Epidemiology of post-stroke behavioural consequences

Liselore Snaphaan

DONDERS
series

This research was carried out at the Radboud University Nijmegen, Medical Centre, at the department of Neurology and at the Donders Institute - Centre for Cognitive Neuroimaging, Radboud University Nijmegen, the Netherlands.

Financial support for printing this thesis by apotheek Heerkens B.V, Janssen-Cilag B.V, Lundbeck B.V, Boehringer Ingelheim is gratefully acknowledged.

Cover design and layout: www.promotie-inzicht.nl
Printed by: Ipskamp Drukkers, Enschede

ISBN 978-90-9025095-3

Epidemiology of post-stroke behavioural consequences

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortman
volgens het besluit van het college van decanen
in het openbaar te verdedigen
op vrijdag 12 maart 2010
om 10:00 uur precies

door

Liselore Johanna Antonia Emeritiana Snaphaan
geboren op 2 augustus 1978
te Druten

Promotor

Prof. dr. G.W.A.M. Padberg

Copromotor

Dr. F.E. de Leeuw

Manuscriptcommissie

Prof. dr. R.P.C. Kessels

Prof. dr. L.J. Kappelle (UMC Utrecht)

Prof. dr. A.C.H. Geurts

Table of contents

General introduction

Stroke is the second most common cause of death (after ischemic heart disease) and a major cause of disability worldwide [1]. It is defined as the rapidly developing loss of brain functions due to occlusion or rupture of the cerebral blood vessels. Hippocrates (460 to 370 BC) was first to describe the phenomenon “stroke” by sudden paralysis. Later, in 1658, Johann Jacob Wepfer (1620–1695) identified two types of stroke, ischemic or haemorrhagic. He also described the rapid recovery of neurological symptoms, which would nowadays be referred to as transient ischemic attacks (TIA’s).
The traditional definition of stroke, devised by the World Health Organisation in the 1970s [2], is a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours". Stroke due to ischemia (80% of all reported stroke incidents) is caused by an occlusion of a blood vessel in the neck or brain due to a thrombosis or embolism. The 24-hour limit arbitrarily distinguishes ischemic stroke from transient ischemic attack (TIA), which is a related syndrome of stroke symptoms that resolve completely within 24 hours.
A haemorrhagic stroke (20%) is caused by rupture of a blood vessel resulting in either an intracerebral haemorrhage (15%) or a subarachnoid haemorrhage (5%).

The clinical symptoms often depend on the location of the stroke. These symptoms include “visible” consequences such as hemiparesis, aphasia, dysarthria or visual deficits. In the first few days to weeks after stroke, common clinical practice mainly focuses on rehabilitation of these “visible” consequences of stroke. Improvement of these motor or language limitations is usually seen in the first days to weeks after the acute stroke event. Then, after these periods with often strenuous rehabilitation medicine, the “non visible” or behavioural consequences after stroke such as depressive symptoms, cognitive decline or fatigue become apparent.

Many studies investigated the prevalence and risk factors of these behavioural consequences of stroke. However, these studies differed tremendously in terms of patient inclusion (age, gender, number of patients that were used) and times following the stroke at which the behavioural assessments were performed. That makes comparison between studies difficult. Furthermore, most studies did not take into account that some so-called post-stroke behavioural consequences may already present before the stroke. Therefore, complete information should be present on the presence of ***pre-***stroke characteristics (for example depression and cognitive decline in the medical history or white matter lesions, previous

stroke and cerebral atrophy) that themselves, independent from the stroke, may be related to depressive symptoms [3-5], impaired cognition [6-10], fatigue [11-13] and consequently could confound the stroke – behaviour relation. Most studies on the epidemiology of post-stroke behavioural consequences are cross sectional in nature and prospective studies are still scare. In addition they usually do not attempt to investigate underlying mechanisms of these behavioural consequences. For example, post-stroke cognitive dysfunction is usually well explained by the size and location of the infarction. An explanation of the occurrence of memory dysfunction after stroke (especially episodic memory dysfunction) is currently lacking, as there is almost never an infarction in the medial temporal lobe (MTL). A proper MTL function is essential for memory encoding and retrieval. With the aid of fMRI we tried to find an explanation for this frequently observed post-stroke memory dysfunction.

The aim of this thesis is to report on frequency, time-course and risk factors of several post-stroke behavioural consequences including depressive symptoms, cognitive dysfunction and fatigue. We wanted to do so by taking the effect of possible confounders from the medical history, pre-stroke neuroimaging and stroke characteristics into account.

The studies presented in this thesis are based on the ongoing Nijmegen Stroke Study. This database has started in 2005 and prospectively investigates short- and long-term consequences of stroke with regular pre-planned assessments after stroke.
The first part of this thesis (chapter 2) is devoted to *post-stroke depressive symptoms* (PSDS) in stroke survivors. It starts with a systematic review that investigates available data on frequency, time-course, possible confounders from the medical history, pre-stroke neuroimaging characteristics and risk factors of PSDS (chapter 2.1). Secondly, chapter 2.2 cross-sectionally investigates the risk factors of post-stroke depressive symptoms among 420 patients with different stroke subtypes by taking possible pre- and stroke related confounders into account.

The second part of this thesis (chapter 3.1) systematically reviews on frequency, time-course and risk factors of *post-stroke memory function*. In chapter 3.2, we attempted to investigate the etiology of a reduced post-stroke memory performance with the aid of fMRI.

In chapter 4 we prospectively investigate the frequency and risk factors of *post-stroke fatigue among 108 patients with a cerebral infarction.*
In the final part of this thesis (chapter 5) the main findings are summarised and discussed. All new findings are put in perspective and suggestions for clinical practice and future research are put forward.

References

1. Donnan GA, Fisher M, Macleod M, et al. Stroke. *Lancet* 2008;371:1612-1623.
2. World health organization. Cerebrovascular disorders : a clinical and research classification. *Cerebrovascular Disorders* (Offset Publications) 1978.
3. Austin MP, Mitchell P, Wilhelm K, et al. Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? *Psychol Med* 1999;29:73-85.
4. Beats B, Levy R, Forstl H. Ventricular enlargement and caudate hyperdensity in elderly depressives. *Biol Psychiatry* 1991;30:452-458.
5. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry* 2000;57:1071-1076.
6. Burns JM, Church JA, Johnson DK, et al. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. *Arch Neurol* 2005;62:1870-1876.
7. Korf ES, Wahlund LO, Visser PJ, et al. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology* 2004;63:94-100.
8. Mungas D, Jagust WJ, Reed BR, et al. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. *Neurology* 2001;57:2229-2235.
9. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992;55:967-972.
10. Vataja R, Pohjasvaara T, Mantyla R, et al. MRI correlates of executive dysfunction in patients with ischaemic stroke. *Eur J Neurol* 2003;10:625-631.
11. Aaronson LS, Teel CS, Cassmeyer V, et al. Defining and measuring fatigue. *Image J Nurs Sch* 1999;31:45-50.
12. de Lange FP, Kalkman JS, Bleijenberg G, et al. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005;26:777-781.
13. Harboe E, Greve OJ, Beyer M, et al. Fatigue is associated with cerebral white matter hyperintensities in patients with systemic lupus erythematosus. *J Neurol Neurosurg Psychiatry* 2008;79:199-201.

Post-stroke depressive symptoms

2.1 Epidemiology of post-stroke depressive symptoms

Abstract

Many studies described the frequency and risk factors of post-stroke depression/ depressive symptoms, although they often lack assessment of confounders (such as depression in the medical history, white matter lesions, atrophy) that may be related to depression, independent from the stroke. We therefore systematically reviewed available data on post-stroke depression by taking the previously mentioned confounding factors into account.

We performed a systematic PubMed and Embase search with the following medical subject heading terms and text words: *cerebrovascular disorder, brain infarction* and *depression*. The search yielded 1796 papers; 107 fulfilled inclusion criteria.

Patients with post-stroke physical/cognitive impairment or depression in their medical history had the highest prevalence of post-stroke depression/depressive symptoms. There were almost no studies that adjusted for confounders in multivariate analysis.

This study reviews the largest number of papers in this area thus far. This review found that psychiatric or depressive disorders in the medical history or post-stroke physical limitations are related with post-stroke depression/depressive symptoms rather than stroke specific (location, size) factors. Virtually no study reported on adjustment for confounding factors.

Liselore Snaphaan and Frank-Erik de Leeuw. Post-stroke depression: a systematic review on pre- and post-stroke clinical and neuroimaging correlates. Aging Health. June 2009, 5:449-449

Introduction

Depression and depressive symptoms after stroke (PSD/PSDS) frequently occur and they interfere with successful stroke recovery [1-3]. Some suggest a causal role for the stroke itself or related factors, whereas others view its occurrence as a reaction on a major life event. PSD and PSDS incidence varies dramatically across studies from 16% to 74% and 11% to 78%, respectively. The interpretation and reproducibility of these figures is limited, in part due to methodological differences between studies. A standardised assessment of depression after stroke may aid in establishing a true estimate of its prevalence and a better understanding of its etiology.

To investigate whether indeed the stroke itself is responsible for the emergence of depression after a stroke this should preferably be assessed in first-ever stroke patients after a standardised stroke – depression assessment time interval. In addition, complete information should be available on the presence of psychiatric or depressive disorders in the medical history, stroke characteristics (including size, location, clinical severity and degree of disability) and pre-stroke neuroimaging characteristics (such as white matter lesions, silent brain ischemia, medial temporal lobe atrophy, cortical atrophy) that themselves may be related to depressive symptoms, independent from the stroke and consequently could confound the stroke – depression relation.

From an etiological point of view one should study first-ever stroke patients that should be as free as possible from the earlier mentioned characteristics. From a clinical (prognostic) point of view one would preferably investigate all stroke patients with complete information on all the previously mentioned items in order to identify prognostic factors for PSD/PSDS. One of the reasons for the controversy around the post-stroke depression concept is because of its poor operationalisation. Secondly, because of a lack of standardised assessment of potential confounders, even in some previous reviews on PSD and PSDS [4-6]. Another explanation for the ongoing controversy is that many separate reports deal with data from one single cohort.

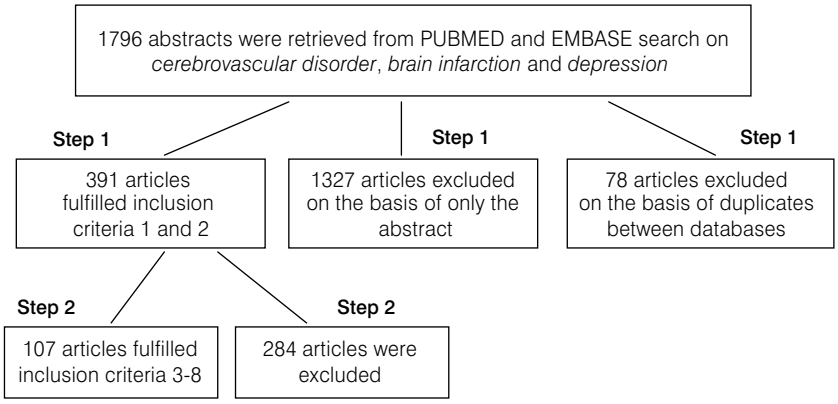
The aim of the present study was therefore to systematically review the available data on frequency, time-course and risk factors of PSD/PSDS in stroke survivors. Secondly, we aimed to evaluate the effect of the previously mentioned possible confounders from the medical history, pre-stroke neuroimaging characteristics and stroke characteristics on the prevalence of PSD/PSDS, by carefully avoiding double counting of multiple reports derived from single cohorts.

Methods

A literature search of PubMed and Embase computerised databases was performed in 2008. We included all papers dealing with stroke and depression and therefore entered the following medical subject heading (MeSH) terms and text words in full and truncated: 'cerebrovascular disorder, brain infarction and depression. In accordance with the literature the term cerebrovascular disorder included both cerebral infarcts and intracerebral haemorrhages. The search was limited to the English language, to those papers with abstracts, and included human studies with participants of 45 years of age or over.

We followed a two-step approach in the selection of eligible articles (see figure 1). First, one reviewer (LS) screened the abstracts for the following characteristics: (1) original paper, published in English on case-control or cohort studies (sample size had to be at least 20), and (2) information about depression and stroke. From screen positive abstracts full papers were collected and went into a second selection step to

Figure 1 The stepwise approach in the selection of eligible and included articles



identify papers that fulfilled the following inclusion criteria: (3) description of the stroke (clinically well defined sudden onset of a neurological deficit with a corresponding lesion on neuroimaging); in addition information on *at least one* of the following five characteristics had to be present: (4) stroke location and severity, (5) description and operationalisation of depression/depressive symptoms according to international diagnostic criteria (6) at least 50% first-ever stroke survivors in the study population (7) information on neuroimaging characteristics (at least one of the following: white matter lesions, silent brain infarction and medial temporal lobe atrophy) and (8) information on pre-stroke (bio)psychological factors (medical history of depression/ depressive episodes and/or psychiatric disease). Papers were evaluated in this second selection criteria by two authors independently (LS and FEdL). In case of disagreement a consensus meeting was held.
The Pubmed and Embase search strategy yielded 1796 papers. After screening of the title and the abstracts, 391 papers were retrieved full-text and examined against the inclusion criteria, of which 107 were included and went on to the data extraction stage (figure 1).

Results

In total 45 studies investigated the presence of PSD at one or more time-points after stroke and 62 studies investigated PSDS at one or more time-points after stroke. PSD was diagnosed on basis of the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM) version III [7] (n=30 studies), DSM version IV [8] (n=12 studies) or Research Diagnostic Criteria [9] (RDC: n=3 studies). PSDS was defined by the following rating scales; Hamilton Depression Rating Scale (HDRS) [10], (n= 14 studies), Beck Depression Inventory (BDI) [11], (n=12 studies), Hospital anxiety and depression scale (HADS) [12], (n=10 studies), Centre for epidemiologic studies depression scale (CES-D)[13], (n=10 studies), Zung Self-Rating Depression Scale (ZDS) [14], (n=6 studies), Montgomery-Asberg Depression Rating Scale (MADRS) [15], (n=6 studies), Geriatric Depression Scale (GDS) [16], (n=2 studies), Cornell Depression Scale (CDS) [17], (n=1 study), Clinical Interview Schedule-Revised (CIS-R) [18], (n=1 study).

Prevalence and time-course of PSD/PSDS

The prevalence of PSD/PSDS measured at more than one time-point within studies (n=25, table 1) varied from 5% to 79% within one month after stroke, which showed a tendency to decline to 8% to 59% one year after stroke, although six studies

[19,20,21,22,23,24] showed a stable time-course (stroke survivors investigated n=976, range n=25-436) while six studies [25,26,27,28,29,30] showed an increase of PSD/PSDS after longer stroke – depression assessment intervals (stroke survivors investigated n=840, range n=80-189). The prevalence of PSD/PSDS that was assessed at one single time-point per study (n=83) varied between 16-74% and 11-78%, respectively (data not shown).

Post-stroke characteristics and PSD/PSDS

Type of stroke (infarction versus haemorrhage), size, side, localisation, stroke severity and aphasia

Most studies (table 2, 3) did not find any relation between type (infarction versus haemorrhage) and size of stroke, nor with aphasia (the Western Aphasia Battery [31] was most commonly used) and the presence of PSD/PSDS. Thirty-three studies (stroke survivors n=5964, range n=26-662) did not find a relationship between lesion side and PSD/PSDS, although seven studies [32-38] (stroke survivors n=506, range n=25-141) found an increased prevalence of PSD/PSDS among those with a left sided lesion, whereas one study [39] (n=145) found this among those with a right sided lesion. Some studies investigated the effect of localisation on PSD and PSDS in more anatomical detail. Most studies [26,40,41,42,43,44,45,46,47,48,49,28,35,50,36,37,51,52,53] (stroke survivors investigated n=2590, range n=20-421) found a relation between PSD/PSDS and infarcts in the anterior part of the brain, especially in the left anterior hemisphere. One study [54](n=120) found an increased prevalence of PSD among patients with infarcts in the posterior part of the brain (hemisphere not specified). Four studies [55,56,20,29] (stroke survivors investigated n=475, range n=89-161) found a higher prevalence of PSD/PSDS among those with a more severe stroke, whereas three studies [38,57,58] (stroke survivors investigated n= 201, range n=33-95) did not (table 2, 3).

Pre-stroke neuroimaging characteristics and PSD/PSDS

There are a number of factors that presumably were already present before stroke (such as a (silent) previous infarction, white matter lesions (WML), medial temporal lobe atrophy (MTA) and cerebral atrophy) that have found to be related with depressive symptoms or depression irrespective of a stroke [59-61]. Consequently, their presence could explain depressive symptoms or depression in stroke patients, not necessarily

related to the stroke. As a result of the fact that stroke survivors usually did not have neuroimaging before the actual stroke, the effects of these factors on PSD/PSDS are difficult to disentangle from the direct stroke effects. Nine [30,52,60-67] studies tried to overcome this problem by rating these characteristics on neuroimaging performed during the stroke diagnosis (table 4). One study [60] (stroke survivors included n=80) found an increased prevalence of PSD among those with the most severe cortical atrophy than those without, whereas others (stroke survivors investigated n=1506, range n=70-395) did not find any relation between any of the mentioned pre-stroke neuroimaging characteristics and PSD/PSDS.

Demographics, pre-stroke (bio)psychological and post-stroke clinical characteristics and PSD/PSDS

Age, sex, education level and marital status

Most studies didn't find any relation between age, sex, education or marital state and PSD/PSDS (table 5, 6).

Pre-stroke psychiatric or depressive disorders in the medical history

Eleven of the 20 studies [59,68,43,69,21,70,71,33,53,52,66] (stroke survivors investigated n=2684, range n=52-739) indicated a higher occurrence of PSD/PSDS among those with a history of depression (table 5, 6). In the remaining studies [30,72,42,44,32,73,74,54,51] (stroke survivors investigated n=1322, range n=50-421) there was no such relation.

Post-stroke physical disability

In 27 studies (stroke survivors investigated n=5201, range n=35-739) a higher prevalence of PSD/PSDS was found among those with a higher degree of physical disability than those without (table 5, 6). In seven studies [30,59,32,2,33,50,75] (stroke survivors investigated n=981, range n=38-285) no such relation was found.

Post-stroke cognitive function

Thirteen studies [59,41,42,2,49,62,63,50,75,74,76,29,23] (stroke survivors investigated n=2030, range n=38-421) found a higher prevalence of PSD/PSDS among those with

Table 1 Prevalence of post-stroke depression and depressive symptoms: a time-course

Depression Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	screenings tool depression
[72]	50	51(1)	100	DSM IV
[26]	80	73(ng)	80	DSM III-R
[80]	70	73(ng)	80	DSM III-R
[82] †	106	66(12)	100	DSM III-R
[83] †	106	66(ng)	100	DSM III-R
[81]	128	71(ng)	100	DSM III
[28]	103	59(13)	76	DSM III
[32]	99	71(10)	76	DSM III
[22]	50	60(12)	84	DSM IV
[30]	189	69(12)	100	DSM IV
Depressive symptoms **Ref**				**screenings tool depressive symptoms**
[66]	202	75(ng)	88	MADRS
[21]	436	75(12)	83	MADRS
				ZDS
[85]	162	67(ng)	100	CES-D
[59]	285	69(ng)	74	HDRS
[20]	161	67(13)	100	BDI
[47]	128	71(14)	100	BDI
[27]	153	35-75	100	HDRS
[25]	190	69(12)	100	BDI/HADS
[56]	100	55(11)	100	BDI
[29]	125	76(ng)	70	HADS
[44]	26	63(9)	100	HDRS
[57]	95	67(11)	100	CESD
[23]	104	59(10)	100	CDS
[24]	145	73(12)	100	MADRS
[86]	200	72(11)	58	GSD

Empty cells: no assessment, ng: not given, DSM: Diagnostic and Statistical Manual of Mental Disorders, MADRS: Montgomery-Asberg Depression Rating scale, ZDS: Zung Self Rating Depression Scale, CES-D: Centre for epidemiological Studies Depression scale, HDRS: Hamilton Depression Rating Scale, BDI: Becks Depression Inventory, HADS: Hospital Anxiety Depression Scale, CDS: Cornell Depression Scale, ↓ Indicates at least a 10% decrease in the prevalence of post-stroke depression/depressive

prevalence of post-stroke depression (%) by stroke – depression assessment interval (months)							change over time
<1	1	2-4	5-6	7-9	12	>12	
20		4					↓
25		31				29(3yr)*	↑
29		30				24	↓
		48			37		↓
		46			36		↓
	43	32			22		↓
35		47	60				↑
35						13	↓
44			40			44	=
	22				39		↑

cut-off	prevalence of post-stroke depressive symptoms (%) by stroke – depression assessment interval (months)							change over time
≥7				43		36	18(3yr)*	↓
≥7			27			22		↓
≥50			22			21		=
≥23		34		25				↓
≥13		79		30				↓
>10		41				42		=
≥13		20				8		↓
>17	29		32	60				↑
9/10 and 7/8		22	26	30	34	39		↑
≥10	27		29	23		24	26	↓
>8	5	16	21					↑
≥13	31		34					=
≥16	69			48				↓
≥11			24			25		=
≥12			55			59		=
≥5	60			35				↓

symptoms between first and last assessment , = Stable prevalence of PSD over time (plus or minus 10% between first and last assessment), ↑ Indicates at least a 10% increase in the prevalence of post-stroke depression/depressive symptoms between first and last assessment,
* indicates the stroke-depression/depressive symptoms assessment Interval, † multiple publication based on virtually the same patient cohort.

Table 2 Relation between the occurrence of ***post-stroke depression*** and stroke characteristics

Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke - depression assessment interval (months)				type of stroke (%)		side (%)	
				<1	1-6	7-12	>12	infarction	relation	left	relation
[51]	159	67(ng)	75		+			100			
[40]	273	64(16)	100		+		+	100		45	N
[64]	70	70(ng)	100		+			100			
[72]	50	51(1)	100	+	+					54	
[98]	126	ng	100		+			I/H		46	N
[99]	301	55(ng)	56	+				80		57	N
[26]	80	44-100	80	+	+	+	+	79		50	
[37]	25	late 50-60	100	+				I/H		56	L↑
[100]	53	59(ng)	100		+			I/H	N	49	N
[101]	30	57(ng)	73		+			I/H		60	L↑
[81]	128	18-96	100		+	+				30	
[73]	94	70(ng)	52		+		+	I/H	N	ng	N
[74]	60	>75=45%	100				+	81		52	
[44]	130	68(ng)	100		+					45	N
[43]	87	63(14)	68		+					36	N
[50]	38	55(ng)	100	+				I/H		76	
[54]	120	58(ng)	100	+				I/H		23	
[33]	141	56(ng)	83	+				79	N	45	L↑
[32]	99	71(10)	76	+				82		47	L↑
[49]	41	70(ng)	100		+			I/H		59	
[77]	190	69(12)	100		+			100		47	N
[52]	275	71(7)	70		+			I/H			
[102]	149	81(5)	73				+	94		ng	N
[30]	189	69(12)	100	+		+		100		47	N

Empty cells: no assessment, ng: not given, Y: Yes, N: No, + indicates timing of post-stroke depression assessment, I: Infarction, H: Haemorrhage, I/H: Infarction/Haemorrhage proportion not given, L: Left hemisphere, R: Right hemisphere, L/R: Left/Right lesion proportion not given, * assessed by NIHSS: (National Institute of Health Stroke Scale) or SSS (Scandinavian Stroke Scale), A: Anterior part of the brain, P: Posterior part of the brain, † anterior cerebral artery, ↑ higher prevalence of post-stroke depression among stroke patients with a left sided stroke/anterior or posterior lesion/larger lesion volume/aphasia, ↓ lower prevalence of post-stroke depression among stroke patients with a smaller lesion volume.

posterior/anterior part of the brain		size (volume)		stroke severity*		aphasia	
left/right	relation	assessed	relation	assessed	relation	assessed	relation
L/R	Anterior ↑ †						
L	Anterior ↑ †	Y	N			Y	↑
L/R		Y	N				
		Y	N	Y			
		Y	N				
L	Anterior ↑	Y	N				
L	Anterior ↑					Y	N
		Y	N				
L/R	Anterior↑						
		Y	N				
		Y	↑				
L/R	Both↑						
L	Anterior ↑	Y	↑				
L/R	Anterior ↑	Y	↓				
L/R	Posterior↑	Y	N				
		Y	N				
L	Anterior ↑	Y					
L/R	N						
L	Anterior ↑	Y	N				
L/R	N	Y	N				

Table 3 Relation between the occurrence of ***post-stroke depressive symptoms*** and stroke characteristics

Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke – depressive symptoms assessment interval (months)				type of stroke (%)		side (%)	
				<1	1-6	7-12	>12	infarction	relation	left	relation
[62]	126	62(13)	100	+				88		42	N
[58]	35	55-91	72			+		87	N		
[66]	202	75(ng)	88		+		+	88		46	
[103]	72	33-85	100		+			I/H		51	N
[39]	145	18-93	75		+			I/H		55	R↑
[21]	436	75(12)	83		+		+	86		49	N
[46]	47	24-79	100		+			88		68	
[48]	20	53(9)	100	+				I/H		45	
[104]	148	62(ng)	100		+			85	N	54	N
[41]	417	68(ng)	81		+			I/H		ng	N
[59]	285	25-80	74		+			81		ng	N
[20]	161	67(13)	100		+	+		85		ng	N
[47]	128	71(14)	100		+	+		81		34	N
[36]	35	66(ng)	100		+			I/H		54	L↑
[28]	48	59(ng)	100	+				46			
[55]	89	55(11)	100	+				100		42	
[105]	60	71(11)	100				+	I/H		52	N
[34]	103	63(11)	74	+	+		+	I/H		46	L↑
[27]	153	35-75	100	+	+						N
[106]	662	63(ng)	71	+				I/H	N	48	N
[107]	50	51-89	100	+						22	N
[42]	421	72(8)	75		+			I/H		34	
[73]	192	62(13)	100	+				83		40	N
[56]	100	55(11)	100	+	+	+	+	I/H		42	N
[29]	125	76(ng)	70	+	+			96			
[108]	165	57(11)	100			+	+	69	↑	45	N
[68]	178	57(13)	59	+				68	N	24	N
[45]	243	65(11)	89		+			I/H			
[19]	26	63(9)	100	+				100		58	N
[78]	178	69(11)	67	+				100		36	N
[38]	73	52(10)	100		+			80		43	L↑

posterior/anterior part of the brain		size (volume)		stroke severity*		aphasia	
left/right	relation	assessed	relation	assessed	relation	assessed	relation
		Y	↑				
				Y	N		
L/R							
				Y			
L/R		Y	↑				
		Y					
L	Anterior ↑ †	Y	N				
L/R	Anterior↑	Y	N				
L/R	N	Y	N				
L/R	Anterior ↑ †						
		Y	N				
				Y	↑		
L/R	Anterior ↑						
R	Both↑	Y	↑				
L	Anterior ↑	Y				Y	N
				Y	↑	Y	N
		Y	↑				
						Y	N
		Y	N				
L/R	Both↑ †			Y			
		Y	N				
				Y	↑	Y	N
				Y	↑		
L/R	N					Y	N
L	Anterior ↑	Y	↑				
				Y	N		
				Y	N		
				Y	N		

Table 3 Continued

Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke – depressive symptoms assessment interval (months)				type of stroke (%)		side (%)	
				<1	1-6	7-12	>12	infarction	relation	left	relation
[57]	95	67(11)	100	+	+			80	N	43	N
[53]	93	37-86	100	+				I/H		46	N
[63]	91	62(13)	100		+			I/H	N	43	N
[23]	104	59(10)	100		+			78	N	49	N
[79]	452	67(12)	85		+			57		ng	N

Empty cells: no assessment, ng: not given, Y: Yes, N: No, + indicates timing of post-stroke depressive symptoms assessment, I: Infarction, H: Haemorrhage, I/H: Infarction/ Haemorrhage proportion not given, L: Left hemisphere, R: Right hemisphere, L/R: Left/Right lesion proportion not given,* assessed by IHSS (National Institute of Health Stroke Scale) or SSS (Scandinavian Stroke Scale), A: Anterior part of the brain,

Table 4 Relation between occurrence of post-stroke depression/depressive symptoms and pre-stroke neuroimaging characteristics

Depression Ref	n	mean age/range (yrs (SD))	proportion first-ever stroke (%)	stroke-depression assessment interval (months)			
				<1	1-6	7-12	>12
[64]	70	70(ng)	100		+		
[60]	80	73(ng)	80				+
[52]	275	71(7)	70		+		
[30]	189	69(12)	100	+		+	
Depressive symptoms Ref							
[62]	126	62(13)	100	+			
[66]	202	75(ng)	88		+		+
[65]	158	55-85	ng		+		
[63]	91	62(13)	100	+			
[67]	395	70(7)	79		+		

Empty cells: no assessment, ng: not given, Y: Yes, N: No, + indicates timing post-stroke depression/ depressive symptoms assessment, WML: White Matter Lesion, MTA: Medial Temporal Lobe Atrophy,

posterior/anterior part of the brain		size (volume)		stroke severity*		aphasia	
left/right	relation	assessed	relation	assessed	relation	assessed	relation
				Y	N		
L/R	Anterior ↑	Y	↑				
L/R	N	Y	↑	Y	N		
		Y	ng				

P: Posterior part of the brain, † anterior/posterior cerebral artery, ↑ higher prevalence of post-stroke depressive symptoms among patients with a left sided stroke/anterior or posterior lesion/larger lesion volume/more severe stroke.

silent infarction		WML		MTA		cortical atrophy	
assessed	relation	assessed	relation	assessed	relation	assessed	relation
		Y	N	Y	N	Y	N
						Y	↑
		Y	N	Y	N	Y	N
Y	N	Y	N				
Y	N	Y	N				
Y		Y	N			Y	N
		Y	N	Y	N	Y	N
Y	N	Y	N				
		Y	N				

↑ higher prevalence of post-stroke depression among stroke patients with more atrophy.

Table 5 Relation between occurrence of ***post-stroke depression*** and demographic/(bio)psychological pre-and post-stroke characteristics

								Demographics			
Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke-depression assessment interval (months)				age		sex	
				<1	1-6	7-12	>12	assessed	relation	assessed	relation
[51]	159	67(ng)	75		+			Y	N	Y	female↑
[40]	273	64(16)	100		+		+				
[72]	50	51(1)	100	+	+			Y		Y	female↑
[26]	80	44-100	80	+	+	+	+	Y			
[70]	52	60(12)	100	+				Y	N	Y	female↑
[109]	88	70(10)	76		+			Y	N	Y	female↑
[2]	49	69(ng)	70		+		+	Y	N	Y	N
[73]	94	70(ng)	52		+		+	Y	N	Y	N
[74]	60	>75 =45%	100				+	Y	older↑	Y	N
[44]	130	68(ng)	100		+			Y	N	Y	N
[43]	87	63(14)	68		+			Y	N	Y	N
[50]	38	55(ng)	100	+				Y	N	Y	N
[49]	94	71(10)	73		+		+	Y	N	Y	N
[54]	120	58(ng)	100	+				Y	N	Y	N
[33]	141	56(ng)	83	+				Y	younger↑	Y	N
[32]	99	71(10)	76	+				Y	N	Y	N
[77]	190	69(12)	100		+			Y		Y	N
[52]	275	71(7)	70		+			Y	N	Y	N
[102]	149	81(5)	73				+	Y	N	Y	N
[30]	189	69(12)	100	+		+		Y	N	Y	N

Empty cells: no assessment, ng: not given, Y: Yes, N: No, + indicates timing of post-stroke depression assessment, ↑ indicates higher prevalence of post-stroke depression among patients who were living alone/had a history of depression or psychiatric disease/had more post-stroke physical disability/ suffered from post-stroke cognitive impairment, BI: Barthel Index, JHFI: John Hopkins Functional Inventory, ADL: Activity Daily Living, MMSE: Mini Mental State.

Demographics				Pre-stroke characteristic		Post-stroke characteristics			
education		living alone		history of depression/ psychiatric disease		physical disability		cognitive impairment	
assessed	relation	assessed	relation	assessed	relation	assessed	relation	assessed	relation
Y	low↑	Y		Y	N				
						BI	↑		
		Y		Y	N				
		Y	↑						
				Y	↑	BI	↑	MMSE	N
		Y	N			BI	N	MMSE	↑
		Y	N						
		Y	N	Y	N	BI	↑	MMSE	N
		Y	N	Y	N	BI	↑	MMSE	↑
		Y	N	Y	N				
Y	N	Y	N	Y	↑	BI	↑	MMSE	N
Y	N	Y	N			JHFI	N	MMSE	↑
		Y	N			BI	↑	MMSE	↑
Y	N	Y	N	Y	N				
				Y	↑	ADL	N	MMSE	N
		Y	N	Y	N	BI	N	MMSE	N
								MMSE	N
Y	N	Y	N	Y	↑	ADL	↑	MMSE	N
				Y	N	BI	N		

Table 6 Relation between occurrence of ***post-stroke depressive symptoms*** and demographic/(bio)psychological pre-and post-stroke characteristics

								Demographics			
Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke-depressive symptoms assessment interval (months)				age		sex	
				<1	1-6	7-12	>12	assessed	relation	assessed	relation
[71]	196	15-49	100				+	Y	N	Y	N
[62]	126	62(13)	100	+				Y		Y	
[66]	202	75(ng)	88		+		+	Y	younger↑	Y	
[103]	72	33-85	100		+			Y		Y	female↑
[39]	145	18-93	75		+			Y	younger↑	Y	
[21]	436	75(12)	83		+		+	Y		Y	female↑
[76]	40	63(ng)	82			+		Y		Y	N
[104]	148	62(ng)	100		+			Y	N	Y	N
[41]	417	68(ng)	81		+			Y	N	Y	N
[87]	508	66(12)	100		+			Y	age 45-85↑	Y	female↑
[59]	285	69 (ng)	74		+			Y	N	Y	female↑
[20]	161	67(13)	100		+	+		Y	older↑	Y	female↑
[36]	35	66(ng)	100		+			Y		Y	
[55]	89	55(11)	100	+				Y	older↑	Y	N
[110]	207	64(12)	100	+				Y	N	Y	female↑
[106]	626	63(13)	71	+				Y	N	Y	N
[42]	421	72(8)	75	+				Y		Y	female↑
[111]	119	61(12)	69				+	Y	N		
[56]	100	55(11)	100	+	+	+	+	Y	N	Y	N/male↑*
[29]	125	76(ng)	70	+	+						
[75]	141	72(11)	84	+	+			Y		Y	
[108]	165	57(11)	100			+	+	Y	N	Y	N
[68]	178	57(13)	59	+				Y	N	Y	female↑

Demographics				Pre-stroke characteristic		Post-stroke characteristics			
education		living alone		history of depression/ psychiatric disease		physical disability		cognitive impairment	
assessed	relation	assessed	relation	assessed	relation	assessed	relation	assessed	relation
		Y	↑	Y	↑	mRS	↑	MMSE	
Y						BI	↑	6 domains	↑
Y				Y	↑	mRS	↑		
Y	N	Y	N			BI			
		Y				BI	↑		
Y		Y		Y	↑	FIM			
						QRS	↑	QRS	↑
Y	N					BI	↑		
		Y	N			BI	↑	GHQ	↑
Y	high↑								
Y	N	Y	↑	Y	↑	BI	N	BCRS	↑
		Y	↑						
						FIM	↑		
Y	N	Y	N			BI/mRS	↑		
		Y	N			BI/mRS	↑		
		Y				BI	↑		
Y	N	Y	N	Y	N	BI	↑	MMSE	↑
		Y	N			BI	↑ †		
						BI	↑	MMSE	↑
Y		Y				ADL	N	ATM	↑
Y	N	Y	N			ADL	↑ *		
				Y	↑				

Table 6 Continued

Ref	n	mean age/ range (yrs(SD))	proportion first-ever stroke (%)	stroke-depressive symptoms assessment interval (months)				Demographics			
								age		sex	
				<1	1-6	7-12	>12	assessed	relation	assessed	relation
[19]	26	63(9)	100	+				Y	N	Y	N
[69]	739	69(13)	88		+			Y	N	Y	N
[78]	178	69(11)	67	+				Y	N	Y	N
[38]	73	52(10)	100		+			Y	younger↑	Y	
[57]	95	67(11)	100	+	+			Y		Y	
[53]	93	37-86	100	+				Y		Y	N
[63]	91	62(13)	100		+			Y	N	Y	female↑
[23]	104	59(10)	100			+		Y	N	Y	N
[79]	452	67(12)	85			+		Y	N	Y	N

Empty cells: no assessment, ng: indicates not given, Y: Yes, N: No, + indicates timing of post-stroke depressive symptoms assessment * only more than one year post-stroke, † relation only at six months post-stroke, ↑ indicates higher prevalence of post-stroke depression among patients who were living alone/ had a history of depression or psychiatric disease/had more post-stroke physical disability/suffered from

post-stroke cognitive impairment compared with those without (table 5, 6). In nine studies [77,43,78,70,32,73,33,52,79] (stroke survivors investigated n=1568, range n=52-452) this relation could not be identified.

Discussion

Data from 107 studies were reviewed on frequency, time-course and risk factors of post-stroke depression/depressive symptoms (PSD/PSDS) in survivors, making it the largest review in this area. In part, some of this has also been addressed in previous reviews [4-6], however they often lacked detailed assessment of possible confounders

Demographics				Pre-stroke characteristic		Post-stroke characteristics			
education		living alone		history of depression/ psychiatric disease		physical disability		cognitive impairment	
assessed	relation	assessed	relation	assessed	relation	assessed	relation	assessed	relation
				Y	↑	ADL	↑		
		Y	N			BI	↑	MMSE	N
Y		Y				FIM	↑		
Y						BI	↑		
				Y	↑				
Y	N							MMSE	↑
						BI	↑	PCRS	↑
								MMSE	N

post-stroke cognitive impairment, BI: Barthel Index, ADL: Activity Daily Living, mRS: modified Rankin Scale, FIM: Functional Independence Measure, QRS: Questionnaire on Resources and Stress, MMSE: Mini Mental State, GHQ: General Health Questionnaire, BCRS: Brief Cognitive Rating Scale, ATM: Abbreviated Mental Test.

from *pre-stroke* (bio)psychological/neuroimaging characteristics in combination with *post-stroke* characteristics on the prevalence of PSD/PSDS.

The prevalence of PSD/PSDS varied from 5% to 79% within one month after stroke, which showed a tendency to decline to 8% to 59% one year after stroke (table 1). Except for post-stroke physical/cognitive disability, there was no relation for post-stroke characteristics and PSD/PSDS. In addition, there was no relation for pre-stroke (bio) psychological/neuroimaging characteristics (including age, sex, education, marital status, silent infarction, WML, medial temporal lobe atrophy, cortical atrophy) and PSD/PSDS. Whereas, psychiatric or depressive disorders in the medical history was significantly related with PSD/PSDS in most studies.

However, some methodological aspects must be considered. A proper identification of risk factors for any outcome requires structured and standardised assessment of that particular outcome. PSD and PSDS have been assessed with the aid of various diagnostic criteria (n=3) or tests (n=16) respectively, making comparisons difficult. Another kind of bias is the fact that multiple publications are based on virtually the same patient cohort; accordingly these results are not entirely based on different study populations (table 1). On the other hand it is almost impossible to exclude these "double counts" at the selection procedure on the basis of unambiguous in-or exclusion criteria as they share, for obvious reasons, the key word upon which selection was based. The sequential assessment of PSD/PSDS *within* studies has been performed in only 25 studies [30,59,26,80,72,27,20,21,47,81,82,83,32,84,22,85, 57,66,23,24,86] that used two different diagnostic criteria (DSM-III or IV) and eight different screening tools to assess PSD/PSDS each with different cut-offs and stroke - depression assessment intervals, which makes it difficult to estimate a reliable PSD/ PSDS time-course. In addition, these studies also differed in terms of patient inclusion (such as number of stroke survivors, first-ever *versus* ever stroke, stroke severity, post-stroke physical disability and post-stroke cognitive impairment), in the collection of pre-stroke neuroimaging data and (bio)psychological factors (such as age, sex, educational level, marital status and medical history of depression). For example, we found considerable a difference in age between the studies making comparisons difficult, as age is an important determinant of depression or depressive symptoms in a number of studies, but not all. [55,20,39,87,33,74,66]

In order to judge the external validity it is essential to have information on the proportion patients that has been included, relative to the stroke population of that particular hospital. Unfortunately, most studies do not report this information. Consequently, all studies report on patients who completed a neuropsychological examination. It seems likely that patients, who could not complete this, presumably had a larger stroke with more severe neurological deficits and suffered more often from aphasia than those who were examined. This could have led to an underestimation of PSD/PSDS. Another source of bias that may lead to underestimation of PSD/PSDS is the fact that all studies only included patients that were actually admitted to the hospital. Many stroke patients, especially the most severely affected, are not admitted to the hospital weeks after stroke and will not be included in studies investigating PSD/PSDS. It seems likely that they are the one with the highest prevalence of PSD/PSDS. On the other hand, people with only a minor stroke may not have been included since they, for example, were not willing to participate months after a stroke from which they had already completely recovered. Theoretically, this could have led to overestimation of PSD/PSDS.

There are several pre-stroke factors, both biological-demographic as well as from the medical history that could, independent from the stroke, relate to PSD/PSDS. Such a confounder could be the presence of vascular white matter lesions, that due do its increased presence in stroke patients [88,89] and its relation with depressive symptoms in the elderly [61] fulfills the criterion of being a confounder. As pre-stroke assessment of depression/depressive symptoms is usually not possible for obvious reasons confounding by (unnoticed) pre-stroke presence or of other pre-stroke factors cannot be excluded. It could therefore be that the differential presence of white matter lesions determines who does and who does not develop PSD/PSDS.

As originally stated by Alexopoulos when proposing his "vascular depression" hypothesis cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults. This means that it may the combination of pre-existent manifestation of cerebrovascular disease (including previous (silent) brain infarctions, vascular white matter lesions) and the acute stroke rather than the acute stroke itself alone that may be related to the emergence of post-stroke depressive symptoms.

In order to assess the relative contribution of this preexistent cerebrovascular disease to the occurrence of post stroke depressive symptoms we reviewed the effect of pre-stroke neuroimaging variables (including white matter lesions and cerebral atrophy) on PSD/PSDS. However, one has to keep in mind that these characteristics were always rated on neuroimaging performed directly *after* the qualifying stroke. Although it seems unlikely, one cannot exclude the fact that early stroke signs (for example the appearance of hypodense areas on a CT) may be misclassified as a white matter lesions. As this misclassification is not related to our outcome (PSD/PSDS), it will most likely be random and, if anything, result in reduced strength of an association between white matter lesions and PSD/PSDS.

Our review shows that only very few studies take possibility of the existence of pre-stroke confounding factors into account. Only nine [30,60,62,63,52,64,65,66,67,67] out of 107 studies assessed their presence and no unequivocal interpretation could be made.

This systematic review clearly points out the methodological limitations and the lack of proof of a clear and predictable relation between stroke characteristics and the occurrence of a depressive episode. It seems therefore plausible that the size, site and severity of a stroke is not causally related to the occurrence of post-stroke depressive symptoms or post-stroke depression [4,6]. This can be understood by taking into consideration the anatomy of the mood regulation system. Anatomically this is a widespread system, involving the frontal lobe (particularly the subgenual

prefrontal cortex), the basal ganglia (particularly the caudate and putamen), the cerebellum, the hippocampus/amygdala complex, and possibly the temporal lobes [90]. It seems unlikely that a single vascular lesion would interrupt such a widely dispersed system to such an extent that it can result in a marked change in mood. This is in line with studies among elderly [91,92] that found a relation between depressive symptoms and WML or cerebral atrophy. This supports the idea that diffuse brain damage, rather than a focal insult, is related with depressive symptoms, possibly by widespread disruptions of the dispersed mood regulation system that may result in accompanying depressive symptoms.

Many studies, (including reviews) have described PSD/PSDS, but almost lacking uniform operationalisation of the outcome and not taken often occurring confounders into account. Our review indicates that, although PSD/PSDS may sound like an attractive concept, there is not much data based on sound methodological studies that support it.

However, there may be no clear proof of a causal relation between stroke and the occurrence of depression or depressive symptoms, from a clinical point of view it is important to identify prognostic factors that could help in early identification of stroke patients at risk for PSD/PSDS. It is known that a previous depressive episode or a previous psychiatric disorder indicates vulnerability for future depression. Any life-event, not only being a stroke, could therefore increase the risk for depression among those patients [93-95]. This systematic review shows indeed that the presence of psychiatric or depressive disorders in the medical history is associated with an increased presence of PSD/PSDS.

Reference List

1. Eriksson M, Norrving B, Terent A, et al. Functional outcome 3 months after stroke predicts long-term survival. *Cerebrovasc.Dis* 2008;25(5), 423-429.
2. Morris PL, Raphael B, Robinson RG. Clinical depression is associated with impaired recovery from stroke. *Med.J.Aust.* 1992;157(4), 239-242.
3. Parikh RM, Robinson RG, Lipsey JR, et al. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. *Arch.Neurol.* 1990;47(7), 785-789.
4. Carson AJ, MacHale S, Allen K et al. Depression after stroke and lesion location: a systematic review. *Lancet* 2000; 356(9224), 122-126.
5. Hackett ML, Yapa C, Parag V, et al. Frequency of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36(6), 1330-1340.
6. Hackett ML , Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36(10), 2296-2301.
7. American Psychiatric Association DSM III. Diagnostic and statistical manual of mental disorders DSM III. In: *Washington D.C:American Psychiatric Press Inc* 1980.
8. American Psychiatric Association DSM IV. Diagnostic and statistical manual of mental disorders DSM IV. In: *Washington D.C:American Psychiatric Press Inc* 1994.
9. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria. *Psychopharmacol.Bull.* 1975;11(3), 22-25.
10. Hamilton M. A rating scale for depression. *J.Neurol.Neurosurg. Psychiatry* 1960;23, 56-62.
11. Beck AT, Ward CH, Mendelsson M, et al. An inventory for measuring depression. *Arch.Gen.Psychiatry* 1961;4, 561-571.
12. Zigmond AS , Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr.Scand.* 1983;67(6), 361-370.
13. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1, 385-401.
14. Zung WW. A self-rating depression scale. *Arch.Gen.Psychiatry* 1965;12, 63-70.
15. Montgomery SA , Asberg M. A new depression scale designed to be sensitive to change. *Br.J.Psychiatry* 1979;134, 382-389.
16. van Marwijk HW, Wallace P, de Bock GH, et al. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Br.J.Gen.Pract.* 1995;45(393), 195-199.
17. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell Scale for Depression in Dementia. *Biol.Psychiatry* 1988;23(3), 271-284.
18. Lewis G, Pelosi AJ, Araya R, et al. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol.Med.* 1992;*22*(2), 465-486.
19. Glodzik-Sobanska L, Slowik A, McHugh P, et al. Single voxel proton magnetic resonance spectroscopy in post-stroke depression. *Psychiatry Res.* 2006;148(2-3), 111-120.
20. Hayee MA, Akhtar N, Haque A, et al. Depression after stroke-analysis of 297 stroke patients. *Bangladesh Med.Res. Counc.Bull.* 2001;27(3), 96-102.
21. Herrmann N, Black SE, Lawrence J, et

al. The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. *Stroke* 1998; 29(3), 618-624.

22. Robinson RG, Murata Y, Shimoda K. Dimensions of social impairment and their effect on depression and recovery following stroke. *Int.Psychogeriatr.* 1999;11(4), 375-384.
23. Wilz G. Predictors of subjective impairment after stroke: influence of depression, gender and severity of stroke. *Brain Inj.* 2007;21(1), 39-45.
24. Lo RS, Cheng JO, Wong EM, et al. Handicap and its determinants of change in stroke survivors: one-year follow-up study. *Stroke* 2008;39(1), 148-153.
25. Aben I, Verhey F, Strik J, et al. A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. *J. Neurol.Neurosurg.Psychiatry* 2003;74(5), 581-585.
26. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke* 1993;24(7), 976-982.
27. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. *Br.J.Psychiatry* 1999;175, 163-167.
28. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients. Importance of location of lesion. *Brain* 1984;107 (Pt 1), 81-93.
29. Townend BS, Whyte S, Desborough T, et al. Longitudinal prevalence and determinants of early mood disorder post-stroke. *J.Clin.Neurosci.* 2007;14(5), 429-434.
30. Aben I, Lodder J, Honig A, et al. Focal or generalized vascular brain damage and vulnerability to depression after stroke: a 1-year prospective follow-up study. *Int.Psychogeriatr.* 2006;18(1), 19-35.
31. Shewan CM , Kertesz A. Reliability and validity characteristics of the Western Aphasia Battery (WAB). *J.Speech Hear. Disord.* 1980;45(3), 308-324.
32. Morris PL, Robinson RG, Raphael B. Prevalence and course of depressive disorders in hospitalized stroke patients. *Int.J.Psychiatry Med.* 1990;20(4), 349-364.
33. Paradiso S , Robinson RG. Minor depression after stroke: an initial validation of the DSM-IV construct. *Am.J.Geriatr.Psychiatry* 1999;7(3), 244-251.
34. Robinson RG , Price TR. Post-stroke depressive disorders: a follow-up study of 103 patients. *Stroke* 1982;13(5), 635-641.
35. Robinson RG, Starr LB, Lipsey JR, et al. A two-year longitudinal study of poststroke mood disorders. In-hospital prognostic factors associated with six-month outcome. *J.Nerv.Ment.Dis.* 1985;173(4), 221-226.
36. Sinyor D, Jacques P, Kaloupek DG, et al. Poststroke depression and lesion location. An attempted replication. *Brain* 1986;109 (Pt 3), 537-546.
37. Starkstein SE, Robinson RG, Berthier ML, et al. Depressive disorders following posterior circulation as compared with middle cerebral artery infarcts. *Brain* 1988;111 (Pt 2), 375-387.
38. Barker-Collo SL. Depression and anxiety 3 months post stroke: prevalence and correlates. *Arch.Clin.Neuropsychol.* 2007;22(4), 519-531.
39. MacHale SM, O'Rourke SJ, Wardlaw JM, et al. Depression and its relation to lesion location after stroke. *J.Neurol.*

Neurosurg.Psychiatry 1998;64(3), 371-374.

40. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. *Neurology* 2005;64(3), 428-433.
41. Dennis M, O'Rourke S, Lewis S, et al. Emotional outcomes after stroke: factors associated with poor outcome. *J.Neurol. Neurosurg.Psychiatry* 2000;68(1), 47-52.
42. Desmond DW, Remien RH, Moroney JT, et al. Ischemic stroke and depression. *J. Int.Neuropsychol.Soc.* 2003;9(3), 429-439.
43. Eastwood MR, Rifat SL, Nobbs H, et al. Mood disorder following cerebrovascular accident. *Br.J.Psychiatry* 1989;154, 195-200.
44. Gonzalez-Torrecillas JL, Mendlewicz J, Lobo A. Effects of early treatment of poststroke depression on neuropsychological rehabilitation. *Int.Psychogeriatr.* 1995;7(4), 547-560.
45. Hama S, Yamashita H, Shigenobu M, et al. Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia. *Eur.Arch.Psychiatry Clin.Neurosci.* 2007;257(3), 149-152.
46. Herrmann M, Bartels C, Schumacher M, et al. Poststroke depression. Is there a patho- anatomic correlate for depression in the postacute stage of stroke? *Stroke* 1995;26(5), 850-856.
47. House A, Dennis M, Warlow C, et al. Mood disorders after stroke and their relation to lesion location. A CT scan study. *Brain* 1990;113 (Pt 4), 1113-1129.
48. Iacoboni M, Padovani A, Di P, et al. Post-stroke depression: relationships with morphological damage and cognition over time. *Ital.J.Neurol.Sci.* 1995;16(4), 209-216.
49. Morris PL, Robinson RG. Personality neuroticism and depression after stroke. *Int.J.Psychiatry Med.*1995;25(1), 93-102.
50. Robinson RG, Bolla-Wilson K, Kaplan E, et al. Depression influences intellectual impairment in stroke patients. *Br.J.Psychiatry* 1986;148, 541-547.
51. Tang WK, Chan SS, Chiu HF, et al. Poststroke depression in Chinese patients: frequency, psychosocial, clinical, and radiological determinants. *J.Geriatr.Psychiatry Neurol.* 2005;18(1), 45-51.
52. Vataja R, Pohjasvaara T, Leppavuori A, et al. Magnetic resonance imaging correlates of depression after ischemic stroke. *Arch.Gen.Psychiatry* 2001;58(10), 925-931.
53. Simis S , Nitrini R. Cognitive improvement after treatment of depressive symptoms in the acute phase of stroke. *Arq Neuropsiquiatr.* 2006;64(2B), 412-417.
54. Starkstein SE, Robinson RG, Honig MA, et al. Mood changes after right-hemisphere lesions. *Br.J.Psychiatry* 1989;155, 79-85.
55. Berg A, Palomaki H, Lehtihalmes M, et al. Poststroke depression in acute phase after stroke. *Cerebrovasc.Dis.* 2001;12(1), 14-20.
56. Berg A, Palomaki H, Lehtihalmes M, et al. Poststroke depression: an 18-month follow-up. *Stroke* 2003;34(1), 138-143.
57. Sit JW, Wong TK, Clinton M, et al. Associated factors of post-stroke depression among Hong Kong Chinese: a longitudinal study. *Psychol.Health Med.* 2007;12(2), 117-125.
58. Stone J, Townend E, Kwan J, et al. Personality change after stroke: some preliminary observations. *J.Neurol. Neurosurg.Psychiatry* 2004;75(12), 1708-1713.

59. Andersen G, Vestergaard K, Ingemann-Nielsen M, et al. Risk factors for post-stroke depression. *Acta Psychiatr. Scand.* 1995;92(3), 193-198.
60. Astrom M. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. *Stroke* 1996;27(2), 270-275.
61. O'Brien J, Desmond P, Ames D, et al. A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. *Br.J.Psychiatry* 1996;168(4), 477-485.
62. Nys GM, van Zandvoort MJ, van der Worp HB, et al. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. *J.Neurol.Sci.* 2005;228(1), 27-33.
63. Nys GM, van Zandvoort MJ, van der Worp HB, et al. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. *J.Neurol.Sci.* 2006;247(2), 149-156.
64. Vataja R, Leppavuori A, Pohjasvaara T, et al. Poststroke depression and lesion location revisited. *J.Neuropsychiatry Clin.Neurosci.* 2004;16(2), 156-162.
65. Vataja R, Pohjasvaara T, Mantyla R, et al. Depression-executive dysfunction syndrome in stroke patients. *Am.J.Geriatr.Psychiatry* 2005;13(2), 99-107.
66. Verdelho A, Henon H, Lebert F, et al. Depressive symptoms after stroke and relationship with dementia: A three-year follow-up study. *Neurology* 2004;62(6), 905-911.
67. Pohjasvaara TI, Jokinen H, Ylikoski R, et al. White matter lesions are related to impaired instrumental activities of daily living poststroke. *J.Stroke Cerebrovasc. Dis.* 2007;16(6), 251-258.
68. Caeiro L, Ferro JM, Santos CO, et al. Depression in acute stroke. *J.Psychiatry Neurosci.* 2006;31(6), 377-383.
69. Hackett ML , Anderson CS. Frequency, management, and predictors of abnormal mood after stroke: the Auckland Regional Community Stroke (ARCOS) study, 2002 to 2003. *Stroke* 2006;37(8), 2123-2128.
70. Loong CK, Kenneth NK, Paulin ST. Post-stroke depression: outcome following rehabilitation. *Aust.N.Z.J.Psychiatry* 1995;29(4), 609-614.
71. Naess H, Nyland HI, Thomassen L, et al. Mild depression in young adults with cerebral infarction at long-term follow-up: a population-based study. *Eur.J.Neurol.* 2005;12(3), 194-198.
72. Cassidy E, O'Connor R, O'Keane V. Prevalence of post-stroke depression in an Irish sample and its relationship with disability and outcome following inpatient rehabilitation. *Disabil.Rehabil.* 2004;26(2), 71-77.
73. Morris PL, Shields RB, Hopwood MJ, et al. Are there two depressive syndromes after stroke? *J.Nerv.Ment.Dis.* 1994;182(4), 230-234.
74. Sharpe M, Hawton K, Seagroatt V, et al. Depressive disorders in long-term survivors of stroke. Associations with demographic and social factors, functional status, and brain lesion volume. *Br.J.Psychiatry* 1994;164(3), 380-386.
75. Saxena SK, Ng TP, Koh G, et al. Is improvement in impaired cognition and depressive symptoms in post-stroke patients associated with recovery in activities of daily living? *Acta Neurol. Scand.* 2007;115(5), 339-346.
76. Thompson SC, Sobolew-Shubin A, Graham MA, et al. Psychosocial adjustment following a stroke. *Soc.Sci. Med.* 1989;28(3), 239-247.

77. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics* 2002;43(5), 386-393.
78. Fure B, Wyller TB, Engedal K, et al. Emotional symptoms in acute ischemic stroke. *Int.J.Geriatr.Psychiatry* 2006;21(4), 382-387.
79. Hama S, Yamashita H, Shigenobu M, et al. Sitting balance as an early predictor of functional improvement in association with depressive symptoms in stroke patients. *Psychiatry Clin.Neurosci.* 2007;61(5), 543-551.
80. Astrom M, Olsson T, Asplund K: Different linkage of depression to hypercortisolism early versus late after stroke. A 3-year longitudinal study. *Stroke* 1993;24(1), 52-57.
81. House A, Dennis M, Warlow C, et al. The relationship between intellectual impairment and mood disorder in the first year after stroke. *Psychol.Med.* 1990;20(4), 805-814.
82. Kauhanen ML, Korpelainen JT, Hiltunen P, et al. Domains and determinants of quality of life after stroke caused by brain infarction. *Arch.Phys.Med.Rehabil.* 2000;81(12), 1541-1546.
83. Kauhanen ML, Korpelainen JT, Hiltunen P, et al. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovasc.Dis.* 2000;10(6), 455-461.
84. Robinson RG, Starr LB, Lipsey JR, et al. A two-year longitudinal study of post-stroke mood disorders: dynamic changes in associated variables over the first six months of follow-up. *Stroke* 1984;15(3), 510-517.
85. Schulz R, Tompkins CA, Rau MT. A longitudinal study of the psychosocial impact of stroke on primary support persons. *Psychol.Aging* 1988;3(2), 131-141.
86. Saxena SK, Ng TP, Yong D, et al. Subthreshold depression and cognitive impairment but not demented in stroke patients during their rehabilitation. *Acta Neurol.Scand.* 2008;117(2), 133-140.
87. Paolucci S, Antonucci G, Pratesi L, et al. Poststroke depression and its role in rehabilitation of inpatients. *Arch.Phys. Med.Rehabil.* 1999;80(9), 985-990.
88. Pantoni L , Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. *Stroke* 1995;26(7), 1293-1301.
89. Leys D, Englund E, Del ST, et al. White matter changes in stroke patients. Relationship with stroke subtype and outcome. *Eur.Neurol.* 1999;42(2), 67-75.
90. Beyer JL , Krishnan KR. Volumetric brain imaging findings in mood disorders. *Bipolar.Disord.* 2002;4(2), 89-104.
91. Abas MA, Sahakian BJ, Levy R. Neuropsychological deficits and CT scan changes in elderly depressives. *Psychol. Med.* 1990;20(3), 507-520.
92. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch.Gen.Psychiatry* 2000;57(11), 1071-1076.
93. Perris H. Life events and depression. Part 3. Relation to severity of the depressive syndrome. *J.Affect.Disord.* 1984;7(1), 37-44.
94. Perris H. Life events and depression. Part 2. Results in diagnostic subgroups, and in relation to the recurrence of depression. *J.Affect.Disord.* 1984;7(1), 25-36.
95. Perris H. Life events and depression.

Part 1. Effect of sex, age and civil status. *J.Affect.Disord.* 1984;7(1), 11-24.
96. Beauregard M, Leroux JM, Bergman s, et al. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. *Neuroreport* 1998;9(14), 3253-3258.
97. Malhi GS, Lagopoulos J, Ward PB, et al. Cognitive generation of affect in bipolar depression: an fMRI study. *Eur.J.Neurosci.* 2004;19(3), 741-754.
98. Gainotti G, Azzoni A, Gasparini F, et al. Relation of lesion location to verbal and nonverbal mood measures in stroke patients. *Stroke* 1997;28(11), 2145-2149.
99. Kishi Y, Kosier JT, Robinson RG. Suicidal plans in patients with acute stroke. *J.Nerv.Ment.Dis.* 1996;184(5), 274-280.
100. Bolla-Wilson K, Robinson RG, Starkstein SE, et al. Lateralization of dementia of depression in stroke patients. *Am.J.Psychiatry* 1989;146(5), 627-634.
101. Robinson RG, Lipsey JR, Bolla-Wilson K, et al. Mood disorders in left-handed stroke patients. *Am.J.Psychiatry* 1985;142(12), 1424-1429.
102. Linden T, Blomstrand C, Skoog I. Depressive disorders after 20 months in elderly stroke patients: a case-control study. *Stroke* 2007;38(6), 1860-1863.
103. Jaracz K , Kozubski W. Quality of life in stroke patients. *Acta Neurol.Scand.* 2003;107(5), 324-329.
104. Kim JS , Choi-Kwon S. Poststroke depression and emotional incontinence: correlation with lesion location. *Neurology* 2000;54(9), 1805-1810.
105. Sharpe M, Hawton K, House A, et al. Mood disorders in long-term survivors of stroke: associations with brain lesion location and volume. *Psychol.Med.* 1990;20(4), 815-828.
106. Ramasubbu R, Robinson RG, Flint AJ, et al. Functional impairment associated with acute poststroke depression: the Stroke Data Bank Study. *J. Neuropsychiatry Clin.Neurosci.* 1998;10(1), 26-33.
107. Popovich JM, Fox PG, Burns KR. The impact of depression on stroke recovery in the U.S. *Int.J.Psychiatr.Nurs.Res.* 2002;7(3), 842-855.
108. van de Port I, Kwakkel G, Bruin M, et al. Determinants of depression in chronic stroke: a prospective cohort study. *Disabil.Rehabil.* 2007;29(5), 353-358 (2007).
109. Morris PL, Robinson RG, Raphael B, et al. The relationship between risk factors for affective disorder and poststroke depression in hospitalised stroke patients. *Aust.N.Z.J.Psychiatry* 1992;26(2), 208-217.
110. Hsieh LP , Kao HJ. Depressive symptoms following ischemic stroke: a study of 207 patients. *Acta Neurol. Taiwan.* 2005;14(4), 187-190.
111. Gesztelyi R, Fekete I, Kellermann M, et al. Screening for depressive symptoms among post-stroke outpatients in Eastern Hungary. *J.Geriatr.Psychiatry Neurol.* 1999;12(4), 194-199.

2.2 Post-stroke depressive symptoms are associated with post-stroke characteristics

Abstract

Several studies have described the frequency and risk factors of post-stroke depressive symptoms (PSDS). However, most studies did not exclude patients with depressive symptoms shortly *before* stroke and paid little attention to pre-stroke risk factors of depression, including previous depressive episodes, white matter lesions, and brain atrophy. These are potential limitations to assess the true effect of stroke on the occurrence of depressive symptoms. Our aim was to investigate the prevalence and risk factors of PSDS with adjustments for the previously mentioned pre-stroke factors. Patients (n=420) with an acute clinical symptomatic TIA or cerebral infarction were eligible for enrolment in this study. The presence of PSDS was rated by the Hospital Anxiety Depression Scale 6-8 weeks post-stroke. The relation between (pre-) stroke factors and PSDS was assessed with multivariate regression analysis.

The prevalence of PSDS was 13% and did not differ between stroke subtype or first-ever/ever occurrence of stroke. Higher degree of post-stroke handicap was related with PSDS (OR 5.39; 95% CI 2.40-12.08) and more functional independence had a protective effect of PSDS (OR 0.88; 95% CI 0.77-1.00).

This is the largest study that investigated the prevalence and risk factors of PSDS by carefully excluded patients with depressive symptoms shortly *before* stroke. PSDS were not related to lesion side or location, but to the degree of post-stroke handicap and functional independence. Early detection of PSDS and its risk factors might help to predict long-term outcome and could promote early interventions of (behavioural) rehabilitation treatment strategies.

Liselore Snaphaan, Sieberen van der Werf, Karin Kanselaar and Frank-Erik de Leeuw. Depressive symptoms early after stroke are associated with pre-and post-stroke characteristics. Cerebrovasc Dis. Oct 2009,28:551-557

Post-stroke depressive symptoms (PSDS) frequently occur and interfere with successful stroke recovery.[1;2] The prevalence of post-stroke depressive symptoms (PSDS) varies between 11% to 78%. [3;4] These large differences are partly due to methodological differences between studies such as the use of different rating scales of depressive symptoms and different time intervals of stroke – depressive symptoms assessment. Another explanation is the inclusion of patients that already have depressive symptoms at the time of stroke. The high prevalence of depressive symptoms, between 8% and 16%, in the general elderly population [5] may affect the prevalence of PSDS, that is at least for this part, not related to the stroke itself.

There is an ongoing debate with respect to the possible causes of PSDS; some investigators stress a biomedical explanation, analogous to for example a hemi-paresis after an infarct in the pyramidal tract, [6] while others view PSDS secondary as a reaction to a threatening major life event [7] and loss of functional independence. [8] Investigating patients with a TIA may help in this respect by disentangling these stroke related factors for PSDS from other factors, as patients with a TIA have shorter duration of symptoms with complete functional recovery to pre-TIA functioning within 24 hours and in most cases without any visible lesion on neuroimaging.

In addition, the relation between stroke and the occurrence of PSDS may be obscured by risk factors related to the stroke (such as type of stroke, lesion location, severity of clinical symptoms and post-stroke degree of disability) and by factors that were presumably already present before the stroke. We aimed at disentangling the effect of symptom duration and severity on the prevalence of PSDS by comparing this between TIA and ischemic stroke patients. In addition, it is known that depressive symptoms are related to vascular white matter lesions, cerebral atrophy or cognitive impairment, irrespective of a stroke. [9-11] Since white matter lesions are more prevalent among stroke patients [12] they may, at least in part, explain the increased prevalence of depressive symptoms. Although, few studies [13] adjust for stroke related risk factors, there are virtually no studies taking pre-stroke confounding factors (such as white matter lesions, cerebral atrophy and the presence of previous depressive episodes in the medical history) into account.

We investigated, in one of the largest stroke cohorts (n=420) thus far, the prevalence of depressive symptoms 6-8 weeks *after* stroke by careful excluding patients with depressive symptoms in the months before the index stroke. We hypothesised that the prevalence of PSDS would be lower following TIA than cerebral infarction. We also aimed to identify risk factors for PSDS using multivariate models to take both pre- and post-stroke risk factors into account.

Materials and Methods

Study population

Consecutive patients that presented with acute symptomatic cerebral ischemia (including TIA and cerebral infarction) according to the WHO diagnostic criteria, [14] and who were admitted to the Neurology department of the Radboud University Nijmegen Medical Centre, the Netherlands between October 2004 and July 2008 were eligible for enrolment in the prospective Nijmegen Stroke Study. The Nijmegen Stroke Study prospectively investigates short- and long-term consequences of stroke with regular pre-planned assessments after stroke. Exclusion criteria for enrolment in this study were: intracerebral haemorrhage (n=84), death at the preplanned ascertainment time of depressive symptoms (n=41, 6-8 weeks after the qualifying stroke), not able to visit the hospital 6-8 weeks post-stroke due to physical limitations, patients with terminal diseases such as cancer but also chronic diseases (such as Parkinson disease, Alzheimer disease, dementia) were excluded even as patients with epileptic seizures, myocardial infarction or head trauma. The local medical ethics committee of the Arnhem Nijmegen region approved the study.
Diagnosis of cerebral ischemia was based on the presence of acute neurological symptoms that could only be explained by a vascular event in a specific arterial territory with a duration of < 24 hours (TIA) or > 24 hours (cerebral infarction) and verified by CT or MRI within the first week after the event. Cerebral ischemia was further subdivided in first-ever (i.e. occurring in patients either without previous clinical cerebral ischemia according to a structured questionnaire nor without ischemic lesions other than the corresponding lesion of the qualifying cerebral ischemia on CT/MRI) and ever cerebral ischemia (defined as patients with a history of previous cerebral ischemia according to a structured questionnaire with or without corresponding ischemic lesions on CT/MRI).

Assessment of depressive symptoms

Six to eight weeks post-stroke patients rated the presence and severity of depressive symptoms on the Hospital Anxiety Depression Scale (HADS). [15] This screening instrument is well-validated in stroke patients. [16] Every patient was checked on their visual acuity, capability of reading and understanding of the questionnaire. A score $>$ 8 on the depression subscale of the HADS was considered indicative for the presence of depressive symptoms and has been found to correlate highly with a formal diagnosis of a depression based on DSM-IV criteria. [16-18]

Assessment of possible pre-stroke risk factors

Standardised structured questionnaires were used to obtain information about age, gender, martial status, educational level (i.e Dutch classification system according to Verhage [19], ranging in ascending order from 1 (less than primary school) to 7 (university degree)). The presence of depressive symptoms in the medical history was assessed with the aid of a standardised, structured questionnaire that has been proven reliable and valid in other epidemiological studies. [11] This questionnaire identifies the occurrence depressive episodes before the stroke and whether the episodes had prompted the patients to seek medical advice. A positive "history of depressive symptoms" was defined as the occurrence of depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist; patients with depressive symptoms within 1 month before the qualifying stroke were excluded.
White matter lesions (WML) were rated semiquantitative (0-3) according to the Age Related White Matter Changes-scale. [20] Cortical atrophy was defined as the mean width of the left and right Sylvian fissure divided by the maximum brain width (at the pineal level). [21] Subcortical atrophy was defined as the mean ventricle-to-brain ratio at the frontal, bicaudate and occipital level. [21]

Assessment of possible stroke-related risk factors

The side of a stroke or TIA was judged on the basis of the acute clinical neurological symptoms at admission (classified as left or right hemispheric stroke or infratentorial stroke (i.e cerebellum or brainstem). Stroke severity was assessed at admission with the National Institute of Health Stroke Scale (NIHSS). [22] The location of lesions (classified as cortical, subcortical white matter, basal ganglia, thalamus, and infratentorial) was scored by an experienced stroke neurologist (FEdL) according to a standard procedure using neuroimaging (either CT or MRI) at which symptomatic lesions were best visible.
Global cognition (MMSE [23]), functional status (Barthel Index (BI) [24][Mahoney and Barthel 1965] ranging from 0 (completely dependent) to 20 (completely independent)) and the degree of handicap (modified Rankin Scale (mRS) [25] ranging from 0 (no symptoms) to 5 (severe disability)) were assessed 6-8 weeks post-stroke. Patients with a mRS 0-1 were classified as 'favourable outcome'. those with with a mRS ≥2 were classified as 'unfavourable'.

Statistical Analysis

Two-sample *t*-tests were used for group comparisons of continuous data, Pearson Chi Square and Mann Whitney U testing were used for nominal (dichotomised variables i.e gender) and for ordinal data (for more than 2 outcome variables i.e education), respectively. All tests were two-tailed with the results considered significant at $p<0.05$. The relation between the PSDS (defined as a HADS > 8) and each individual pre- and post-stroke risk factor separately was assessed with age and sex adjusted logistic regression analysis. Subsequently, the predictor variables that turned out to be significantly related in the age and sex adjusted logistic model were then introduced into a step-backward logistic regression (conditional) analysis to calculate independent risk factors for PSDS, presented as odds ratios (OR), with 95% confidence interval (95% CI).

Results

The final study population consisted of 420 patients with cerebral ischemia (TIA n=137 and infarction n=283) with a mean age of 64.3 years (SD 14.0), a mean HADS depressive items score of 4.4 (SD 4.1) and 42% of them were female. The median educational level was 5 (high school level) and 24% of the patients were living alone (data not shown).

Prevalence of PSDS

The overall prevalence of PSDS 6-8 weeks after stroke was 13% and varied between 10% (TIA) to 15% (cerebral infarction) (table 1). There were 329 patients with a first-ever manifestation of stroke (TIA n=113 and cerebral infarction n=216) and 91 patients who had suffered a stroke before (TIA n=24 and cerebral infarction n=67). PSDS prevalence did not significantly differ across stroke subtypes (TIA versus cerebral infarction p=0.11) nor between first-ever and ever stroke with respect to PSDS (p=0.52, data not shown).

Stroke related risk factors of PSDS

Patients with a higher MMSE score after stroke had a reduced risk for PSDS (OR 0.87; 95% CI 0.80-0.94, per each point increase in the MMSE, table 2), as had patients with

less functional independency after stroke (OR 0.84; 95% CI 0.76-0.93, per each point increase in the Barthell index). Those with an unfavourable outcome (mRS ≥ 2) or with a more severe stroke had an increased risk for PSDS (OR 4.54; 95% CI 2.29-9.01 and OR 1.08; 95% CI 1.01-1.15, per point increase on the NIHSS, respectively, table 3).

Pre-stroke risk factors of PSDS

A pre-stroke history of depression was not a risk factor for PSDS at 6-8 weeks post-stroke (OR 1.02; 95% CI 0.37-2.85), as there were no other pre-stroke risk factors for PSDS.

Multivariate model

The variables, in the age and sex adjusted logistic regression model, that turned out to be significantly related with PSDS (bold in table 2), were then introduced into a step-backward regression analysis to calculate predictors of PSDS. Unfavourable outcome (mRS ≥ 2) was related with an increased risk of PSDS (OR 2.46; 95% CI 1.12-5.38), whereas more functional independency had a protective effect on PSDS (OR 0.88; 95% CI 0.77-1.00 per each point increase on the post-stroke BI). There was no significant relation between pre-stroke predictors and PSDS in multivariate models.

Discussion

The prevalence of PSDS was 13% six to eight weeks post-stroke; there were neither significant differences between stroke subtypes with respect to the prevalence of PSDS nor for first-ever or ever stroke patients. Although others have investigated the frequency and predictors of PSDS, [3;13;26;27] this is the largest hospital based study (n=420), that in addition explicitly excluded patients with depressive symptoms in the weeks before stroke in order to obtain unbiased prevalence figures. Another novel aspect was that risk factors for PSDS were calculated with adjustments for possible pre- and post-stroke risk factors. A higher degree of post-stroke handicap and less post-stroke functional independency, independent from each other as well as from other risk factors, were related with an increased risk of PSDS.

A methodological aspect that should be noted is the possible selection bias. Non-responders in our study were significantly more TIA patients. As TIA patients, by

Table 1 Patients' characteristics classified by type of stroke and by presence or absence of post-stroke depressive symptoms

	TIA n=137		
	post-stroke depressive symptoms		
	Present (10%)	**Absent (90%)**	**P-value**
Characteristics			
Demographics			
Age mean (SD)	61.5(9.7)	61.2(13.7)	0.95
Female gender (%)	31	34	0.81
Living alone (%)	23	15	0.47
Education median (range)	5(4-6)	5(2-7)	0.53
Post-stroke characteristics			
Behavioural			
Depressive Items mean (SD)	12.3(3.0)	2.8(2.5)	**<0.01**
MMSE mean (SD)	27.8(2.4)	28.4(1.8)	0.23
Clinical			
Barthel Index median (range)	20(-)	20(16-20)	0.76
Rankin Scale median (range)	0(-)	0(-)	na
NIHSS median (range)	0(-)	0(-)	na
First-ever stroke (%)	92	81	0.31
Left/Right/Infratentorial (%) **	46/39/15	46/47/7	0.50
Neuroimaging			
Cortical/Subcortical/Both/Infratentorial (%)	-	-	na
Subcortical structures			
White matter/Basal ganglia/Thalamus (%)	-	-	na
Pre-stroke characteristics			
History depressive symptoms (%)	0	17	0.14
Mean grade subcortical atrophy (SD) §	0.3(0.04)	0.3(0.03)	0.53
Mean grade cortical atrophy(SD) ‖	0.1(0.03)	0.1(0.02)	0.23
ARWMC median (range)	0(0-12)	0(0-26)	0.99

Age and sex adjusted differences between absence or presence of PSDS, were P-values were calculated by * Univariate t-test (continue data), † Pearson Chi-square analyses (categorical data), ‡ Mann-Whitney U Test (ordinal data); significant values ($p < 0.05$) are printed bold; § mean of ventricle to brain ratio at the frontal, bicaudate or occipital level; ‖ mean width of the left and right sylvian fissure divided by the

	Cerebral infarction n=283			Total study population n=420		
	post-stroke depressive symptoms			post-stroke depressive symptoms		
	Present (15%)	Absent (85%)	P-value	Present (13%)	Absent (87%)	P-value
	64.9(13.1)	65.9(14.3)	0.67	64.1(12.4)	64.3(14.3)	0.92*
	51	44	0.40	46	41	0.42†
	36	27	0.27	33	23	0.14†
	4(1-7)	5(1-7)	**<0.01**	5(1-7)	5(1-7)	**<0.01**‡
	12.7(3.2)	3.4(2.5)	**<0.01**	12.6(3.1)	3.2(2.5)	**<0.01***
	25.2(4.3)	26.9(3.3)	**<0.01**	25.9(4.0)	27.4(2.9)	**<0.01***
	20(4-20)	20(4-20)	**<0.01**	20(4-20)	20(4-20)	**<0.01***
	2(0-5)	1(0-4)	**<0.01**	1(0-5)	0(0-4)	**<0.01**‡
	3(0-19)	3(0-27)	0.06	3(0-19)	2(0-27)	**0.02***
	70	77	0.28	75	79	0.54†
	50/38/12	41/44/15	0.58	46/38/13	43/45/12	0.63†
	7/38/41/14	16/48/26/10	0.26	9/41/38/12	18/48/25/9	0.33†
	91/0/9	74/15/11	0.35	92/0/8	76/13/11	0.34†
	24	14	0.23	16	15	0.92†
	0.3(0.04)	0.3(0.04)	0.59	0.3(0.04)	0.3(0.04)	0.75*
	0.1(0.03)	0.1(0.03)	0.27	0.1(0.03)	0.1(0.03)	0.12*
	0(0-12)	0(0-29)	0.42	0(0-12)	0(0-29)	0.48*

maximum brain width (at the pineal level); na not applicable; ** refers to left or right hemisphere or infratentorial ischemia; - no (or little) visible lesions on MRI or CT scan.

Table 2 Pre-and post-stroke risk factors for post-stroke depressive symptoms

	Cerebral infarction	Total study population
Characteristics	n=283	n=420
Demographics		
Age	1.00(0.97-1.02)	1.00(0.98-1.02)
Gender *(reference male)*	1.33(0.69-2.54)	1.27(0.72-2.23)
High education ≥ level 5 *(reference low education <5)*	0.50(0.24-1.05)	0.64(0.34-1.20)
Post-stroke Characteristics		
MMSE	**0.88(0.81-0.96)**	**0.87(0.80-0.94)**
Barthel Index	**0.84(0.76-0.93)**	**0.84(0.76-0.93)**
Rankin Scale ≥ 2 *(reference rankin scale <2)*	**4.50(2.45-8.26)**	**4.54(2.29-9.01)**
NIHSS	1.07(0.99-1.15)	**1.08(1.01-1.15)**

Values are Odds Ratios (95% Confidence Intervals) adjusted for age and gender; significant OR are printed bold ($p < 0.05$).

definition, had no post-stroke neurological deficits, the prevalence for PSDS could therefore be an overestimation. On the other hand, we excluded patients with more severe neurological deficits including those who were physically not able to visit the hospital 6-8 weeks post-stroke that are likely to have more PSDS. In turn, this could have led to underestimation of PSDS. We therefore consider the prevalence of 13% as a small overestimation because we excluded more patients with TIA's than patients with severe deficits. Although, we aimed to investigate pre-stroke neuroimaging variables (including WML and subcortical/cortical atrophy) in relation to PSDS, one has to keep in mind that neuroimaging was performed directly *after* the qualifying stroke. Therefore, one cannot fully exclude the fact that early stroke signs (for example the appearance of hypodense areas on a CT) may have been misclassified as WML. For this reason WML were not rated in areas in which the infarction was suspected. As this possible misclassification is not related to our outcome (PSDS), it will most likely be random and, if anything, result in reduced strength of an association between WML and PSDS.

Furthermore, it is known that several pharmacologic agents are associated with onset of depression including selective antihypertensive agents, cimetidine, indomethacin,

alcohol, barbiturates, stimulant withdrawal, corticosteroids. However, the prescription of most of these drugs were not changed before the assessment of PSDS making a relation with emerging PSDS less likely. If any, it seems likely that patients with PSDS have a higher usage of these previously mentioned drugs. Due to an expected power problem we could not adjust for all these individuals variables separately.

In favor of our study is that we have included both TIA patients and patients with cerebral infarction. Including TIA patients, with usually short lasting symptoms with complete functional recovery and without any visible lesion on neuroimaging, gave us the opportunity to investigate whether stroke related factors itself would be related to PSDS or that other, for example adaptive mechanisms to a life event could also play a role.

In addition, most previous studies predominantly focused on the relation between PSDS and post-stroke characteristics, without appropriate control for possible pre-stroke confounding. Our study has taken possible pre- and post-stroke risk factors into account, by introducing them into a multivariate analysis.

The prevalence of PSDS obtained from our study are consistent with hospital and rehabilitation-based cross-sectional data. However some studies found a higher prevalence of PSDS because of the use of a more sensitive, but less specific cut-off ≤ 7 on the HADS to identify depressive symptoms. [28] Another reason for our prevalence at the lower end of the spectrum could be that in contrast to our study, most studies [8;28] did not attempt to exclude individuals that suffered from a depression or depressive symptoms just weeks before the qualifying stroke. It seems likely that the prevalence of PSDS will be increased by including these patients. Our study explicitly excluded patients with depressive symptoms at the time of the stroke and therefore we consider the 13% prevalence of post-stroke depressive symptoms as a reliable estimate.

We hypothesised that the prevalence of PSDS would be lower among TIA patients than cerebral infarction as TIA's experience (by definition) no functional loss, a factor we found to be related with PSDS. Our study, however, did not find such a difference. A methodological explanation could be that the response among TIA patients was related with more psychological complaints after stroke. In other words, the persistence of depressive or psychological symptoms after the TIA could be related with visiting our outpatient clinic, leading to selection bias. Particularly, as our response among TIA patients was lower (about 60%) than in stroke patients, this may have played a role.

Some found a relation between side of lesion (left/right hemisphere), [29] lesion location (subcortical/cortical) [30] and PSDS. However they used univariate analysis to investigate this relation and were not able to adjust for possible risk factors. As most other studies, [31] we did not find a relation between PSDS and lesion size/

location or post-stroke physical disabilities. This seems plausible as anatomically the mood regulation system is a widespread system, involving the frontal lobe (particularly the subgenual prefrontal cortex), the basal ganglia (particularly the caudate and putamen), the cerebellum, the hippocampus/amygdala complex, and possibly the temporal lobes. It seems therefore unlikely that a single vascular lesion would interrupt such a widely dispersed system to such an extent that it can result in a marked change in mood. This is in line with studies among elderly [11;32] that found a relation between depressive symptoms and WML or cerebral atrophy and supports the idea that a more diffuse brain damage is related with depressive symptoms. Possibly by global diffuse disruptions of the connecting mood regulation fibre tracts that may result in accompanying mood dysfunction. Although, despite our large sample size, we must not ignore the fact that type II errors may play a role of not finding a relation between lesion size/location.

Some investigators [6] found a relation between cerebral atrophy and depressive symptoms long after stroke (2-3 years), others [33] (including ours) did not found this relation weeks to months after stroke. It could be that cerebral atrophy among depressive stroke patients develops during time and that this relation becomes only apparent after longer (years) follow up. This explanation could also apply for WML, however studies investigating WML after stroke a risk factor for PSDS are scarce. Our study found no relation between WML and depressive symptoms early after stroke and to our knowledge no other studies found a relation between WML and PSDS thus far.

Furthermore, relatively little studies paid attention on pre-stroke characteristics (such as depressive symptoms in their medical history) when investigating risk factors for PSDS. We did not found a relation between history of depressive symptoms and PSDS. Although, some studies [34;35] did found a relation, they often lacked a description of how a history of depressive symptoms was defined and virtually no study reported on actions taken with patients that were depressive at the time of stroke. We defined “history of depressive symptoms” as those depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist [11] and patients with depressive symptoms just before the qualifying stroke were excluded to provide a reliable as possible prevalence of PSDS. It seems likely that patients with depressive symptoms just before their stroke, still had their depressive symptoms at the 6-8 weeks assessment after stroke. This might explain differences in the prevalence of PSDS between the above mentioned studies and ours.

The main outcome of our study is that unfavourable outcome (mRS $\geq$ 2) and less functional independence (BI) both at 6-8 weeks post-stroke are risk factors for PSDS. The relationship between post-stroke functional impairment and PSDS is poorly

understood. [36] Some have argued that stroke patients may develop depressive symptoms as a psychological reaction to limited physical functioning [37] others speculate that depressive symptoms itself produce functional impairment as a result of fatigue, hopelessness, and diminished motivation [38] and a third point of view is that physical disabilities can both be a cause or a consequence of depressive symptoms. [39]

For patients, caregivers and their therapists it is clinically important to identify prognostic factors for PSDS because these can interfere with successful stroke recovery. [1;2] Early detection of PSDS and associated factors might help to predict long-term outcome and could provide opportunities for early interventions, including (behavioural) rehabilitation treatment strategies. Prospective studies are needed to provide more insight in the time-course of PSDS and to identify which prognostic factors are associated with the persistence or development of PSDS in the long-term.

Reference List

1. Morris PL, Raphael B, Robinson RG. Clinical depression is associated with impaired recovery from stroke. *Med J Aust*. 1992;157:239-242.
2. Parikh RM, Robinson RG, Lipsey JR, et al. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. *Arch Neurol*. 1990;47:785-789.
3. Desmond DW, Remien RH, Moroney JT, et al. Ischemic stroke and depression. *J Int Neuropsychol Soc*. 2003;9:429-439.
4. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients. Importance of location of lesion. *Brain*. 1984;107 (Pt 1):81-93.
5. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003;58:249-265.
6. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke*. 1993;24:976-982.
7. Bush BA. Major life events as risk factors for post-stroke depression. *Brain Inj*. 1999;13:131-137.
8. Singh A, Black SE, Herrmann N, et al. Functional and neuroanatomic correlations in poststroke depression: the Sunnybrook Stroke Study. *Stroke*. 2000;31:637-644.
9. Austin MP, Mitchell P, Wilhelm K, et al. Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? *Psychol Med*. 1999;29:73-85.
10. Beats B, Levy R, Forstl H. Ventricular enlargement and caudate hyperdensity in elderly depressives. *Biol Psychiatry*. 1991;30:452-458.
11. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry*. 2000;57:1071-1076.
12. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996;27:1274-1282.
13. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke*. 2005;36:2296-2301.
14. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58:113-130.
15. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-370.
16. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;43:386-393.
17. American Psychiatric Association DSM IV: Diagnostic and statistical manual of mental disorders DSM IV. *Washington D.C:American Psychiatric Press Inc*, 1994.
18. O'Rourke S, MacHale S, Signorini D, et al. Detecting psychiatric morbidity after stroke comparison of the GHQ and the HAD Scale. *Stroke*. 1998;29:980-985.
19. Verhage, F. Intelligentie en leeftijd [Inteligence and age]. 1964. *Assen, Van Gorcum*.

20. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318-1322.
21. Gomori JM, Steiner I, Melamed E, et al. The assessment of changes in brain volume using combined linear measurements. A CT-scan study. *Neuroradiology*. 1984;26:21-24.
22. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-870.
23. Folstein M, Folstein S, McHugh PR. Clinical predictors of improvement after electroconvulsive therapy of patients with schizophrenia, neurotic reactions, and affective disorders. *Biol Psychiatry*. 1973;7:147-152.
24. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Md State Med J*. 1965;14:61-65.
25. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-607.
26. Eriksson M, Asplund K, Glader EL, et al. Self-reported depression and use of antidepressants after stroke: a national survey. *Stroke*. 2004;35:936-941.
27. Hackett ML, Yapa C, Parag V, et al. Frequency of depression after stroke: a systematic review of observational studies. *Stroke*. 2005;36:1330-1340.
28. Aben I, Denollet J, Lousberg R, et al. Personality and vulnerability to depression in stroke patients: a 1-year prospective follow-up study. *Stroke*. 2002;33:2391-2395.
29. Sinyor D, Jacques P, Kaloupek DG, et al. Poststroke depression and lesion location. An attempted replication. *Brain*. 1986;109 (Pt 3):537-546.
30. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain*. 1987;110 (Pt 4):1045-1059.
31. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. *Lancet*. 2000;356:122-126.
32. Abas MA, Sahakian BJ, Levy R. Neuropsychological deficits and CT scan changes in elderly depressives. *Psychol Med*. 1990;20:507-520.
33. Vataja R, Pohjasvaara T, Leppavuori A, et al. Magnetic resonance imaging correlates of depression after ischemic stroke. *Arch Gen Psychiatry*. 2001;58:925-931.
34. Caeiro L, Ferro JM, Santos CO, et al. Depression in acute stroke. *J Psychiatry Neurosci*. 2006;31:377-383.
35. Hackett ML, Anderson CS. Frequency, management, and predictors of abnormal mood after stroke: the Auckland Regional Community Stroke (ARCOS) study, 2002 to 2003. *Stroke*. 2006;37:2123-2128.
36. Ramasubbu R, Robinson RG, Flint AJ, et al. Functional impairment associated with acute poststroke depression: the Stroke Data Bank Study. *J Neuropsychiatry Clin Neurosci*. 1998;10:26-33.
37. Tanner DC, Gerstenberger DL. The grief response in neuropathologies of speech and language. *Aphasiology*. 1988;2:79-84.
38. Schubert DS, Taylor C, Lee S, et al. Physical consequences of depression in the stroke patient. *Gen Hosp Psychiatry*. 1992;14:69-76.
39. Eastwood MR, Rifat SL, Nobbs H, et al. Mood disorder following cerebrovascular accident. *Br J Psychiatry*. 1989;154:195-200.

3

Post-stroke cognitive dysfunction

3.1 Epidemiology of post-stroke cognitive dysfunction

Abstract

Post-stroke memory dysfunction is a prerequisite for the diagnosis of post-stroke dementia. This diagnosis is made within months after a stroke, apparently assuming a relatively stable course of the post-stroke memory function. Clinical experience added to anecdotal evidence from the literature suggests that post-stroke memory function may be reversible. The aim of the present study was to systematically review the available data on the time course of post-stroke memory function in non-demented stroke survivors. In addition, we wanted to investigate the role of (pre-)stroke characteristics on post-stroke memory function. We performed systematic literature search of PubMed, with the following medical subject heading (MeSH) terms: *memory* and *stroke*. The search strategy yielded 798 papers of which 65 fulfilled our inclusion criteria and went on to the data extraction stage. Five studies reported the prevalence of post-stroke memory dysfunction at different post-stroke intervals. The prevalence of post-stroke memory dysfunction varied from 23 to 55% three months post-stroke, which declined from 11 to 31% one year post-stroke. Larger stroke volume, pre-stroke medial temporal lobe atrophy and white matter lesions were related with decreased post-stroke memory function. Not all patients with post-stroke memory dysfunction three months after a stroke had memory dysfunction one year post-stroke. Consequently, not all criteria for the dementia diagnosis were fulfilled anymore. This may indicate that post-stroke dementia may be reversible in a substantial proportion of stroke patients. Preferably, standardised re-assessment of cognitive function should be performed in each patient diagnosed with PSD.

Liselore Snaphaan and Frank-Erik de Leeuw. Post-stroke memory function in non-demented patients: a systematic review on frequency and neuroimaging correlates. Stroke, Jan 2008, 38:198-203

Introduction

Post-stroke memory dysfunction (PMD) is, by definition, a prerequisite for the diagnosis of post-stroke dementia (PSD) or vascular dementia (VaD) [1], albeit not a prominent clinical feature of the post-stroke cognitive profile [2]. This diagnosis is made within months after a stroke [1, 3], apparently assuming a relatively stable course of PMD. This is in contrast to what is common in clinical practice, since the prevalence of PMD is known to vary from 50% within the first few weeks after a stroke, gradually decreasing to 12% six months after a stroke [4, 5]. The presence of PMD is required to fulfill clinical diagnostic criteria for dementia. This may suggest that post-stroke dementia may be reversible in a substantial proportion of stroke patients that initially have been diagnosed with PSD.

Surprisingly, formal studies investigating the time course of post-stroke memory function (PMF) are scarce. This may allow for potential misclassification of post-stroke dementia or VaD when memory function changes over time (the presence of memory dysfunction is a symptom needed to fulfill this clinical diagnosis).

Another reason for investigating the true occurrence of PMD is that a stroke only seldom occurs in the brain structure that is predominantly involved in memory encoding and retrieval (the medial temporal lobe) [6-8]. Despite this, the frequency of PSD or VaD is estimated to be over 30% [9], which may suggest that other ***(pre-)*** stroke characteristics are related to ***post***-stroke memory function (PMF) such as white matter lesions (WML), medial temporal lobe atrophy (MTA), previous (silent) infarcts, and pre-stroke cognitive function. Many studies have investigated the epidemiology of PMF. However, some methodological limitations must be considered, including small sample size, inability to adjust for confounding factors and unclear operationalisation and description of the timing of assessment of memory function. Only a few addressed the role of stroke characteristics and that of the previously mentioned presumed pre-stroke characteristics in patients with PMD. It is important to know the course of PMF, since albeit the pre-eminent factor in the PSD and VaD diagnosis, it may not even be present (to the same extent) over three months after the stroke, as it was during the diagnosis of PSD and VaD (within three months after stroke).

We systematically reviewed the available data on frequency, time course and risk factors of post-stroke memory function in non-demented stroke survivors. Secondly, we evaluated the effect of location and severity of stroke on PMF. In addition, we wanted to investigate the role of pre-stroke structural brain changes including WML, MTA, previous (silent) infarcts and pre-stroke cognitive decline on the frequency of PMF.

Methods

A literature search of the electronic database PubMed was performed at 03-05-2006. We entered the following medical subject heading (MeSH) terms and text words in full and truncated: *memory* and *stroke*. In accordance with the literature the term stroke includes both cerebral infarcts and intracerebral haemorrhages. The search was limited to the English language, and included human studies with participants of 45 years of age or over. We followed a two-step approach in this selection of eligible articles (see figure). First, one reviewer (LS) screened the abstracts for the following characteristics: (1) original paper, published in English on case-control or cohort studies (sample size had to be at least 15), and (2) information about memory and stroke had to be present. From screen positive abstracts full papers were collected that then went to a second selection step to identify papers that fulfilled the following inclusion criteria; (3) description and operationalisation of post-stroke memory function; (4) description of the stroke (at least one of the following characteristics had to be present: location, severity and first-ever stroke); (5) description of presumed pre-stroke factors that could possibly influence post-stroke memory (WML, previous stroke, MTA and pre-stroke cognitive function). Papers were evaluated against the inclusion criteria by two authors independent from each other (LS and FEdL); in case of disagreement a consensus meeting was held.

Results

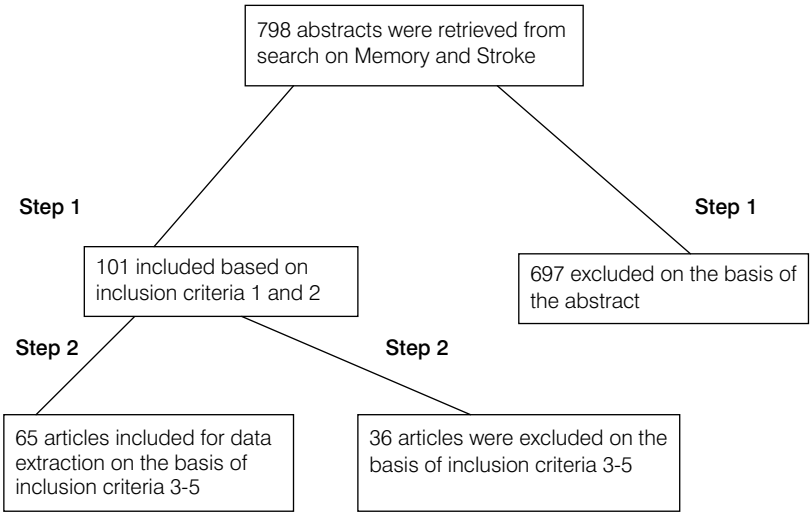
The search strategy yielded 798 papers. After screening of the title and the abstracts, 101 papers were retrieved full-text and examined against the in- and exclusion criteria, of which 65 were included and went on to the data extraction stage (figure 1).

Time course of post-stroke memory function

The most common tests that were used to assess verbal memory function were: the Wechsler Memory Scale (WMS) [10], the Rey Auditory Verbal Learning Test (RAVLT) [11], the Rivermead Behavioural Memory Test (RBMT) [12], the Cambridge Assessment Of Mental Disorders (CAMCOG) [13], the California Verbal Learning Test (CVLT) [14], and the Verbal Learning Task (VLT) [15].

Five studies [16-19] investigated the formal time course of post-stroke memory dysfunction, that had all included first-ever stroke patients, at different post-stroke

Figure 1 The stepwise approach in the selection of eligible and included articles



intervals (table 1). There was a general tendency [20-34] of a reduced (verbal) memory function (table 2) among stroke survivors as compared to controls (healthy controls or normative data).

There were ten studies that attempted to operationalise PMD, each with their own defined cut-offs (see details table 1) [4, 5, 16-19, 35-38].

The prevalence of PMD ranged from 50% weeks after the stroke to 11% more than a year after the stroke (see for details table 1).

Relation between post-stroke memory function and stroke characteristics

Table 2 presents an overview of post-stroke memory function (assessed at different stroke – memory assessment intervals) in relation to possible ***(pre-)*** stroke confounding factors.

Table 1 Prevalence of post-stroke memory dysfunction: a time-course

		Stroke survivors		
Single memory assessment	Number	Mean age yrs(SD)	First-ever stroke	Memory test
Ref				
4	16	59(NS)	Y	AVLT
37	78	NS	NS	RBMT
38	220	59(13)	NS	WMS
35	30	76(8)	NS	WMS
36	229	56(11)	Y	AVLT
Multiple memory assessment				
Ref				
18	196	69(13)	Y	AVLT
5	139	69(12)	Y	AVLT
16	60	61(NS)	Y	WMS
19	23	56(16)	Y	AVLT
17	111	60(14)	Y	AVLT

Verbal memory tests
AVLT: Auditory Verbal earning Test
RBMT: Rivermead Behavioural Memory Test
WMS: Wechsler Memory Scal

Abbreviation
NS: Not Specified
Empty cells indicate no assessment
Y: Yes

Several studies provided a clear description of the size (volume) [26, 39-43] and the location [4, 16, 25, 33, 34, 38, 42-51] of the infarction, however the relation with PMF was only seldom investigated. In one study [42] a linear relation between the size of the infarction and the degree of PMF was found. More circumstantial evidence for a role of stroke severity with respect to PMF comes from a study [41] that found a larger total volume of infarction among those patients who developed post-stroke dementia.

Cerebral infarcts in the left middle temporal gyrus and the and/or left dorsal lateral frontal cortex were significantly correlated with PMF [46]. Four studies [33, 38, 44, 48] found a lower PMF in left-sided stroke compared to right hemispheric stroke. Most studies found left hemispheric stroke to be related to more severe PMD as compared

	Prevalence of post-stroke memory dysfunction						
Cut-off	stroke – memory assessment interval (months)						
	0.25	1	3	6	7	12	>12
< 10 percentile	50%						
Score failed 7 or more items					49%		
<2SD			23%				
< 1SD		50%					
<15 percentile			31%				
< 10 percentile		24%		17%		15%	
< 10 percentile		22%		12%			
NS			55%			31%	
< 2SD	13%						11%
Z-Score < -1.65	22%				6%		

to the right hemisphere, presumably since most memory tasks rely on intact language function. Although these studies also included non-verbal memory tasks.

Relation between pre-stroke characteristics and post-stroke memory function

There are a number of factors that presumably were already present prior to the stroke (including WML [52-54], MTA [55, 56] previous (silent) infarcts, and pre-stroke cognitive decline), that could be related to PMF. Due to the fact that stroke patients usually did not have neuroimaging and/or neuropsychology before the actual stroke, the effects of these factors on PMD are difficult to disentangle from the direct stroke effects. Some studies tried to overcome this problem by making adjustments for WML and MTA.

Table 2 The relation between post-stroke memory function and presumed pre-stroke and stroke characteristics

Ref	*Study population*					
	Index	Number	Mean age yrs(SD)	Control	Number	Mean age yrs(SD)
28	Stroke (CIND)	41	66(10)	Stroke (NCI)	62	64(8)
22	Stroke	96	80(4)	Healthy	23	80(6)
30	Stroke	99	71(14)	Healthy	99	70(NS)
27	Stroke	238	70(8)	Healthy	38	67(5)
26	Stroke (Moderate MTA)	54	74(7)	Stroke (no MTA)	100	67(8)
25	Stroke 2months PS	65	56(11)	Same patients 27months PS	65	56(11)
21	Stroke	40	65(11)	Healthy	20	65(12)
34	Silent incident stroke	396	NS	Healthy	619	71(7)
23	Stroke	53	75(7)	Healthy	1171	72(7)
31	Stroke	259	80(4)	Healthy	66	80(4)
33	Stroke	22	55(NS)	Healthy	15	53(6)
20	Multiple Strokes	23	63(NS)	Healthy	11	63(9)
49	Stroke	25	61(9)	Normative data	213	61(3)
32	Stroke	227	71(8)	Healthy	240	71(7)

	Post-stroke memory function			***Stroke characteristics***			***PMF related pre-stroke characteristics***		
Memory test	Performance on memory test compared to controls*			Location (left side)	Size (ml)	First-ever	WML	MTA	Silent stroke
	1-3	4-7	>12						
	Stroke-memory assessment interval (months)								
WMS		-							
CAMCOG	-†						Y		
AVLT	=			53%		100%			
WMS	=†				29	0%	Y	Y	
WMS(R)	-†					0%	Y	Y	
ALVT		-		54%		92%			
WMS(R)	-			50%					
VLT			-†		1.3		Y	Y	Y
AVLT		-							
CAMCOG(R)	=								
WMS-R	-			45%					
CVLT	-								
WMS(R)	=			0%		100%			
CVLT	-								
SRT	-								

Table 2 Continued

Ref	*Study population*					
	Index	Number	Mean age yrs(SD)	Control	Number	Mean age yrs(SD)
24	Stroke	198	68(12)	Healthy	242	65(14)
29	Stroke	123	72(9)	Healthy	78	71(6)

Verbal memory tests
WMS(R): Wechsler Memory Scale(Revised)
CAMCOG(R): Cambridge Assessment of Mental Disorders(Revised)
(R)AVLT: (Rey)Auditory Verbal earning Test
CIND: Cognitive Impairment No Dementia
CVLT: California Verbal Learning Test
SRT: Selective Reminding Test
VLT: Verbal Learning Task

White Matter Lesions

WML was scored in only 5 out of 12 studies [17, 18, 22, 43, 47]. Their presence, as assessed by means of semi-quantitative rating scales, varied from 15% to 45%. In general there was a lower PMF among patients with WML compared to those without, with otherwise identical demographical and stroke characteristics. WML were associated with global cognitive impairment in stroke patients [22, 57, 58]. Independent of this finding, there was a significant association between left frontal WML volume

Post-stroke memory function				*Stroke characteristics*			*PMF related pre-stroke characteristics*		
Memory test	Performance on memory test compared to controls*			Location (left side)	Size (ml)	First-ever	WML	MTA	Silent stroke
	1-3	4-7	>12						
	Stroke-memory assessment interval (months)								
VLT			-			86%			
WMS(R)	-†		-†				Y		

Abbreviation
WML: White Matter Lesions
MTA: Medial Temporal lobe Atrophy
NCI: No Cognitive Impairment
PS: Post-Stroke
NS: Not Specified
The grey cells indicate the post-stroke time interval of memory function assessment
Empty cells indicate no assessment or not specified
* - : indicates significantly worse performance compared to the controls
(as defined in the original article)
+ : indicates significantly better performance compared to the controls
(as defined in the original article)
= : indicates equal performance compared to the controls
(as defined in the original article)
† : adjusted for at least one of the confounding factors mentioned
Y : Yes, indicates that the article describes one or more pre-stroke characteristics

and post-stroke working memory and between both left and right temporal WML volumes and memory function (not otherwise specified) [22].

Medial temporal lobe atrophy

The degree of MTA was assessed in only two studies. Their presence (as assessed on a semi-quantitative scale) [59] was strongly related to immediate and delayed post-stroke memory function (not otherwise specified) among 260 stroke survivors

[26]. This is in line with findings among 22 stroke survivors, in which there was a relation between post-stroke verbal memory as assessed with the Verbal Learning Task and pre-stroke MTA [47].

Previous (silent) infarcts

Information on previous (silent) infarction was lacking in most studies. Twenty-one articles included first-ever stroke survivors and 44 articles included also patients with multiple strokes or did not specify this. One article related silent stroke to memory [34]. They found that silent infarctions located in the thalamus, were associated with a greater decline in memory performance (z-score=-0.50; 95% confidence interval, -0.87 to –0.13).

Pre-stroke cognition

None of the 65 included articles investigated pre-stroke cognition in relation with post-stroke memory function.

Discussion

Data from 65 studies were reviewed. The prevalence of post-stroke memory dysfunction in non-demented stroke survivors varied from 13 to 50% weeks after the stroke, which declined to 11 to 31% one year (or more) after stroke (table 1). It could be that post-stroke dementia is reversible in some stroke patients that have initially been diagnosed with PSD. Preferably, standardised re-assessment of cognitive function should be performed in each patient diagnosed with PSD. Unfortunately, this is not part of current diagnostic criteria (DSMIV [60] or NINDS-AIREN [1]). A prerequisite for the description of a reliable time course of PMD is the presence of a stable source population and a complete as possible follow-up, otherwise the prevalence may appear to decrease when cases (those with PMD) selectively die.
However, some methodological aspects must be considered. The measurement of PMD at several post-stroke intervals was assessed in five studies [5, 16-19]. Therefore, the ascertainment of a time course of PMD prevalence relies on different studies that investigated PMD at different post-stroke intervals. However, these studies differed tremendously in terms of patient inclusion, assessment of memory function and in the collection of stroke and pre-stroke (imaging) characteristics.

In addition, and not always explicitly mentioned, most studies included patients who were able to complete neuropsychological examination. As a consequence, patients who could not complete testing (with a presumably larger stroke than those who could be examined) and those with aphasia were not examined. This could have led to an underestimation of PMD. On the other hand, people with only a minor stroke may not have been included since they, for example, were not willing to participate months after a stroke from which they had completely recovered already.

Some studies [5, 18, 23, 25, 26, 34, 50, 58, 61] investigated patients derived from a larger cohort (also includes one population based study [34]) that apparently had manifestations of cerebral ischemia, either on a scan (in that case it was unclear whether the infarct had been symptomatic or not) or based on history taking. These results are most likely not to be compared with "recent" stroke patients since it seems likely that both stroke characteristics and memory function differ between early stroke survivors and "ever stroke" patients.

Another source of bias that may lead to underestimation of PMD is the fact that all studies only included patients that were actually admitted to the hospital. Many stroke patients, especially the most severely affected with presumably pre-stroke cognitive impairment or even dementia, are not admitted to the hospital. It seems likely that they are the one with the highest prevalence of PMD and the highest risk of PSD. Some studies excluded patients that appear demented immediately after stroke. Consequently, the remaining sample (that then does not encompass any demented patient) has a lower risk of developing PSD.

We found a considerable age difference between the studies making comparisons difficult, as age is an important determinant of memory [24, 38, 62]. In addition, age is an important determinant of both MTA and WML, the latter being one of the most important confounders or effect modifiers in the relation between stroke and PMD. The possibility that differences in MTA or WML underlie (at least in part) the observed differences of PMD between studies can therefore not be ruled out.

There was a wide variability in assessment of verbal memory function and the definition of memory dysfunction. From most studies the memory dysfunction (for example expressed as the number SD's below the mean) could not be calculated due to lack of raw data. Therefore the prevalence of PMD across different post-stroke intervals is rather limited and difficult to compare. Others studies used normative data or controls to define memory function. However, the problem with normative data could be that there is not much known about the persons investigated and they certainly did not undergo neuroimaging. Therefore, normative data could also include people with a silent stroke or white matter lesions.

The above mentioned methodological considerations may lead to questioning the validity of the concept of PMD and consequently of the diagnosis of VaD and PSD. These diagnoses are based (analogous to the diagnosis of Alzheimer's disease) on the assumption of a stable or gradual decline of post-stroke memory function among patients without pre-stroke characteristics that could be related to PMD [1, 9]. Our review indicates that this is not true. Patients with PMD three months after a stroke (who could then have been diagnosed with VaD or PSD when also all other dementia criteria were fulfilled) could very well have recovery of memory dysfunction half a year after the stroke, and consequently not fulfill dementia diagnosis anymore. We also found that patients with PMD appear to constitute a population with many other (pre-) stroke factors that could, independent from the stroke, be related to PMD, both structural as well cognitive.

The development of PMD also seems counter intuitive, since the stroke does usually not affect structures known to be involved in memory [6-8]. However, the emergence of post-stroke memory dysfunction fits in current thinking of memory as a function of an intact cerebral network, connecting several parts of the brain, including medial temporal lobes, anterior thalamic nucleus, mammillary body, fornix, and the prefrontal cortex which each other (the so called circuit of Papez) [4, 33, 34, 43, 46, 47, 63]. Any stroke in either these structures or in the connections in between could result in PMD. Presumably, patients with already preexisting damage in either compartments of the network (MTA) or in the connections (WML) are at increased risk for PMD. Perhaps these are also the patients who are therefore at the highest risk for PSD, although formal studies are lacking. Therefore, future studies should include well characterized stroke patients (both in terms of stroke and pre-stroke characteristics) that assess memory function at several predefined post-stroke intervals. They should particularly include information on whether an ever or first-ever stroke survivors are included since a previous stroke may influence cognitive function assessed immediately after another, novel stroke. Care should be given to proper registration of those patients that cannot complete memory testing. Novel imaging techniques such as task related, but also resting state fMRI may be of use in the detection of what part of the brain (or what network) shows altered function in patients with PMD. These techniques could then, when established, perhaps also be of use in the early prediction of those with PMD, or even post-stroke dementia and as such possibly guide early (cognitive) rehabilitation medicine.

Reference List

1. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. *Report of the NINDS-AIREN International Workshop Neurology* 1993;43:250-60.
2. Bowler JV. Vascular cognitive impairment. *J Neurol Neurosurg Psychiatry* 2005;76:v35-v44.
3. De Leeuw FE, van Gijn J. Vasculaire dementie. *Ned Tijdschr Geneeskd* 2004; 148:1181-6.
4. Kumral E, Evyapan D, Balkir K, et al. Bilateral thalamic infarction. Clinical, etiological and MRI correlates. *Acta Neurol Scand* 2001;103:35-42.
5. Rasquin SM, Verhey FR, Lousberg R, et al. Vascular cognitive disorders: memory, mental speed and cognitive flexibility after stroke. *J Neurol Sci* 2002;203-204:115-9.
6. Buckner RL, Kelley WM, Petersen SE. Frontal cortex contributes to human memory formation. *Nat Neurosci* 1999;2:311-4.
7. Kelley WM, Miezin FM, McDermott KB, et al. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron* 1998;20:927-36.
8. Wagner AD, Schacter DL, Rotte M, et al. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 1998;281:1188-91.
9. Leys D, Henon H, Mackowiak-Cordoliani MA, et al. Poststroke dementia. *Lancet Neurol* 2005;4:752-9.
10. Wechsler D. A standarized memory scale for clinical use. *J.Psychology* 1945;19:87-95
11. Rey A. L'examen clinique en psychologie 183 Paris: *Presses Universitaires de France* 1964.
12. Wilson C. The rivermead behavioural memory test Tichfield:*Thames Vally Test Company* 1985.
13. Roth M. CAMDEX: a standardisedinstrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* 1986;149:698-709.
14. Delis. California Verbal Learning Test. Research edition. *New York: The Psychological Corporation Harcourt Brace Jovanovich Inc* 1987.
15. Brand N&JJ. Learning and retrieval rate of words presented auditorily and visually. *Journal of General Psychology* 1985; 112: 201-210.
16. Kotila M, Waltimo O, Niemi ML, et al. The profile of recovery from stroke and factors influencing outcome. *Stroke* 1984;15:1039-44.
17. Nys GM, van Zandvoort MJ, de Kort PL, et al. Domain-specific cognitive recovery after first-ever stroke: a follow-up study of 111 cases. *J Int Neuropsychol Soc* 2005;11:795-806.
18. Rasquin SM, Lodder J, Ponds RW, et al. Cognitive functioning after stroke: a one-year follow-up study. *Dement Geriatr Cogn Disord* 2004;18:138-44.
19. van Zandvoort MJ, Kessels RP, Nys GM, et al. Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. *Clin Neurol Neurosurg* 2005;107:385-92.
20. Babikian VL, Wolfe N, Linn R, et al. Cognitive changes in patients with multiple cerebral infarcts. *Stroke* 1990;21:1013-8.

21. Berrin-Wasserman S, Winnick WA, Borod JC. Effects of stimulus emotionality and sentence generation on memory for words in adults with unilateral brain damage. *Neuropsychology* 2003;17:429-38.
22. Burton EJ, Kenny RA, O'Brien J, et al. White matter hyperintensities are associated with impairment of memory, attention, and global cognitive performance in older stroke patients. *Stroke* 2004;35:1270-5.
23. Dik MG, Deeg DJ, Bouter LM, et al. Stroke and apolipoprotein E epsilon4 are independent risk factors for cognitive decline: A population-based study. *Stroke* 2000;31:2431-6.
24. Engstad T, Almkvist O, Viitanen M, et al. Impaired motor speed, visuospatial episodic memory and verbal fluency characterize cognition in long-term stroke survivors: the Tromso Study. *Neuroepidemiology* 2003;22:326-31.
25. Hochstenbach JB, den OR, Mulder TW. Cognitive recovery after stroke: a 2-year follow-up. *Arch Phys Med Rehabil* 2003;84:1499-504.
26. Jokinen H, Kalska H, Ylikoski R, et al. Medial temporal lobe atrophy and memory deficits in elderly stroke patients. *Eur J Neurol* 2004;11:825-32.
27. Jokinen H, Kalska H, Mantyla R, et al. Cognitive profile of subcortical ischaemic vascular disease. *J Neurol Neurosurg Psychiatry* 2006;77:28-33.
28. Nyenhuis DL, Gorelick PB, Geenen EJ, et al. The pattern of neuropsychological deficits in Vascular Cognitive Impairment-No Dementia (Vascular CIND). *Clin Neuropsychol* 2004;18:41-9.
29. Sachdev PS, Brodaty H, Valenzuela MJ, et al. Progression of cognitive impairment in stroke patients. *Neurology* 2004;63:1618-23.
30. Srikanth VK, Thrift AG, Saling MM, et al. Increased risk of cognitive impairment 3 months after mild to moderate first-ever stroke: a Community-Based Prospective Study of Nonaphasic English-Speaking Survivors. *Stroke* 2003;34:1136-43.
31. Stephens S, Kenny RA, Rowan E, et al. Neuropsychological characteristics of mild vascular cognitive impairment and dementia after stroke. *Int J Geriatr Psychiatry* 2004;19:1053-7.
32. Tatemichi TK, Desmond DW, Prohovnik I, et al. Confusion and memory loss from capsular genu infarction: a thalamocortical disconnection syndrome? *Neurology* 1992;42:1966-79.
33. Vakil E, Blachstein H, Soroker N. Differential effect of right and left basal ganglionic infarctions on procedural learning. *Cogn Behav Neurol* 2004;17:62-73.
34. Vermeer SE, Prins ND, den HT, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348:1215-22.
35. Cartoni A, Lincoln NB. The sensitivity and specificity of the Middlesex Elderly Assessment of Mental State (MEAMS) for detecting cognitive impairment after stroke. *Neuropsychol Rehabil* 2005;15:55-67.
36. Hochstenbach J, Mulder T, van Limbeek J, et al. Cognitive decline following stroke: a comprehensive study of cognitive decline following stroke. *J Clin Exp Neuropsychol* 1998;20:503-17.
37. Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. *Br J Clin Psychol* 1989;28:61-5.
38. Madureira S, Guerreiro M, Ferro JM. Dementia and cognitive impairment three months after stroke. *Eur J Neurol* 2001;8:621-7.

39. Bowler JV, Hadar U, Wade JP. Cognition in stroke. *Acta Neurol Scand* 1994;90:424-9.
40. Corbett A, Bennett H, Kos S. Cognitive dysfunction following subcortical infarction. *Arch Neurol* 1994;51:999-1007.
41. Desmond DW, Moroney JT, Bagiella E, et al. Dementia as a predictor of adverse outcomes following stroke: an evaluation of diagnostic methods. *Stroke* 1998;29:69-74.
42. Elwan O, Hashem S, Helmy AA, et al. Cognitive deficits in ischemic strokes: psychometric, electrophysiological and cranial tomographic assessment. *J Neurol Sci* 1994;125:168-74.
43. Exner C, Weniger G, Irle E. Implicit and explicit memory after focal thalamic lesions. *Neurology* 2001;57:2054-63.
44. Hom J, Reitan RM. Generalized cognitive function after stroke. *J Clin Exp Neuropsychol* 1990;12:644-54.
45. Malhotra P, Jager HR, Parton A, et al. Spatial working memory capacity in unilateral neglect. *Brain* 2005;128:424-35.
46. Reed BR, Eberling JL, Mungas D, et al. Memory failure has different mechanisms in subcortical stroke and Alzheimer's disease. *Ann Neurol* 2000;48:275-84.
47. Van der Werf YD, Scheltens P, Lindeboom J, et al. Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia* 2003;41:1330-44.
48. von Cramon DY, Hebel N, Schuri U. Verbal memory and learning in unilateral posterior cerebral infarction. A report on 30 cases. *Brain* 1988;111:1061-77.
49. Welte PO. Indices of verbal learning and memory deficits after right hemisphere stroke. *Arch Phys Med Rehabil* 1993;74:631-6.
50. Yaretzky A, Raviv S, Netz Y, et al. Primary visual memory of stroke patients. *Disabil Rehabil* 1995;17:293-7.
51. Zwinkels A, Geusgens C, van de Sande P, et al. Assessment of apraxia: inter-rater reliability of a new apraxia test, association between apraxia and other cognitive deficits and prevalence of apraxia in a rehabilitation setting. *Clin Rehabil* 2004;18:819-27.
52. Burns JM, Church JA, Johnson DK, et al. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. Arch Neurol 2005;62:1870-6.
53. Mungas D, Jagust WJ, Reed BR, et al. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. Neurology 200;57:2229-35.
54. Vataja R, Pohjasvaara T, Mantyla R, et al. MRI correlates of executive dysfunction in patients with ischaemic stroke. *Eur J Neurol* 2003;10:625-31.
55. Korf ES, Wahlund LO, Visser PJ, et al. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology* 2004 ;63:94-100.
56. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992;55:967-72.
57. Ballard C, Stephens S, Kenny R, et al. Profile of neuropsychological deficits in older stroke survivors without dementia. *Dement Geriatr Cogn Disord* 2003;16:52-6.
58. Burton E, Ballard C, Stephens S, et al. Hyperintensities and fronto-subcortical atrophy on MRI

are substrates of mild cognitive deficits after stroke. *Dement Geriatr Cogn Disord* 2003;16:113-8.
59. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 199;67:66-72.
60. Lewis G. DSM-IV. Diagnostic and statistical manual of mental disorders, 4th edn - AmerPsychiatAssoc. *Psychological Medicine* 1996;26:651-2.
61. Larson E, Kirschner K, Bode R, et al. Construct and predictive validity of the repeatable battery for the assessment of neuropsychological status in the evaluation of stroke patients. *J Clin Exp Neuropsychol* 2005;27:16-32.
62. Desmond DW, Moroney JT, Paik MC, et al. Frequency and clinical determinants of dementia after ischemic stroke. *Neurology* 2000;54:1124-31.
63. Budson AE, Price BH. Memory dysfunction. *N Engl J Med* 2005;352:692-9.
64. Blake H, McKinney M, Treece K, et al. An evaluation of screening measures for cognitive impairment after stroke. *Age Ageing* 2002;31:451-6.
65. Bohannon RW, Ahlquist M, Lee N, et al. Functional gains during acute hospitalization for stroke. *Neurorehabil Neural Repair* 2003;17:192-5.
66. Clark PC, Dunbar SB, Shields CG, et al. Influence of stroke survivor characteristics and family conflict surrounding recovery on caregivers' mental and physical health. *Nurs Res* 2004;53:406-13.
67. Dagenbach D, Kubat-Silman AK, Absher JR. Human verbal working memory impairments associated with thalamic damage. *Int J Neurosci* 2001;111:67-87.
68. Exner C, Weniger G, Irle E. Cerebellar lesions in the PICA but not SCA territory impair cognition. *Neurology* 2004;63:2132-5.
69. Hajek VE, Rutman DL, Scher H. Brief assessment of cognitive impairment in patients with stroke. *Arch Phys Med Rehabil* 1989;70:114-7.
70. Hochstenbach J, van Spaendonck KP, Cools AR, et al. Cognitive deficits following stroke in the basal ganglia. *Clin Rehabil* 1998;12:514-20.
71. Hochstenbach JB, Anderson PG, van Limbeek J, et al. Is there a relation between neuropsychologic variables and quality of life after stroke? *Arch Phys Med Rehabil* 2001;82:1360-6.
72. Hoffmann M, Schmitt F. Cognitive impairment in isolated subtentorial stroke. *Acta Neurol Scand* 2004;109:14-24.
73. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. *Br J Psychiatry* 1988;152:209-13.
74. Koning dI, Dippel DW, van Kooten F, et al. A short screening instrument for poststroke dementia : the R-CAMCOG. *Stroke* 2000;31:1502-8.
75. Mosch SC, Max JE, Tranel D. A matched lesion analysis of childhood versus adult-onset brain injury due to unilateral stroke: another perspective on neural plasticity and recovery of social functioning. *Cogn Behav Neurol* 2005;18:5-17.
76. Mysiw WJ, Beegan JG, Gatens PF. Prospective cognitive assessment of stroke patients before inpatient rehabilitation. The relationship of the Neurobehavioral Cognitive Status Examination to functional improvement. *Am J Phys Med Rehabil* 1989;68:168-71.

77. Pohjasvaara T, Erkinjuntti T, Vataja R, et al. Dementia three months after stroke. Baseline frequency and effect of different definitions of dementia in the Helsinki Stroke Aging Memory Study (SAM) cohort. *Stroke* 1997;28:785-92.
78. Prescott RJ, Garraway WM, Akhtar AJ. Predicting functional outcome following acute stroke using a standard clinical examination. *Stroke* 1982;13:641-7.
79. Riepe MW, Riss S, Bittner D, et al. Screening for cognitive impairment in patients with acute stroke. *Dement Geriatr Cogn Disord* 2004;17:49-53.
80. Stephens S, Kenny RA, Rowan E, et al. Association between mild vascular cognitive impairment and impaired activities of daily living in older stroke survivors without dementia. *J Am Geriatr Soc* 2005;53:103-7.
81. Sunderland A, Stewart FM, Sluman SM. Adaptation to cognitive deficit? An exploration of apparent dissociations between everyday memory and test performance late after stroke. *Br J Clin Psychol* 1996;35:463-76.
82. Sze KH, Sim TC, Wong E, et al. Effect of nimodipine on memory after cerebral infarction. *Acta Neurol Scand* 1998;97:386-92.
83. Tham W, Auchus AP, Thong M, et al. Progression of cognitive impairment after stroke: one year results from a longitudinal study of Singaporean stroke patients. *J Neurol Sci* 2002;203-204:49-52.
84. Wade DT, Parker V, Langton HR. Memory disturbance after stroke: frequency and associated losses. *Int Rehabil Med* 1986;8:60-4.

3.2 Memory performance after stroke associated with reduced medial temporal lobe functionality

Abstract

Stroke is a leading cause of disability, not only because of motor limitations, but also because of the frequent occurrence of post-stroke cognitive impairment. This is illustrated by the fact that the risk of post-stroke dementia is reportedly higher than a recurrent stroke. The loss of subcortical and cortical functions in the post-stroke cognitive dysfunction spectrum is usually well explained by the size and location of the infarction. However, this does not apply for post-stroke memory dysfunction (especially episodic memory dysfunction), as there is almost never an infarction in the medial temporal lobe (MTL). Involvement of the MTL in post-stroke memory dysfunction seems likely since this structure is essential for memory encoding and retrieval. For a proper episodic memory function the MTL depends on intact connections with virtually the whole brain. Disconnection from other brain areas due to the infarction could lead to a reduced MTL function and the attendant reduced episodic memory function. We investigated MTL functionality in 28 first-ever stroke patients and 22 healthy controls with the aid of fMRI. Stoke patients with a reduced episodic memory function 6-8 weeks after infarction had a reduced medial temporal lobe functionality. Post-stroke reduced MTL functionality may be responsible for the frequent observation of impaired post-stroke episodic memory function. Insight in this mechanism could be helpful in identifying which stroke patient may be at increased risk for developing post-stroke dementia and who could benefit from early cognitive rehabilitation.

Liselore Snaphaan, Mark Rijpkema, Inge van Uden, Guillén Fernández, Frank-Erik de Leeuw. Reduced medial temporal lobe functionality in stroke patients: A functional Magnetic Resonance Imaging study. Brain. Jul 2009, 132:1882-8.

Introduction

Stroke is a devastating disease that affects millions of people worldwide every year. It is a leading cause of disability; in the acute phase this is predominantly determined by limitations of motor function that usually show a fairly good tendency to recover in the first weeks, whereas in the subacute and chronic phase post-stroke cognitive impairment is an important determinant of recovery [Hofgren *et al. 2007].* Cognitive impairment within the first month after stroke affects up to 10-82% [Rasquin et al. 2004] of stroke survivors that surprisingly often goes unnoticed by treating physicians, usually due to a lack of a standardised assessment. The importance of post-stroke cognitive function as a major determinant of post-stroke Activity-of-Daily-Life (ADL) is illustrated by the fact that the risk of dementia after a stroke is reportedly higher than the risk of a recurrent stroke [Yokota et al. 2004].

Most of the spectrum of post-stroke cognitive dysfunction is usually well explained by the size and location of the infarction, whereas an explanation of the occurrence of memory dysfunction after stroke (especially episodic memory dysfunction) is currently lacking, as there is almost never an infarction in the medial temporal lobe (MTL) [Snaphaan and de Leeuw 2007]. Despite the absence of direct ischemic structural damage of the MTL, an impaired post-stroke function of the MTL presumably plays a role in the development of episodic memory dysfunction after stroke, as a proper MTL function is essential for memory encoding and retrieval [Brierley et al. 2002]. After all, for an optimal episodic memory function the MTL depends on intact connections with virtually the whole brain [Suzuki 2007]. Disconnection from these other brain areas due to the infarction could lead to a reduced MTL function and in addition to a reduced episodic memory function. Therefore we hypothesised that the reduced episodic memory functionality found in stroke survivors is related with a reduced MTL function.

The n-back task activates a so-called working memory (WM) network that consists of bilateral prefrontal cortex, parietal cortex, thalamus, anterior cingulate, and bilateral cerebellum [Callicott *et al.* 1999;Callicott *et al.* 2000]. In addition to these working memory related activations medial temporal deactivations were observed as well with the n-back task [Egan et al., 2003]. Previous studies showed that this deactivations can be used as a marker of the MTL function [Egan et al., 2003; Meyer-Lindenberg et al. 2001;Weinberger et al. 1996]. The n-back task is a relatively simple task that can equally well be executed by patients with impaired episodic memory performance and controls, thereby excluding the possibility that differences in test performance (i.e n-back task) can explain differences in MTL activation. Consequently, the n-back task is used to assess functionality of the MTL in this study, but it is not a measure of episodic memory

performance. We investigated MTL activation by fMRI using the n-back task in 28 consecutive first-ever supratentorial stroke survivors and 22 healthy controls.

Methods

Patients

Patients were eligible for inclusion if they had an acute symptomatic first-ever supratentorial cerebral infarction between September 2005 and May 2007 and were admitted to the department of Neurology of the Radboud University Nijmegen Medical Centre. The diagnosis of stroke was based on both the presence of acute neurological symptoms that could only be explained by vascular lesion in a specific vascular territory and a compatible lesion on CT or MRI scan. Patients were excluded on the basis of the following criteria: age > 75 years, preexistent cognitive decline (considered present when the patient had a score of <78 on the short Informant Questionnaire on cognitive decline in elderly (IQCODE) [de Jonghe *et al.* 1997]) or concurrent cognitive impairment (considered present when the patient had a score of ≤ 23 on the Mini Mental State examination (MMSE) [Folstein *et al.* 1973]), history of concomitant neurological disease, presence of diseases or the use of medication that were likely to affect cognition, history of alcohol or drug abuse, severe white matter lesions (operationalised as a score ≥ 2 in two or more regions as assessed with the ARWMC scale [Wahlund *et al.* 2001]), clinical or radiological evidence of a previous infarction, aphasia and MRI contra-indications (metal implants, pacemaker, claustrophobia). In total 52 patients fulfilled in- and exclusion criteria; 38 of them agreed to participate in the study (response 73%). There were no differences between responders and non-responders with respect to the baseline characteristics described in table 1. Ten of them were left out of the analysis because of distortion of MRI data by movements (n=3), lack of adherence to task instructions (n=2) or early break off during scanning (anxiety, n=5), which resulted in a study population of 28 patients.

Controls

Healthy control subjects (n=29) were recruited from the general population through advertising. They were closely matched to the patient group with respect to age, gender and education. Both patients and controls underwent an identical neuro-psychological examination. Seven controls were left out of the analysis because of the presence of silent brain infarcts (n=4) or pre-existent cognitive decline (n=3).

The medical ethics committee (CMO Arnhem-Nijmegen, The Netherlands) approved the study protocol. All subjects gave written informed consent to participate in this study and only travel costs were reimbursed.

Episodic memory assessment

All patients underwent a complete, standardised neuropsychological examination between 6-8 weeks after their qualifying stroke covering all cognitive domains, including assessment of mood. Episodic memory was assessed with the California Verbal Learning Task, Dutch version (CVLT) [Delis 1987]. We were particularly interested in the delayed-recall because this measure is most sensitive to MTL function [Hermann *et al.* 1987;Mungas *et al.* 1985]). Other relevant tests for the purpose of this particular study included; global cognition (MMSE), pre-existent cognitive decline (IQCODE), and anxiety and depressive symptoms (Hospital Anxiety Depression Scale (HADS) [Zigmond and Snaith 1983]). In addition, educational level was assessed in all subjects using the Dutch classification system [Verhage 1964], ranging in ascending order from 0 (less than primary school) to 7 (university degree).

Other covariates

Clinical stroke severity at admission was assessed with the National Institute of Health Stroke Scale (NIHSS)[Brott *et al.* 1989]. Infarcts were classified according to location by an experienced stroke neurologist (FEdL) according to a standard procedure using neuroimaging (either CT or MRI) at which the symptomatic lesion was best visible. We also assessed the post-stroke functional status 6-8 weeks after stroke by the Barthel Index (BI) [Mahoney and Barthel 1965];[Mahoney and Barthel 1965] ranging from 0 (completely dependent) to 20 (completely independent), and degree of handicap (modified Rankin Scale (mRS) [van Swieten *et al.* 1988]; ranging from 0 (no symptoms) to 5 (severe disability).

fMRI Task design

Patients were scanned 9-12 weeks after the stroke. As fMRI task design we used a number variant version of the n-back working memory paradigm [Gevins and Cuttilo, 1993]. The n-back task is a paradigm which activates a so-called working memory (WM) network that consists of bilateral prefrontal cortex, parietal cortex, anterior cingulate, and bilateral cerebellum [Callicott et al. 1999;Callicott et al. 2000], whereas

MTL deactivation is also observed [Callicott et al. 2000;Meyer-Lindenberg et al. 2001]. In this study an n-back task was used with a sequence of 0-back (minimal WM load) and 2-back conditions (moderate WM load) arranged in a blocked design.
In the scanner, subjects viewed single digits (digits 1-9) in white arial font on a black background on a screen in pseudo-random order. Each digit appeared 0.6 s, after which the subjects had to react within 1.5 s by pressing the response button for the target digit. The two conditions (0-back and 2-back) were applied in alternating blocks of 15 digits. The whole experiment consisted of 10 cycles and thus each subject had to respond to 300 digits. The task took about 12 minutes and 19 seconds, in which 308 whole brain images were recorded. In the 0-back task subjects had to respond to target digit '1'. The 2-back task required the subject to press the response button when a digit occurred which matched the one presented two digits before. Both conditions contained 15% target digits. Subjects were instructed in detail with task examples on a computer outside the scanner until they understood the task procedure. During the experiment subjects were reminded of the actual condition by continuous presentation of the following symbols on the screen: '–' indicated the 0-back condition and '←' indicated the 2-back condition.

Data acquisition

MR data were acquired with a 1.5T Siemens (Erlangen, Germany) Sonata MR scanner, equipped with a circularly polarised head coil. One run of T2*-weighted blood oxygenation level-dependent (BOLD) images was acquired using echo-planar imaging (EPI) with each image volume consisting of 35 axial slices [voxelsize 3 mm x 3.5mm x 3.5mm; repetition time (TR), 2.40 s; echo time (TE), 30 ms; 64x64 matrix; field of view (FOV), 224 mm x 224; flip angle, 90°]. After the functional run, a high-resolution T1-weighted structural MR image was acquired for coregistration and spatial normalisation procedures [3D MP-RAGE (magnetisation-prepared rapid gradient-echo); TR, 2.25 s; TE, 3.68 ms; 176 contiguous 1mm slices; 256x256 matrix; FOV, 256 mm].
Total brain volume was calculated as the sum of the volumes of grey matter (G) and white matter (W) which were assessed by automated segmentation of high-resolution T1-weighted structural MR images using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). All segmented volumes were visually checked using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/) .
Hippocampal volume was assessed by manual segmentation using the interactive software program 'ITK-SNAP' (http://www.itksnap.org) according to a standardised protocol [Brierley *et al.* 2002;Geuze *et al.* 2005] with a high interrater agreement (intraclass

correlation coefficient for the left and right hippocampus of 97% and 96%, respectively). Hippocampal volumes were adjusted for total brain volume. This segmentation was done without prior knowledge of both performances on memory tasks and degree of MTL activation during the fMRI experiment.

Data analysis

The first three EPI volumes were discarded to allow for T1 equilibration. Data were analysed in MATLAB 7.1 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 with the following preprocessing steps: spatial realigning to correct subject motion (none of the subjects exceeded 3 mm motion), coregistration to the mean of functional images using mutual information optimisation, slice time correction, spatial normalisation to the Montreal Neurological Institute (MNI) T1 template, and spatial smoothing with a Gaussian kernel of 8 mm full-width at half-maximum.

A general linear model [Friston *et al.* 1995] was used to analyse the data. Regressors for the 0-back and 2-back task were convolved with the canonical hemodynamic response function (HRF). To adjust for movement-related activation, the realignment parameters were also added to the model as regressors. The data were high pass-filtered (128 s) to account for low-frequency effects. Contrast images were created for each subject summarising the differences between conditions (0-back minus 2-back, and 2-back minus 0-back contrast). The single-subject contrast images were entered into second-level random-effects analysis. Group level SPM(t) maps were thresholded at $p=0.001$ (uncorrected) and the cluster-size statistics FWE (Familywise Error) corrected were used as the test statistics. Only clusters at $p(FWE)\leq 0.05$ were considered significant. As we had an a priori hypothesis about the MTL (reduced MTL functionality is linked to impaired episodic memory function after stroke), a small volume correction was used for the MTL [Worsley *et al.* 1996]. For this purpose the MTL region of interest from the SPM anatomy toolbox (version 1.5 S. Eickhoff, institute for Medicin, research centre Jülich) was used. A two-sample *t*-test was applied to investigate the differences in brain activity between patients and control group during the 0-back minus 2-back contrast and 2-back minus 0-back contrast.

Baseline and clinical characteristics were analysed using SPSS version 14.0. Two-sample t-tests were used for between group comparison for continuous data, Chi Square tests for nominal data and Mann Whitney U analyses were used for non-parametric data. All effects were tested at the $p<0.05$ level (two-tailed).

Results

Subjects' characteristics

The study population consisted of 50 subjects with a mean age of 54.2 years (SD12.8), 46% of them were female, median educational level was 5 and 84% was right handed. Baseline characteristics of both patients and controls are presented in table 1. No significant differences were found for age, gender, education and handedness between patients and controls. Total brain volume, grey matter volume, white matter volume, and hippocampal volume did not significantly differ between patients and controls.
Clinical and behavioural characteristics of patients and controls are presented in table 2. There were no differences between patients with a left or right sided stroke. There were nine patients who had an infarction in the internal capsule (six left; three right), five in the corona radiata (four right; one left), three in the thalamus (one right; two left), four in the occipital lobe (two right; two left), four in the brain stem and three in the parietal lobe (two right; one left).

Table 1 Baseline characteristics

	patients (n=28)	controls (n=22)
Age in years (SD) †	53.7(12.6)	51.5(12.9)
Male % $	57.1	50.0
Education (range) #	5(0-7)	5(2-7)
Right handed % $	85.7	81.8
Left sided infarction %	46.4	
Total brain volume (SD) †	1159(129.3)*	1143(122.9)**
Grey matter volume (SD) ††	661(67.9)*	659(77.1)**
White matter volume (SD) ††	498(68.6)*	484(58.5)**
Hippocampal volume (SD) ††	7.1(1.0)	6.7(0.9)

Values represent means (SD), median (range), proportions (%) or ml (volume), empty cells Indicates no assessment, * data available for n=27, ** data available for n=21, † Univariate Analysis, † †corrected for total brain volume, $ Chi Square Analysis, # Mann Whitney U analysis; score 5 means 10-11 years of education. No significant differences were found between patients and controls for all these baseline characteristics ($p<0.05$).

Table 2 Clinical and behavioural characteristics of participants

	Patients n=28	Controls n=22
MMSE (SD) †	28.1(1.7)*	29.4(0.8)#
Delayed recall words (SD) †	9.2(4.6)	12.4(2.0)#
HADS anxiety (range) †	5.5(0-12)**	4.5(0-14)
HADS depressive symptoms (range) †	4.0(0-17)**	2.5(0-14)
Modified BI (SD)	20(0.0)**	20(0.0)
Modified Rankin scale (range)	1(0-3)**	
NIHSS score (range)	2(0-16)***	
Correct responses on n-back task (%)		
0-back condition mean (SD) †	99.1(2.3)	99.7(0.7)
2-back condition mean (SD) †	93.3(4.7)	94.9(2.8)

Values represent means (SD), median (range) or proportions (%), empty cells indicates no assessment, * data available for n=27, ** data available for n=26, *** data available for n=25, † Univariate Analysis, # Significant differences between patients and controls ($p<0.05$)

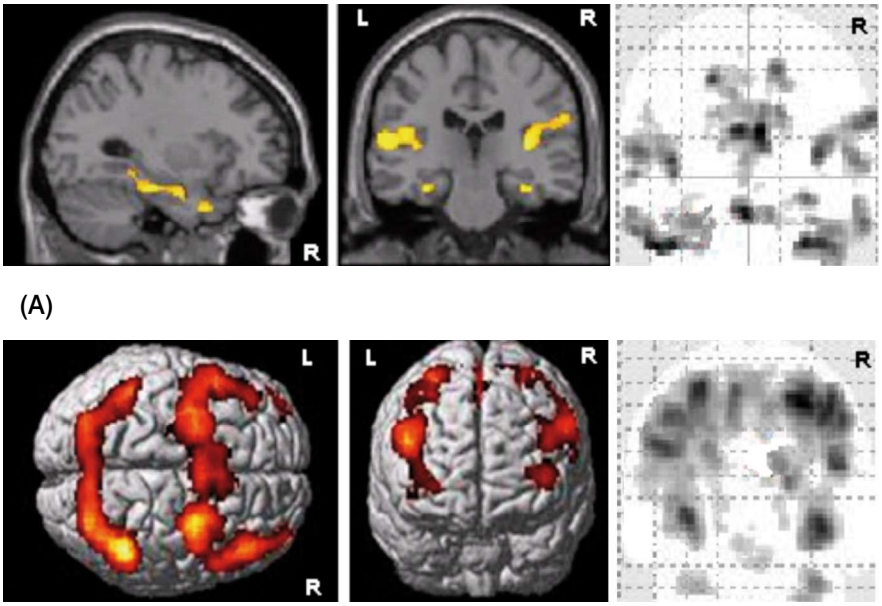
Patients performed significantly worse (mean words 9.2(SD 4.6)) than controls (mean words 12.4 (SD 2.0)) on the delayed recall task of the CVLT ($p= 0.004$). There was no difference between other clinical and behavioural characteristics, except for the MMSE score. Despite the difference in episodic memory function, patients and controls did not perform significantly different on the n-back task in the scanner.

fMRI responses

Patients and controls

In the 0-back minus 2-back contrast brain activation was observed bilaterally in the frontal lobe, medial temporal lobe, cingulate gyrus, insula, occipital lobe and cerebellum (figure 1A). In the 2-back minus 0-back contrast brain activation was observed bilaterally in the frontal lobe, brain stem (pons), cerebellum and temporal lobe (figure 1B). These two activation patterns (figure 1A,B) correspond with brain areas typically activated by the n-back paradigm [Callicott *et al.* 1999;Callicott *et al.* 2000;Meyer-Lindenberg *et al.* 2001]. These activation patterns were similar for patients and controls.

Figure 1 Whole brain activation pattern of 22 controls during (A) 0-back minus 2-back contrast and (B) 2-back minus 0-back contrast, thresholded at P=0.001 uncorrected



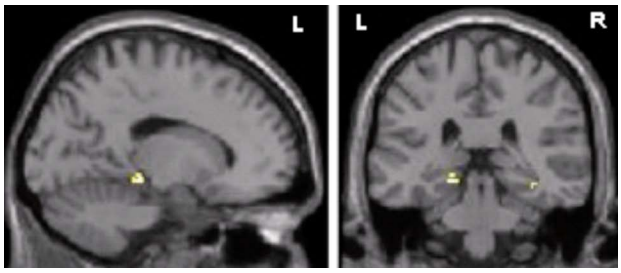
Furthermore, we found a positive correlation between MTL activation (in the 0-back minus 2-back contrast) and CVLT performances in controls (ß=0.48, p=0.02), that was significantly different from patients.

Patients versus Controls

Exploratory whole brain analysis revealed no significant differences (p(FEW) >0.05) between stroke patients and controls, probably due to limited power as the study was designed to look exclusively at MTL functionality in a heterogenous group of stroke patients.

As we wanted to compare MTL functionality (assessed with the n-back task) between patients and healthy controls, we subsequently focused specifically on the MTL. Both patients and controls showed MTL activation during the 0-back minus 2-back contrast, however patients showed significantly less left sided MTL activation ($x = -18$, $y = -32$, $z = -10$, $t = 4.42$, $k = 27$, $p(FWE) = 0.02$) than healthy matched controls (figure 2). Additionally, there was a trend for the right sided MTL activation ($x = 32$, $y = -38$, $z = -10$, $t = 3.70$, $k = 13$, $p(FWE) = 0.12$). No significant differences were observed in the opposite contrast (2 minus 0 back).

Figure 2 Difference in MTL activation between healthy controls (n=22) and stroke patients (n=28) during 0-back minus 2-back contrast. Healthy controls showed significantly more MTL activation than patients during the 0-back minus 2-back contrast, thresholded at P=0.001 uncorrected



Discussion

To our knowledge, this is the first study that investigates medial temporal lobe function and episodic memory performance among stroke patients. We found reduced MTL activation assessed by an n-back paradigm in stroke patients. In addition, stroke patients had a reduced episodic memory function compared to healthy matched controls.

A strong element in our study is the large sample size (28 stroke patients), in contrast with many other fMRI studies that often investigated less than 20 patients [Meyer-

Lindenberg *et al*. 2001;Harvey *et al.* 2005;Meisenzahl *et al.* 2006] leading to the possibility of finding false negative results (type II error). Another strong element is our high response of 73%, which may imply a high external validity. Furthermore, episodic memory was assessed blinded to MTL function. Another important issue is the generalisability of our study, because we included *all* stroke patients regardless of the size and side of the infarction. This was done intentionally because a recent systematic review [Snaphaan and de Leeuw, 2007] found no evidence between lesion location and memory dysfunction. Therefore, our findings may be generalized towards any first-ever stroke patient with an acute symptomatic supratentorial cerebral infarction.

However, there are also some methodological aspects that need to be considered. We used the activations in the MTLs in a working memory task to assess the 'functionality' of the MTLs in an episodic memory task. This is in line with previous research that used a similar approach [Johnson *et al*, 2001; Egan *et al,* 2003]. In accordance with these studies we also found a positive correlation between MTL activation in the 0-back minus 2-back contrast and CVLT performances in controls (ß=0.48, p=0.02), that, differed significantly from the stroke patients. This finding suggests that reduced MTL functionality may be responsible for the impaired post-stroke episodic memory function. Furthermore, one could question the validity of functional MRI in patients with a compromised cerebrovascular circulation. fMRI relies on the Blood Oxygen Level Dependent (BOLD) signal that is presumably dependent on intact cerebrovascular responses. However, the fact that we were able to detect fMRI responses as predicted from previous studies that used the n-back task [Callicott *et al*. 1999;Callicott *et al.* 2000;Meyer-Lindenberg *et al.* 2001] makes this unlikely. In addition, recent methodological studies on the validity of fMRI in stroke patients confirmed its usefulness [Kimberley *et al.* 2007].

Critics could argue that reduced MTL activation is simply a consequence of impaired performance on the n-back task by the stroke patients. However, despite the fact that patients performed worse on the delayed recall task, they did <u>not</u> on the n-back task; making this explanation rather unlikely. Another explanation for our finding of a reduced MTL activation among stroke patients could be differential selection of patients with already pre-existing cognitive decline. However, this seems unlikely as we only included patients that showed no signs of prestroke cognitive decline, as assessed with the IQCODE. Furthermore, memory function is known to be affected by many environmental factors and structural brain correlates including depressive symptoms, anxiety, total brain volume and hippocampal volume [Kauhanen *et al.* 1999;Kizilbash *et al.* 2002;Sullivan *et al.* 1996;Lupien *et al.* 1998]. As patients were carefully matched with controls with respect to these factors, we consider it unlikely

that this differential MTL activation is explained by other group differences, except for the stroke.

Another explanation for a reduced MTL functionality could be a systemic reaction as a response on a cerebral event. Support from this notion comes from a study that found increased glucocorticoids levels in acute stroke patients compared with controls [Szczudlik *et al.* 2004]. Subsequently, several studies have demonstrated that elevated glucocorticoids levels results in a reduction of hippocampal volume and deficits in hippocampus dependent memory tasks compared to normal glucocorticoids controls [Elgh *et al.* 2006;Lupien *et al.* 1998;de Quervain *et al.* 2003]. However, we consider this explanation unlikely as both episodic memory assessment and the fMRI experiments were performed about 2-3 months after the qualifying stroke. Longitudinal studies on the time course of glucocorticoids levels after stroke have shown normalization within weeks after the stroke [Cohan *et al.* 2005;Ibrahimagic *et al.* 2005;Marklund *et al.* 2004;O'Neill *et al.* 1991].

Emerging evidence from functional neuroimaging, neurophysiology and computational modeling highlights the importance of interaction between the MTL, parietal cortex, thalamus and prefrontal cortex for a proper episodic memory function [Simons and Spiers 2003]. Any lesion or disconnection in this network (due to for example an infarction in white matter structures that connect the MTL with the other relevant structures or due to underlying psychiatric disease including schizophrenia [Callicott *et al.* 2000]) may result in an accompanying memory dysfunction, possibly due to a lesser functionality of the MTL or of any other element of the network. Support for this notion comes from a diffusion tensor imaging study among patients with traumatic brain injury [Kraus *et al.* 2007]. In this study, Kraus and colleagues found that focal traumatic white matter abnormalities (not located in the MTL) were related with memory dysfunction. So, MTL functionality seems to depend on intact connections of the MTL with other brain regions and this functionality can be reduced due to disruptions of the connecting fibre tracts. Consequently, one could argue that stroke patients with an episodic memory function comparable with controls presumably would have a "normal" MTL functionality as well. Unfortunately our sample of stroke patients was too small to reliably compare "normal" with "impaired" episodic memory performers.

Clinically, our study could contribute to the early identification of stroke patients with reduced episodic memory function due to impaired MTL functionality. By enlarge, stroke patients are at increased risk for developing post-stroke dementia [Loewenstein *et al.* 2004] (which is even three times higher than the risk of a recurrent stroke [Yokota *et al.* 2004]). To date it is not possible to identify the ones at risk, but our study may

provide diagnostic opportunities in this identification. Prospective studies are now needed to determine whether those with impaired MTL functionality are indeed at increased risk for post-stroke dementia. To unravel the underlying mechanisms of impaired MTL functionality some of these studies should investigate stroke patients with infarcts at similar locations with the aid of diffusion tensor imaging to study their effect on (loss of) connectivity within the episodic memory network.

Reference List

Brierley B, Shaw P, David AS. The human amygdala: a systematic review and meta-analysis of volumetric magnetic resonance imaging. Brain Res Brain Res Rev 2002; 39: 84-105.

Brott T, Adams HP, Jr., Olinger CP *et al*. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20: 864-870.

Callicott JH, Bertolino A, Mattay VS *et al*. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex 2000; 10: 1078-1092.

Callicott JH, Mattay VS, Bertolino A *et al*. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 1999; 9: 20-26.

Carlson S, Martinkauppi S, Rama P *et al*. Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. Cereb Cortex 1998; 8: 743-752.

Cohan P, Wang C, McArthur DL *et al*. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit Care Med 2005; 33: 2358-2366.

de Jonghe JF, Schmand B, Ooms ME *et al*. Abbreviated form of the Informant Questionnaire on cognitive decline in the elderly. Tijdschr Gerontol Geriatr 1997; 28: 224-229.

de Quervain DJ, Henke K, Aerni A *et al*. Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. Eur J Neurosci 2003; 17: 1296-1302.

Delis. California Verbal Learning Test. Research edition. New York: The Psychological Corporation Harcourt Brace Jovanovich Inc; 1987.

Egan MF, Kojima M, Callicott JH, *et al*. The BDNF val66met Polymorphism Affects Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function. Cell 2003; 112: 257-269.

Elgh E, Lindqvist AA, Fagerlund M, Eriksson S, Olsson T, Nasman B. Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. Biol Psychiatry 2006; 59: 155-161.

Folstein M, Folstein S, McHugh PR. Clinical predictors of improvement after electroconvulsive therapy of patients with schizophrenia, neurotic reactions, and affective disorders. Biol Psychiatry 1973; 7: 147-152.

Friston KJ, Holmes AP, Worsley KJ *et al*., Frackowiak R.S.J. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995; 2: 189-210.

Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: Review of methodologies currently employed. Mol Psychiatry 2005; 10: 147-159.

Harvey PO, Fossati P, Pochon JB *et al*. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. Neuroimage 2005; 26: 860-869.

Hermann BP, Wyler AR, Richey ET *et al*. Memory function and verbal learning ability in patients with complex partial seizures of temporal lobe origin. Epilepsia 1987; 28: 547-554.

Hofgren C, Bjorkdahl A, Esbjornsson E *et al*. Recovery after stroke: cognition, ADL function and return to work. Acta Neurol Scand 2007; 115: 73-80.

Ibrahimagic OC, Sinanovic O, Cickusic A *et al*. Ischemic stroke as reaction to an acute stressful event. Med Arh 2005; 59: 79-82.

Johnson SC, Saykin AJ, Flashman LA *et al*. Brain activation on fMRI and verbal memory ability: Functional neuroanatomic correlates of CVLT performance. Journal of the International Neuropsychological Society 2001; 7: 55-62.

Kauhanen M, Korpelainen JT, Hiltunen P *et al*. Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke 1999; 30: 1875-1880.

Kimberley TJ, Khandekar G, Borich M. fMRI reliability in subjects with stroke. Exp Brain Res 2007.

Kizilbash AH, Van der ploeg RD, Curtiss G. The effects of depression and anxiety on memory performance. Arch Clin Neuropsychol 2002; 17: 57-67.

Kraus MF, Susmaras T, Caughlin BP *et al*. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 2007; 130: 2508-2519.

Loewenstein DA, Acevedo A, Czaja SJ *et al*. Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. Am J Geriatr Psychiatry 2004; 12: 395-402.

Lupien SJ, de LM, de SS *et al*. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1998; 1: 69-73.

Mahoney F.I., Barthel D.W. Functional evaluation: The Barthel Index. Md State Med J 1965; 14: 61-65.

Marklund N, Peltonen M, Nilsson TK *et al*. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J Intern Med 2004; 256: 15-21.

Meisenzahl EM, Scheuerecker J, Zipse M *et al*. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci 2006; 256: 522-531.

Meyer-Lindenberg A, Poline JB, Kohn PD *et al*. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 2001; 158: 1809-1817.

Mungas D, Ehlers C, Walton N *et al*. Verbal learning differences in epileptic patients with left and right temporal lobe foci. Epilepsia 1985; 26: 340-345.

O'Neill PA, Davies I, Fullerton KJ *et al*. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke 1991; 22: 842-847.

Rasquin SM, Lodder J, Ponds RW *et al*. Cognitive functioning after stroke: a one-year follow-up study. Dement Geriatr Cogn Disord 2004; 18: 138-144.

Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in long-term memory. Nat Rev Neurosci 2003; 4: 637-648.

Snaphaan L, de Leeuw FE. Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. Stroke 2007; 38: 198-203.

Sullivan EV, Shear PK, Lim KO *et al*. Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. Biol Psychiatry 1996; 39: 234-240.

Suzuki WA. Integrating associative learning signals across the brain. Hippocampus 2007; 17: 842-850.

Szczudlik A, Dziedzic T, Bartus S *et al.* Serum interleukin-6 predicts cortisol release in acute stroke patients. J Endocrinol Invest 2004; 27: 37-41.

van Swieten JC, Koudstaal PJ, Visser MC *et al.* Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604-607.

Verhage F. Inteligence and age. Assen, Van Gorcum.; 1964.

Wahlund LO, Barkhof F, Fazekas F *et al.* A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318-1322.

Weinberger DR, Mattay V, Callicott J *et al.* fMRI applications in schizophrenia research. Neuroimage 1996; 4: S118-S126.

Worsley K.J, Marrett S, Neelin P *et al.* A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 1996; 4: 58-73.

Yokota C, Minematsu K, Hasegawa Y, *et al.* Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-based study over a 20-year period. Cerebrovasc Dis 2004; 18: 111-116.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-370.

4

Post-stroke Fatigue

4.1 Prospective study about post-stroke fatigue and possible predictors

Abstract

Post-stroke fatigue (PSF) often occurs after stroke and has a negative impact on the rehabilitation process. Several studies focused either on short- or on long-term PSF and their direct relations with stroke characteristics. However, possible pre-stroke confounders like history of depression, pre-existent white matter lesions or brain atrophy were hardly taken into account. Therefore the precise mechanisms underlying PSF remain still unclear. This study was aimed to assess the possible contributions of (pre-) stroke factors to both short-term PSF and its subsequent course over time.

This study pertains to 108 patients with an acute cerebral infarction. PSF was rated by the Checklist Individual Strength at two months and 1.5 year post-stroke. The relation between (pre-)stroke factors and PSF was assessed with multivariate regression analysis.

The prevalence of baseline PSF was 35% and at follow-up 33%. Older age had a protective effect on PSF at baseline (OR 0.95; 95% CI 0.91-0.98), whereas depressive symptoms and infratentorial infarctions were an increased risk for PSF (OR 1.40; 95% CI 1.21-1.63 and OR 4.69; 95% CI 1.03-21.47, respectively). Baseline fatigue was related to an increased risk of PSF at follow-up (OR 1.15; 95% CI 1.09-1.22). Depressive symptoms and baseline fatigue were associated with PSF deterioration over time (OR 1.32; 95% CI 1.04-1.67 and OR 1.11; 95% CI 1.00-1.24, respectively).

Predictors for PSF were younger age, depressive symptoms and infratentorial infarctions. Baseline fatigue did predict fatigue outcome over time, suggesting that early interventions might be useful to prevent deteriorated PSF.

Liselore Snaphaan, Sieberen van der Werf, and Frank-Erik de Leeuw. Time course and risk factors of post-stroke fatigue:A prospective cohort study. submitted.

Introduction

The prevalence of post-stroke fatigue (PSF) varies between 39% and 72% and it is one of the greatest barriers to rehabilitation and has a negative impact on post-stroke quality of life [1-3]. Fatigue has a high prevalence in many neurological disorders with predominantly focal cerebral lesions (multiple sclerosis [4]) as well as in disorders with a more diffuse cerebral pathology (Parkinson disease [5]), but also in disorders with primarily neuromuscular involvement (muscular dystrophy [6]). This suggests that fatigue encompasses the clinical spectrum of many neurological disorders and is not so much due to a lesion in a certain brain area rather than any disease affecting both the central and peripheral nervous system and the attendant limitations in daily living. This corresponds with studies that suggested post-stroke fatigue (PSF) to be secondary to post-stroke functional impairment, psychological distress or recovery process [7, 8].
The prevalence of (PSF) is high, but reportedly highly variable [9] due to methodological differences between studies including patient inclusion, assessment of fatigue, assessment at different time-points after the stroke, and in the collection of (post-) stroke characteristics.

The post-stroke course of fatigue is virtually unknown. From a clinical perspective knowledge on risk factors for PSF, and more particularly, for persistent PSF may lead to early identification of those at risk for persistent PSF. This recognition is important as nowadays there is ample proof of effective treatment strategies for PSF [10].
From the etiologic perspective the relation between stroke and the occurrence of fatigue may be obscured by possible confounders, like type of stroke, location of lesion and physical disability. Although some studies [1, 7, 11] took these possible confounders into account, there are no studies taking *pre-stroke* confounders (factors that were presumably already be present before the stroke) into account, like depression [12], vascular white matter lesions (WML) [13], cerebral atrophy [14]. For example, since white matter lesions are more prevalent among stroke patients [15] they may, at least in part, explain the increased prevalence of fatigue symptoms.
The aim of the present study was to investigate the prevalence, course and possible risk factors of PSF. In addition, we wanted to estimate the risk of baseline and long-term course of PSF, adjusted for stroke and pre-stroke related factors by the use of multivariate models.

Methods

Study population

All patients that presented with acute symptomatic ischemic infarction according to the WHO diagnostic criteria [16] who were admitted to the Neurology department of the Radboud University Nijmegen Medical Centre, the Netherlands were eligible for enrolment in the prospective Nijmegen Stroke Study. The Nijmegen Stroke Study prospectively investigates short- and long-term consequences of stroke with regular preplanned assessments after stroke.
Inclusion criteria for enrolment in this study were: acute ischemic infarction and fatigue assessment at 6-8 weeks post-stroke and 1.5 year post-stroke. Therefore, the final study population included 108 patients who were screened for PSF at two time point after the stroke (figure 1). The local medical ethics committee of the Arnhem Nijmegen region approved the study.
The diagnosis of ischemic infarction was based on the presence of acute neurological symptoms that could only be explained by a vascular event in a specific arterial territory with a duration of > 24 hrs and verified by CT or MRI. Ischemic infarction was further classified as first-ever (i.e. occurring in patients either without previous clinical stroke according to a structured questionnaire nor without ischemic lesions other than the corresponding lesion of the acute clinical stroke on CT/MRI) and ever stroke (defined as patients with a history of previous stroke according to a structured questionnaire with or without corresponding ischemic lesions on CT/MRI).

Assessment of PSF

The presence of fatigue was rated by self-assessment of the Checklist Individual Strength (CIS [17] at two time points after the stroke (i.e at 6-8 weeks post-stroke (baseline) and 1.5 year post-stroke (follow-up)). This screening instrument is well-validated in studies among stroke patients [1, 8]. The fatigue subscale indicates the level of experienced fatigue over the past 2-week period and contains 8 fatigue items that have to be answered on a 7-point scale. The score can range from 8 (no fatigue) to 56 (severe fatigue). A score above 35 is considered indicative for severe fatigue [17] and has been found to correlate highly with a formal diagnosis of a fatigue based on DSM-IV criteria.

Course of PSF

The course of PSF was classified as follows: *no PSF* (patients without fatigue (CIS fatigue ≤ 35) at baseline and follow-up); *persistent PSF* (patients with severe fatigue (CIS fatigue>35) both at baseline and follow-up); *recovered from PSF* (patients with fatigue at baseline and without fatigue at follow-up) and *incident PSF* (patients without fatigue at baseline but with fatigue at follow-up).

Assessment of possible pre-stroke confounders

Standard questionnaires were used to obtain information about age, gender, martial status, educational level (i.e Dutch classification system [18], ranging in ascending order from 1 (less than primary school) to 7 (university degree)) and pre-stroke depression (defined as "history of depressive symptoms" as depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist) [19]. White matter lesions (WML) were rated at admission according to the Age Related White Matter Changes-scale [20]. Subcortical atrophy was defined as the mean ventricle-to-brain ratio at the frontal, bicaudate and occipital level [21]. Cortical atrophy was defined as the mean width of the left and right Sylvian fissure divided by the maximum brain width (at the pineal level [21]), or in absence of either of these (in 1% of all cases), the width of one Sylvian fissure divided by the maximum brain width, multiplied with two, was used. Subcortical atrophy was defined as the mean ventricle-to-brain ratio at the frontal, bicaudate and occipital level [21], the three ventricle-to-brain ratio were available in all cases.

Assessment of possible stroke-related confounders

The side of a stroke was judged on the basis of the acute clinical neurological symptoms at admission (classified as left or right hemispheric stroke or infratentorial stroke (i.e cerebellum or brainstem). Stroke severity was assessed at baseline with the National Institute of Health Stroke Scale (NIHSS) [22]. Cortical lesions (ie frontal, parietal, temporal, occipital lobes), subcortical lesions (white matter, basal ganglia, thalamus), both cortical and subcortical, and infratentorial lesions were identified and rated by an experienced stroke neurologist (FEdL), according to a standard procedure using neuroimaging (either CT or MRI) at which symptomatic lesions were best visible.

Global cognition (MMSE), functional status (Barthel Index (BI) [23][Mahoney and Barthel 1965] ranging from 0 (completely dependent) to 20 (completely independent)) and the degree of handicap (modified Rankin Scale (mRS) [24] ranging from 0 (no symptoms) to 5 (severe disability)) were assessed at baseline. Patients with a mRS 0-1 were classified as 'favourable', those with with a mRS ≥2 were classified as 'unfavourable'.

Statistical Analysis

Two-sample t-tests were used for group comparison of continuous data, Chi Square and Mann Whitney U testing were used for nominal and for non-parametric data, respectively. To investigate significant differences within the four groups, univariate analysis with post-hoc Scheffé corrections were used. All tests were two-tailed with the results considered significant at $p<0.05$.

The relations between the risk of PSF (defined as a fatigue score > 35 on CIS) and the several pre- and post-stroke risk factors were assessed with age and sex adjusted logistic regression analyses. Subsequently, the predictor variables that turned out to be significantly related in the age and sex adjusted logistic model were then introduced into a step-backward logistic regression (conditional) analysis to calculate independent risk factors for PSF, presented as odds ratios (OR), with 95% confidence interval (95% CI).

Results

The final study population consisted of 108 stroke patients with a mean age of 65.0 years (SD12.9) at baseline, 36% of them were female, median educational level was 5 (high school level) and 24 % were living alone, the mean fatigue (CIS) score at baseline was 30.3 (SD 14.6) and at follow-up 29.5 (SD 13.9, data not shown).

Prevalence of PSF at baseline and follow-up

The prevalence of PSF was 35% within 2 months after stroke and 33% at 1.5 year post-stroke (follow-up). Younger age ($p<0.01$), higher score of post-stroke anxiety ($p<0.01$) and depressive symptoms ($p<0.01$) were significantly related with PSF at baseline (adjusted for age and gender), as was a higher degree of post-stroke handicap (mRS $p=0.03$). There were no significant differences between patients *with*

PSF and patients *without* PSF for pre-stroke characteristics at baseline (table 1). In addition, younger age ($p<0.01$), higher score of anxiety ($p=0.03$) and depressive symptoms ($p<0.01$) assessed at baseline were also significantly related with PSF at follow-up (adjusted for age and gender, table 1), whereas there was no relation between higher degree of handicap and PSF at follow-up ($p=0.14$).

Course of PSF

In total 108 stroke patients were followed with a mean follow-up of 1.5 year, 57% of the patients did not have PSF at all, whereas 26% of the patients had PSF at both time points. Nine percent of the patients had fatigue at baseline but recovered at follow-up and 8% of the patients had no PSF at baseline but they did at follow-up. In univariate analysis, patients without fatigue at both time points were significantly older compared to those who developed PSF ($p=0.02$) and also had lower score of depressive symptoms ($p=0.01$) compared to those with PSF at both post-stroke time points or to those who recovered from PSF (table 2).

Stroke related risk factors of PSF at baseline or follow-up

In age and gender adjusted logistic regression analysis (table 3), the presence of an infratentorial infarct was a risk factor for PSF *at baseline* (OR 4.10; 95% CI 1.04-16.12) compared with those with an infarction at another location. In addition, post-stroke anxiety and/or depressive symptoms were significantly associated with an increased risk of PSF at baseline (OR 1.18; 95% CI 1.03-1.35 per each point increase on the HADS anxiety items, OR 1.36; 95% CI 1.17-1.57 per each point increase on the HADS depressive symptoms items, respectively). Whereas older age had a protective effect on PSF at baseline and follow-up (OR 0.94; 95% CI 0.91-0.98 and OR 0.95; 95% CI 0.92-0.98 per increase of age, respectively). Risk factors for PSF *at follow-up* were those with a higher fatigue level at baseline (OR 1.15; 95% CI 1.09-1.21 per each point increase on the CIS fatigue items) as had patients with anxiety or depressive symptoms, OR 1.15; 95% CI 1.01-1.31 per each point increase on the HADS anxiety items, OR 1.30; 95% CI 1.14-1.49 per each point increase on the HADS depressive symptoms items, respectively). In an age and sex adjusted regression analysis, patients with an infratentorial infarction were not at risk for PSF at follow-up (OR 1.78; CI 0.48-6.56) compared with those with an infarction at another location.

Table 1 Demographics and patients' characteristics classified by presence or absence of post-stroke fatigue at baseline or follow-up

	Fatigue at baseline	
Demographics	**Absent N=70**	**Present N=38**
Age mean (SD) *	68.2(12.1)	59.0(12.3)
Female gender (%)†	30	47
Living alone (%)†	28	18
Education median (range) ‡	5(1-7)	5(1-7)
Post-stroke characteristics		
Behavioural characteristics		
MMSE mean (SD) *	27.1(2.7)	27.6(2.7)
Anxiety mean (SD) *	3.8(3.2)	6.4(4.0)
Depressive symptoms mean (SD) *	2.7(2.8)	7.1(4.6)
Clinical characteristics		
Barthel index median (range) *	20(10-20)	20(9-20)
Modified Rankin Scale median (range) ‡	0(0-3)	1(0-3)
NIHSS median (range) *	0(0-5)	1(0-8)
First-ever stroke (%)†	71	76
Left hemisphere/Right hemisphere (%)†	47/47	46/35
Infratentorial (%)†	6	19
Imaging characteristics		
Lesion location cortical/subcortical/both (%)†	13/79/8	33/44/23
Subcortical structures:		
White matter/Basal ganglia/Thalamus (%)	74/16/10	75/0/25
Pre-stroke characteristics		
History depressive symptoms (%)†	6	8
ARWMC median (range) *	0(0-29)	0(0-4)

Values represent means (SD), median (range) or proportions (%), P-values were calculated between presence and absence of fatigue at baseline adjusted for age (for continues data), significant values ($p < 0.05$) are printed bold, * Univariate t-test (continue data), † Chi-square analyses (categorical data),

		Fatigue at follow-up	
P-value	Absent N=72	Present N=36	P-value
<0.01	67.8(11.8)	59.3(13.3)	**<0.01**
0.07	32	44	0.22
0.37	23	28	0.55
0.87	5(1-7)	5(1-7)	0.29
0.37	27.3(2.6)	27.3(2.9)	0.33
<0.01	3.9(3.1)	6.3(4.3)	**0.03**
<0.01	2.9(2.8)	7.0(4.9)	**<0.01**
0.38	20(10-20)	20(9-20)	0.81
0.03	0(0-3)	1(0-3)	0.14
0.09	0(0-8)	0(0-5)	0.55
0.58	74	72	0.88
0.54	49/43	43/43	0.78
0.03	8	14	0.34
0.07	16/72/12	29/53/18	0.44
0.36	72/17/11	78/0/22	0.36
0.65	6	8	0.61
0.10	0(0-29)	0(0-5)	0.17

‡ Mann-Whitney U Test (ordinal data), # mean of ventricle to brain ratio at the frontal, bicaudate or occipital level, ** mean width of the left and right sylvian fissure divided by the maximum brain width (at the pineal level).

Table 2 Demographics, stroke and behavioural characteristics at post-stroke fatigue patients during 1.5 year

	No fatigue*
Demographics	**N=62**
Age mean (SD)	68.5(11.9)
Female gender (%)	71
Living alone (%)	23
Education median (range)	5(1-7)
Post-stroke characteristics	
Baseline behavioural characteristics	
Fatigue items CIS mean (SD)	20.7(8.9)
MMSE mean (SD)	27.2(2.7)
Anxiety items mean (SD)	3.5(3.0)
Depressive symptoms items mean (SD)	2.5(2.6)
Baseline clinical characteristics	
Barthel index median (range)	20(10-20)
Modified Rankin Scale median (range)	0(0-3)
NIHSS median (range)	0(0-5)
First-ever stroke (%)	73
Lesion side left/right (%)	47/47/6
Infratentorial lesions (%)	6
Pre-stroke characteristics	
History depressive symptoms (%)	5
Subcortical atrophy ratio mean (SD) #	0.34(0.04)
Cortical atrophy ratio mean (SD) **	0.03(0.01)
ARWMC median (range)	0(0-29)

P-values were calculated with an univariate t-test (continue data), Pearson Chi-square analyses (categorical data), Kruskall-Wallis (ordinal data), significant values ($p < 0.05$) are printed bold, * no fatigue: no fatigue at baseline and follow-up, persistent fatigue: fatigue at both time-points, incident fatigue: fatigue at follow-up not at baseline, recovery fatigue: only fatigue at baseline not at follow-up, † significant differences between no fatigue versus persistent fatigue, ‡ significant differences between no fatigue versus persistent fatigue, and no fatigue versus recovery from fatigue, and recovery from fatigue versus incident fatigue, and incident fatigue versus persistent fatigue, ‖ significant differences between no fatigue versus persistent fatigue, and no fatigue versus recovery from fatigue, # mean of ventricle to brain ratio at the frontal, bicaudate or occipital level, ** mean width of the left and right sylvian fissure divided by the maximum brain width (at the pineal level).

	Persistent fatigue*	Incident fatigue*	Recovery fatigue*	P-value
	N=28	N=8	N=10	
	57.4(12.6)	65.8(14.2)	63.3(10.7)	**0.02**†
	46	38	50	0.32
	18	63	20	0.07
	5(1-7)	5(2-6)	1(0-1)	0.62
	48.0(6.9)	27.8(7.3)	42.5(4.7)	**<0.01**‡
	27.4(3.0)	26.8(2.6)	28.2(1.8)	0.67
	6.5(4.3)	5.6(4.6)	6.1(3.0)	**0.02**†
	7.6(5.2)	5.0(3.1)	5.9(2.4)	**<0.01**‖
	20(9-20)	20(20-20)	20(10-20)	0.73
	1(0-3)	1(0-2)	1(0-3)	0.15
	1(0-5)	0(0-1)	1(0-8)	0.22
	75	63	80	0.86
	41/41/19	50/50/0	60/20/20	0.61
	19	0	20	0.18
	7	13	11	0.79
	0.33(0.04)	0.35(0.03)	0.31(0.03)	0.10
	0.03(0.01)	0.04(0.02)	0.03(0.01)	0.28
	0(0-4)	0(0-5)	0(0-2)	0.07

Table 3 Risk factors for post-stroke fatigue at baseline or follow-up (OR and 95% CI)

	Fatigue at baseline	Fatigue at follow-up
Demographics		
Age	**0.94(0.91-0.98)**	**0.95(0.92-0.98)**
Gender *(reference male)*	2.20(0.92-5.30)	1.71(0.72-4.09)
Post-stroke baseline characteristics		
Fatigue CIS	na	**1.15(1.09-1.21)**
Anxiety	**1.18(1.03-1.35)**	**1.15(1.01-1.31)**
Depressive symptoms	**1.36(1.17-1.57)**	**1.30(1.14-1.49)**
Rankin Scale ≥ 2 *(reference Rankin Scale <2)*	1.78(0.68-4.66)	1.04(0.39-2.74)
Infratentorial lesion (clinical)	**4.10(1.04-16.12)**	1.78(0.48-6.56)

Values are Odds Ratios (95% Confidence Intervals) adjusted for age and gender, significant OR are printed bold ($p < 0.05$); na, not applicable because part of the baseline fatigue definition is based on the CIS score.

Stroke related risk factors for PSF course over time

Patients with incident fatigue (fatigue at follow-up, not at baseline) had higher fatigue score and more post-stroke depressive symptoms at baseline (OR 1.11; 95% CI 1.00-1.24, per each point increase on the CIS fatigue items and OR 1.32; 95% CI 1.04-1.69, per each point increase on the HADS depressive symptoms, respectively) compared to patients without PSF at both time-points. No significant differences could be found in (pre-)stroke related risk factors between patients with persistent fatigue compared to patients who made recovery.

Multivariate model

The variables that turned out to be significantly related in the logistic regression analysis (in bold table 3), were then introduced into an age and gender adjusted step-backward logistic regression model to calculate independent predictors of PSF at baseline and follow-up. Older age has a protective effect on PSF *at baseline* (OR 0.95; 95% CI 0.91-0.98, per increase of age). Post-stroke depressive symptoms and infratentorial infarctions were related with an increased risk of PSF *at baseline* (OR

1.40; 95% CI 1.21-1.63 per point increase on the HADS depression items, OR 4.69; 95% CI 1.03-21.47, respectively). Whereas higher score on baseline fatigue was related with an increased risk of PSF *at follow-up* (OR 1.15; 95% CI 1.09-1.22, per point increase on the CIS fatigue items). To calculate independent predictors of PSF over time, the significant predictors (in bold in table 4) were introduced into a step-backward regression analysis with never fatigue as reference category compared to incident fatigue (fatigue at follow-up, not at baseline). Higher fatigue score at baseline and post-stroke depressive symptoms assessed at baseline were related with an increased risk of PSF at patients with incident fatigue (OR 1.11; 95% CI 1.00-1.24, per point increase on the CIS fatigue items and OR 1.32; 95% CI 1.04-1.67 per point increase on the HADS depression items).

Table 4 Risk factors for post-stroke fatigue during time (OR and 95% CI)

Demographics	Incident fatigue*	Recovery fatigue †
Age	0.98(0.93-1.04)	1.04(0.98-1.11)
Female gender	1.48(0.32-6.87)	1.04(0.23-4.64)
Post-stroke baseline characteristics		
Fatigue CIS	**1.11(1.00-1.24)**	0.86(0.74-0.99)
Anxiety	1.18(0.96-1.45)	1.02(0.83-1.26)
Depressive symptoms	**1.32(1.04-1.69)**	0.86(0.71-1.08)

Values are Odds Ratios (95% Confidence Intervals) adjusted for age and gender, significant OR are printed bold ($p < 0.05$), never fatigue and persistent fatigue were reference variables,* *reference*: those without PSF during baseline and follow-up, † *reference*: those with fatigue during baseline and follow-up

Discussion

This large prospective study showed that the prevalence of baseline and follow-up PSF did not differ significantly ($p=0.82$). In multivariate models, younger age, depressive symptoms and infratentorial infarcts were related with an increased risk of PSF at baseline, whereas higher fatigue score at baseline was related with an increased risk of PSF at follow-up. Those who develop PSF over time, had more often depressive symptoms and a higher fatigue score at baseline.

The prevalence of both baseline and long-term PSF seems lower than other studies that used the same fatigue rating scale. One could argue that patients who could not complete assessment of fatigue, might have had more severe neurological deficits and therefore suffered more often from fatigue. This could have led to an underestimation of PSF even as by excluding patients with an intracerebral hemorrhage that suffered more often from severe neurological deficits. Therefore our study does not represent the whole stroke population, although the majority of strokes constitutes of ischemic stroke. Another reason for our prevalence at the lower end of the spectrum could be that in contrast to our study, no study attempted to adjust for possible confounding factors that were already be present before the qualifying stroke like depression or white matter lesions, that, independent from the stroke, could also be related with fatigue [12, 13]. Our study explicitly controls for these pre-stroke factors and therefore we consider the 35% baseline prevalence of PSF as a reliable estimate.

In favour of our study are its large sample size that gave us the opportunity to investigate pre- and post-stroke risk factors for PSF, independent from each other as well as independent from other risk factors, by introducing them into a multivariate analysis. Another strong element of our study is that this is a single centre study, with two investigators that performed a structured and standardised assessment with a well validated fatigue screenings instrument, which strengthens the uniformity and validity of our findings.

In contrast to many other studies, our study found that patients with infratentorial infarctions were at risk for PSF at baseline and is consistent with a study from Staub and colleagues [25]. The brain stem is an important regulator in the autonomic nervous system and also plays a major role in sleep and consciousness as well as modulation of fatigue, and motivation to perform various activities. Imaging studies [26, 27] have shown abnormal activity in the brain stem in people with chronic fatigue syndrome. This may indicate that damage in this particular brain area may be associated with fatigue, for thusfar unknown reasons. Novel imaging techniques such as task related, but also resting state fMRI may be of use in the detection of what part of the brain (or what network) shows altered function in patients with PSF. These techniques could then, when established, perhaps also be of use in the early prediction of those with PSF and as such possibly guide early (cognitive) rehabilitation medicine.

Furthermore, higher degree of post-stroke depressives symptoms found in this study were related with an increased risk of PSF over time, independent from other risk

factors. This is an important finding because recent research showed a significantly improvement in fatigue by the use of cognitive behavioural therapy [10], and therefore could provide a positive effect on rehabilitation participation and/or post-stroke quality of life. To date, there is a paucity of prospective studies with a sufficient size of patients to allow stable multivariate predictive models of PSF over time, even as proper registration of pre-stroke characteristics collected from the medical history and from neuroimaging. Future research should overcome these limitations when investigating PSF from an etiological as well as for a prognostic perspective. In addition, rehabilitation studies should investigate whether early fatigue interventions might be useful to prevent deterioration of PSF.

Reference List

1. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Arch Phys Med Rehabil* 1999;80:173-8.
2. Michael K. Fatigue and stroke. *Rehabil Nurs* 2002;27:89-94.
3. Morley W, Jackson K, Mead GE. Post-stroke fatigue: an important yet neglected symptom. *Age Ageing* 2005;34:313.
4. Lerdal A, Celius EG, Moum T. Fatigue and its association with sociodemographic variables among multiple sclerosis patients. *Mult Scler* 2003;9:509-14.
5. Friedman JH, Brown RG, Comella C, et al. Fatigue in Parkinson's disease: a review. *Mov Disord* 2007;22:297-308.
6. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry* 2005;76:1406-9.
7. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke* 2002;33:1327-33.
8. van der Werf SP, van den Broek HL, Anten HW, et al. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *Eur Neurol* 2001;45:28-33.
9. Colle F, Bonan I, Gellez Leman MC, et al. Fatigue after stroke. *Ann Readapt Med Phys* 2006;49:272-4.
10. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001;357:841-7.
11. Schepers VP, Visser-Meily AM, Ketelaar M, et al. Poststroke fatigue: course and its relation to personal and stroke-related factors. *Arch Phys Med Rehabil* 2006;87:184-8.
12. Aaronson LS, Teel CS, Cassmeyer V, et al. Defining and measuring fatigue. *Image J Nurs Sch* 1999;31:45-50.
13. Harboe E, Greve OJ, Beyer M, et al. Fatigue is associated with cerebral white matter hyperintensities in patients with systemic lupus erythematosus. *J Neurol Neurosurg Psychiatry* 2008;79:199-201.
14. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005;26:777-81.
15. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;27:1274-82.
16. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ* 1980;58:113-30.
17. Vercoulen JH, Swanink CM, Fennis JF, et al. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38:383-92.
18. Verhage F. Intelligentie en leeftijd [Inteligence and age].*Assen,Van Gorcum* 1964.
19. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry* 2000;57:1071-6.

20. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001;32:1318-22.
21. Gomori JM, Steiner I, Melamed E, et al. The assessment of changes in brain volume using combined linear measurements. A CT-scan study. *Neuroradiology* 1984;26:21-4.
22. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20:864-70.
23. Mahoney FI., Barthel DW. Functional evaluation: The Barthel Index. *Md State Med J* 1965;14:61-5.
24. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.
25. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis* 2001;12:75-81.
26. Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 1995;88:767-73.
27. Tirelli U, Chierichetti F, Tavio M, et al. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* 1998;105:54S-8S.

5

Summary and Discussion

This thesis investigates the epidemiology and pathophysiology of several behavioural consequences after stroke such as depressive symptoms, cognitive dysfunction and fatigue. Although it may seem that many studies did so before, our study is to be distinguished from previous studies because of its prospective nature and the fact that we were able to control for potential pre-stroke behavioural confounders (such as depression and cognitive decline in the medical history) and pre-stroke neuroimaging confounders (such as white matter lesions, previous brain ischemia, cerebral atrophy). This final chapter provides a summary of the main findings of the studies described in this thesis. In addition, the most important methodological considerations and recommendations for future research will be discussed.

Summary of the main findings

Post-stroke depressive symptoms

In chapter 2.1 the literature on the prevalence and risk factors of post-stroke depressive symptoms was systematically reviewed. The prevalence of post-stroke depressive symptoms varied between studies from 5% to 79% within one month after stroke, with a tendency to decline to 8% to 59% one year after stroke. Risk factors for post-stroke depressive symptoms included pre-stroke depression in the medical history and post-stroke physical/cognitive disability.
In our own, cross-sectional part of the study (chapter 2.2), the prevalence of post-stroke depressive symptoms among 420 patients was 13% two months after the qualifying stroke. There was no relation between post-stroke depressive symptoms and pre-stroke depressive symptoms and/or neuroimaging characteristics (such as lesion side or location, previous stroke, white matter lesions). In contrast, a higher degree of post-stroke handicap and functional dependence were risk factors for post-stroke depression.

Post-stroke memory dysfunction

We performed a systematic review on the prevalence and risk factors of post-stroke memory dysfunction as described in chapter 3.1. The prevalence of post-stroke memory dysfunction varied between studies from 13 to 50% within one month post-stroke, which declined from 11 to 31% one year post-stroke. Risk factors for

post-stroke memory dysfunction included a larger stroke volume, medial temporal lobe atrophy and white matter lesions.
A possible explanation for post-stroke memory dysfunction was provided in chapter 3.2. We found that stroke patients with lower episodic memory performance had lower medial temporal lobe (MTL) activation compared to healthy controls. It could be that this lower MTL activation is responsible for the frequent observation of post-stroke memory dysfunction. In our study, this reduced MTL activation was seen in all stroke patients, independent of the location of the infarct, as we intentionally included patients with strokes at any location in order to achieve maximum generalisability. This differential medial temporal lobe activation between patients and controls was independent of structural brain changes (such as total brain volume, grey matter volume, white matter volume and hippocampal volume).

Post-stroke fatigue

In chapter 4 we studied the prevalence, incidence and risk factors of post-stroke fatigue after two and 18 months post-stroke. The prevalence of post-stroke fatigue among 108 stroke patients was 35% two months after stroke and this proportion of patients with post-stroke fatigue remained stable even at 18 months post-stroke. The incidence of post-stroke fatigue was 8%, meaning that patients who suffered from fatigue 18 months after stroke did not report such complaints at baseline. Risk factors for post-stroke fatigue at two months were post-stroke depressive symptoms and infratentorial infarctions, whereas older age appeared protective for post-stroke fatigue at two and 18 months post-stroke. The presence of fatigue two months after stroke was a risk factor for fatigue 18 months after the stroke.

General discussion of the main findings

Whereas many studies described the prevalence and risk factors of depressive symptoms, memory dysfunction and fatigue after stroke, there is still an ongoing debate with respect to the possible causes of these post-stroke behavioural symptoms. Some researchers have stressed a biomedical explanation in terms of a direct stroke effect on these symptoms, analogous to for example a hemi-paresis after an infarct in the pyramidal tract [1, 2], while others view these post-stroke behavioural consequences secondary as a psychological reaction to a major life event [3-5] and loss of functional independence [6].

One of the reasons for the ongoing controversy on these possible causes of post-stroke behavioural consequences may be the lack of its structured and standardised assessment (chapter 2.1 and 3.1). For example, there was a wide variability in assessment of behavioural deficits (and if the same questionnaire is used, quite often each investigator uses his/her own cut off criteria in the operationalisation of presence or absence of the symptoms) and varying time intervals between stroke and the assessment of the behavioural symptoms. Keeping in mind that the prevalence of most post-stroke behavioural symptoms does not exhibit a stable time-course, one can easily understand that a comparison between studies about prevalence and risk factors is at least difficult, not to say unreliable. A standardised assessment of post-stroke behavioural deficits at well defined post-stroke intervals may aid in establishing a true estimate of its prevalence and risk factors and a better understanding of its etiology.

Another explanation for the ongoing controversy is a lack of standardised assessment of pre-stroke characteristics (such as depression in the medical history, cognitive decline, white matter lesions, silent brain ischemia and cerebral atrophy) which by themselves may be related to behavioural symptoms, independent from the stroke, and consequently could confound the "stroke – behavioural symptom" relation.

In our study (chapter 2.2), the prevalence of post-stroke depressive symptoms was considerably lower than in most previous studies (see chapter 2.1). This may be explained by our exclusion of patients with depressive episodes within one month before the qualifying stroke, while none of the studies described in chapter 2.1 reported on baseline (pre-stroke) depressive symptoms. Therefore the post-stroke prevalence of depressive symptoms in those studies could simply be higher by the inclusion of individuals who already suffered from depressive symptoms before stroke.

To investigate whether indeed the stroke itself is responsible for the emergence post-stroke behavioural symptoms, complete pre-stroke information should be available from the medical history (presence of psychiatric/depressive disorders, cognitive decline, previous stroke) in combination with neuroimaging data that may show lesions (white matter lesions, silent brain ischemia, cerebral atrophy) that have also been related with these behavioural symptoms.

A way to possible disentangle the post-stroke behavioural symptoms as a secondary result of the stroke due to a psychological reaction of a major life event, we postulated to study TIA patients. These patients experience a more or less similar life event as patients with a cerebral infarction, but do usually not develop the ischemic lesion.

We found that the prevalence of post-stroke depressive symptoms did not differ between TIA patients and patients with a cerebral infarction two months after stroke. This may suggest that the development of post-stroke depressive symptoms, at least in part, is a psychological reaction to this major life event rather than a result of permanent post-stroke consequences, such as physical disabilities, that influence the occurrence of post-stroke depressive symptoms most [7, 8].

As with post-stroke depressive symptoms, the cause of post-stroke memory dysfunction also remains unclear. In the systematic review we performed (chapter 3.1), post-stroke memory dysfunction was related to a larger lesion volume and pre-stroke medial temporal lobe atrophy and white matter lesions. However, these 65 studies differed tremendously in terms of patient inclusion (sample size, age, first-ever or ever stroke patients), assessment of memory function and in the collection of stroke and pre-stroke (imaging) characteristics. Consequently the results should be interpreted carefully.

The diagnosis of post-stroke dementia (the presence of post-stroke memory dysfunction is a symptom needed to fulfill this clinical diagnosis) is often made within a few months after a stroke, apparently assuming a relatively stable course of the post-stroke memory function. However, in our systematic review, only five of the 65 studies [9-13] reported the prevalence of post-stroke memory dysfunction at different post-stroke intervals and showed that post-stroke memory dysfunction is not based on a reliable time course. This may allow for potential misclassification of post-stroke dementia when memory function changes over time. Preferably, standardised re-assessment of cognitive function should be performed in each patient diagnosed with post-stroke dementia.

Chapter 3.2 reports on a study investigating the underlying mechanism of post-stroke memory dysfunction. The medial temporal lobe (MTL) is an important brain area for an effective formation of episodic memory. Surprisingly, many stroke patients exhibit memory deficits, despite the fact that most stroke patients do not have an infarction in MTL. This may indicate that the MTL depends, for a proper memory function, on connections with other brain regions and that lesions (like infarcts) disconnect the MTL from the network. In our fMRI study, where we used a number variant version of the n-back working memory paradigm [14] as fMRI task design. The n-back task is a paradigm which activates a so-called working memory (WM) network, including the MTL. We found that post-stroke memory dysfunction could not be explained by a reduction of MTL volume, but by a reduction of MTL function.

Critics could argue that reduced MTL activation (assessed with the n-back task) by stroke patients is simply a consequence of impaired performance on this task rather than a result of memory dysfunction. However, despite the fact that patients performed worse on the memory task, they did ***not*** on the n-back task; making this explanation rather unlikely. Another explanation for our finding of a reduced MTL activation among stroke patients could be differential selection of patients, for example by including stroke patients with already pre-existing cognitive decline. Therefore, reduced MTL activation is related with cognitive decline and not due to the stroke. However, this seems unlikely as we only included patients that showed no signs of pre-stroke cognitive decline, as assessed with the Informant Questionnaire on cognitive decline in elderly. Furthermore, memory function is known to be affected by many environmental factors and structural brain correlates including depressive symptoms, anxiety, total brain volume and hippocampal volume [15-18]. As patients were carefully matched with controls with respect to these factors, we consider it unlikely that this differential MTL activation is explained by other group differences, except for the stroke.
MTL functionality seems to depend on connections of the MTL with other brain regions and this functionality can be reduced due to disruptions of the connecting fibre tracts.

In chapter 4.1, we investigated an often neglected but nevertheless disabling post-stroke symptom, namely post-stroke fatigue. We investigated the prevalence of post- stroke fatigue within two months after the stroke (baseline) and after just over one year (follow up). We found a lower prevalence of post-stroke fatigue than other studies that used the same fatigue rating scale during the same time period after stroke. An explanation for this could be that in contrast to our study, no study attempted to adjust for possible risk factors that were already present before qualifying stroke like depression or white matter lesions, that, independent from the stroke, also have found to be associated with fatigue [19, 20]. In contrast to many other studies, we found that patients with infratentorial infarctions were at higher risk for PSF at baseline compared to patients with a cerebral infarction elsewhere in the brain. Although there have been others that reported similar findings [2].
The brain stem is an important regulator in the autonomic nervous system and also plays a major role in sleep and consciousness and thereby, either cause or consequence, modulates fatigue and motivates to perform various activities. The brain stem consists anatomically of the medulla oblongata, the pons and mesencephalon and all of these structures are connected with the formatio reticularis, a regulatory network of the arousal system. Functional brain imaging

studies [21, 22] have shown abnormal activity in the brain stem in people with chronic fatigue syndrome. This may indicate that damage due to a infarction in either one of the previously mentioned structures or in the connections in between may be associated with fatigue.
We observed a relatively stable time-course of post-stroke fatigue until just over one year after the stroke. Several rehabilitation studies showed that recovery of function usually occurs in the first weeks to months after stroke. Therefore, our study does not support the notion that post-stroke fatigue is a direct result of functional impairment, or part of a recovery process.

Methodological considerations

There are three types of biases that should be acknowledged in order to judge the methodological merits of a study, namely selection bias, information bias and confounding.

Selection bias

Selection bias can occur due to selective participation of patients. For example, patients who were not able to complete neuropsychological testing were not included in the study. They presumably had a larger stroke with more severe neurological deficits, and most likely more often suffered from severe post-stroke behavioural deficits (such as depressive symptoms, memory dysfunction or fatigue). This selection bias could results in an underestimation of the post-stroke depressive symptoms prevalence. On the other hand an overestimation of this prevalence could have occured when only patients with a minor stroke or TIA were not to be included in the study since they, for example, were not willing to participate months after a stroke from which they already had completely recovered. Non-responders in our study were significantly more TIA patients than patients with severe deficits. The prevalence of post-stroke depressive symptoms could therefore be a small overestimation. Special care should be given to proper registration of those that were excluded from the study.

Information bias

Information bias may occur by misclassification of the risk factor, dependent on the outcome. For example, we aimed to investigate the relation between pre-stroke

neuroimaging variables (including white matter lesion, silent brain ischemia and cerebral atrophy) and several behavioural consequences after stroke, but one has to keep in mind that neuroimaging was performed directly *after* the qualifying stroke. Therefore, one cannot fully exclude the fact that early stroke signs (for example the appearance of hypodense areas on a CT) may have been misclassified as white matter lesions. For this reason white matter lesions were not rated in areas in which the infarction was suspected.

Another example of an information bias is the use of medication. It is known that several pharmacologic agents are associated with depressive symptoms, memory dysfunction or fatigue including selective antihypertensive agents, cimetidine, indomethacin, alcohol, barbiturates, stimulant withdrawal, corticosteroids. More specific, patients using antidepressants may provide lower scores on the Hospital Anxiety Depression Scale compared to patients that do not take antidepressants. Therefore, medication use could result in information bias. However, the prescription of these drugs were not changed before the assessment of the above mentioned behavioural characteristics, making this source of bias less likely.

Confounding; 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. Possible confounders in our studies includes pre-stroke depression, white matter lesions and cerebral atrophy, as they are associated with both the independent variable (stroke) and the outcome variable (depressive symptoms, memory dysfunction, fatigue). For example, we aimed to investigate the prevalence and risk factors of post-stroke depressive symptoms and therefore patients with pre-stroke depression were excluded as they could confound this relation. In general, study populations need to be large in order to adjust for confounders in a statistical reliable way. Our study included over 400 participants and therefore fulfilled this “size” condition.

Clinical relevance

We found that the incidence of post-stroke depressive symptoms among 420 stroke patients was 13%. Depressive symptoms after stroke may have a negative influence on successful stroke recovery [23, 24]. Vice versa, stroke patients with a higher degree of post-stroke handicap and/or less functional independence were at increased risk for post-stroke depressive symptoms. Therefore, early treatment of stroke patients with post-stroke depressive symptoms could possibly result in a better stroke recovery.

A bit to our surprise was the observation of an identical prevalence of post-stroke depressive symptoms among TIA and ischemic stroke patients. Especially as these patients with no post-stroke handicap or functional dependency often go home with no (medical) support or follow-up appointment, mainly due to the fact that all "visual" complaints related to the stroke event no longer exist. More care should be given to these patients as these disabling complaints often go unnoticed while recent research suggests, that behavioural rehabilitation may have a positive effect on post-stroke depressive symptoms, albeit this is not investigated in TIA patients yet.

Post-stroke memory dysfunction is a prerequisite for the diagnosis of post-stroke dementia. In common clinical practice, this diagnosis is made within three months after a stroke, apparently assuming a relatively stable course of the post-stroke memory function. We found that not all patients with memory dysfunction three months post-stroke still had their memory deficits one year post-stroke. Consequently, not all criteria for the post-stroke dementia diagnosis were fulfilled anymore after one year. This may indicate that post-stroke dementia may be reversible in a substantial proportion of stroke patients. Preferably, standardised re-assessment of cognitive function should be performed in each patient diagnosed with post-stroke dementia in order to exclude false positives, and most importantly not to diagnose patients with a dramatic disease, that on hindsight, was merely based on immediate post-stroke effects on cognitive performance.
Till now, the underlying mechanism of post-stroke memory dysfunction was still unclear. In our fMRI study, we showed that loss of the MTL function plays a role in the development of memory dysfunction after stroke. A possible explanation for this could be that MTL functionality depends on intact connections of the MTL with other brain regions and this functionality can be reduced due to disruptions of the connecting fibre tracts. These new insights may be helpful in identifying specific locations of stroke that may particularly be associated with the development post-stroke dementia.

Stroke patients with an infratentorial infarction and/or post-stroke depressive symptoms (two months after stroke) were at increased risk for (long-term) post-stroke fatigue. These patients may benefit from cognitive behavioural therapy [25] that focuses on the reduction of fatigue. Fatigue reduction may have a positive effect on rehabilitation participation and/or post-stroke quality of life [26-28].

Bottomline is that most patients with cerebrovascular disease suffer from disabling post-stroke behavioural complaints that often go unnoticed, unless one is specifically asked for. In our view the results of this thesis plea for a standardised structured assessment of frequent occurring post stroke behavioural symptoms including mood, memory (as part of the assessment of the functionality of other cognitive domains) and fatigue.

Future perspectives- methodology

Although, our study did not found a relation between post-stroke behavioural consequences and pre-stroke behavioural characteristics (such as depression or cognitive deficits in the medical history), pre-stroke neuroimaging characteristics (such as white matter lesions, silent brain ischemic, cerebral atrophy), formal studies investigating these possible risk factors are scare. Therefore, we suggested future stroke studies that aim to examine the behavioural consequences after stroke to take account of pre-stroke characteristics and to report whether patients were excluded from analysis based on these pre-stroke behavioural/ neuroimaging characteristics.
To gain a more detailed insight into the etiology of several post-stroke behavioural deficits, we suggest future stroke studies (preferably prospective in nature) to include TIA patients. Those could give researchers the opportunity to investigate whether stroke related factors itself would be related to behavioural deficits or that other, for example adaptive mechanisms to a life event could play a role.

Future perspectives – “clinical prediction”

Prospective studies are needed to provide more insight into the time-course of the several behavioural consequences after stroke (described in this thesis) and to identify which factors are associated with the persistence or development of these consequences in the long-term.
Stroke patients are at increased risk for developing post-stroke dementia [29] (which is even three times higher than the risk of a recurrent stroke [30]). To date, it is not possible to identify stroke patients that are at risk for post-stroke dementia. Our fMRI study may provide diagnostic opportunities for this identification. We found evidence that despite the absence of direct ischemic structural damage

of the MTL, an impaired function of the MTL plays a role in the development of memory dysfunction after stroke. Longitudinal studies are now needed to determine whether those with impaired MTL functionality are indeed at increased risk for post-stroke dementia. Furthermore, these fMRI studies may be combined with diffusion tensor imaging (DTI) in order to study the possible underlying structural correlate of the functional network. DTI is increasingly being used to investigate the structural integrity of white matter tracts and networks and can provide insight into the physiology and pathophysiology of organisation of cerebral networks during the development of several behavioural consequences after stroke. The execution of these so called multimodal MRI studies will be one of the research objectives for the near future of stroke related behavioural complaints.

Reference List

1. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke 1993;24:976-982.*
2. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis 2001;12:75-81.*
3. Bush BA. Major life events as risk factors for post-stroke depression. *Brain Inj 1999;13:131-137.*
4. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke 2002;33:1327-1333.*
5. van der Werf SP, van den Broek HL, Anten HW, et al. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *Eur Neurol 2001;45:28-33.*
6. Singh A, Black SE, Herrmann N, et al. Functional and neuroanatomic correlations in poststroke depression: the Sunnybrook Stroke Study. *Stroke 2000;31:637-644.*
7. Herrmann N, Black SE, Lawrence J, et al. The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. *Stroke 1998;29:618-624.*
8. Kauhanen ML, Korpelainen JT, Hiltunen P, et al. Domains and determinants of quality of life after stroke caused by brain infarction. *Arch Phys Med Rehabil 2000;81:1541-1546.*
9. Kotila M, Waltimo O, Niemi ML, et al. The profile of recovery from stroke and factors influencing outcome. *Stroke 1984;15:1039-1044.*
10. Nys GM, van Zandvoort MJ, de Kort PL, et al. Domain-specific cognitive recovery after first-ever stroke: a follow-up study of 111 cases. *J Int Neuropsychol Soc 2005;11:795-806.*
11. Rasquin SM, Verhey FR, Lousberg R, et al. Vascular cognitive disorders: memory, mental speed and cognitive flexibility after stroke. *J Neurol Sci 2002;203-204:115-119.*
12. Rasquin SM, Lodder J, Ponds RW, et al. Cognitive functioning after stroke: a one-year follow-up study. *Dement Geriatr Cogn Disord 2004;18:138-144.*
13. van Zandvoort MJ, Kessels RP, Nys GM, et al. Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. *Clin Neurol Neurosurg 2005;107:385-392.*
14. Gevins A, Cutillo B. Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr Clin Neurophysiol 1993;87:128-143.*
15. Kauhanen M, Korpelainen JT, Hiltunen P, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke 1999;30:1875-1880.*
16. Kizilbash AH, Van der ploeg RD, Curtiss G. The effects of depression and anxiety on memory performance. *Arch Clin Neuropsychol 2002;17:57-67.*
17. Sullivan EV, Shear PK, Lim KO, et al. Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. *Biol Psychiatry 1996;39:234-240.*
18. Lupien SJ, de LM, de SS, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci 1998;1:69-73.*
19. Aaronson LS, Teel CS, Cassmeyer V, et al. Defining and measuring fatigue.

Image J Nurs Sch 1999;31:45-50.

20. Harboe E, Greve OJ, Beyer M, et al. Fatigue is associated with cerebral white matter hyperintensities in patients with systemic lupus erythematosus. *J Neurol Neurosurg Psychiatry 2008;79:199-201.*
21. Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM 1995;88:767-773.*
22. Tirelli U, Chierichetti F, Tavio M, et al. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med 1998;105:54S-58S.*
23. Chemerinski E, Robinson RG, Kosier JT. Improved recovery in activities of daily living associated with remission of poststroke depression. *Stroke 2001;32:113-117.*
24. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. *Biol Psychiatry 2003;54:376-387.*
25. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet 2001;357:841-847.*
26. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. *Arch Phys Med Rehabil 1999;80:173-178.*
27. Michael K. Fatigue and stroke. *Rehabil Nurs 2002;27:89-94, 103.*
28. Morley W, Jackson K, Mead GE. Post-stroke fatigue: an important yet neglected symptom. *Age Ageing 2005;34:313.*
29. Loewenstein DA, Acevedo A, Czaja SJ, et al. Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. *Am J Geriatr Psychiatry 2004;12:395-402.*
30. Yokota C, Minematsu K, Hasegawa Y, et al. Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-based study over a 20-year period. *Cerebrovasc Dis 2004;18:111-116.*

Nederlandse samenvatting

Cerebrovasculair accident (CVA) is wereldwijd een belangrijke doodsoorzaak en heeft een grote invloed op de kwaliteit van leven. Na een intensieve medische behandeling treedt het meeste lichamelijke herstel kort na een CVA op. Deze "zichtbare" gevolgen (zoals hemiparese, afasie en visuele problematiek) die vaak kort na een CVA op de voorgrond treden, verdienen de meeste aandacht van zowel dokters als familieleden. Domweg doordat deze zo zichtbaar zijn. Dit proefschrift richt zich juist op de "niet-zichtbare" (of secundaire) gevolgen van een CVA, die vaak pas later duidelijk worden of pas duidelijk worden als er expliciet naar wordt gevraagd. Voorbeelden hiervan zijn depressieve symptomen, geheugenklachten en vermoeidheid. De studies beschreven in dit proefschrift proberen meer inzicht te krijgen in de epidemiologie en pathophysiologie van de hierboven genoemde secundaire gevolgen van een CVA. Daarvoor is in 2005 de Nijmeegse Stroke Studie opgericht. Deze prospectieve database verzamelt van alle CVA patiënten die opgenomen zijn geweest op de afdeling neurologie van het Radboud Universiteit Nijmegen, Medisch Centrum de demografische, klinische, radiologische en neuropsychologische gegevens.
Er bestaat een doorlopend debat over de oorzaak van de bovengenoemde secundaire gevolgen van een CVA. Een aantal wetenschappers is van mening dat de locatie van een laesie belangrijk is, net zoals een verlamming na een herseninfarct in de pyramidebaan. Andere wetenschappers beweren dat de secundaire gevolgen na een CVA een psychologische reactie is op een "major life event" of als een reactie op lichamelijke afhankelijkheid.

Hoofdstuk 2: Depressieve symptomen ná een CerebroVasculair Accident

Hoofdstuk 2.1 beschrijft van 107 studies de prevalentie van depressieve symptomen na een CVA, het beloop van deze symptomen gedurende de tijd en de risicofactoren voor depressieve symptomen na een CVA. In tegenstelling tot laesie locatie of grootte, werd in dit overzichtsartikel, fysieke beperkingen na een CVA en depressiviteit in de medische geschiedenis wel gerelateerd aan depressieve symptomen na een CVA. Echter, al deze studies corrigeren nauwelijks voor factoren die reeds aanwezig zijn vóór de CVA, de zogenaamde confounders. Deze confounders (bijv depressieve symptomen in de medische geschiedenis, witte stof afwijkingen, stille infarcten, cerebrale atrofie) kunnen gerelateerd zijn aan depressieve symptomen ongeacht een CVA en kan daardoor de relatie tussen uitkomst en CVA mogelijk vertroebelen.

Hoofdstuk 2.2 onderzoekt bij 420 patienten de prevalentie en risicofactoren van depressieve symptomen, twee maanden ná een CVA. Mogelijke confounders zoals depressieve symptomen in de medische geschiedenis, witte stof afwijkingen en cerebrale atrophy, werden nadrukkelijk in acht genomen. De prevalentie van depressieve symptomen twee maanden na de CVA was 13%. De mate van handicap en functionele afhankelijkheid na de CVA waren risicofactoren voor depressieve symptomen na een CVA. Om meer inzicht te krijgen in de achterliggende oorzaak van depressieve symptomen ná een CVA werden ook TIA patiënten onderzocht. Deze patiënten maken een soort gelijke episode mee in vergelijking tot patiënten met een herseninfarct, maar bij TIA's herstellen de "zichtbare" gevolgen na een CVA binnen 24 uur en radiologische afwijkingen in het brein zijn nauwelijks waar te nemen. Ondanks dat TIA patiënten geen blijvende "zichtbare" beperkingen laten zien, is de prevalentie van depressieve symptomen na een CVA vergelijkbaar met die van patiënten met een herseninfarct.

Hoofdstuk 3: Cognitieve klachten ná een CerebroVasculair Accident

Hoofdstuk 3.1 beschrijft van 65 studies de prevalentie, risicofactoren en beloop van geheugenklachten na een CVA. De diagnose vasculaire dementie (waarbij de aanwezigheid van geheugenklachten/geheugenstoornissen een belangrijke voorwaarde is) wordt vaak binnen drie maanden na een CVA vastgesteld. Daarbij wordt gemakshalve er vanuit gegaan dat de geheugenklachten na een CVA een stabiel beloop hebben. Echter, onze gestructureerde literatuurstudie laat zien dat maar weinig studies (n=5) het beloop van geheugenklachten na een CVA over meerdere momenten hebben bestudeerd. Deze studies laten juist een hogere prevalentie zien van geheugenklachten kort na een CVA en een lagere prevalentie langere tijd na een CVA. Het is dus zeer goed mogelijk dat de diagnose vasculaire dementie (die per definitie binnen drie maanden na een CVA wordt vastgesteld) bij sommige patiënten niet meer van toepassing is naarmate de tijd na een CVA verstrijkt. Opnieuw diagnosticeren van vasculaire dementie na een CVA zou daarvoor wenselijk zijn. Risicofactoren voor geheugenklachten na een CVA zijn toename laesie volume, cerebrale atrofie en wittestof afwijkingen. Voor de interpretatie van deze uitkomsten moeten wel een aantal methodologische aandachtspunten in acht genomen worden. De 65 studies variëren sterk in: 1) patiënt inclusie (hoeveelheid, leeftijd, geslacht, eerste CVA of eerdere CVA's), 2) verschillende meetinstrumenten voor geheugenklachten, 3) wisselende tijdsmomenten van geheugentesten na een CVA en 4) verzamelen van karakteristieken

ná de CVA (laesie locatie, volume) en vóór de CVA (wittestof afwijkingen, cerebrale atrofie). Deze variatie maakt het lastig studies onderling te vergelijken en dus ook de etiologie van geheugenklachten vast te stellen. Het is daarom belangrijk om gegevens structureel en gestandaardiseerd te verzamelen.
Met behulp van functionele MRI wordt in **hoofdstuk 3.2** onderzocht wat de achterliggende oorzaak van geheugenklachten is. Cognitieve klachten kunnen veelal verklaard worden door de grootte en locatie van een herseninfarct, maar voor geheugenklachten geldt dit niet. Geheugenklachten worden frequent genoemd na een CVA, echter een infarct in dat deel van het brein wat essentieel is voor het geheugen (de mediale temporaal kwab) komt zelden voor. In dit hoofdstuk onderzoeken we met behulp van fMRI de functionaliteit van de mediale temporaal kwab bij 22 gezonde controles en 28 patiënten met een herseninfarct. De functionaliteit van de mediale temporaal kwab hangt af van intacte verbindingen met andere hersengebieden verspreid over het gehele brein. Geheugenklachten na een herseninfarct zijn niet gerelateerd aan vermindering in structuur van de mediale temporaal kwab, maar in verminderding van functie van de mediale temporaal kwab. Verder onderzoek moet uitwijzen of patiënten met verminderde mediale temporaal kwab functionaliteit ook een verhoogd risico hebben op het ontwikkelen van vasculaire dementie.

Hoofdstuk 4: Vermoeidheid ná een CerebroVasculair Accident

Bij veel neurologische aandoeningen speelt vermoeidheid een belangrijke rol, zeker omdat het een negatieve impact heeft op het rehabilitatieproces. De meeste studies bestuderen vermoeidheid kort na een CVA of juist alleen langere tijd na een CVA. Daarbij wordt nauwelijks rekening gehouden met confounders die vóór de beroerte reeds aanwezig waren (bijv depressieve symptomen in de medische geschiedenis, wittestof afwijkingen, cerebrale atrofie) en gerelateerd zijn aan vermoeidheid ongeacht een CVA. **Hoofdstuk 4.1** bestudeert de prevalentie van vermoeidheid na een CVA, het beloop van vermoeidheid gedurende de tijd en de risicofactoren voor vermoeidheid na een CVA. Meer dan 100 CVA patiënten werden twee maanden én 1.5 jaar na een CVA onderzocht. Mogelijke confounders (zoals depressieve symptomen in de medische geschiedenis, wittestof afwijkingen en cerebrale atrophy) werden nadrukkelijk in acht genomen. De prevalentie van vermoeidheid twee maanden én 1.5 jaar na de CVA was respectievelijk 35% en 33%. Risicofactoren voor vermoeidheid twee maanden na een CVA zijn: lagere leeftijd, depressieve symptomen en infratentoriële infarcten. De risicofactor voor

vermoeidheid 1.5 jaar na een CVA is vermoeidheid twee maanden na een CVA. Voorspellers voor het ontwikkelen van vermoeidheid 1.5 jaar na een CVA zijn: depressieve symptomen en vermoeidheid twee maanden na een CVA. Vroegtijdige vermoeidheidsinterventies, die momenteel worden ontwikkeld, kunnen mogelijk helpen bij het voorkómen van vermoeidheid langere tijd na een CVA.

Hoofdstuk 5: Samenvatting en discussie

In dit laatste hoofdstuk worden de belangrijkste bevindingen van het proefschrift beschreven. Verder worden methodologische aspecten aangedragen om niet alleen de verschillende studies beschreven in dit proefschrift kritisch te kunnen interpreteren, maar ook de hiaten van de bestaande literatuur. Als laatste wordt de klinische relevantie van de desbetreffende studies beschreven en worden suggesties aangedragen voor zowel methodologisch als klinisch wetenschappelijk onderzoek.

Dankwoord

Allereerst gaat mijn dank uit naar alle patiënten en controle personen die mee hebben gewerkt om dit onderzoek te verwezenlijken.

Mijn dank voor Prof. Dr. Padberg, dat u mijn promotor bent en voor het feit dat ik dit promotie-onderzoek op uw afdeling heb kunnen vervullen.
Mijn copromotor Dr. de Leeuw wil ik graag bedanken, Frank-Erik jouw doortastendheid en zakelijk inzicht waren verhelderend. Jij wist vaak de vinger op de zere plek te leggen en dat heeft dit onderzoek des te sterker gemaakt. Ik ben trots dat ik jouw eerste promovendus ben, mijn dank voor de samenwerking al die jaren!

Karin Kanselaar, super leuk dat jij mijn paranimf wil zijn. Toen ik als junior onderzoeker begon had ik weinig ervaring met CVA-patiënten, jij als CVA verpleegkundige (inmiddels Nurse Practitioner) en gevoelsmens liet me zien hoe met patiënten om te gaan en daarbij mis ik de “patiënten-overlegjes” op maandag en donderdag nog steeds! Nu heb je zelf de keuze gemaakt om het promotietraject te volgen, wat je ook zeker gaat lukken…als je je maar aan de planningen houdt! Heel veel succes meid en ik houd PubMed in de gaten.
De afdeling neurologie wil ik bedanken voor een kijkje achter de schermen in de wereld van neurologen, arts-assistenten, poli-medewerkers, secretaresses en co-assistenten. De geneeskundestudenten, Guus Bökkering en Inge van Uden wil ik in het bijzonder danken voor hun (soms ook slopende) werkzaamheden, die mede hebben bijgedragen aan verschillende artikelen in dit proefschrift. Hopelijk zien we elkaar nog op een of ander congres?
Natuurlijk wil ik mijn kamergenoten van de kleine onderzoekskamer mijn dank overbrengen; Lars (mijn vaste roomie, fijne vent, befaamd fietser en enige man op de kamer), Charlotte (expert in de ziekte van Parkinson en onze dokter), Loes (nieuwste aanwinst van de kamer), Nicol (altijd fanatiek in wat ze ook doet), Maja (oftewel Dr. Stulemeijer, perfectionisme op en top…zelfs op de blokfluit) en Teuntje (welliswaar geen stekkie op de kamer maar altijd bereid tot een gesprekje). Aangezien we allen zo verschillend zijn, waren onze gesprekken/discussies ook erg divers, maar interesse vóór elkaar en lol mét elkaar waren toch wel de dingen die ons een heus team maakte en mede daarom ook het promoveren leuk maakte. Heel veel succes de komende tijd voor ieder van jullie en ik zal het intensieve contact missen!

Ook aan mijn 'niet neurologie' collega's wil ik graag mijn dank overbrengen; Doctor Carlijn Hooijmans, al hebben we maar kort met elkaar gewerkt (1 week om precies te zijn!) hadden we gelijk een band die we sindsdien (>4 jaar) niet meer hebben losgelaten, jammer dat je momenteel op wereldreis bent!? Clemens Jansen, mijn FCDC maatje! Naast al die uren analyseren, wist jij mijn brein te voeden met muzikale/filosofische/psychologische bijzonderheden. Sieberen van der Werf, dank voor alle inspanningen wat tot twee artikelen in dit proefschrift heeft geleid. Mark Rijpkema, voor het wegwijs maken in de wereld van fMRI en voor de hulp bij "ongelukken" met SPM. Paul Gaalman, voor het leren omgaan met een 1.5 Tesla MRI-scanner waardoor ik zelfs certified user werd! Last but not least, Norbert Janssen voor het meedenken en het opzetten van de CVA database, maar ook voor de ontelbare keren dat ik weer patiënten wilde verwijderen, jumpjes, instructieschermpjes en vragenlijsten wilde toevoegen of veranderen!
Ik heb gemerkt dat wetenschap bedrijven het beste gaat als je zo nu en dan uit dat wereldje wordt getrokken en wie kunnen dat beter dan je beste vrienden… Eelkje, Bram, Heleen, Martijn, Laura en Sjoert, door de jaren heen hebben we vele leuke dingen (en soms ook wel domme) gedaan, en zoals jullie weten ben ik blij met zulke echte vrienden, dat wil ik jullie even laten weten! Verder wil ik de baasjes, Klup Met, Karin Mentink, Nicole Verstappen, Eveline Kamping, Laura Koster, Anne Kan en Ellen Meuleman bedanken voor alle afleiding die ik het afgelopen jaar steeds meer nodig had…hopelijk gaan we op deze voet verder.

Lieve Leone, mijn grote zus, alhoewel onze interesses en ideeën vroeger heel ver van elkaar af lagen, komen ze nu wel héél dichtbij. Ik ben blij dat je als paranimf op dit belangrijke moment in mijn leven aan mijn zijde wilt staan. Stan (gesprekstof hebben we genoeg), Joep (heerlijk neefje dat je bent), Lobke (klein als je bent en al zó belangrijk), Ben (pesten lijkt je hobby), Ineke (vol interesse in eigenlijk alles), Daan (stoere zelfstandige kerel met een klein hartje) en Annemien (vanaf moment één, zat het goed) wat is het toch fijn om te weten dat je familie altijd achter je staat!

Lieve mamma en pappa, een warm nest, jezelf ontplooien, optimisme en genieten, zijn kenmerkend voor jullie. Met die ideeën in mijn binnenzak ben ik gekomen waar ik nu ben. Bedanken is in deze context zo formeel, ik wil jullie gewoon laten weten dat ik ontzettend veel van jullie hou en hoop dat ik nog heel wat gezellige en interessante gesprekken met jullie mag voeren!

Jeroen, mijn mannetje, jij bent de afgelopen tijd mijn stabiele factor geweest en het is heerlijk om te weten dat jij dat ook de komende tijd zult zijn. We koesteren bijzondere momenten in Europa, Azië, Afrika, Amerika en Australië… ik kan niet wachten tot ons volgend avontuur!!!

Publications

1. de Jong T, Snaphaan L, Pattij T, Veening J, Waldinger M, Cools A, Olivier B. Effects of chronic treatment with fluvoxamine and paroxetine during adolescence on serotonin-related behavior in adult male rats. *Eur Neuropsychopharmacol.* 2006 Jan;16(1):39-48. Epub 2005 Aug 16.

2. Liselore Snaphaan and Frank-Erik de Leeuw. Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. *Stroke* 2007 Jan;38(1):198-203. Epub 2006 Dec 7.

3. Liselore Snaphaan and Frank-Erik de Leeuw. Post-stroke depression: a systematic review on pre- and post-stroke clinical and neuroimaging correlates. *Aging Health* 2009 Jun; 5(3): 427-443. [Epub ahead of print]

4. Liselore Snaphaan, Karin Kanselaar, Sieberen van der Werf, Frank-Erik de Leeuw. Post-stroke depressive symptoms are associated with post-stroke characteristics. *Cerebrovasc Dis* 2009 Oct;28(6):551-557. [Epub ahead of print]

5. Liselore Snaphaan, Mark Rijpkema, Inge van Uden, Guillen Fernandez and Frank-Erik de Leeuw. Reduced medial temporal lobe functionality in stroke patients: A functional Magnetic Resonance Imaging study. *Brain* 2009 Jul;132(Pt 7):1882-8. Epub 2009 May 29.

6. Liselore Snaphaan, Sieberen van der Werf, Frank-Erik de Leeuw. Time course and risk factors of post-stroke fatigue: a prospective cohort study.(submitted 2009).

Curriculum Vitae

Liselore Snaphaan werd geboren op 2 augustus 1978 te Druten. In 1995 behaalde zij haar MAVO diploma aan het Johannes Bosco College te Druten, in datzelfde jaar startte zij de laboratorium opleiding Klinische Chemie aan het ROC de Leijgraaf te Oss. In 1998-1999 vervulde zij haar onderzoeksstage (detecteren van Mola zwangerschappen) op de afdeling Chemische Endocrinologie aan het Radboud Universiteit Nijmegen, Medisch Centrum. Na het behalen van haar MBO diploma is zij in 1999 gestart met de laboratorium opleiding Medische Microbiologie aan de Hogeschool van Arnhem en Nijmegen. In 2001-2002 heeft zij een klinische stage gedaan op de afdeling Medische Microbiologie in het Rijnstate Ziekenhuis te Arnhem en een onderzoeksstage (valideren van desinfectiemiddelen) op de afdeling Kwaliteitsbewaking bij het farmaceutisch bedrijf Organon te Oss. In 2002 behaalde ze haar HBO diploma en startte tevens de opleiding Clinical and Experimental Neurosciences aan de Universiteit te Utrecht. Haar onderzoeksstage (functie van astrocyten bij HIV-dementie) heeft ze uitgevoerd bij Eijkman-Winkler Centre for Microbiology aan het Universitair Medisch Centrum, Utrecht. Haar afstudeerstage (lange termijn effect van antidepressiva) heeft ze vervuld op de afdeling Anatomie aan het Radboud Universiteit Nijmegen, Medisch Centrum en behaalde in oktober 2004 haar Master of Science degree. Van 2005 tot en met 2008 werd zij aangesteld als junior-onderzoeker op de afdeling Neurologie aan het Radboud Universiteit Nijmegen, Medisch Centrum, waar dit proefschrift het resultaat van is. Momenteel is zij werkzaam voor het project Zichtbare Zorg ziekenhuizen als wetenschappelijk onderzoeker/projectmanager op de afdeling IQ healthcare aan het Radboud Universiteit Nijmegen, Medisch Centrum.

Series Donders Institute for Brain,
Cognition and Behaviour

1. van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection.* Maastricht University, Maastricht, The Netherlands.
2. Schoffelen, J.M. (2007). *Neuronal communication through coherence in the human motor system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
3. de Lange, F.P. (2008). *Neural mechanisms of motor imagery.* Radboud University Nijmegen, Nijmegen, The Netherlands.
4. Grol, M.J. (2008). *Parieto-frontal circuitry in visuomotor control.* University Utrecht, Utrecht, The Netherlands.
5. Bauer, M. (2008). *Functional roles of rhythmic neuronal activity in the human visual and somatosensory system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
6. Mazaheri, A. (2008). *The Influence of Ongoing Oscillatory Brain Activity on Evoked Responses and Behaviour*. Radboud University Nijmegen, Nijmegen, The Netherlands.
7. Hooijmans, C.R. (2008). *Impact of nutritional lipids and vascular factors in Alzheimer's Disease.* Radboud University Nijmegen, Nijmegen, The Netherlands.
8. Gaszner, B. (2008). *Plastic responses to stress by the rodent urocortinergic Edinger-Westphal nucleus.* Radboud University Nijmegen, Nijmegen, The Netherlands.
9. Willems, R.M. (2009). *Neural reflections of meaning in gesture, language and action.* Radboud University Nijmegen, Nijmegen, The Netherlands.
10. Van Pelt, S. (2009). *Dynamic neural representations of human visuomotor space.* Radboud University Nijmegen, Nijmegen, The Netherlands.
11. Lommertzen, J. (2009). *Visuomotor coupling at different levels of complexity.* Radboud University Nijmegen, Nijmegen, The Netherlands.
12. Poljac, E. (2009). *Dynamics of cognitive control in task switching: Looking beyond the switch cost.* Radboud University Nijmegen, Nijmegen, The Netherlands.
13. Poser, B.A. (2009) *Techniques for BOLD and blood volume weighted fMRI.* Radboud University Nijmegen, Nijmegen, The Netherlands.
14. Baggio, G. (2009). *Semantics and the electrophysiology of meaning. Tense, aspect, event structure*. Radboud University Nijmegen, Nijmegen, The Netherlands.
15. van Wingen, G.A. (2009). *Biological determinants of amygdala functioning*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
16. Bakker, M. (2009). *Supraspinal control of walking: lessons from motor imagery.* Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

17. Aarts, E. (2009). *Resisting temptation: the role of the anterior cingulate cortex in adjusting cognitive control.* Radboud University Nijmegen, Nijmegen, The Netherlands.
18. Prinz, S. (2009). *Waterbath stunning of chickens – Effects of electrical parameters on the electroencephalogram and physical reflexes of broilers.* Radboud University Nijmegen, Nijmegen, The Netherlands.
19. Knippenberg, J.M.J. (2009). *The N150 of the Auditory Evoked Potential from the rat amygdala: In search for its functional significance.* Radboud University Nijmegen, Nijmegen, The Netherlands.
20. Dumont, G.J.H. (2009). *Cognitive and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') in combination with alcohol or cannabis in humans.* Radboud University Nijmegen, Nijmegen, The Netherlands.
21. Pijnacker, J. (2010). *Defeasible inference in autism: a behavioral and electrophysiogical approach.* Radboud Universiteit Nijmegen, The Netherlands.
22. de Vrijer, M. (2010). *Multisensory integration in spatial orientation.* Radboud University Nijmegen, Nijmegen, The Netherlands.
23. Vergeer, M. (2010). *Perceptual visibility and appearance: Effects of color and form.* Radboud University Nijmegen, Nijmegen, The Netherlands.
24. Levy, J. (2010). *In Cerebro Unveiling Unconscious Mechanisms during Reading.* Radboud University Nijmegen, Nijmegen, The Netherlands.
25. Treder, M. S. (2010). *Symmetry in (inter)action.* Radboud University Nijmegen, Nijmegen, The Netherlands.
26. Horlings C.G.C. (2010) *A Weak balance; balance and falls in patients with neuromuscular disorders.* Radboud University Nijmegen, Nijmegen, The Netherlands
27. Snaphaan, L.J.A.E. (2010). *Epidemiology of post-stroke behavioural consequences.* Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.