Long-term cognitive impairment after first-ever ischemic stroke in young adults:

a neuroimaging study

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Pauline Schaapsmeerders

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Voor mijn ouders

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Introduction

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Chapter

General introduction, aims and outline

Stroke

Stroke is the second most common cause of death and major cause of disability worldwide.[1] Eighty percent of all strokes are ischemic and are caused by an occlusion of a blood vessel, leading to an ischemic area and accompanying stroke-related neurologic deficit. Besides possible debilitating physical impairments, ischemic stroke has been frequently associated with cognitive impairments[2-5] and dementia in stroke survivors aged 60 years and over.[6] Although stroke often occurs in these older individuals, up to 14% of all ischemic strokes occur in young adults (18 through 50 years of age).[7-13] Furthermore, the incidence of ischemic stroke in the young seems to rise over time.[14]

Cognitive outcome after ischemic stroke in young adults

The traditionally held view is that the younger the patient with stroke, the more likely the patient will recover. However, studies on stroke outcome are often limited to motor recovery. Although physical disabilities are the most visible disabilities after an ischemic stroke, cognitive impairments, which are often less apparent to others, could have devastating consequences for these young adults. That is, these patients are in a period of life where they start forming a family, will get an education or are preparing for future career steps.

Surprisingly, only a handful of studies focused on cognitive outcome up to one year after stroke in young adults.[15, 16] These studies showed that cognitive impairments were frequent in these young patients, but motor recovery was generally favorable.[15, 16] As young stroke patients have a long life expectancy, information on long-term cognitive performance exceeding one year is very important to these young individuals.[17] Currently, data on the long-term follow-up prognosis of cognitive performance (ten years or more) are lacking. Therefore, it remains unknown if, or to what extent, cognitive decrements can be found years after their ischemic stroke. Providing adequate information is one of the first steps in treatment and management of patients, making it relevant for rehabilitation services.

Cognitive performance and the association with neuroimaging markers after stroke

Apart from identifying the spectrum of cognitive impairment after ischemic stroke, knowledge on its underlying cerebral substrate is of utmost importance to get insight in post-stroke cognitive performance and perhaps compensatory mechanisms. As an ischemic stroke is a focal event, cognitive impairment cannot always be explained by lesion characteristics itself. This is nicely illustrated by the frequent occurrence of episodic memory impairment after stroke, in the absence of a stroke in brain structures known to be important for memory formation: the medial temporal lobe. Furthermore, often multiple cognitive domains are affected in a patient, suggesting that brain regions that are remote from the site of the infarction may be affected by the stroke.
Despite the existing literature on neuroimaging markers for post-stroke cognitive impairments, these studies are often limited to stroke in older individuals (≥60 years of age).[2, 3] In these older stroke patients post-stroke cognitive deficits may also be explained by co-existing neurodegenerative pathology, which is less likely to occur in younger patients, such as cerebral small vessel disease,[18] amyloid pathology,[19, 20] and other comorbidities that affect cognitive functioning. Therefore, newer techniques that can assess subclinical brain injury, such as diffusion tensor imaging, are potentially important tools in the assessment of cognitive impairments after ischemic stroke, since remote white matter integrity might play a role in cognitive outcome after ischemic stroke.[2] This could therefore be another target for prevention.[2]

Aims of the thesis and the study design

The aim of this thesis was to describe the spectrum of long-term cognitive impairments after first-ever ischemic stroke in young adults and to better understand cognitive impairments using neuroimaging techniques. This thesis is part of the 'Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation' (FUTURE) study.[21-25] This is a large, prospective cohort study designed to investigate causes and consequences of stroke in young adults (18 through 50 years of age). For the studies reported in this thesis, first-ever ischemic stroke patients were recruited that were admitted to the Radboud University Medical Centre between January 1, 1980 until November 1, 2010. Exclusion criteria for ischemic stroke in the FUTURE study were cerebral venous sinus thrombosis and retinal infarction. Follow-up cognitive assessment was conducted between November, 2009 and January 1, 2012, with subsequent MRI scanning.

Outline of this thesis

Part I of the present thesis consists of the study design and protocol of the FUTURE study (**chapter 2**). **Chapter 3** reviews the literature on stroke in young adults and addresses the underlying etiology of young stroke.
Part II, chapter 4 addresses the prevalence and mean cognitive outcome after first-ever ischemic stroke in young adults compared with a non-stroke population about 11 years after stroke. **Part III** describes the relationship between long-term memory performance and remote hippocampal volume (**chapter 5**) and hippocampal integrity (**chapter 6**) after ischemic stroke in young adults. **Chapter 7** describes the white matter integrity remote from the stroke location and the association with long-term cognitive impairment in multiple cognitive domains, incorporating cerebral small vessel disease (lacunes, microbleeds, and white-matter hyperintensities). Finally, **part IV** addresses the summary of this thesis and general discussion (**chapter 8**).

2

Chapter

The FUTURE study: a prospective cohort study
Study rationale and protocol

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Van Alebeek ME, Schaapsmeerders P, Schoonderwaldt HC, Dorresteijn LD, Overeem S, Drost G, Janssen MC, van Heerde WL, Kessels RP, Zwiers MP, Norris DG, van der Vlugt MJ, van Dijk EJ, de Leeuw FE.

Risk factors and prognosis of young stroke. The FUTURE study: a prospective cohort study. Study rationale and protocol.

BMC Neurology. 2011; 11: 109-116

Abstract

Background and objective

Young stroke can have devastating consequences with respect to quality of life, the ability to work, plan or run a family, and social participation. Better insight into risk factors and the long-term prognosis is extremely important, especially in young stroke patients with a life expectancy of decades. To date, detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific risk of mortality or recurrent vascular events, remains scarce.

Methods

The FUTURE study is a prospective cohort study on risk factors and prognosis of young ischemic and hemorrhagic stroke among 1006 patients, aged 18 through 50 years, included in our study database between January 1, 1980 and November 1, 2010. Follow-up visits at our research center take place from the end of 2009 until the end of 2011. Control subjects will be recruited among the patients' spouses, relatives, or social environment. Information on mortality and incident vascular events will be retrieved via structured questionnaires. In addition, participants are invited to the research center to undergo an extensive sub study including MRI.

Conclusion

The FUTURE study has the potential to make an important contribution to increase the knowledge on risk factors and long-term prognosis in young stroke patients. Our study differs from previous studies by having a maximal follow-up of more than 30 years, including not only TIA and ischemic stroke but also hemorrhagic stroke, the addition of healthy controls and prospectively collect data during an extensive follow-up visit. Completion of the FUTURE study may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

Introduction

Up to 12% of all strokes occur in patients between 18-50 years ('young stroke'),[26] affecting about 5000 patients each year in the Netherlands and about 2 million young people each year worldwide. In a substantial proportion of roughly one third the etiology remains unelucidated. In terms of prognosis a young stroke has a dramatic influence on independency and quality of life as it occurs in the period of life that people start to form families, make decisive career moves, and have an active social life. Uncertainty about long-term prognosis affects choices and planning affiliated with these life events.
Whereas risk factors and prognosis in patients who develop a stroke at higher ages (usually over 70 years) are among the best studied topics in clinical medicine, this does not hold true for young stroke. At higher ages, almost all risk factors have atherosclerosis in their final common pathway. However, this cannot simply be extrapolated to young stroke as the underlying cause of stroke is usually different from that in elderly and may therefore also have a different prognosis both with respect to functional stroke outcome as to risks of recurrent stroke or other major vascular events. Even more, the identification of risk factors for young stroke so far has often been based on the occurrence of presumed risk factors in consecutive series of young stroke patients, without methodological sound comparison with controls.
The 'long-term' perspective in an on average over 70 years old stroke patient differs from that of a 30 years young stroke patient, and particularly studies with a long-term follow-up of more than 10 years are lacking in the young stroke field. Studies thus far, usually with a mean follow-up duration of less than 7 years, report highly variable post-stroke mortality and risk of incident vascular disease.[26-31] These large differences across studies are well explained because young stroke is a heterogeneous disease and most studies were small, had different selection criteria, did not investigate patients in person but relied on telephone interviews, and outcome assessments and follow-up planning was not uniform and often suboptimal. Although stroke includes both ischemic and hemorrhagic stroke, almost all studies have excluded the investigation of etiology and prognosis of young hemorrhagic stroke.
Except for recurrent vascular disease and persistent motor and language impairments, post-young stroke quality of life will most likely also be determined by cognitive dysfunction, depressive symptoms, fatigue, and specific post-stroke complications such as epilepsy, because those determine the ability to (return to) work and to have a normal family and social life. Data on those aspects in the very long-term follow-up of young stroke patients are even more scarce.
Although the absolute number of young stroke is lower than stroke among the elderly, the total number of years that young stroke patients as a whole will live with the consequences of the stroke exceeds that of older stroke survivors due to far longer survival.

This justifies a properly designed and executed study on risk factors and prognosis of young stroke, compared with controls. We therefore set up the *FUTURE* study (*F*ollow-*U*p of *T*ransient ischemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation study), the largest single-center prospective cohort study on risk factors and prognosis of young TIA, ischemic stroke and hemorrhagic stroke patients (n=1006) and controls.

Methods

The FUTURE study is a prospective cohort study that aims to investigate the causes and consequences of a young stroke. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Patients

The department of neurology has a long-standing interest in the etiology and prognosis of young stroke and therefore maintains a prospective registry of all consecutive young stroke patients with a standardized collection of baseline and clinical characteristics (see 'baseline') since the 1970'ies.[32] For the current *FUTURE* study, all consecutive TIA, ischemic stroke patients with presumed arterial origin or those with an intracerebral hemorrhage that sought medical attention for these disorders at the department of neurology of the Radboud University Medical Centre between 1-1-1980 and 1-11-2010 will be eligible for participation in the study.

Inclusion criteria

1. TIA, ischemic stroke of presumed arterial origin or intracerebral hemorrhage
2. Date of onset between 1-1-1980 and 1-11-2010
3. Age 18-50 at onset

Exclusion criteria

1. Traumatic hemorrhagic stroke
2. Intracerebral hemorrhage in known cerebral metastasis or primary brain tumor
3. Ischemic/hemorrhagic stroke due to cerebral venous sinus thrombosis
4. Intracerebral hemorrhage due to ruptured cerebral aneurysm
5. Any subarachnoid hemorrhage
6. Retinal infarct

TIA was defined as a rapidly evolving focal neurological deficit with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours. On the basis of radiological findings, stroke was further subdivided into hemorrhagic and ischemic stroke.

As the diagnostic process may have changed during a more than 30-year period all initial diagnoses were reviewed by a panel of 2 experts from a pool of 4 (FEdL, EvD, RA, LJD) and in cases of disagreement a consensus meeting was held to adjudicate the event.
1006 patients who had sought medical attention at our University Medical Centre between 1-1-1980 and 1-11-2010 fulfilled inclusion and exclusion criteria for our study. Characteristics of our baseline population (at the time of their qualifying event) are reported in Table 1.

Table 1 | Baseline population characteristics

	Total population	Time of index event		
		1980-1989	1990-1999	2000-2010
No.	1006	223	249	534
Men, No. (%)	470 (46.7)	110 (49.3)	128 (51.4)	232 (43.4)
Age at index event, mean (SD), y	40.2 (7.9)	39.3 (8.3)	39.7 (8.6)	40.8 (7.4)
Index event				
TIA, No. (%)	277 (27.5)	52 (23.3)	40 (16.1)	185 (34.6)
Ischemic stroke, No. (%)	630 (62.6)	146 (65.6)	189 (75.9)	295 (55.2)
Hemorrhage, No. (%)	99 (9.8)	25 (11.2)	20 (8.0)	54 (10.1)

Controls

Control subjects will be recruited among the patients' spouses, relatives or social environment. They have to be at least 18 years old without a history of any TIA or stroke before the age of 50 at the moment of inclusion.

Baseline

At baseline (during the occurrence of the qualifying event for the study) a minimal dataset has been collected that consists of demographics, stroke subtype, risk factors, and additional investigations (Table 2). The completeness of the baseline dataset varies among patients due to changes in standard diagnostic procedures over the last 30 years.
Current common rating scales for the severity and cause of stroke did not exist at the time when a substantial proportion of our patients experienced their qualifying event. Therefore, a rating of both the severity (NIHSS) and cause (TOAST) was done for all cases retrospectively by a validated approach.[33]

Follow-up

Information on the vital status will be available either from hospital data or through coupling of patient records with data from the municipality registry. All patients alive will be approached for the follow-up assessment according to a 2-step approach.

First, all patients will be contacted by letter to inform them about the study; subsequently they will be contacted by phone. In case the patient has moved, the municipality register of the last known residence will be contacted to trace the patient. In cases of an invalid phone number, a second letter will be sent asking the patient to contact our center to provide a correct phone number. Subsequently, when a patient does not respond to the second letter, the last known general practitioner will be contacted to provide us with updated contact details. The patient will be considered lost to follow-up when known alive, but when untraceable via the procedure described above.

Subsequently, patients will be given the opportunity to participate in an extensive sub study. If they agree to do so, they will be invited to visit our research center for additional investigations including a structured interview, cognitive assessment, physical and neurological examination, an extensive MRI protocol, an electrocardiogram, and an ultrasonography of the carotid arteries (Table 2). In addition, blood samples (serum/plasma/DNA) will be taken for future analysis. When patients are not able to visit our research center the same investigations will be performed at their homes, except for the ultrasonography of the carotid arteries, electrocardiogram, and MRI scan. Controls will undergo the same protocol as patients.

The follow-up has started at the end of 2009 and is planned to finish at the end of 2011. All these participants signed an informed consent.

Outcome events

The primary outcome of the study will be all-cause mortality and the composite endpoint of death from all vascular causes; non-fatal stroke, non-fatal (silent) myocardial infarction, cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy, and other arterial revascularisation procedures), whichever occurred first. We will perform separate analysis for the occurrence of fatal or non-fatal stroke. Causes of death will be categorized into ischemic stroke, intracerebral hemorrhage, cardiac causes, other vascular causes or non-vascular causes. If we cannot obtain information about the cause of death, the event will be classified as unspecified.

Secondary outcomes are seizures (classified according to the ILAE[34]) and dementia (according to DSM-IV).

Table 2 | Schedule of assessments in the FUTURE study

Assessment	Baseline	Follow-up
Demographics		
Ethnicity		X
Education		X
Marital status		X
Social/living status		X
Stroke Characteristics		
Qualifying event	X	
Symptoms at onset	X	
Discharge date and destination	X	
TOAST	X	
NIHSS at admission and at discharge	X	
Modified Ranking Scale at discharge	X	
Medical History		
History of any cardiovascular disease	X	X[a]
Cardiovascular risk factors	X	X[a]
Family history of cardiovascular disease	X	X
Medication use	X	X[a]
Stroke related surgical procedures	X	X[a]
Epilepsy	X	X[a]
Neuropsychologic examination		
Global cognitive function		
Mini Mental State Examination (MMSE)		X
Verbal memory function		
Rey Auditory Verbal Learning Test		X
Visuospatial memory		
Rey's Complex Figure Test		X
Speed of information processing		
Symbol-Digit Substitution Task		X
Stroop test		X
Working memory		
Paper and Pencil Memory Scanning Tasks		X
Executive functioning		
Animal Fluency task		X

Table 2 | Continued

Assessment	Baseline	Follow-up
Neuropsychologic examination		
Attention		
Verbal series attention test		X
Subjective cognitive failures		
Cognitive failures questionnaire		X
Depressive symptoms		
Structured questionnaire depressive symptoms		X[a]
Mini International Neuropsychiatric Interview (MINI)		X
Centre of Epidemiological Studies Depression Scale (CES-D)		X
Hospital Anxiety and Depression Scale (HADS)		X
Physical examination		
Length and weight	X	X
Waist circumference		X
Blood pressure	X	X
Heart rate	X	X
Neurological examination		
Babinski sign	X	
Sensory system		
Quantitative measurement by vibration tuning fork		X
Muscle strength		
Medical Research Council Scale (MRC)		X
Mobility and activities of daily living		
TUG-test		X
Exercise expressed in metabolic equivalent value		X[a]
Tinetti test (body balance and gait)		X
Modified Rankin Scale (mRS)	X	X
Barthel Index		X
Instrumental activities of daily living questionnaire (IADL)		X
Additional questionnaires		
Fatigue		
CIS-20R		X

Table 2 | Continued

Assessment	Baseline	Follow-up
Additional questionnaires		
Health related quality of life		
Short Form 36		X
EQ-5D		X
Stroke impact scale 3.0		X
Sleep disturbances		X[a]
List of Threatening Experiences (LTE)		X[a]
Work		X[a]
Radiological examination		
Confirmation of index event (CT or MRI)	X	
Angiography	X	
MRI		
T1 magnetization-prepared rapid gradient echo		X
FLAIR pulse sequences		X
Transversal T2* weighted gradient echo sequence		X
Diffusion Tensor imaging		X
Resting state imaging		X
Time-of-flight angiography		X
Ancillary investigation		
Electrocardiogram	X	X
Ultrasonography of the carotid arteries	X	X

[a] Variables were collected both for the period before and after the index event.

Whenever an outcome event is suspected with the aid of a standardized, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty. In case a patient has died, this information will be retrieved from their general practitioner or a relative. If there is no information available, the event will be classified as a possible event.

Assessment of variables during follow-up

Demographics and life style

Standardized questionnaires on demographics, education (classified using 7 categories; '1' being less than primary school and '7' reflecting an academic degree),[35] marital status, living conditions, and life style habits (alcohol consumption, smoking, exercise) will be administered. Alcohol consumption will be defined as units per day and the age at which alcohol consumption had started (and ended if stopped) will be noted. Cigarette smoking behavior will be defined as never, former, and current. Subsequently, former and current smoking behavior will be quantified as the number of pack-years, calculated as the number of packs of cigarettes smoked per day multiplied by the number of years a participant had smoked. Exercise will be expressed in the metabolic equivalent value (MET) according to accepted standards.[36]

Medical history

Structured, standardized questionnaires will be used to assess participants history of hypertension, diabetes mellitus, atrial fibrillation, TIA, stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy and other arterial revascularization procedures, [37-40] migraine with or without aura,[41] pregnancy, and malignancy. Whenever a primary or secondary outcome event is suspected with the aid of this standardized, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty (see outcome events). The presence of a family history of myocardial infarction, cerebrovascular disease, and diabetes mellitus in next of kin will be recorded.

Epilepsy

Each patient will be evaluated for a history of epilepsy by means of a standardized, structured questionnaire. Whenever epilepsy is suspected, information will be retrieved from the treating physician and verified and adjudicated by a neurologist (FEdL). Epilepsy will be classified according to the ILAE criteria.[34] Post-stroke epilepsy will be subdivided into early (≤7 days post-stroke) and late (>7 days) post-stroke epilepsy.

Current medication

Current medication use and the age at which medication use started will be noted and classified according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization, WHO Collaborating Centre for drug statistics and methodology, http://www.whocc.no/atcddd/).

Neuropsychological assessment

We will administer an extensive neuropsychological test battery that encompasses items from other large-scale epidemiological studies covering the main cognitive domains.[42, 43] Global cognitive function will be assessed using the Mini Mental State Examination (MMSE).[44] Verbal episodic memory function will be assessed by the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT) that also includes a delayed free-recall and recognition trial, a test used to evaluate the ability to acquire and retain new verbal information.[45] Visuospatial episodic memory will be administered by the Rey Complex Figure Test (RCFT), that consists of 3 trials: a copy trial, an immediate recall trial after 3 minutes and a delayed-recall trial after 30 minutes.[46] To evaluate speed of information processing and executive function, 2 tests will be used; the abbreviated Stroop Color Word Test (3 subtasks, the interference trial measuring response inhibition)[47] and the Symbol-Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test.[48] A verbal fluency task in which as many animals as possible have to be named within 60 seconds will be used to test semantic memory and executive functioning (response generation). To assess working memory, the Paper and Pencil Memory Scanning Task (4 subtasks)[49] will be used. To evaluate attention, the verbal series attention test (VSAT) will be used. [50] To register subjective cognitive failures we will administer the modified Cognitive Failures Questionnaire (CFQ).[51] The assessments will be carried out under standardized circumstances in quiet rooms.

A standardized structured questionnaire used in previous large-scale epidemiological studies will be used to assess the history of depressive symptoms; normal reactions to stressful events or normal grief will carefully be excluded.[52] In case of a depressive episode, age of onset, the medical advice and medication use will be registered. We defined 'depression' as those depressive episodes that have required attention of a general practitioner, psychologist or psychiatrist. This definition includes minor depression, as well as more severe depression syndromes such as major depression and bipolar depression.[52]

In addition, participants will be screened for current depressive symptoms by means of the Mini International Neuropsychiatric Interview (MINI), part A, which is a short diagnostic structured interview based on the DSM IV.[53] Additionally, presence of actual depressive symptoms will be assessed by 2 self report questionnaires, the Centre of Epidemiologic Studies Depression Scale (CES-D)[54] and the Hospital Anxiety and Depression Scale (HADS).[55]

Physical and Neurological Examination

Height and weight will be measured without shoes in light clothing. The body mass index (BMI) will be calculated as weight divided by height (in meters) squared. The maximal waist circumference will be measured without shirt, in standing position,

between the lowest rib and the iliac crest, at the end of normal expiration.[56] Blood pressure and pulse rate will be measured in triplicate in supine position after 5 minutes rest. Subsequently, one measurement is performed after 1 minute in upright position.[39] The strength of the biceps, hand grip, iliopsoas, quadriceps, and foot extensor muscles on both sides will be scored according to the medical research council scale (MRC). The sensory system will be assessed by a quantitative measurement by vibration tuning fork (Rydel-Seiffer®) on both first toes and both medial malleolus, also registering ankle edema and the ankle jerk reflex.

Gait and balance

We will use a widely used modified version of the original Tinetti test with 17 items: 9 for body balance (score 0-16) and 8 for gait (score 0-12), with a maximum score of 28.[57] It grades balance while sitting, standing with eyes open and closed, nudging and turning, gait initiation, stride length and width and symmetry. Functional mobility will be classified by using the widely-used timed-up-and-go(TUG)-test which is a timed test during which the participant is asked to rise from a standard armchair, walk 3 m, turn, walk back, and sit down again.[58] Each participant will perform the test 3 times.

Functional performance

As a measure of disability the Barthel Index and modified Rankin Scale will be used.[59] The activities of daily living will be assessed by the instrumental activities of daily living questionnaire.[60]

Additional self-report questionnaires

Several primary sleep disorders are addressed using a number of screening questions. The presence of possible sleep disordered breathing is based on a history of snoring, witnessed sleep-related apneas, and non-restorative sleep. Non-REM and REM parasomnias are addressed based on a history of sleepwalking or dream-enacting behavior. Excessive daytime sleepiness will be assessed based on the presence of continuous feelings of sleepiness, sleep attacks or a combination of both. Finally, the presence of sleep-onset and/or sleep-maintenance insomnia is recorded.
For the assessment of fatigue we will use the Checklist on Individual Strength (CIS-20R).[61] The overall health status (quality of life) will be assessed with the Short Form 36 (SF-36),[62, 63] the EQ-5D,[64] and the Stroke Impact Scale 3 (SIS-3).[65]
Adverse life events will be assessed with the 12-item List of Threatening Events (LTE), 6 months before the index event and subsequently the period after the index event.[66] Patients will be asked for their employment status in the month before their index event, within the first year after their index event and at time of the follow-up visit. Each period includes a description of occupation, working hours a week, adjustments in tasks, use of supporting devices and reasons for not working.

Ancillary Investigations

MRI protocol

MRI scanning will be performed on a 1.5-Tesla Magnetom scanner (Siemens, Erlangen, Germany). The scanning protocol includes whole brain 3D T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE/TI 2730/2.95/1000ms; flip angle 7°; voxel size 1.0x1.0x1.0mm); FLAIR pulse sequences (TR/TE/TI 12220/85/2200ms; voxel size 1.0x1.2x3.0mm; slice gap 0.6mm); transversal T2-weighted turbo spin echo sequence (TR/TE 7440/96ms; voxel size 0.9x0.9x3.0 mm; slice gap 0.6 mm); Multi-slab 3D time of flight angiography sequence (TR/TE 24/7ms; voxel size 0.8x0.5x1.0mm) will be made of the carotid arteries and the circle of Willis. Gradient echo susceptibility weighted imaging sequence (TR/TE 49/40ms; voxel size 0.8x0.7x1.0mm); DTI (TR/TE 9100/98ms; voxel size 2.2x2.2x2.2mm; 7 unweighted scans, 61 diffusion weighted scans, with non co-linear orientation of the diffusion-weighting gradient, and b value 1000s/mm^2) and resting state imaging using a gradient echo EPI (TR/TE 1870/35ms; voxel size 3.5x3.5x3.0 mm; slice gap 0.5mm). During resting state, participants will be told not to concentrate on any particular subject, but just to relax with their eyes closed. The complete scanning protocol takes approximately 60 minutes.

ECG

An electrocardiogram (ECG) will be performed and evaluated by a standardized assessment by an experienced cardiologist, registering frequency, cardiac rhythm, cardiac ectopias, cardiac axis, conduction time over the PQ, QRS, and QTC intervals, conduction disturbances, left ventricle hypertrophy, pathologic Qs, infarction, repolarization disturbances, and acute ischemia. A final diagnosis is defined as normal, abnormal without clinical significance, abnormal with clinical consequences or pathologic ECG with immediate consultation of a cardiologist when necessary.

Carotid ultrasound

A carotid ultrasound assessment will be performed at which the intima media thickness (IMT) will be measured in the distal (near the bulbus) left and right common carotid artery. All measurements will be performed using a phased array real-time scanner (Philips i-u22, The Netherlands) with a 17-5 MHz broadband linear transducer. The IMT will be automatically measured by QLab® qualification software (V.4.2.1.) according to previously described procedures.[67] All ultrasound measurements will be performed by 3 experienced and specific trained clinical neurophysiology technicians.

Vena puncture

Fasting blood samples will be taken. Immediate analysis will include glucose, creatinine, lipid profile and complete blood count. Additional serum, plasma and DNA will be stored (-80°C) for future biochemical and genetic analyses.

Statistical analyses

Cumulative risk of primary and secondary outcomes will be estimated with Kaplan-Meier analysis. In the analysis of vascular events, patients who had died from other than the defined fatal endpoints will be censored at the time of death. Cox proportional hazard models will be used to calculate the risk of suffering from any of the primary or secondary outcomes in the follow-up period, with adjustments for the necessary covariates. The relative risk (hazards ratios) will be calculated with their corresponding 95% confidence intervals.

Cross-sectional analysis (for example in the comparison between patients and controls of data acquired during the follow-up) of continuous variables will be done with Student's *t*-test or analysis of variance or in case of skewed distributions which cannot be normalized corresponding non-parametric tests will be used. Chi-squared test will be used for cross-sectional analysis of categorical variables.

Discussion

Detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific the risk of mortality and recurrent vascular events, remains scarce. These data are often derived from selected patients (often with the exclusion of TIA and hemorrhagic stroke patients) in small sized studies with short follow-up without in person assessment of risk factors and outcomes. We therefore performed the FUTURE study, designed to investigate risk factors and to prospectively assess prognosis in a large cohort of young stroke patients.

Strong elements of our study are the inclusion of both TIA and hemorrhagic and ischemic stroke patients, the very long follow-up (up to 30 years), its sample size of over 1 000 potential participants and the availability of baseline data of all consecutive patients in a single university medical center. In addition, the extensive investigation during a follow-up visit, including advanced neuroimaging has the potential of major contributions to the field. Our study differs from many other young stroke studies due to the inclusion of controls that enable us to compare the frequency of some presumed, but also unknown, risk factors between patients and controls. Detailed risk factor analysis can be done, not only for commonly documented risk factors but also for

those that are rarely documented in medical records, like physical inactivity and sleep disturbances. Moreover, the inclusion of healthy controls provides the opportunity to distinguish consequences of a young stroke from other factors like ageing effects.
We feel that completion of our study may contribute to a better understanding of the etiology of young stroke and may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

3

Chapter

Ischemic stroke in young adults: risk factors and long-term consequences

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Abstract

Contrary to trends in most other diseases, the average age of ischemic stroke onset is decreasing, owing to a rise in the incidence of stroke among 'young' individuals (under 50 years of age). This review provides a critical overview of the risk factors and etiology of young ischemic stroke and addresses its long-term prognosis, including cardiovascular risk, functional outcome and psychosocial consequences. We highlight the diminishing role of 'rare' risk factors in the pathophysiology of young stroke in light of the rising prevalence of 'traditional' vascular risk factors in younger age groups. Long-term prognosis is of particular interest to young patients, because of their long life expectancy and major responsibilities during a demanding phase of life. The prognosis of young stroke is not as favorable as previously thought, with respect either to mortality or cardiovascular disease, or to psychosocial consequences. Therefore, secondary stroke prevention is probably a lifelong endeavor in most young stroke survivors. Due to under-representation of young patients in past trials, new randomized trials focusing on this age group are needed to confirm the benefits of long-term secondary preventive medication. The high prevalence of poor functional outcome and psychosocial problems warrants further study to optimize treatment and rehabilitation for these young patients.

Introduction

Stroke is a devastating disease that affects 15 million patients worldwide each year, resulting in death in about one-third of patients and severe disability in two-thirds of the survivors.[68, 69] Approximately 80% of all strokes are ischemic strokes, of which roughly 10% occur in individuals under the age of 50 years — so-called 'young stroke'.[30] In this article, we review the literature on ischemic stroke in these young patients. Age limits defining young stroke differ across studies,[12, 25, 30, 70] but we chose to define young stroke as an ischemic stroke in adults aged 18-49 years, as this was the age range generally used in large studies.[12, 71, 72] For the sake of inclusivity, however, we will also report on results from some studies that used upper age limits of 45, 50 or 55 years.[25, 73] Risk factors and management strategies for young stroke differ across the world, depending on factors such as genetic differences, environmental influences, and the development and accessibility of health services. In this review, we will focus on the situation in Western societies, unless otherwise specified.

In recent years, we have witnessed a remarkable, unprecedented decrease in the average age of onset of ischemic stroke in the overall population, which is mainly attributable to an increased incidence of stroke in young adults.[14, 74] Ischemic stroke in young adults is often thought to be related to 'rare' risk factors and etiological features that are very different from the 'traditional' vascular risk factors and etiology seen in older stroke patients. However, the increase in stroke incidence in young adults has been found to be associated with a rising prevalence of some important 'traditional' vascular risk factors, including hypertension, hypercholesterolemia, diabetes mellitus, and obesity, in this age group.[14, 75] We will discuss the role of these risk factors from the perspective of the increased incidence of young stroke.

In addition to the identification of risk factors and etiology, long-term prognosis after stroke is of particular interest from the perspective of young patients, as they usually have a life expectancy of several decades. Following a stroke, these individuals are suddenly confronted with uncertainties about their future in a period of life during which they might be preparing for decisive career moves or planning a family. Therefore, information on long-term prognosis should include not only the risk of vascular and other diseases, but also the expected psychosocial consequences related to life after stroke — a topic reported to be among the top 10 research priorities for patients.[76]

In the first part of this review, we provide a critical overview of the existing literature on risk factors and etiology of young ischemic stroke. This section will include a methodological discussion on the rare risk factors and etiology that have conventionally been regarded as specific for young stroke, followed by a discussion of the growing prevalence of traditional vascular risk factors among younger individuals. We will then review the lifelong consequences of stroke in young adults, not only in terms of cardiovascular disease recurrence, but also with respect to less frequently studied

but equally relevant consequences, including cognitive and social impairments, mood disorders, and fatigue.

Risk factors and etiology

The view that ischemic stroke in young adults is different from 'old stroke' with respect to risk factors and etiology originated predominantly from the many publications — mainly based on case series from tertiary hospitals — that reported on the high prevalence of unusual, rare conditions and risk factors among young patients with stroke.[77] These rare risk factors and etiologies are extensively summarized in previous reviews and textbooks,[77,78] and will not be outlined in detail here. The term 'risk factor' is used to indicate that a certain factor was found to be associated with stroke in young adults. However, the mere identification of a risk factor does not imply that the etiology is fully understood. Sometimes the risk factor is somewhere in the 'causal pathway' of the disease, and may give rise to a certain etiology that in turn is associated with the disease; for example, hypertension is a risk factor, but atherosclerosis might be the underlying causal etiology of the stroke. For the purposes of this review, we will categorize the etiology according to the Trial of Org 10172 Acute Stroke Treatment (TOAST) classification, with 'large-artery atherosclerosis', 'small-vessel disease', 'cardio-embolic', 'other determined', and 'cryptogenic' as important etiological subgroups.[79]

'Rare' risk factors and etiologies

In Tables 1 and 2, we summarize data on 5 rare risk factors and 5 rare etiologies that have been linked chiefly to stroke in young patients. The choice was based on the relatively high prevalence of these factors and etiologies in large, Western young stroke cohorts.[12,72] In other populations, the distribution of conditions in the TOAST category 'other determined etiologies' differs. For example, in Japan, moyamoya disease will be diagnosed more frequently in young patients with stroke, because the incidence and prevalence of this disease is much higher there than in other parts of the world, such as Europe.[80]

Etiological subgroups, as described in Table 2, vary across sex and age categories. Extracranial arterial dissections are the most common 'rare' etiological subgroup. Dissections are found throughout all age categories and account for approximately 20% of strokes in patients under 45 years of age, but only for 2% of all ischemic strokes. The highest incidence of dissections lies in the fifth decade; men and women are about equally affected, although women are, on average, 5 years younger when the dissection manifests.[108,109]

Inflammatory arteriopathies, such as vasculitis, are a heterogeneous group, mostly consisting of multisystemic inflammatory disorders affecting arteries of all sizes,

Table 1 | Top 5 most prevalent 'rare' risk factors for stroke in young[a] Western populations

Risk factor	TOAST classification[b]	Prevalence in young patients with stroke[c]	Strength of association	Highest level of evidence[d]
Migraine[81-85, e]	Unknown cause	20-24%	Pooled effect estimate ~2.0[86]	A1, association proven for migraine with aura only
Illicit drug use[87-91]	Other (rare) causes	9-20%	OR 2.0 for cocaine;[87] OR 2.3 for cannabis;[90, f] no significant association for amphetamines[87]	A2 for cocaine; B for amphetamines, cannabis and heroin
Patent foramen ovale[92-95]	Possible cardiac embolism; low-risk source	24%, up to 50% in stroke, classified as cryptogenic	Hazard ratio ~1.5 (non-significant)[93]	A2, contrasting with evidence from B-level studies
Oral contraceptives[84, 96-101]	Other (rare) cause/ unknown	10-40%	Summary OR 2.1[97]	B
Pregnancy/puerperium[102-106]	Other (rare) cause/ unknown	7.5% in women	Relative risk 8.7 during puerperium, not during pregnancy[104]	A2, conflicting results

[a] Under 50 years of age;
[b] TOAST classification, according to Ay et al. (2005)[79];
[c] Sum of all prevalences exceeds 100%, because data were extracted from different study populations. In addition, conditions are not mutually exclusive in an individual patient;
[d] Levels of evidence: A1, systematic review, based on at least 2 independent A2-level studies; A2, prospective cohort study of sufficient sample size and duration of follow-up, adequately adjusted for confounding and selective follow-up sufficiently excluded; B, prospective cohort study, not meeting the criteria of A2, or retrospective cohort study, or case-control study; C, non-comparative study; D, expert opinion;
[e] Note that migrainous stroke is very rare;[107] however, reports on the role of migraine as a risk factor for stroke are abundant;
[f] Not significant after correction for tobacco use.

Table 2 | Top 5 most prevalent 'rare' etiologies for stroke in young[a] Western populations

Etiology	TOAST classification[b]
Non-inflammatory arteriopathies	
Arterial dissection (cervical or intracranial)[108-112]	Other (rare) causes
Reversible cerebral vasoconstriction syndrome[72, 113-115]	Other (rare) causes
Inflammatory arteriopathies	
Inflammatory arteriitis[116, e]	Other (rare) causes
Cardioembolic	
Cardiomyopathy[12, 72, 117]	Cardioembolism, high-risk source
Prothrombotic state	
Coagulation factors[118-124]	Other (rare) cause/unknown

[a] Under 50 years of age;
[b] TOAST classification, according to Ay et al. (2005)[79];
[c] Sum of all prevalences exceeds 100%, because data were extracted from different study populations. In addition, conditions are not mutually exclusive in an individual patient;
[d] Levels of evidence: A1, systematic review, based on at least 2 independent A2-level studies; A2, prospective cohort study of sufficient sample size and duration of follow-up, adequately adjusted for

depending on the disease.[116] Some of these conditions virtually never occur in young adults; for example, giant cell arteriitis almost exclusively affects individuals over 50 years of age. However, other conditions, such as Takayasu disease, predominate in young females.[116] Of note, infectious diseases underlie a considerable proportion of cases of secondary vasculitis. In the developed world, hepatitis B and C remain the most common underlying infections, whereas HIV is a large problem in the developing world.[126]

Within the subgroup of cardioembolic stroke, cardiomyopathy is one of the most prevalent conditions in young patients with ischemic stroke.[12, 72] One would expect cardiomyopathy to be associated with strokes earlier in life, because this condition often has an early age of onset. However, one study that stratified young patients with

	Prevalence in young patients with stroke[c]	Strength of association	Highest level of evidence[d]
	10-25%	Not reported	A2
	1-5%	Not reported	B
	3-5% (all autoimmune vasculitides combined)	Not reported	B or C, depending on the underlying autoimmune disorder
	2-3%	Not reported	A2
	Antiphospholipid syndrome: 10%[f] Factor V Leiden: 3.0-7.5% Antithrombin III deficiency: 5-8% Protein C deficiency: 4-11% Protein S deficiency: 6% (up to 23% in occasional studies) Prothrombin mutation: 2-6%	OR 2.2[125] OR 1.02[118] Not reported Not reported Not reported Not reported	A2 for antiphospholipid syndrome, conflicting results; B for other factors, conflicting results

confounding and selective follow-up sufficiently excluded. B, prospective cohort study, not meeting the criteria of A2, or retrospective cohort study, or case-control study; C, non-comparative study; D, expert opinion;

[e] Including primary vasculitis and vasculitis secondary to collagen vascular diseases, and other systemic conditions (excluding those secondary to infections)[116];

[f] Up to 46% in selected populations.

stroke by age category found no significant difference in prevalence between patients under 42 years of age and those aged 42 years or older. In this study, cardiomyopathy was more than twice as prevalent in men than in women (15.5% versus 6.1%).[72]

Antiphospholipid syndrome is an important example of a prothrombotic state that is related to stroke in young adults. This condition has predominantly been studied in women. An increased risk of ischemic stroke was found in association with this condition in women under 50 years of age (OR 43.1, 95%-CI 12.2-152.0).[127] Although some studies showed a clearer relationship in younger women than in older populations, another study showed no age differences in a young stroke population.[128]

Of note, some of the risk factors mentioned in Table 1, such as illicit drug abuse or the presence of a patent foramen ovale (PFO), are seen as being quite specific to young

adults, but they can actually occur throughout the human life span. In older adults, however, the relative presence of these risk factors is much lower than in young adults, as the absolute numbers of patients with traditional cardiovascular risk factors and a proven etiology, such as large-artery atherosclerosis, small-vessel disease or cardioembolic stroke, is much higher.

For most of the risk factors in Table 1, only weak associations with respect to young stroke have been reported. Moreover, the extent to which a risk factor is judged to be causal in the origin of a disease might depend on the quality of the study. To increase the likelihood of causality, studies would have to show that the effects of risk factors are, among other criteria, dose-dependent and time-dependent.[129] Double-blind randomized trials or large, prospective cohort studies would be needed to meet these requirements.

Associations for most of the reported risk factors were derived from case-control studies or case series, which are prone to various forms of bias because they are hospital-based and often limited with respect to sample size. First, information bias — in particular, recall bias — needs to be considered. Remarkable events in the recent past, such as infections, might be more readily remembered by a patient in the aftermath of a stroke than by a person who has not experienced a stroke. Acute respiratory tract infections have been implicated as trigger factors for stroke, as have chronic infections, such as chronic bronchitis.[130] The potential role of these infections as trigger factors was supported by the fact that their association with stroke was time-dependent and dose-dependent. However, the evidence derives mostly from case-control studies with methodological limitations.

Second, referral bias could be an issue. Young stroke cases described in the literature are often selected from a population that was referred for a second opinion to a tertiary academic center. These cases usually represent a selection of patients in whom no etiology could be established on the initial investigations. Subsequent additional investigations may have revealed incidental or presumed abnormal findings (for example, a PFO) that were not necessarily causal factors.

Last, confounding can contribute to bias; for example, in many small studies, traditional risk factors were not appropriately adjusted for in the analysis.

Traditional vascular risk factors

Whereas the role of rare risk factors in the pathophysiology of young stroke seems overestimated, the role of traditional vascular risk factors may have been underestimated.[8, 12, 14, 24, 26, 30, 73, 131-133] The rising incidence of stroke in young adults coincides with an increasing prevalence of traditional vascular risk factors in this age group,[12, 73, 113, 132] which is at least supportive of a relationship between the two, but causality remains to be proven. Hypertension is reported in 19-39% of all young patients with stroke, dyslipidemia in 17-60%, diabetes in 2-10%, smoking in 42-57%,

and obesity in 10-20%.[12, 24, 26, 30, 73, 131, 132] Figure 1 illustrates the increase in prevalence of the traditional vascular risk factors with age, indicating a sharp rise in the prevalence of hypertension — and, to a lesser extent, hypercholesterolemia — over the age of 35 years.

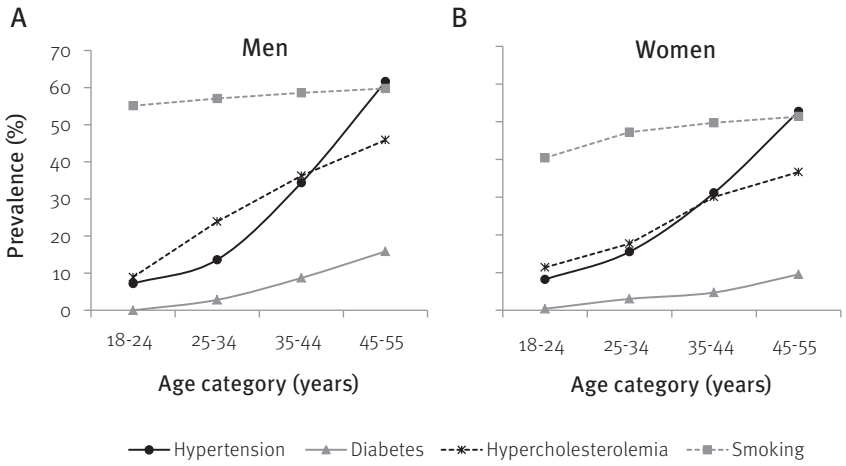

Figure 1 | Prevalence of traditional vascular risk factors in young patients with stroke

Graphs show the prevalence of various traditional vascular risk factors by age category, for **(A)** men and **(B)** women. Data were pooled from the 15 Cities study,[132] FUTURE study,[24] and SIFAP1 study.[73]

Figure 2 shows that the number of traditional vascular risk factors per patient increases with age: in patients over 35 years of age, only a small fraction of patients has no vascular risk factors.

Despite the high prevalence of traditional vascular risk factors in young adults with stroke, a proven causal etiology, such as large-artery atherosclerosis, remains to be identified in a large proportion of cases.[113] However, improved diagnostics, including high-resolution plaque and vessel wall imaging, might increase the likelihood of diagnosing a causal etiology, especially among patients with vascular risk factors, by enabling detection of earlier stages of atherosclerosis.[134]

Given the abundance of traditional vascular risk factors, the proven presence of large-artery atherosclerosis might obviate the need for further diagnostic work-up, although the safety of this strategy requires confirmation in diagnostic studies. In patients without any proven etiology, ancillary investigations are indicated to further unravel potentially treatable rare risk factors and etiologies.

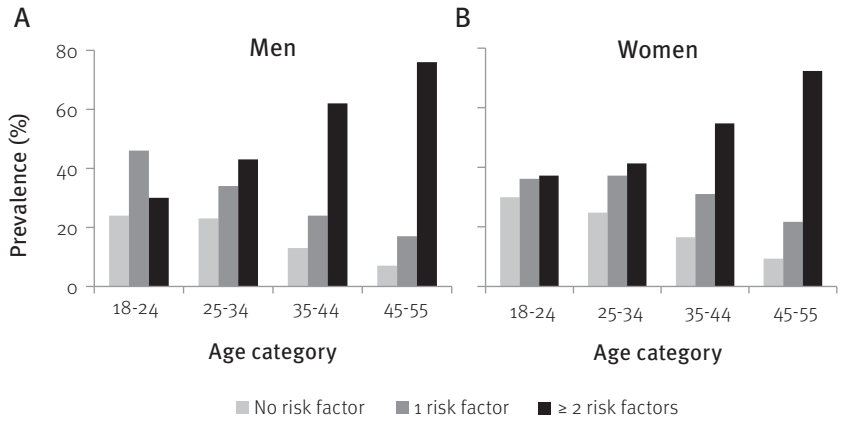

Figure 2 | Age-specific proportions of patients with traditional vascular risk factors, stratified by sex

Graphs show the prevalence of no, 1, or 2 or more traditional vascular risk factors in different age categories, for **(A)** men and **(B)** women. Traditional vascular risk factors that were considered were diabetes, hypertension, smoking, and hypercholesterolemia. Data are extracted from the SIFAP1 study.[73]

Cardiovascular prognosis

Mortality

Prognosis in terms of mortality was usually considered to be favorable in young patients with stroke, given the lower short-term mortality rates compared with older patients.[135] However, long-term follow-up studies in young patients found 5-year cumulative mortality ranging from 9-11%, while the 10-year cumulative risk of death ranged from 12-17%.[23, 26, 70, 136-138] In 30-day survivors of a young ischemic stroke, 20-year cumulative mortality was reported to be 27%, which is 4 times higher than that of individuals in the general population matched for age and sex.[23] As Figure 3 shows, excess mortality is present across all age groups of young patients with stroke, but especially in those over 35 years of age, in whom vascular risk factors are also highly prevalent.

In young adults who died during a 5-year[137] or a 20-year[23] follow-up period after stroke, vascular disease was the main cause of death. More than half of the deaths resulting from vascular disease were attributable to a vascular cause other than stroke. These findings suggest that the underlying (vascular) disease that caused stroke at a relatively young age continues to put these patients at an increased long-term risk of vascular disease.

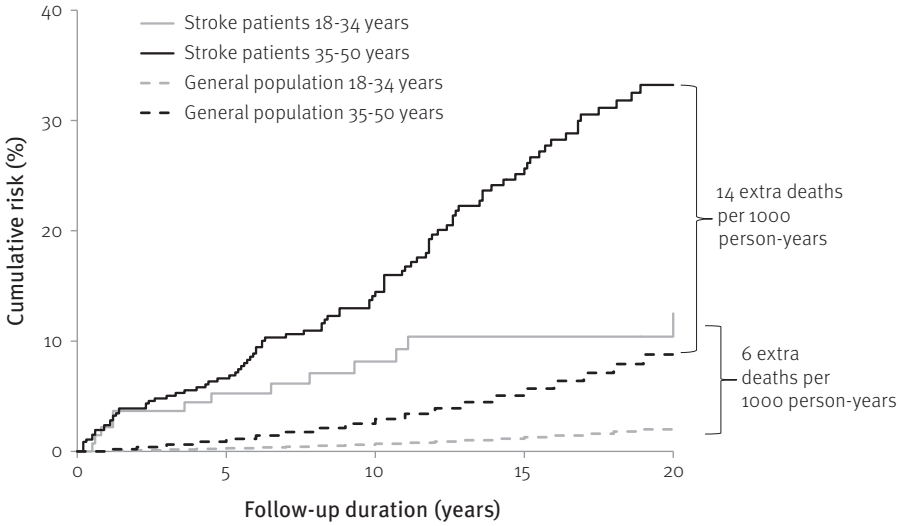

Figure 3 | Long-term cumulative mortality in young patients with stroke and the general population with similar age, sex and calendar-year characteristics

Figure shows the excess mortality of young patients with stroke, compared with the general population, stratified by age <35 years or ≥35 years. Based on data from the FUTURE study.[23]

Recurrent vascular events

In the first few years following a young stroke, patients are at a substantial risk of stroke recurrence (annual risk 1-3%)[24, 27, 29-31, 70] and, to a lesser extent, other cardiovascular vascular events (annual risk 0.5-1.0%).[24, 29, 31] In the decades that follow, the risk of recurrent events continues to be elevated, leading to a cumulative risk of 20% for recurrent stroke and 17% for other cardiovascular events.[24, 26, 29]

Identification of high-risk groups

High-risk groups in terms of recurrent mortality and cardiovascular events were identified on the basis of the TOAST classification.[79] The atherothrombotic stroke category was found to have the highest risk of mortality and recurrent stroke, compared with the other TOAST categories.[23, 24, 107, 139]

Risk factors that were associated with the highest 5-year risk of recurrent stroke predominantly included the traditional vascular risk factors, including age over 40 years, history of transient ischemic attack, type 1 diabetes, and the use of antihypertensive medication.[31] The studies available found that the risk of mortality[137, 138, 140] and recurrent vascular events[24, 31] increased in parallel with the number of traditional

cardiovascular risk factors present (Figure 4). Cardioembolic strokes were also associated with higher risks of mortality and recurrent vascular events.[23, 24]

Racial disparities in cardiovascular prognosis after young stroke have also been observed. In a short-term follow-up study of young stroke patients aged 18-45 years, black individuals had the highest 30-day risk of mortality: 10%, about 4 times the risk in Asians.[141] White individuals had an approximately 3.5-fold increased risk of 30-day mortality compared with Asians. These differences were independent of the presence of traditional vascular risk factors.

These findings indicate that prognosis in terms of long-term risk of cardiovascular disease after a young stroke is not as favorable as previously thought.[70, 136, 140, 142] Young patients with stroke, especially those who resemble older stroke patients with respect to the presence of traditional vascular risk factors and etiology, also seem to show similarity to older patients in terms of long-term cardiovascular mortality and disease.

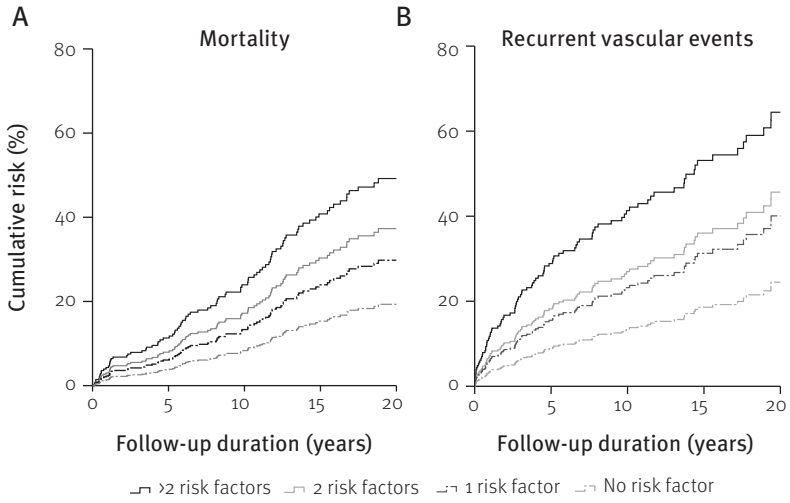

Figure 4 | Risk of death or recurrent vascular events, stratified by number of traditional vascular risk factors

Figure shows risk of **(A)** mortality and **(B)** recurrent vascular events, stratified by the number of risk factors present. Risks are adjusted for age and sex. Traditional vascular risk factors that were considered were diabetes, hypertension, smoking, and hypercholesterolemie. Based on data from the FUTURE study.[23, 24]

Of note, the prognosis for stroke patients in the 'other determined' category, which includes arterial dissection, seemed relatively favorable compared with the other categories.[24, 109, 139] However, one must keep in mind that this category includes a mixture of conditions, each with a different disease course and treatment options and, thus, variable prognoses.

Secondary prevention

Young patients with stroke are often under-represented in large secondary prevention trials on antiplatelet drugs, statins and blood pressure lowering agents.[107] Nonetheless, it is common practice to treat young stroke patients in accordance with guidelines based on extrapolated data from elderly patients with stroke.[143] This might be a sensible approach, given that a considerable proportion of these young patients have the risk factors that are targeted in these trials, and some of the trials showed greater benefits in younger individuals (under 65 years) than in the older ones (65 years or over).[144] These conclusions are, however, mainly based on *post hoc* analyses, as no studies were specifically designed to investigate secondary prevention strategies in young adults with stroke. Although no evidence exists that long-term secondary prevention is particularly harmful in young patients, the question of whether these long-term prevention strategies are truly beneficial in all young adults with stroke — for example, in those patients in whom no risk factor or presumed etiology could be found — remains to be answered. In addition, treatment strategies without proven benefit are not particularly cost-effective.

Secondary prevention strategies in some subgroups with a specific risk factor or etiology have been investigated in young adults, for example, those with PFO or anti-phospholipid syndrome. For a PFO, current evidence does not show superiority of closure, compared with medical treatment, in preventing recurrent strokes in adults under 60 years of age.[145] Two randomized controlled trials included *post hoc* subgroup analyses in patients aged 45 years or younger (approximately 45% of the study cohort), which showed no beneficial effects of closure in this subgroup.[146, 147] For patients with antiphospholipid syndrome, guidelines from the American Heart Association and American Stroke Association recommend treatment with oral anticoagulants, with an international normalized ratio (INR) between 2.0 and 3.0.[148] However, an expert panel could not reach consensus and noted that the evidence supporting higher or lower INR intensities or other strategies, such as antiplatelet therapy, was uniformly weak.[149]

To discover which patients will benefit the most from secondary prevention strategies, we suggest that recruitment of patients for future (multicenter) trials should be based on etiological subgroups rather than age, so that younger patients are not excluded.

Physical impairments and complications

The risk factors and etiology underlying a stroke have a substantial impact on cardiovascular mortality and morbidity. With respect to functional outcome and psychosocial consequences, however, the prognosis is more likely to be determined by a combination of factors, including not only etiology, but also stroke severity and subsequent cerebral damage, co morbidity, demands from the patient's environment, and the patient's coping strategies. The sections that follow provide an overview of prognosis in terms of physical problems (functional outcome, pain, and epilepsy) and psychosocial consequences (cognitive impairment, depression, anxiety, fatigue, sexual dysfunction, and return to work) after a young stroke.

Functional outcome

Neurological deficits due to a stroke are often registered during hospital admission and discharge, as a measure of stroke severity on the NIH Stroke Scale. However, as no studies have described these neurological deficits in the years after discharge, the frequency of neurological deficit over time is not known.

Functional outcome is assessed in terms of disability, most commonly with the modified Rankin Scale (mRS), a scale that predominantly assesses motor function. Using this scale, functional outcome is usually found to be better in younger than in older adults after short-term follow-up.[150] For young adults, however, information on long-term physical disability is equally important, because of their long life expectancy. Only a few studies have reported long-term functional outcomes after young ischemic stroke. Proportions of individuals with poor functional outcome (mRS score >2) among young stroke survivors range from 6-20% after a mean follow-up duration of 3-12 years,[26, 142, 151, 152] compared with 40% after short-term follow-up in older stroke survivors.[153]

Independence with regard to basic activities of daily living may not necessarily mean a good outcome for young patients: the ability to live independently as a young adult also requires independence in performing more complex tasks. In addition, demands from society on these young patients might be higher than in the elderly, because of occupational obligations and, in many cases, their role as a caregiver for a young family. The studies performed to date have not addressed these issues. Moreover, one must keep in mind that young stroke survivors with a poor functional outcome have to cope with this consequence for a considerable number of years, given their generally long life expectancy.

Epilepsy

Post-stroke epilepsy is reported to affect 2.4-14.4% of young patients with ischemic stroke.[26, 29, 142, 154-156] The highest prevalence was found in a study that included patients

aged 50 years and under;[156] most other studies only included patients up to 45 years of age. The lowest prevalence was found in a study that only included cryptogenic stroke.[154] Factors that were associated with epilepsy, either with or without recurrent seizures, included a more severe stroke and involvement of cortical structures.[29, 156] A study with a decade of follow-up revealed a long-term association between post-stroke epilepsy and a poor functional outcome, as measured with the mRS.[152]

Pain

The prevalence of post-stroke pain has frequently been studied in the older stroke population, and estimates vary considerably, from as low as 1% to as high as almost 50%.[157-160] This broad range is probably explained by the wide variation in methods used to assess post-stroke pain. Moreover, post-stroke pain originates from multiple sources, including central pain from both thalamic and extrathalamic lesions, and peripheral pain from musculoskeletal abnormalities, such as joint contractures.[157] No studies have specifically addressed the prevalence of pain after stroke in young adults. A recent report suggested a link between post-stroke pain and increased mortality in young patients with stroke.[161]

Psychosocial consequences

Cognitive impairment

Cognitive performance is an important determinant of social functioning in a young patient with stroke.[162] One year after stroke, up to 60% of young stroke patients had impaired cognitive performance compared with stroke-free controls, depending on the cognitive domain tested.[15, 16] In younger patients in particular, cognitive recovery is likely to continue beyond one year after stroke. However, one study reported that after a mean follow-up of 11 years, 50% of young patients with stroke still had to cope with impairment or below average performance on at least one cognitive domain.[163] Elderly patients with stroke commonly exhibit prominent frontal executive impairment,[5] whereas young patients generally show deficits in multiple cognitive domains, including visuo-construction, delayed verbal memory, attention, and executive function. Most of these deficits are especially pronounced in patients with left-hemispheric lesions, with the exception of visuoconstruction, which seems to be more impaired after right-hemispheric strokes.[163] These findings suggest that cognitive impairment in young patients with stroke displays a more global pattern than one would expect on the basis of a focal lesion,[163] perhaps as a result of diffuse network dysfunction remote from the site of the lesion.[163, 164]

Aphasia has not been specifically tested in long-term follow-up studies.[163] One study that assessed language disturbances in the subacute phase after stroke found

that young patients (under 51 years) were prone to non-fluent aphasia, whereas older patients were more likely to exhibit fluent aphasia, probably owing to a higher proportion of posterior infarcts in the older age group.[165]

Cognitive impairment can have life-changing consequences for young adults. For example, return to work may be impaired due to memory problems.[71] A short-term follow-up study found that the number of cognitive deficits predicted later inability to return to work.[166] This is not a surprising finding, as disturbances in multiple domains might interact, thereby diminishing the ability to compensate for impairments. For example, visual field defects can lead to reading disorders, and alexia could exaggerate this effect.[167]

Depression

Depressive symptoms are present in 28-46% of young patients with stroke[70, 71, 168] after follow-up durations of 6-12 years. Depressive symptoms can have a large impact on recovery and daily life after stroke. These symptoms have been associated with poor functional outcome in an unadjusted analysis, but this association might have been confounded, for example, by recurrent vascular events.[71]

Patients with stroke were also found to have an increased risk of suicide (up to 7%), or suicidal ideations (6-15%) in both the acute and the chronic phase, especially when patients had current or past mood disorders.[169, 170] Young adults seemed to be at particular risk.[170]

In one study conducted in the general population, younger individuals tended to be classified as having a 'non-vascular depression' profile, which was characterized by a higher risk of suicide and more psychotic features, whereas older individuals more often displayed a 'vascular depression' profile, with a higher prevalence of functional disability and anhedonia.[171] The small study sample resulted in large confidence intervals, and the findings need further confirmation in large stroke cohorts. One might expect that the proportions of vascular and non-vascular depression profiles would not differ markedly between young and older patients in a stroke cohort, since both age groups have vascular lesions. However, elderly individuals might still exhibit a greater propensity towards a vascular depression profile owing to accumulation of vascular damage with age.

Depressive symptoms should not be confused with emotionalism (that is, emotional expressions outside a patient's normal control), which was reported in 22.5% of the general stroke population the first month post-stroke.[172] Although the 2 conditions co-occurred in 1 patient, and depressed mood was more likely to be present in patients with emotionalism, most patients with emotionalism were found not to be depressed. No studies on emotionalism versus depression have been conducted specifically in young patients with stroke.

Anxiety

Anxiety is present in 19% of patients with young ischemic stroke after 12 years of follow-up,[71] but no studies exist on its influence on daily life.

Fatigue

Post-stroke fatigue is present in about 50% of young patients with stroke,[173] and seems to be associated with poor functional outcome[173] and inability to regain pre-stroke activities.[174, 175] However, most of the studies that assessed this complaint were limited with respect to sample size[175] or follow-up duration.[174, 175]

Some short-term follow-up studies in older stroke patients found fatigue to be associated with certain lesion locations.[176, 177] In young patients with stroke, however, fatigue could be the result of an imbalance between demands from society and reduced cognitive or physical capacity after stroke. Moreover, factors that underlie fatigue in the short term after stroke may differ from those in the long term, but these factors remain to be clarified.

Sexual dysfunction

One short-term follow-up study on sexual dysfunction, focusing on young patients with stroke (aged 18-45 years), found diminished sexual function in 22.5% of patients.[155] In the general stroke population, sexual dysfunction is caused by multiple factors, varying from neurological deficits (for example, hemisensory neglect[178] or aphasia) to psychological problems such as depression.[179] The relative contributions and long-term effects of the various factors in a young stroke population are unknown.

Hypersexuality may also be an issue after a young stroke. One study found this problem in just 1 of 71 young stroke patients, which may have been an underestimation, as the opinion of the patients' partners was not investigated.[155] Hypersexuality is thought to result from disinhibition due to lesions in the frontostriatal circuits, and also in the temporal lobe after ischemic stroke.[180]

Return to work

Return to work after young stroke is an important determinant of life satisfaction,[181, 182] and might even be a necessity for many people to provide for themselves. In addition to the personal implications for patients, inability to return to work after stroke imposes an economic burden on society as a whole, owing to loss of productive years of employment.[183] However, only a few studies have addressed this important subject.

Reports to date indicate that 50-80% of stroke patients returned to work after a maximum follow-up of 4 years.[175, 184-187] However, most young patients with stroke will be of vocational age for more than a decade of their remaining life, which stresses the need for further studies on the very long-term prognosis with respect to return to work. In one study with a follow-up of almost 12 years,[71] only 40% of patients had

returned to full-time employment by the end of the study period. However, these data must be regarded with caution, since the study was retrospective with a relatively low response rate.

Screening and treatment

Cognitive impairment, mood disorders, and fatigue seem to be very common in young patients with stroke, and functional outcome is poor in a substantial proportion of these young adults. If not actively screened for, these consequences often go unnoticed by caregivers, possibly leading to frustration in young patients when they are not able to return to their pre-stroke activities.[188] The first step in treatment of these 'invisible' psychosocial issues, therefore, is their recognition.

The next step is to start treatment for these symptoms. The current treatment strategies, which are suboptimal, consist primarily of occupational therapy[189] or medical treatment, for example, with antidepressants.[190, 191]

Directions for future research

Currently, only limited data exist on long-term psychosocial consequences and their impact on daily life functioning after stroke in young adults. Future studies should focus on the influence of these psychosocial factors on daily life and try to find clinical and demographic factors that can predict future psychosocial effects. Large, prospective cohort studies are needed for this purpose. These predictors might, in turn, provide insight into the pathophysiological mechanisms that underlie these psychosocial consequences, although imaging studies, postmortem studies or animal models would provide us with more fundamental insights.

In addition, treatment strategies should be developed, and their effects quantified, in clinical trials. Individuals who experience a stroke at a younger age have different rehabilitation goals from their older counterparts,[188] and specific programs need to be developed that are adjusted to the specific needs of these young patients.

Conclusions and recommendations

In the past, stroke in individuals under 50 years of age ('young stroke') has been viewed as a disease with different risk factors and etiology — and usually a better prognosis — in comparison with stroke in older patients. After a critical review of the available literature, however, this view may be challenged.

Traditional vascular risk factors in young adults with stroke have been somewhat neglected in the literature, which seems unjustified given their high prevalence,[107]

especially in young patients between 35 and 50 years of age. This high prevalence coincides with a rising incidence of stroke in young adults, suggesting that traditional vascular risk factors might contribute more to the etiology of young stroke than was previously thought. The presence of these risk factors, however, is not always related to causal etiologies such as large-artery atherosclerosis, as assessed with current diagnostic tools.

Young patients with stroke are at increased risk of cardiovascular mortality and morbidity compared with the general population, sometimes even approaching the risks observed in the older stroke population. The patients whose condition is classified as atherothrombotic stroke, with highly prevalent traditional risk factors, have the highest risk. In these patients, lifelong treatment with secondary prevention seems to be a plausible approach. However, further trials are needed to establish which patients will benefit from different forms of secondary prevention. Recruitment of patients for these trials should be based on etiological subgroups rather than age.

Although many 'young' stroke patients are 'old' with respect to etiology and prognosis, they are 'young' when psychosocial consequences come into play, as most patients have a life expectancy of decades that includes phases of their lives in which important life-changing decisions have to be made. To fulfil these needs, treatment strategies tailored to the needs of young patients must be developed.

Stroke in young adults is an acute disease, but its lifelong consequences are becoming increasingly recognized. Treatment and guidance, accompanied by a lifelong perspective, should be offered to each young stroke survivor in order to attain the highest possible quality of post-stroke life.

II

Part

Long-term cognitive outcome after ischemic stroke in young adults

4

Chapter

Long-term cognitive impairment after first-ever ischemic stroke in young adults

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Long-term cognitive impairment after first-ever ischemic stroke in young adults.

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Abstract

Background and objective

Up to 14% of all ischemic strokes occur in young adults (≤ 50 years). Post-stroke cognitive performance is a decisive determinant of their quality of life. However, virtually no studies report on cognition after young stroke, especially not on the long-term. This long-term perspective is important since young patients have a long life expectancy during which they start forming a family, have an active social life and make decisive career moves. We aimed to evaluate the long-term cognitive outcome.

Methods

All consecutive patients between January 1, 1980 and November 1, 2010 with a first-ever young ischemic stroke were recruited for cognitive assessment, using a matched stroke-free population as a reference. Composite Z-scores for seven cognitive domains were calculated and the ANCOVA model was used (Bonferroni correction). A below average performance was defined as >1.0 SD below the age-adjusted mean of the controls and cognitive impairment as >1.5SD.

Results

277 patients and 146 matched controls completed cognitive assessment (mean follow-up = 11.0 years, SD 8.2; age = 50.9 years, SD 10.3). Long-term cognitive outcome after an ischemic stroke was worse in most cognitive domains compared with a non-stroke population. Up to 50% of the patients had a below average performance or cognitive impairment. Deficits in processing speed, working memory, and attention were most common.

Conclusion

Even eleven years after ischemic stroke in young adults, a substantial proportion of patients must cope with permanent cognitive deficits. These results have implications for information given to patients and rehabilitation services.

Introduction

Approximately 10% to 14% of all ischemic strokes occur in young adults (aged 18-50).[8-13, 192] The incidence of stroke in young adults is rising, which is a major concern.[14] Their outcome is usually considered fairly good, since these patients usually have a good motor recovery,[142, 193] and outcome after stroke is usually assessed with rating scales that predominantly measure motor performance.[194] However, post-stroke outcome is also very much dependent on cognitive performance after stroke. Surprisingly, there are only a few studies that addressed cognitive outcome on the short-term (4-12 months)[15, 16] and none on the long-term. Although these short-term studies found somewhat lower cognitive performance in ischemic stroke patients compared with controls, that may still very well be compatible with the common observation of gradual cognitive recovery, that may continue for at least one year or longer after stroke.[17, 195]

Since life expectancy of most of these patients exceeds by far one year,[137] patients need to be informed about their cognitive prognosis, not only on the short-term, but particularly for the coming decades as they are in a period of life in which they start forming a family, have an active social life, and make decisive career moves. It is exactly this long term perspective that is currently missing. The aim of the present study was to investigate the long-term cognitive performance after a first-ever young ischemic stroke.

Patients and methods

Study design

This study is part of the "*F*ollow-*U*p of *T*ransient ischemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation" (*FUTURE*) study, a large cohort study which investigates causes and consequences of stroke in young adults.[25] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and the recruitment of controls.

The present study comprises all consecutive patients with a first-ever ischemic stroke of presumed arterial origin, aged 18-50 years, admitted to Radboud University Medical Centre from January 1, 1980, until November 1, 2010. This hospital is a large academic center, receiving patients from both the direct environment as well as serving as a tertiary referral center. Our hospital is the only academic medical center in our region. Patients were identified through a prospective registry of all consecutive young ischemic stroke patients that has been kept at the department since the 1970s with a standardized collection of baseline, clinical characteristics, and neurological exam. Ischemic stroke was defined as focal neurologic deficit persisting more than 24 hours.

The diagnosis of ischemic stroke and lesion location were based on medical records and radiological findings.
The diagnostic techniques has been improved during a 30-year period and to minimize bias all initial diagnoses were reviewed by a panel of two experts from a pool of four (FEdL, EvD, RA, LJD) and in cases of disagreement a consensus meeting was held to adjudicate the event.
Primary exclusion criteria for ischemic stroke patients in the FUTURE study were cerebral venous sinus thrombosis and retinal infarction. There were additional exclusion criteria for cognitive assessment based on the neurological exam, which was also a part of the FUTURE study (Figure 1).
Controls were recruited among patients' spouses, relatives, or social environment. They had to be at least 18 years old without a history of TIA or stroke. The control group and patient group were matched for age, sex, and level of education. Controls were all living independently, none fulfilled the clinical criteria of dementia. They were recruited from the same environment as patients. Written informed consent was obtained from all participants.

Cognitive assessment

Neuropsychological tests were administered between November 2009 and end 2011. They covered the main cognitive domains and these tests have been previously applied in large-scale epidemiological studies of cerebrovascular disease.[42, 43] Strict instruction protocols were used to assess cognitive performance and researchers were trained. The following cognitive domains were examined: *Processing speed* (the written administration of the Symbol-Digit Modalities Test, Abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure [ROCF] – Copy trial), *Working memory* (Paper and Pencil Memory Scanning Task [PPMST]), *Immediate memory* (ROCF – Immediate recall and the total number of words immediately recalled in the three-trial version of the Rey Auditory Verbal Learning Test [RAVLT]), *Delayed memory* (delayed recall on the ROCF and the RAVLT), *Attention* (Verbal Series Attention Task [VSAT], and *Executive functioning* (Verbal Fluency and Stroop Interference). To account for speed-accuracy trade-off on the Stroop test, PPMST, and VSAT, composite scores were calculated [accuracy(%)/reaction time].[196] Stroop Interference was computed by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II. To prevent potential bias in scoring the ROCF, two researchers independently rated 10% of the complex figures in both patients and controls, with high inter-rater reliability using the Spearman's correlation coefficients (Copy: r_s=0.90; Immediate recall: r_s=0.97; Delayed recall r_s=0.95). Detailed information on the neuropsychological examination is described extensively elsewhere.[25]

Other measurements

Age, sex, level of education, depressive symptoms, and fatigue were considered possible confounders. Level of education was scored with a Dutch scoring system (1=less than primary school; 7=university degree).[197]

Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS),[55] and fatigue was assessed using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[61, 198]

Marital status (married, divorced, widowed, and never married) at follow-up was reported. Employment status at follow-up was defined as the number of patients who worked/studied at the time of their event and were unemployed, still employed, or retired at follow-up assessment. Employment status of controls was defined as employed, unemployed, and retired at follow-up assessment. Functional outcome during follow-up visit was evaluated using the Barthel Index[199] and modified Rankin Scale (mRS).[194] A good functional outcome was defined as an mRS score of 0-1 and a Barthel Index of ≥85.[200]

Furthermore, assessment of both the etiology (TOAST)[7] and severity (National Institutes of Health Stroke Scale; NIHSS)[201] was performed retrospectively in all cases using a validated approach,[33, 202] because these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event.

We assessed vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking (current/former/never), current alcohol use (>2 units/day)), and vascular disease (myocardial infarction and recurrent stroke) on the basis of medical history using a standardized, structured questionnaire and/or the use of medication. Whenever a myocardial infarction or recurrent stroke was suspected information retrieved was verified and adjudicated by physicians. The Body-mass index (BMI) at follow-up was calculated as weight (kilograms) divided by height (meters) squared.

Statistical analysis

Baseline characteristics were presented as means (±SD), median (Q1-Q3), or number of cases (%). All statistical analyses were performed with SPSS 20.0 software for Windows. Baseline characteristics in young ischemic stroke participants and ischemic stroke patients who refused cognitive assessment were compared using a Pearson's chi-square test, Mann-Whitney *U* test, or Student's *t*-test when appropriate. To adjust for multiple comparisons in all analyses a Bonferroni correction was applied (p-values <0.0071 were considered significant, since there were seven pairwise comparisons for each analysis)

The mean raw cognitive test scores (±SD) for each test were calculated. The Rey Complex Figure – Copy trial showed a left skewed distribution, therefore this variable was transformed (e^5) to obtain a normal distribution to use in all subsequent analyses.[203] For the purpose of data reduction, across-domain comparison, and statistical considerations,

raw test scores were converted to Z-scores, using the mean and standard deviation of the controls. Z-scores of tests assigned to the same cognitive domain were averaged and were used in all subsequent analyses as composite Z-score, or domain score. If one test of a particular domain was missing, the domain score was occasionally based on the remaining tests of that domain (always<5.1%).
An one-way ANCOVA model was used for each cognitive domain with a two-level factor adjusting for age, sex, level of education, depressive symptoms, and fatigue severity. All p-values reported were two-sided and confidence intervals were calculated at the 95% CI.
Linear regression was used to explore the effect of differences in follow-up duration and performance on cognitive domains adjusting for age, sex, level of education, depressive symptoms, and fatigue. Results were reported as standardized beta coefficients.

Below average performance and cognitive impairment

Due to the long-term follow-up patients differed in age at follow-up cognitive assessment. Obviously, age has an influence on cognitive performance apart from stroke.[204] To account for differences in age, age-adjusted Z-scores for each neuropsychological test were calculated using the mean and SD of the controls in three different strata of age at follow up: 20-40, 40-60 and 60-80 years. Next, Z-scores of cognitive tests assigned to the same cognitive domain were averaged.
The frequency of a below average performance (>1.0SD below age-adjusted mean of controls) and cognitive impairment (>1.5SD) was determined.[5]
A Pearson's chi-square test (or Fisher's exact test when an expected cell count was less than five) was used to investigate differences between patients and controls in the proportion of participants with cognitive impairment

Lesion location and cognitive outcome

The frequency of cognitive impairment or a below average performance for each cognitive domain in patients with supratentorial infarction (left vs. right) and infratentorial infarction was determined. The proportion of patients with cognitive impairments were compared with controls using a Pearson's chi-square test (or Fisher's exact test when an expected cell count was less than five).

Recurrent stroke

All above described analyses were conducted including and excluding patients with a recurrent stroke to investigate whether patients with recurrent events influenced the results.

Results

The study population consisted of 277 ischemic stroke participants and 146 controls (Figure 1).

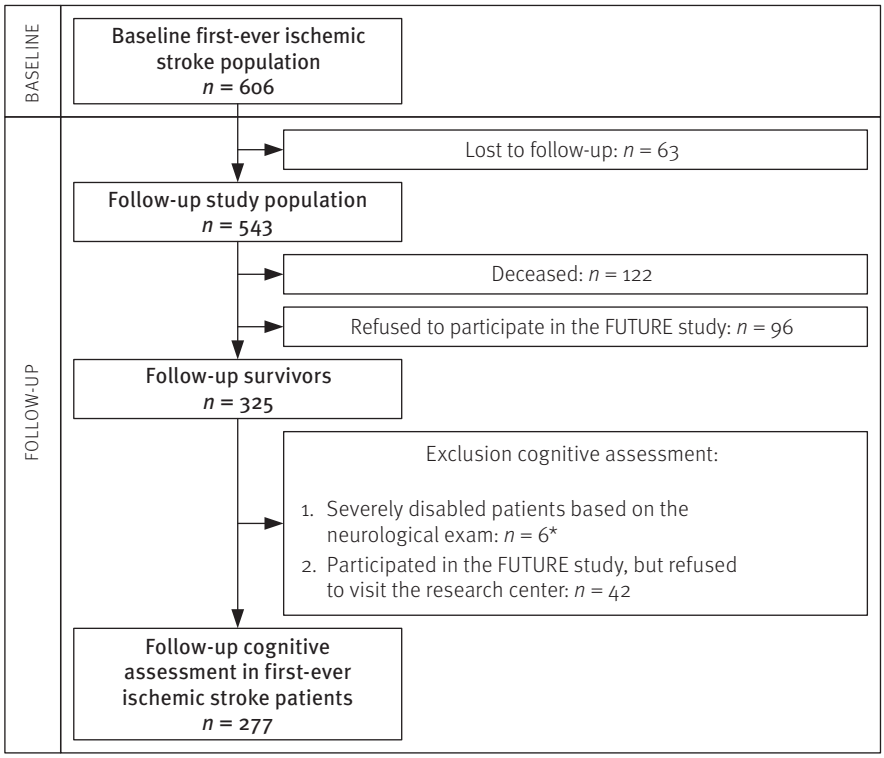

Figure 1 | Flowchart of the study population

*Severe psychiatric disorder (n=1), inability to communicate in Dutch (n=1), blind and deaf (n=1), severe fatigue (n=1), severe aphasia (only sounds), bilateral hemianopia (n=1), and severe physical disabilities (n=1).

Basic demographic and clinical characteristics of the study population are described in Table 1 and neuropsychological test scores are presented in Table 2.
Mean age of patients was 40.0 years (SD 7.7) at stroke onset; 55.6% was female. Mean follow-up of the study population was 11.0 years (SD 8.2), while 48.0% had a follow-up of ten years or longer. Participants did not significantly differ on basic demographical and clinical characteristics from ischemic stroke patients who refused

Table 1 | Demographic and clinical characteristics of the study population and ischemic stroke patients who refused cognitive assessment

	Ischemic stroke participants	Refusals[b]	p-value[c]	Controls
No.	277	138		146
Age at index event, mean (SD), y	40.0 (7.7)	40.1 (8.0)	0.84	
Men, No. (%)	123 (44.4)	59 (42.8)	0.75	61 (41.8)
Follow-up duration, mean (SD), y	11.0 (8.2)			
<10 years, No. (%)	144 (51.9)			
≥10 years, No. (%)	133 (48.0)			
Age at follow-up examination, mean (SD), y	50.9 (10.3)			48.6 (11.7)
Education, median (Q1-Q3)	5 (4-6)			5 (5-6)
NIHSS score at admission, median (Q1-Q3)	4 (2-8)	4 (2-7.75)	0.79	
Barthel Index at follow-up, mean (SD)	96.9 (9.7)			99.6 (1.5)
Good outcome (BI ≥85), No. (%)	262 (94.6)			146 (100)
modified Rankin Scale at follow-up, median (Q1-Q3)	1 (1-2)			0 (0-0)
Good outcome (mRS 0-1), No. (%)	191 (69.0)			139 (95.2)
MMSE at follow-up, mean (SD)	26.3 (2.6)			27.2 (1.9)
HADS - depressive symptoms, mean (SD)	4.0 (3.6)			2.5 (2.7)
CIS-20R - fatigue severity, mean (SD)	30.3 (13.9)			22.5 (12.8)
Marital status at follow-up				
Married, No. (%)	180 (65.7)			97 (66.4)
Widowed, No. (%)	5 (1.8)			4 (2.7)
Divorced, No. (%)	22 (8.0)			6 (4.1)
Never married, No. (%)	67 (24.5)			39 (26.7)
Employment status at follow-up[a]				
Working, No. (%)	120 (51.9)			101 (70.1.2)
Unemployed, No. (%)	94 (40.7)			35 (24.3)
Retired, No. (%)	17 (7.4)			8 (5.6)

TOAST			0.21	
Large-artery atherosclerosis, No. (%)	66 (23.8)	42 (30.4)		
Cardiac source of embolism, No. (%)	26 (9.4)	10 (7.25)		
Small-vessel occlusion (lacune), No. (%)	38 (13.7)	16 (11.6)		
Stroke of other determined etiology, No. (%)	47 (17.0)	33 (23.9)		
Multiple etiologies, No. (%)	7 (2.5)	3 (2.2)		
Stroke of undetermined etiology, No. (%)	93 (33.6)	24 (24.6)		
Vascular medical history				
Myocardial infarction, No. (%)	16 (5.8)			3 (2.1)
Recurrent stroke, No. (%)	30 (10.8)			
Vascular risk factors				
Hypertension, No. (%)	150 (54.2)			44(30.1)
Diabetes mellitus, No. (%)	34 (12.3)			6 (4.1)
Dyslipidemia, No. (%)	185 (66.8)			26 (17.8)
BMI at follow-up, mean (SD)	26.9 (5.1)			26.9 (4.7)
Smoking, No. (%)				
Current	78 (28.2)			38 (26.0)
Ex-smoker	129 (46.6)			55 (37.7)
Never	70 (25.3)			53 (36.3)
Alcohol (>2 units/day), No. (%)	19 (6.9)			14 (9.6)

NIHSS=National Institutes of Health Stroke Scale, MMSE=Mini-Mental State Examination, HADS=Hospital Anxiety and Depression Scale, CIS-20R=Checklist Individual Strength, TOAST=Trial of Org 10172 in Acute Stroke Treatment. Missing data in ischemic stroke participants: Lesion location=0.4%, education=1.1%, NIHSS at admission=0.7%, marital status=1.1%, employment status: 2.5%. MMSE=2.9%, HADS depression=1.1%, CIS-20R=1.1%, BMI=3.2%, alcohol=0.4%. Missing in the control group: employment status=1.4%, BMI=1.4%. Missing in the refusals: NIHSS at admission=1.4%.

[a] The proportion of ischemic stroke patients with baseline employment (n=231) and who were unemployed, still employed, or retired at follow-up. Controls: employment status at follow-up.

[b] Ischemic stroke patients who refused to participate in the FUTURE study (n=96) + patients who participated in the FUTURE study, but refused to visit the research center (n=42).

[c] Comparison between ischemic stroke participants and those who refused cognitive assessment.

Table 2 | Neuropsychological test scores of patients with a previous young stroke and controls

Cognitive domain & test	Ischemic stroke	Controls
Processing speed, mean (SD)		
SDMT	42.6 (13.7)	53.3 (10.2)
Stroop part I[a]	4.0 (1.1)	4.7 (0.8)
Stroop part II[a]	3.2 (0.9)	3.7 (0.6)
Visuoconstruction, mean (SD)		
ROCF copy	30.7 (5.4)	32.4 (2.8)
Memory, mean (SD)		
Working memory		
PPMST "%"[a]	2.8 (1.0)	3.6 (0.8)
PPMST "S"[a]	2.4 (0.8)	3.1 (0.7)
PPMST "MP"[a]	1.6 (0.5)	2.0 (0.5)
PPMST "DHN"[a]	1.3 (0.4)	1.6 (0.4)
Immediate memory		
RAVLT trial 1-3	18.3 (6.3)	22.1 (6.1)
ROCF immediate recall	16.4 (6.5)	18.3 (5.8)
Delayed memory		
RAVLT delayed recall	5.3 (2.8)	6.9 (2.8)
ROCF delayed recall	15.8 (6.3)	18.0 (5.7)
Attention, mean (SD)		
VSAT score[a]	1.2 (0.5)	1.5 (0.4)
Executive functioning, mean (SD)		
Verbal fluency	21.3 (6.8)	24.4 (5.8)
Interference[a]	0.51 (0.1)	0.56 (0.1)

SDMT = Symbol-Digit Modalities Test, ROCF = Rey-Osterrieth Complex Figure, PPMST = Paper & Pencil Memory Scanning Test, RAVLT = Rey Auditory Verbal Learning Test, VSAT = Verbal Series Attention Test.
[a] Speed-accuracy composite score. Higher scores indicate better performance on all measures.

to participate or who did participate in the FUTURE-study but did not want to visit the research center (Table 1).

Ischemic stroke patients had a worse cognitive performance on six cognitive domains after a mean follow-up of 11 years compared with controls (processing speed: $F(1,406)=35.4$, $p<0.0001$; working memory: $F(1,407)=41.7$, $p<0.0001$; immediate memory: $F(1,412)=14.0$, $p=0.0002$; delayed memory: $F(1,408)=17.7$, $p<0.0001$;

attention: F(1,396)=28.6, p<0.0001; executive functioning: F(1,409)=17.2, p<0.0001) (Figure 2).

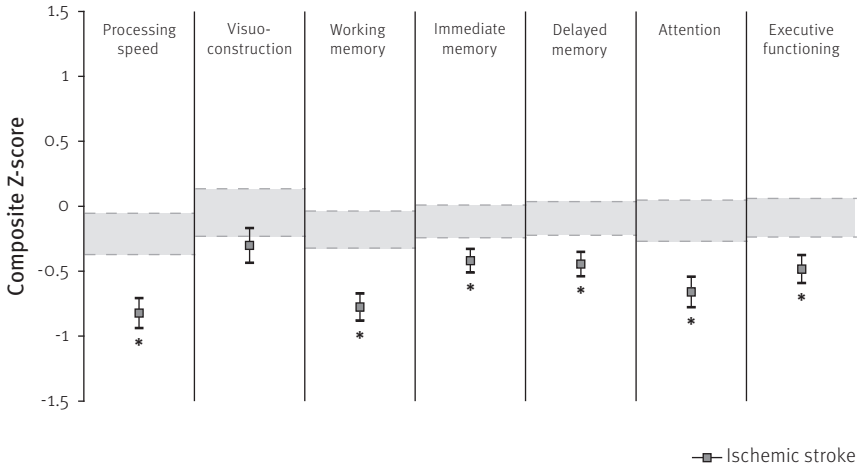

Figure 2 | Cognitive performance about 11 years after first-ever ischemic stroke in young adults compared with controls

Adjusted mean composite Z-score (95% CI) per cognitive domain (adjusted for age, sex, education, depressive symptoms, and fatigue). Gray band represents the 95% CI of the adjusted mean composite Z-score of controls. Missing values in different domains: 0.7-6.5%. No missing values in the control group.

* Denotes a significant difference between ischemic stroke patients and controls. p-value ‹0.0071 was considered significant.

Follow-up duration

In ischemic stroke patients longer follow-up duration was associated with a lower immediate memory (β=-0.23, p=0.001), delayed memory (β=-0.30 , p<0.0001), and executive functioning score (β=-0.22, p=0.004).

Below average performance and cognitive impairment

Ischemic stroke patients showed a substantial higher proportion of patients with a below average performance (›1.0 SD below the mean composite Z-score of controls) or cognitive impairment (>1.5 SD) compared with controls (Figure 3A). Up to 50% of all ischemic stroke patients had a below average performance or cognitive impairment. Cognitive impairments were frequent among patients, affecting up to 34.8%. Deficits in processing speed, working memory, and attention were most common.

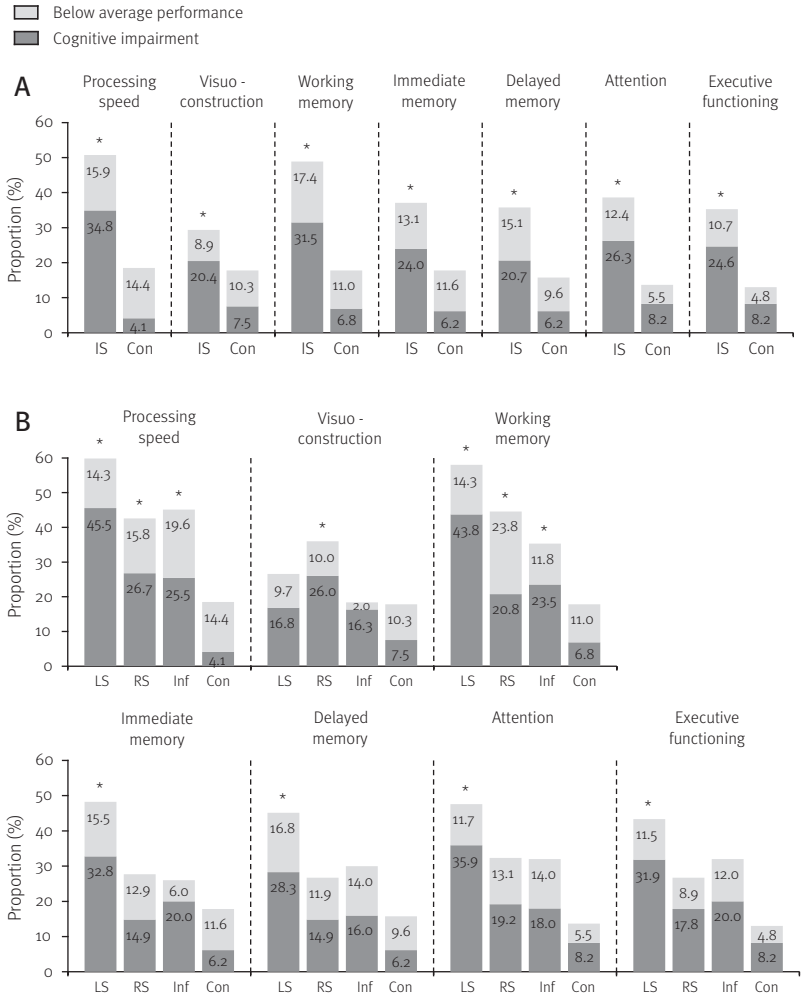

Figure 3 | The prevalence of long-term cognitive impairment or a below average performance in ischemic stroke patients and controls

The proportion (%) of ischemic stroke patients and controls with a below average performance (composite Z-score >1.0SD below the age-adjusted mean of controls) or a cognitive impairment (>1.5SD) about 11 years after stroke **(3A)**. The relationship between lesion location and the proportion of patients with a below average performance or a cognitive impairment compared with controls **(3B)**. IS=Ischemic stroke, Con=Control group, LS=left supratentorial ischemic stroke, RS=right supratentorial ischemic stroke, Inf=Infratentorial ischemic stroke.
*Denotes a significantly higher proportion of patients with cognitive impairment compared with controls. *P*-value <0.0071 was considered significant.

Lesion location and cognitive outcome

One patient could not be classified as supratentorial or infratentorial infarction (infarction in basal ganglia or brainstem). Seven patients with bilateral supratentorial infarction were excluded from the analyses since the number of patients was too small for further analyses. The results showed that patients with a left supratentorial infarction had the worst cognitive outcome, up to 45.5% of patients had cognitive impairments on the long-term (Figure 3B).

Recurrent stroke

After excluding patients with a recurrent stroke (n=30), there was no longer a significant negative relation between follow-up duration and executive functioning score in ischemic stroke patients.

Discussion

This study showed that a substantial proportion of young ischemic stroke patients after a mean follow-up of eleven years showed a worse cognitive performance on a wide range of cognitive domains compared with a matched stroke-free population. Patients with a left surpratentorial infarction had the worst cognitive outcome.

Strong elements of our study include a large sample size in a single center, with a high response rate.[15, 16] We used extensive neuropsychological testing rather than a short cognitive screen and we included a representative control group as a reference for neuropsychological examination.

However, some methodological issues need to be addressed. First, the study was not community-based, but hospital-based and therefore our sample may not represent all young stroke survivors in general. However, we believe that our stroke population is representative to the wider Dutch stroke population. Those who survive usually visit a university medical center during the course of their disease. Furthermore, the age- and sex- standardized prevalence of stroke in our region equals that of the age- and sex- standardized prevalence of stroke in the Netherlands.[205] We therefore believe that our cohort has a good external validity. This is also underlined by the fact that we included all consecutive cases admitted to our hospital.

Second, cognitive data of patients who refused to participate obviously was lacking, but their baseline characteristics did not differ from participants in the present study, making a selection bias unlikely.

Although we investigated a wide range of cognitive domains, agnosia or language comprehension[15] were not included in our neuropsychological assessment. Based on the neurological exam we considered the proportion of patients with these symptoms to be small and therefore we believe that this has not largely influenced cognitive performance.

We found relatively low MMSE scores in both the patients and the controls, compared with others[15] and healthy older adults.[206] However, all controls lived independently and none fulfilled the clinical criteria for dementia. Furthermore, the diagnostic accuracy of the MMSE in detecting cognitive impairment is generally poor, especially outside the Alzheimer domain.[207] Hence, we believe this finding is of little clinical relevance.

Longer follow-up, adjusted for age effects, was associated with a decrease in cognitive functioning in ischemic stroke patients. Longer time interval might be associated with incident co morbidity that could in turn have negatively affected cognitive performance. Another explanation is that these patients are older and that, apart from the stroke, neurodegenerative pathology might have emerged that interacts with the cerebrovascular disease.[208] A better understanding of this interaction is important as especially those with the longest follow-up are the oldest patients who might be at risk for further cognitive decline, due to this interaction of vascular lesions and neurodegenerative pathology.

Two studies have investigated cognitive performance in 24[16] and 40[15] young ischemic stroke patients 4-12 months after stroke. Malm and colleagues[16] examined 24 patients with cerebellar infarcts and cognitive domains most affected were mental speed, cognitive flexibility, and working memory. We also found that an infratentorial infarction was associated with impairments in processing speed and working memory. Cao and colleagues[15] investigated 40 young ischemic stroke patients and assessed other domains and found language comprehension, reasoning and verbal memory to be most affected. Processing speed was not assessed in these patients.[15] Comparing our results with these two studies we found similar deficits in verbal memory, working memory and processing speed, but also deficits in executive functioning and attention are common on the long-term in ischemic stroke patients. These two domains were not addressed in the reported studies.[15, 16]

A substantial proportion up to 50% of young ischemic stroke patients had a below average cognitive performance or impairment, despite the fact that the median of initial stroke severity was relatively mild. This highlights the influence of cerebrovascular lesions on cognitive performance, even decades after the stroke. It could also be that a severity rating scale, which includes predominantly motor signs (NIHSS), may underestimate the effect of stroke on other than motor symptoms. This would justify a basic careful neuropsychological examination of stroke patients in the (sub)acute phase of the disease.

Interestingly, a focal stroke on the long-term seems to have a widespread impact on cognition, affecting multiple cognitive domains. Increasing evidence suggests that focal lesions can have a widespread, diffuse impact on brain network organization,[164] which may explain the cognitive impairments attributable to dysfunction of the brain, remote from the site of the infarction.[209]

It appears that stroke in young adults seems to have a relatively better cognitive prognosis as compared with stroke in the elderly, as we found cognitive deficits in 20.4-34.8% of our young ischemic stroke patients, whereas 31-77%[210] was reported in elderly stroke survivors. This difference in cognitive prognosis is perhaps due to a better collateral blood supply with an attendant lower volume of the infarction, a more pronounced neuronal plasticity and the absence of neurodegenerative pathology in younger adults.[211]

To conclude, in young ischemic stroke patients, with in general a good motor recovery, long-term cognitive impairments are common. Given the importance of cognitive performance for post-stroke quality of life cognitive functioning should be monitored in clinical practice. This may also yield valuable information for treating rehabilitation services and return to work.

III

Part

Neuroimaging biomarkers for long-term cognitive outcome after stroke in young adults

5

Chapter

Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults

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Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults.

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Abstract

Background and objective

Memory impairment after stroke in young adults is poorly understood. In elderly stroke survivors memory impairments and the concomitant loss of hippocampal volume are usually explained by coexisting neurodegenerative disease (for example amyloid pathology) in interaction with stroke. However, neurodegenerative disease, such as amyloid pathology, is generally absent at young age. Accumulating evidence suggests that infarction itself may cause secondary neurodegeneration in remote areas. Therefore, we investigated the relation between long-term memory performance and hippocampal volume in young patients with first-ever ischemic stroke.

Methods

We studied all consecutive first-ever ischemic stroke patients, aged 18-50 years, admitted to our academic hospital center between 1980-2010. Episodic memory of 173 patients was assessed using the Rey Auditory Verbal Learning Test and the Rey Complex Figure and compared with 87 stroke-free controls. Hippocampal volume was determined using FSL-FIRST, with manual correction.

Results

On average 10 years after stroke, patients had smaller ipsilateral hippocampal volumes compared with controls after left-hemispheric stroke (5.4%) and right-hemispheric stroke (7.7%), with most apparent memory dysfunctioning after left-hemispheric stroke. A larger hemispheric stroke was associated with a smaller ipsilateral hippocampal volume (b=-0.003, p<0.0001). Longer follow-up duration was associated with a smaller ipsilateral hippocampal volume after left-hemispheric stroke (b=-0.028ml, p=0.002) and right-hemispheric stroke (b=-0.015ml, p=0.03).

Conclusion

Our results suggest that infarction is associated with remote injury to the hippocampus, which may lower or expedite the threshold for cognitive impairment or even dementia later in life.

Introduction

Episodic memory deficits are common after ischemic stroke with high risk of conversion to poststroke dementia over time.[6, 212-214] These memory deficits in elderly stroke survivors are often explained by coexisting neurodegenerative pathological changes (e.g., amyloid pathology) that directly affects hippocampal volume, in interaction with the infarction (e.g., post-stroke Wallerian degeneration) as hippocampal strokes are rare.[213, 215-217]

Also, up to 37.1% of young stroke patients (18-50 years) suffer from episodic memory impairment or below average memory performance independent of site and severity of the infarction, even up to eleven years after stroke.[163] However, these memory impairments in young stroke patients are poorly understood, as the presence of coexisting neurodegenerative pathology observed in elderly stroke survivors (e.g., presence of amyloid pathology) is very unlikely to occur at such a young age.[218]

Infarctions located anywhere in the brain can induce widespread effects causing disruption of functional networks of the cortical regions.[209, 219] Furthermore, apart from these functional changes, atrophy of nonischemic remote brain regions, presumably due to neuropathological consequences of ischemic stroke, has been observed.[220-222]

Hippocampal lesion studies have shown that the hippocampus is an important brain structure for episodic memory formation, i.e., encoding and long-term consolidation of new information.[223] These processes can be assessed using the Rey-Auditory Verbal Learning Test (RAVLT)[224] and the Rey-Osterrieth Complex Figure (ROCF).[225]

One smaller study of 36 younger patients with medial cerebral artery occlusion found a smaller ipsilateral hippocampal volume compared with the contralateral hippocampus and concomitant impairment in episodic verbal memory dysfunction, up to two years after stroke.[221]

Memory performance is of utmost importance in young stroke patients as they are in a demanding time of life and usually have a life expectancy of decades ahead. Therefore, understanding the long-term underlying structural correlates of decline in memory functioning after stroke is of key importance and may provide opportunities to tailor post-stroke treatment and rehabilitation. However, currently these data are lacking. Therefore, we investigated the relation between long-term memory performance and hippocampal volume in young patients with first-ever ischemic stroke. We hypothesized that infarction in these young adults is associated with long-term ipsilateral hippocampal atrophy and longer follow-up duration to be associated with a smaller ipsilateral hippocampal volume. We further hypothesized that stroke has a generalized effect on the ipsilateral hemisphere, not only restricted to the hippocampus. To investigate this, we determined thalamic volume after stroke, because the thalamus, apart from the hippocampus, has also been found to be associated with memory

function[226] and previous studies have shown that ipsilateral thalamic volume is reduced after medial cerebral artery occlusion.[227, 228]

Patients and methods

Study design

This study is part of the "*F*ollow-*U*p of *T*ransient ischemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation"-study (*FUTURE* study), a prospective cohort study of prognosis after young stroke or TIA in adults aged 18 through 50 years admitted to the Radboud University Medical Centre, the Netherlands, between January 1, 1980, and November 1, 2010.[23, 25, 163] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and written informed consent was obtained from all participants. Patients were identified through a prospective registry of all consecutive young stroke/TIA patients that has been kept at the department since the 1970s with a standardized collection of baseline and clinical characteristics (including demographics, stroke subtype, vascular risk factors, and a history of epilepsy). The present MRI study comprises all consecutive patients with a first-ever ischemic stroke. Ischemic stroke was defined as focal neurologic deficit persisting more than 24 hours. Primary exclusion criteria for ischemic stroke in the FUTURE study were previous stroke or TIA, cerebral venous sinus thrombosis, and retinal infarction. Additional exclusion criteria for the present MRI study were recurrent stroke/TIA and hippocampal stroke.

Participants had the opportunity to undergo an extensive neuropsychological examination after long follow-up which was administered between November 2009 and December 2011.

Lesion location (left hemisphere, right hemisphere, and infratentorial) was based on medical records and radiological findings. The exact lesion location (frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, thalamus, brainstem, and cerebellum) was determined using the T1-weighted images and FLAIR sequence.

Stroke-free control participants were recruited among the patients' spouses, relatives, or social environment. Controls had to be at least 18 years old without a history of TIA or stroke. Controls were all living independently, none fulfilled the clinical criteria of dementia.

Episodic memory

Verbal episodic memory was assessed using the three-trial version of the Rey Auditory Verbal Learning Test (RAVLT)[224, 229] and visuospatial episodic memory was assessed using the Rey-Osterrieth Complex Figure (ROCF).[225] The verbal and visual memory indices derived from these tests are considered to be associated with hippocampal

functioning,[209, 230] integrity,[231-233] and volume.[232, 234-236] The encoding phase of memory functioning was assessed using the 'Immediate verbal recall' (total number of correctly recalled words over the three consecutive learning trials of the RAVLT), and 'immediate visuospatial recall' (immediate recall score/copy trial score of the ROCF). Storage of previously acquired information is reflected by 'delayed verbal recall' (number correctly reproduced words 30 minutes after Trial 3) and 'delayed visuospatial recall' (delayed recall score after 30 minutes/copy trial). However, as delayed recall performance might be confounded by a retrieval deficit, i.e., the inability to access previously stored information, the RAVLT also incorporates 'delayed verbal recognition' (number of hits and correct rejections on a list of 30 items consisting of 15 target items among 15 distractor items) that bypasses retrieval and reflects successful storage.[224]

Other measurements

Age, sex, level of education, depressive symptoms, and fatigue, were considered possible confounders for memory performance. Level of education was scored with a widely-used Dutch scoring system (1=less than primary school; 7=university degree). Depressive symptoms and fatigue were assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS)[55] and the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[61] Functional outcome during follow-up visit was evaluated using the modified Rankin Scale (mRS).[237] The mRS is a measure for degree of disability or dependence in daily activities of patients with stroke (0=no symptoms; 6=death).

Furthermore, assessment of stroke etiology (TOAST)[7] and severity (NIHSS: National Institutes of Health Stroke Scale)[201] was done retrospectively for all cases by a validated approach,[33, 202] as these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event. The TOAST is a system to categorize subtypes of ischemic stroke based on etiology. It includes six categories: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small artery occlusion (lacune), (4) rare causes, (5) multiple causes, and (6) unknown cause. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effects of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extra-ocular movement, motor strength, ataxia, dysarthria, and sensory loss.

Neuroimaging data acquisition

Participants underwent 1.5-T MRI scanning on the Siemens, Magnetom Avanto. The scanning protocol included a T1-weighted MPRAGE whole-brain scan (TI /TR/TE 1000ms/2730ms/2.95ms; flip angle 7°; field of view [FOV] = 256 mm, voxel size 1.0×1.0×1.0 mm^3) and a FLAIR pulse sequence (TI /TR/TE 2200ms/12220ms/85ms; interslice gap: 0.6mm ; voxel size 1.2x1.0x3.0mm^3).

Neuroimaging data processing

Matlab 7 was used to perform all MRI data analyses. We used optimized Voxel-Based Morphometry toolbox (VBM8) (http://dbm.neuro.uni-jena.de/vbm.html) within SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm) for each T1-weighted image to determine the relative proportion of gray matter, white matter, and CSF per voxel. We used the thorough clean up option, turned the final masking and skull-striping with graph-cut off to have better segmentation of CSF in case of large cortical infarction. Still, in patients with large cortical infarcts the CSF was underestimated and manual correction was needed based on visual inspection. FSLview (FMRIB Software Library release 5.0, http://www.fmrib.ox.ac.uk/fsl) was used to draw a mask using the dura mater as the boundary for intracranial space.[238] Total brain volume was taken as the sum of total gray and white matter. Intracranial volume (ICV) was taken as the sum of total gray and white matter and CSF volume. T1-weighted images were used to segment the hippocampus using FSL-FIRST.[239] Each mask was manually corrected using FSLview.[238] One experienced investigator, blinded for memory performance scores and baseline characteristics (PS), corrected all masks. Anatomical boundaries were determined in the coronal section, actual segmentation was performed using a previously published standardized protocol in which segmentation correction was performed from posterior to anterior.[229] We used a standard neuroanatomical atlas as a guide.[240] The slice before the level in which the crura of the fornices appeared in full view was defined as the posterior border of the hippocampus. The anterior border of the hippocampus was defined as the slice in which the hippocampus was no longer present, and the amygdala fully covered the hippocampus. The inferior horn of the lateral ventricle was used as the superior border. The inferior border was determined by the white matter. The lateral border was defined by the temporal horn of the lateral ventricle and the white matter adjacent to the hippocampus. To correct for differences in head size, normalized total brain volumes and normalized hippocampal volumes (ml) were calculated with the following formula: (average intracranial volume of the total population * (total brain or hippocampal volume of the participant/intracranial volume of the participant)).[229] Inter-rater reliability on a random sample of 10% of all cases showed an intra-class correlation coefficient for the left hippocampus of 0.81, and for the right hippocampus of 0.83. The intra-rater reliability for hippocampal volumes yielded an intra class correlation coefficient for the left hippocampus of 0.93 and for the right hippocampus 0.96.

Lesion volume and lesion probability maps

Cerebral infarctions were defined as hypointense areas on a T1-weighted MPRAGE whole-brain scan with corresponding gliotic rim on FLAIR. The T1-weighted image from each patient was used to manually trace lesions, with the aid of corresponding slices

on the FLAIR image. One experienced investigator (PS) traced all the lesions and was blinded for baseline characteristics and outcome measures (hippocampal volume and memory performance). Normalized lesion volumes (ml) were calculated with the same formula used to normalize hippocampal volume. Next, the T1-weighted images were brain-extracted (FSL-BET: Brain Extraction Tool)[241] and subsequently, along with the lesion mask, registered to the Montreal Neurological Institute (MNI) standard space by an affine transformation with 12 degrees of freedom using FSL-FLIRT (FMRIB's Linear Image Registration Tool; Software Library release 5.0, http://www.fmrib.ox.ac.uk/fsl), followed by non-linear registration using FNIRT (FMRIB's Non-linear Image Registration Tool).[242] Next, for each patient group all lesion masks were merged and averaged, which resulted in a lesion probability map for left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke patients.

Thalamic volume

To determine whether ipsilateral stroke specifically affects the hippocampus we additionally investigated thalamic volumes using FSL-FIRST.[239] Patients with a thalamic stroke were excluded from the analysis. Normalized thalamic volumes were calculated with the same formula used to normalize hippocampal volumes.

Statistical analyses

Baseline characteristics were presented as mean (±SD), median (Q1-Q3), or number of cases (%) and group differences were tested with a Pearson's chi-square test, Mann-Whitney *U* test, or Student's *t*-test when appropriate. Two-sided p-values<0.05 were considered statistically significant. We compared lesion volumes between the three patient groups (left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke) with ANCOVA (adjusted for age at follow-up, sex, and follow-up duration).

The mean memory performance for patients with left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke were compared with controls by means of ANCOVA, adjusted for age at follow-up, sex, education, depressive symptoms, and fatigue. Aphasia may negatively influence verbal memory performance and therefore we examined the effect of excluding aphasic patients from the memory analyses.

Mean hippocampal volumes were calculated for each of the three lesion locations and were compared with controls using an ANCOVA model, adjusted for age at follow-up and sex.

We investigated whether ipsilateral hippocampal volume was associated with immediate verbal recall, delayed verbal recall, immediate visuospatial recall, and delayed visuospatial recall (in Z-scores) after left-hemispheric stroke and right-hemispheric stroke. Linear regression was used for this purpose (b-weights; 95%CI), adjusted for age, sex, level of education, follow-up duration, normalized lesion volume,

and ipsilateral thalamic volume. The analysis was adjusted for thalamic volume to investigate whether ipsilateral hippocampal volume was independently associated with memory performance. Patients with thalamic stroke were excluded from this analysis.
To investigate whether lesion volume was related to ipsilateral and contralateral hippocampal volume after hemispheric stroke linear regression was used (b-weights; 95%CI), adjusted for age at follow-up, sex, lesion location (left or right), and follow-up duration.
The association between follow-up duration and left and right hippocampal volume was analyzed by left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke separately by means of linear regression, corrected for age at follow-up, sex, and normalized lesion volume.
Finally, mean thalamic volumes were calculated for each of the three lesion locations and compared with controls using an ANCOVA model, adjusted for age at follow-up and sex. Patients with thalamic stroke were excluded. For left and right-hemispheric stroke patients separately, we were also interested whether ipsilateral thalamic volume was associated with immediate verbal recall, delayed verbal recall, immediate visuospatial recall, and delayed visuospatial recall (in Z-scores). The same linear regression model as described in the section on hippocampal volume and memory functioning was used for this purpose and we subsequently reported whether there was an independent association between thalamic volume (b-weights; 95%CI) and memory performance.

Results

The study population consisted of 176 ischemic stroke participants and 87 controls. No differences were observed in baseline characteristics between participants (n=176) and those who refused (n=96) or were lost follow-up (n=63). Basic demographical and clinical characteristics of those who did participate in the FUTURE study, but did not participate in the present sub study are presented in Table 1.
The mean follow-up duration was 10.1 (SD 7.9) years and the mean age at follow-up was 49.7 years (SD 9.7). Eighty seven controls (mean age: 49.0, SD 11.7) with memory assessment and T1-weighted whole-brain image were available. The number of patients with bilateral infarction (n=3) was too small for subsequent analyses, therefore they were excluded and 173 patients remained for subsequent analyses.
Table I shows the exact lesion location of patients. Left-hemispheric stroke patients and right-hemispheric stroke patients showed the highest lesion probability in the Medial Cerebral Artery (MCA) territory (Figure 1). Infratentorial stroke patients had the highest lesion probability in right cerebellum and pons (Figure 1).

Strokes in the right hemisphere were on average larger than strokes in the left hemisphere (F(1,128)=8.03, *p*=0.005) and than infratentorial strokes (F(1,95)=14.09, *p*=0.0003) (Table 1 and Figure 1). Left-hemispheric stroke patients had larger strokes compared with infratentorial stroke patients (F(1,108)=3.93, *p*=0.049). Patients with a right-hemispheric stroke had a more severe stroke (higher NIHSS score at stroke onset) compared with left-hemispheric stroke patients (Mann-Whitney U test, *p*=0.002), but not compared with infratentorial stroke patients (*p*=0.7) (Table 1). Infratentorial stroke patients had a more severe stroke compared with left-hemispheric stroke patients (*p*=0.009).

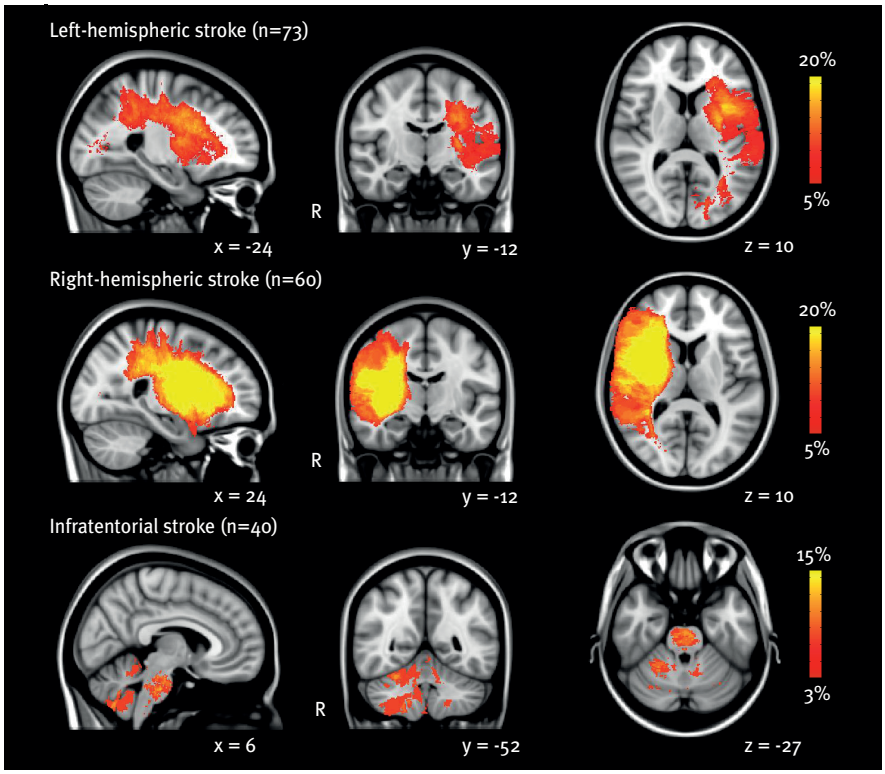

Figure 1 | Lesion probability maps in patients with left-hemispheric stroke

The color overlay created on top of the Montreal Neurologic Institute (MNI) standard brain template shows the probability of each voxel containing a lesion in each patient group. The color bar denotes the probability range.

Table 1 | Demographic and clinical characteristics of participants, controls, and non-participants in present MRI study

Characteristics	Total Ischemic stroke population	Hemispheric stroke		Infratentorial stroke	Controls	No memory assessment/ no MRI
		Left	Right			
No.	176	73	60	40	87	84
Age at event, mean (SD), y	39.6 (8.0)	39.9 (7.7)	39.1 (8.5)	39.9 (7.8)		41.8 (7.0)[a]
Follow-up duration, mean (SD), y	10.1 (7.9)	10.0 (7.8)	9.9 (7.7)	10.7 (8.5)		10.5 (9.7)
Follow-up ≥ 15 yr, No. (%)	47 (26.7)	18 (24.7)	14 (23.3)	14 (35.0)		
Age at follow-up (SD), No. (%), y	49.7 (9.7)	49.9 (9.0)	49.1 (9.5)	50.6 (11.0)	49.0 (11.7)	52.3 (11.1)
Men, No. (%)	78 (44.3)	26 (35.6)	25 (41.7)	26 (65.0)	39 (44.8)	30 (35.7)
NIHSS at stroke onset, median (Q1-Q3)	4 (2-8)	3 (1-5)	6 (2.25-10)	5 (3-8)		5 (2-12)
Education, median (Q1-Q3)	5 (4-6)	5 (4-6)	5 (4-5)	5 (5-6)	5 (5-6)	5 (4-5)[a]
MRS at follow-up, median (Q1-Q3)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	0 (0-0)	1 (1-2)[a]
HADS – depressive symptoms, mean (SD)	3.6 (3.5)	4.4 (3.8)	3.1 (3.1)	2.8 (3.2)	2.5 (2.8)	
CIS-20R – subjective fatigue, mean (SD)	29.3 (14.0)	32.6 (14.1)	27.5 (11.9)	25.7 (15.9)	22.9 (12.6)	
Normalized lesion volume, mean (SD), ml		16.5 (32.4)	36.9 (54.4)	2.8 (5.5)		
Normalized total brain volume, mean (SD), ml		1133.0 (57.3)	1110.4 (62.4)	1149.1 (32.5)	1159.4 (32.8)	
Intracranial volume, mean (SD), ml		1401.5 (159.4)	1385.7 (147.5)	1450.9 (130.5)	1387.2 (119.7)	
TOAST						
Atherothrombotic stroke, No. (%)	39 (22.2)	13 (17.8)	16 (26.7)	9 (22.5)		22 (26.2)
Cardioembolic stroke, No. (%)	12 (6.8)	9 (12.3)	1 (1.7)	2 (5.0)		12 (14.3)
Lacunar stroke, No. (%)	21 (11.9)	12 (16.4)	5 (8.3)	4 (10.0)		13 (15.5)
Rare causes, No. (%)	34 (19.3)	12 (16.4)	13 (21.7)	9 (22.5)		19 (22.6)
Multiple causes, No. (%)	4 (2.3)	1 (1.4)	1 (1.7)	1 (2.5)		3 (3.6)
Unknown cause, No. (%)	66 (37.5)	26 (35.6)	24 (40.0)	15 (37.5)		15 (17.9)[a]

Lesion location						
Left hemisphere stroke, No. (%)	73 (41.5)					34 (40.5)
Right hemisphere stroke, No. (%)	60 (34.1)					35 (41.7)
Infratentorial stroke, No. (%)	40 (22.7)					13 (15.5)
Bilateral stroke, No. (%)	3 (1.7)					2 (2.4)
Cortical stroke,[b] No. (%)						
Frontal lobe		33 (45.2)	37 (61.7)			
Parietal lobe		30 (41.1)	30 (50.0)			
Temporal lobe		25 (34.2)	31 (51.7)			
Occipital lobe		19 (26.0)	8 (13.3)			
Subcortical stroke,[b] No. (%)						
Basal ganglia		28 (38.4)	30 (50.0)			
Thalamus		8 (11.0)	16 (26.7)			
Brainstem stroke,[b] No. (%)				27 (67.5)		
Cerebellar stroke,[b] No. (%)				19 (47.5)		
Language						
Aphasia at stroke onset, No. (%)	35 (20.1)	29 (40.3)	3 (5.0)	2 (5.3)		
Aphasia at discharge, No. (%)	20 (11.4)	17 (23.6)	2 (3.3)	0 (0.0)		

NIHSS=National Institutes of Health Stroke Scale, mRS= modified Rankin scale. HADS=Hospital Anxiety and Depression Scale, CIS-20R=Checklist Individual Strength. TOAST=Trial of Org 10172 in Acute Stroke Treatment. First-ever ischemic stroke, no recurrent events with no memory assessment/MRI: No RAVLT + No ROCF: n=4, no MRI: n=47, participated in the FUTURE study, but refused to visit the research center: n=33. Missing data in ischemic stroke participants: education=0.6%, NIHSS at admission=1.1%, HADS-depressive symptoms= 0.6%, CIS-20R=0.6%, aphasia at discharge= 0.6%. Missing data in non-participants: education=3.6%. [a] $P<0.05$, denotes a significant difference between ischemic stroke participants in present MRI study and patients with no memory assessment/ no MRI. [b] Stroke could be located in more than one region in a patient.

Memory performance

Table 2 shows the mean memory performance of patients (expressed in Z-scores) compared with controls. Left-hemispheric stroke patients performed significantly worse on immediate verbal recall (unadjusted mean Z-score:-0.67, 95% CI: -0.88 to -0.46) and delayed verbal recall (mean:-0.56, 95% CI: -0.80 to -0.32), delayed visuospatial recall (mean=-0.49, 95% CI: -0.78 to -0.19), and delayed verbal recognition (mean:-0.73, 95% CI: -1.02 to -0.45) compared with controls (mean Z-score for every measure=0.00, 95% CI: -0.21to 0.21) (Table 2). Right-hemispheric stroke patients only performed significantly worse than controls on delayed verbal recognition (mean Z-score=-0.54, 95% CI: -0.82 to -0.27). Infratentorial stroke patients performed significantly worse on immediate verbal recall (mean=-0.44, 95% CI: -0.74 to -0.15) and delayed verbal recognition (mean=-0.63, 95% CI: -1.01 to -0.25) compared with controls.

Exclusion of patients with aphasia (n=19) did not affect our results, except for a change into a trend towards significance for the delayed visuospatial recall (p=0.058) in left-hemispheric stroke patients.

Table 2 | 10-year follow-up of mean memory performance (Z-scores) for patients compared with controls

	Hemispheric stroke		Infratentorial stroke
	Left	Right	
No.	73	60	40
Verbal memory (RAVLT), mean (SD)			
Immediate verbal recall	-0.70 (0.9)***	-0.25 (0.9)	-0.44 (0.9)*
Delayed verbal recall	-0.57 (1.0)**	-0.28 (0.9)	-0.46 (0.9)
Delayed verbal recognition (hits + correct negatives)	-0.73 (1.2)***	-0.53 (1.1)**	-0.60 (1.2)*
Visuospatial memory (ROCF), mean (SD)			
Immediate visuospatial recall	-0.42 (1.1)	0.13 (1.1)	0.18 (1.1)
Delayed visuospatial recall	-0.51 (1.2)*	0.13 (1.2)	0.00 (1.1)

RAVLT= Rey Auditory Verbal Learning Test, ROCF= Rey-Osterrieth Complex Figure. Missing data in patients: no ROCF: 1.7%, no RAVLT: 1.2%. Controls (n=87) are not displayed since their mean Z-score is zero (SD=1) for each measure. A star denotes a significant worse performance for patients compared with controls after adjustments for age at follow-up, sex, education, depressive symptoms, and fatigue. *P ‹0.05, **P ‹0.01, ***P ‹0.001.

Hippocampal volume after stroke

After a mean follow-up duration of 10 years patients with left-hemispheric stroke showed a smaller left hippocampal volume (2.98ml, SD 0.4) compared with controls (3.15ml, SD 0.3)($F(1,156)=8.28$, $p=0.005$), which was an unadjusted mean difference of 5.4% (adjustment for age and sex did not affect this difference) (Figure 2). Right-hemispheric stroke was associated with smaller right hippocampal volume (3.11ml, SD 0.4) compared with controls (3.36ml, SD 0.4)($F(1,143)=16.79$, $p<0.0001$), which was a difference of 7.4% (after adjustment for age and sex: 7.7%)(Fig. 2). The mean contralateral hippocampal volume of both left and right-hemispheric stroke patients did not significantly differ from controls (Figure 2). There were no differences between mean hippocampal volume of patients with infratentorial stroke and controls (Figure 2).

After adjusting for age, sex, level of education, follow-up duration, normalized lesion volume, and left thalamic volume, there was a significant positive association between left hippocampal volume and immediate visuospatial recall (b=0.90, 95% CI= 0.20 to 1.60, t=2.58, $p=0.012$) and delayed visuospatial recall (b=1.01, 95%CI= 0.27 to 1.75, t=2.74, $p=0.008$) in left-hemispheric stroke patients. No association was observed between left hippocampal volume and verbal memory performance after left-hemispheric stroke. In right-hemispheric stroke patients no significant associations between right hippocampal volume and memory performance were observed.

Relationship between lesion volume and hippocampal volume

Even after adjustment for age at follow-up, sex, lesion location (left/right), and follow-up duration, a larger hemispheric stroke was significantly associated with a smaller ipsilateral hippocampal volume (b=-0.003, 95%CI= -0.005 to -0.002 per ml increase

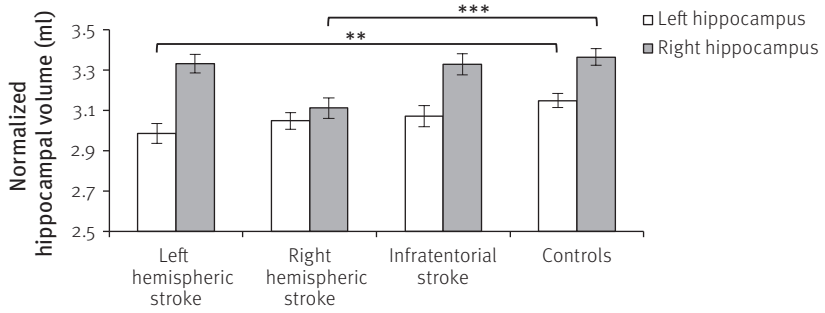

Figure 2 | Unadjusted mean hippocampal volume (±SEM) 10 years after ischemic stroke in young adults compared with stroke-free controls

Significant differences are shown after adjusting for age at follow-up and sex.
*$P<0.05$, **$P<0.01$, ***$P<0.001$.

in lesion volume, t=-4.46, p<0.0001), not contralateral hippocampal volume (b=-0.001, 95%CI= -0.002 to 0.000, t=-1.36, p=0.18).

Relationship between follow-up duration and hippocampal volume

After controlling for age, sex, and normalized lesion volume, in patients with left-hemispheric stroke there was a negative association between follow-up duration and left hippocampal volume (b= -0.028 ml, 95% CI=-0.04 to -0.01, t=-3.25, p=0.002). After each decade the left hippocampus is estimated to be 0.28 ml smaller. In right-hemispheric stroke patients longer follow-up duration was associated with a smaller right hippocampal volume (b= -0.015 ml, 95% CI=-0.03 to -0.003, t=-2.54, p=0.03). This is an estimated reduction of 0.15 ml after a decade. We did not observe a relationship between duration of follow-up and contralateral hippocampal volume after hemispheric stroke. No associations were observed after infratentorial stroke.

Thalamic volume after stroke

To investigate whether the results were specific to the hippocampus, thalamic volumes after stroke were also examined. In left-hemispheric stroke patients a significantly smaller mean left thalamic volume (7.00ml, SD 0.9) was found compared with controls (7.60ml, SD 0.6)(F(1,148)=24.66, p<0.0001). Right-hemispheric stroke patients had a smaller mean right thalamic volume (6.38ml, SD 1.1) compared with controls (7.39ml, SD 0.6)(F(1,127)=49.5, p<0.0001). Hemispheric stroke was not associated with smaller contralateral thalamic volume compared with controls. Patients with infratentorial stroke did not have significantly smaller thalamic volumes compared with controls.
After adjustment for age, sex, level of education, follow-up duration, ipsilateral hippocampal volume, and normalized lesion volume, no independent association between ipsilateral thalamic volume and memory performance was found in hemispheric stroke patients (all p-values>0.05).

Discussion

We showed that on average 10 years following ischemic stroke in adults 18 through 50 years, hemispheric stroke outside the medial-temporal lobe is associated with a smaller ipsilateral hippocampal volume compared with a stroke-free population, accompanied by a worse memory performance.
We showed that patients with a left-hemispheric stroke after a mean follow-up of 10 years had a worse memory performance on almost all memory measures with an attendant smaller ipsilateral hippocampal volume compared with controls. Although the memory performance was only very mildly affected in right-hemispheric stroke patients compared with controls, we observed a smaller ipsilateral hippocampal volume.

Possibly, aphasia limits the proper assessment of verbal memory performance in left-hemispheric stroke patients. However, these patients also had a worse *visual* memory performance and the exclusion of patients with aphasia did not significantly alter our findings making this a very unlikely explanation. Other studies also found that left hippocampal atrophy is more evidently related to poorer memory function than right hippocampal atrophy.[235, 243-245] This finding is in line with hippocampal lesion data.[246, 247] These previous results and our present findings suggest that volumetric changes in the left hippocampus may be more important to memory performance than volumetric changes in the right hippocampus.

In left-hemispheric stroke patients, our results suggest poorer encoding ability as well as a decay of acquired visuospatial information over time, both of which have been found to correlate with hippocampal volume and functioning.[230, 233, 235]

Somewhat surprisingly, the regression analyses yielded no association between *verbal* memory and ipsilateral hippocampal volume, whereas this relationship has been found in patients with Alzheimer's disease.[248] In patients with Alzheimer's disease larger reductions in hippocampal volume have been observed (left: 30% and right: 35%) compared to our young stroke patients (left: 5.4% and right: 7.7%).[249] Possibly, once volume loss exceeds a certain volume, as for example in Alzheimer's disease, the relation between hippocampal volume and verbal episodic memory may become more evident.[249, 250]

A previous study by Xie et al. (2011)[221] investigated 36 relatively young patients up to two years after middle cerebral artery occlusion. However, life expectancy of most of these young patients exceeds by far two years. Our findings therefore extend those of Xie et al. (2011) as we found a relation between hippocampal volume and hemispheric stroke, but not infratentorial stroke, with a much longer follow-up of 10 years. Data on lesion side (left/right) was lacking in the study of Xie et al. (2011), which is important since the asymmetry between left and right hippocampal volume, with larger right than left volumes, is established in healthy adults.[251] Therefore, we compared volumes of patients with volumes of controls within each hemisphere.

Furthermore, another important finding of our study is the inverse relation between follow-up duration in years and ipsilateral hippocampal volume, reflecting decreasing hippocampal volume from the early months after stroke up to 30 years after stroke. This relation persisted even after adjusting for age. This might explain the negative association between follow-up duration and memory performance previously observed in these young adults.[163]

Finally, our results suggest that hemispheric stroke has a generalized effect on ipsilateral brain structures remote from the infarction, such as a smaller ipsilateral hippocampus and thalamus. However, after adjusting for age, sex, education, follow-up duration, normalized lesion volume, and ipsilateral hippocampal volume no independent relation was found between thalamic volume and memory performance. Ipsilateral

hippocampal volume was still associated with visual memory function in left-hemispheric stroke patients after excluding patients with thalamic stroke and adjusting for left thalamic volume in the regression analysis, suggesting an independent association between ipsilateral hippocampal volume and memory performance.

Underlying mechanism of smaller ipsilateral hippocampal volume

Rodent studies showed loss of pyramidal cells in the CA1 area of the hippocampus after ischemia in other areas of the brain,[252] possibly caused by spreading depression (SD), causing secondary neuronal damage and infarct expansion. SD is associated with failure of brain ion homeostasis, efflux of excitatory amino acids from neurons, resulting in increased energy metabolism and changes in cerebral blood flow.[253] Support for SD as underlying mechanism of hippocampal damage after infarction comes from the finding that inhibition of SD propagation by blocking intercellular communication via gap junction channels after ischemic stroke in rodents, results in less hippocampal damage and fewer deficits in memory.[221]

The observation of a smaller ipsilateral hippocampus dependent on follow-up duration after stroke may induce a vulnerability of the hippocampus in the affected hemisphere to the effect of ageing, possibly leading to accelerated cognitive decline at an already earlier age. When these patients finally come to an age when neurodegenerative features come into play, their remaining hippocampal volume may already be lower or expedite the threshold for cognitive impairment or even dementia, compared with persons without a stroke at young age. This notion is in agreement with the finding that patients who develop Alzheimer's disease, loss of hippocampal volume seems to be present years before the clinical diagnosis.[234]

Strengths and limitations

The strengths of our study include its large sample size and the long follow-up. This single center study allowed us to collect baseline and follow-up information according to identical procedures in all patients, with high inter-rater and intra-rater agreement for hippocampal volumes. We used strict protocols and researchers were trained, in order to reduce the risk of information bias.

Some limitations of our study need to be addressed. Although the FUTURE study has a prospective design, the current analysis is cross-sectional and we therefore can only report on smaller hippocampal volume after stroke. While this may be due to post-stroke hippocampal atrophy, a longitudinal design is required to further support causality. However, our data clearly demonstrate a relation between the stroke and future loss of ipsilateral hippocampal volume, since we did not observe smaller contralateral hippocampal volumes and longer follow-up duration was associated with smaller ipsilateral hippocampal volume. Additional support comes from our finding that a larger hemispheric stroke was associated with smaller ipsilateral

hippocampal volume. In contrast with one smaller study (n=36),[221] we did observe an inverse relationship between lesion volume and ipsilateral hippocampal volume. Possibly, in the previous study low statistical power due to a small sample size resulted in no association.[221] Thus, our findings suggest that it is highly unlikely that these patients already had smaller ipsilateral hippocampal volumes before stroke onset.
Second, selection bias might have occurred, since patients who refused or were not eligible for MRI scanning had a poorer outcome compared with participants. However, bias would only have occurred when the relation between the stroke and hippocampal volume would be selectively different in non-participants, which does not seem likely. However, non-participants might have had more vascular risk factors, which may accelerate decline of hippocampal volume.
Third, MRI quantification (with manual correction of hippocampal volume and ICV in case of large cortical infarcts) could not have been done blindly for lesion location and size. This might have biased the results. However, *automated* analyses on thalamic volume showed the same results as compared with *manually* corrected hippocampal volume, suggesting no bias due to unblinded reading.

Conclusions and clinical implications

To conclude, the greater (probable lifelong) memory impairment after stroke may be explained by a smaller ipsilateral hippocampus. At present the mean memory performance of our patients was not within the "impaired" range (i.e., less than 1.5 standard deviations below the mean of the controls). Given their young age, these patients are expected to live on for several decades and the reduced ipsilateral hippocampal volume accompanied by a worse memory score may point towards a lower neural reserve in these patients, making them at risk for further cognitive decline, especially when neurodegenerative disease comes into play. Also, in these young patients even small decrements in memory function may affect vocational and academic achievements, which makes our findings highly relevant.
The stronger association between left-hemispheric stroke, a smaller left hippocampal volume, and worse memory performance has clinical implications, since it seems that especially small baseline left hippocampal volume is associated with higher risk of conversion into dementia.[254] These patients with memory decline and smaller hippocampal volumes therefore might be especially at risk for further cognitive decline. It is important to inform patients on these long-term consequences and provide realistic outlooks given the underlying structural changes. Future studies are needed that prospectively investigate the underlying structural changes of cognitive decline to support causality.

6

Chapter

Lower ipsilateral hippocampal integrity after ischemic stroke in young adults: a long-term follow-up study

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Lower ipsilateral hippocampal integrity after ischemic stroke in young adults: A long-term follow-up study.

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Abstract

Background and objective

Memory impairment after stroke is poorly understood as stroke rarely occurs in the hippocampus. Previous studies have observed smaller ipsilateral hippocampal volumes after stroke compared with controls. Possibly, these findings on macroscopic level are not the first occurrence of structural damage and are preceded by microscopic changes that may already be associated with a worse memory function. We therefore examined the relationship between hippocampal integrity, volume, and memory performance long after first-ever ischemic stroke in young adults.

Methods

We included all consecutive first-ever ischemic stroke patients, without hippocampal strokes or recurrent stroke/TIA, aged 18-50 years, admitted to our academic hospital between 1980 and 2010. One hundred and forty-six patients underwent T1 MPRAGE, DTI scanning and completed the Rey Auditory Verbal Learning Test and were compared with 84 stroke-free controls. After manual correction of hippocampal automatic segmentation, we calculated mean hippocampal fractional anisotropy (FA) and diffusivity (MD).

Results

On average 10 years after ischemic stroke, lesion volume was associated with lower ipsilateral hippocampal integrity ($p<0.05$), independent of hippocampal volume. In patients with a normal ipsilateral hippocampal volume (volume is less than or equal to 1.5 SD below the mean volume of controls) significant differences in ipsilateral hippocampal MD were observed ($p<0.0001$). However, patients with a normal hippocampal volume and high hippocampal MD did not show a worse memory performance compared with patients with a normal volume and low hippocampal MD ($p>0.05$).

Conclusion

Patients with average ipsilateral hippocampal volume could already have lower ipsilateral hippocampal integrity, but at present with no attendant worse memory performance compared with patients with high hippocampal integrity. Longitudinal studies are needed to investigate whether a low hippocampal integrity after stroke might lead to exacerbated memory decline with increasing age.

Introduction

Although episodic memory dysfunction frequently occurs after ischemic stroke at young age (18 through 50 years), it's underlying mechanism is poorly understood. That is, stroke typically does not affect brain structures that are crucial for memory formation and retrieval, such as the hippocampus.[209] However, recent studies started to unravel potential underlying mechanisms by demonstrating smaller *ipsilateral* hippocampal volumes in patients who experienced an ischemic stroke outside the medial temporal lobe at young age, with an accompanying worse memory performance.[255]
Most likely, these findings on the macroscopic level are not the first manifestation of structural damage of the hippocampus after ischemic stroke as they are presumably preceded by microstructural changes with already (subtle) cognitive correlates. Diffusion Tensor Imaging (DTI) is able to detect these early manifestations of damage on the microstructural level.[233] Therefore, in young stroke patients these microstructural changes may explain lower verbal memory performance, even before structural changes on conventional MRI appear. However, to the best of our knowledge, this has never been investigated in patients with stroke at young age, whereas understanding of the pathophysiology of post-stroke memory dysfunction is of particular importance in young patients, since they are in a period of life in which they start forming a family, have an active social life, and make decisive career moves, requiring optimal cognitive function.
Therefore, we investigated long-term hippocampal integrity in patients with first-ever young ischemic stroke. This study is embedded within the "*F*ollow-*U*p of *T*ransient ischemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation"-study (*FUTURE* study) that addresses risk factors and prognosis after stroke in young adults.

Patients and methods

Study design

This study is part of the *FUTURE* study, a prospective cohort study of prognosis after transient ischemic attack (TIA), ischemic stroke, or hemorrhagic stroke in adults aged 18 through 50 years admitted to the Radboud university medical centre, the Netherlands, between January 1, 1980, and November 1, 2010.[24, 25, 163] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and written informed consent was obtained from all participants.
Patients were identified through a prospective registry of all consecutive young stroke/TIA patients that has been kept at the department since the 1970s with a standardized collection of baseline and clinical characteristics (including demographics, stroke subtype, vascular risk factors, and a history of epilepsy). Ischemic stroke was defined as focal

neurologic deficit persisting more than 24 hours. Lesion location (left hemisphere, right hemisphere, and infratentorial) was based on medical records and radiological findings. Lesion location was further specified into frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, thalamus, brainstem, and cerebellum based on the T1-weighted images and FLAIR sequence. Patients had the opportunity to undergo an extensive neuropsychological examination after long follow-up which was administered between November 2009 and December 2011.[163]

The present substudy comprises all consecutive patients with a first-ever ischemic stroke. Primary exclusion criteria for ischemic stroke in the FUTURE study were previous stroke or TIA, cerebral venous sinus thrombosis, and retinal infarction.[25] Additional exclusion criterion for the present substudy were recurrent stroke/TIA and hippocampal stroke.

Stroke-free control participants were recruited among the patients' spouses, relatives, or social environment. Inclusion criteria were: 18 years or older without a history of TIA or stroke. The control group and patient group were matched for age, sex, and level of education. Controls were all living independently, none fulfilling the clinical criteria of dementia.

Episodic memory

Episodic memory performance was evaluated with the Rey Auditory Verbal Learning Test [RAVLT],[229] a widely used word-list learning test tapping verbal memory function. The RAVLT consists of three consecutive learning trails, followed by a delayed free recall test as well as a delayed recognition test. In the present study we used the immediate verbal recall score (total number of correctly recalled words over the three consecutive learning trials) and the delayed verbal recall score since these measures are most sensitive to hippocampal (dys)function and previous studies found a clear association with hippocampal integrity.[232, 234, 256-258] Immediate verbal recall reflects the encoding phase of memory functioning. Delayed verbal recall after the learning trials of the RAVLT reflects storage and retrieval success of previously acquired information.[224]

Other measurements

Level of education was scored with a widely-used Dutch scoring system (1=less than primary school; 7=university degree). Functional outcome during follow-up visit was evaluated using the modified Rankin Scale (mRS).[237] Furthermore, assessment of stroke etiology (TOAST)[7] and severity (National Institutes of Health Stroke Scale, NIHSS)[201] was done retrospectively for all cases by a validated approach,[33, 202] as these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event. The etiology of stroke using TOAST was classified as atherothrombotic stroke, cardioembolic stroke, lacunar stroke, rare causes (vasculitis, moyamoya, migraine, coagulopathy, systemic disease, genetic, toxic,

post-surgery, traumatic, pregnancy related), multiple causes, or unknown cause. Depressive symptoms and fatigue were assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS)[55] and the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[61]

We assessed vascular risk factors at follow-up (hypertension, diabetes mellitus, dyslipidemia, smoking (current/former/never), current alcohol use (>2 units/day)) on the basis of medical history using a standardized, structured questionnaire and/or the use of medication. The Body-mass index (BMI) at follow-up was calculated as weight (kilograms) divided by height (meters) squared.

Neuroimaging data acquisition

Participants underwent a 1.5-T MRI scanning on the Siemens, Magnetom Avanto. A T1-weighted whole-brain scan was collected (magnetization-prepared rapid acquisition with gradient echo [MPRAGE], TI 1000 ms, repetition time [TR] 2730 ms, echo time [TE] 2.95 ms, flip angle 7°, field of view [FOV] = 256 mm, voxel size 1.0×1.0×1.0 mm^3) as well as a set of whole-brain diffusion-weighted images (TR 9100 ms, TE 98 ms, diffusion directions 61, with non co-linear orientation of the diffusion-weighting gradient and b-value 1000 s/mm^2. Seven unweighted images, FOV = 220 mm, voxel size 2.2×2.2×2.2 mm^3) and a FLAIR pulse sequence (TI /TR/TE 2200ms/12220ms/85ms; interslice gap: 0.6mm; voxel size 1.2x1.0x3.0mm^3).

Neuroimaging data processing

Hippocampal and intracranial volumetry

Neuroimaging data analyses are extensively described elsewhere.[255] In short, neuroimaging data were analyzed using Matlab 7. Voxel-Based Morphometry toolbox (VBM8) within SPM8 was used for each T1-weighted image to determine the volume of gray matter, white matter, and CSF to calculate the intracranial volume (ICV).

Hippocampal volumes were determined by automatic segmentation (FSL-FIRST: FMRIB Software Library release 5.0, http://www.fmrib.ox.ac.uk/fsl) with manual correction using FSLview by one experienced investigator (PS) who was blinded for baseline characteristics and memory performance. The anatomical boundaries were determined using a previously published standardized protocol in which segmentation correction was performed from posterior to anterior.[229, 259] Normalized brain volume and hippocampal volume (ml) were calculated with the following formula: (average intracranial volume of the total population * (brain or hippocampal volume of the participant/intracranial volume of the participant)).[260] Inter-rater reliability on 10% of all cases showed an intra-class correlation coefficient for the left hippocampus of 0.81, and for the right hippocampus of 0.83. The intra-rater reliability for hippocampal volumes yielded an intra class correlation coefficient for the left hippocampus of 0.93 and for the right hippocampus 0.96.

Thalamus

To determine whether the results are specific for the hippocampus or not, we additionally investigated thalamic integrity. Lesion studies have shown that, apart from the hippocampus, thalamic lesions have also been found to be associated with memory dysfunction[226] and previous studies have shown that ipsilateral thalamic volume is reduced after ischemic stroke.[227, 228, 255] Thalamic volume was determined using FSL-FIRST.[239] Patients with a thalamic stroke were excluded from the analysis. Normalized thalamic volumes were calculated with the same formula used to normalize hippocampal volumes.

DTI analysis

First, diffusion data were preprocessed to detect and correct head and cardiac motion artifacts, using an in-house developed iteratively re-weighted-least-squares algorithm named 'PATCH'.[261] Eddy current corrections and motion artifacts from affine misalignment are performed simultaneously by minimization of the residual diffusion tensor errors. Using DTIFit within the Functional MRI of the Brain Diffusion Toolbox, we created FA en MD images. Next, the mean unweighted image (b=0) was used to coregister to the anatomical T1 image using SPM8 with default settings, which were then applied to the FA en MD images. All images were visually inspected for severe motion artefacts and co-registration errors. To reduce partial volume effects for hippocampal and thalamic MD and FA, we eroded the hippocampus and thalamic volumes by one voxel in all directions.[232] All images were checked for not including peri-hippocampal CSF. The mean FA and MD were calculated for the right and left hippocampus and thalamus.

Ischemic stroke volume and lesion probability maps

Ischemic lesions were defined as hypointense areas on a T1-weighted MPRAGE whole-brain scan with corresponding gliotic rim on FLAIR. The T1-weighted image from each patient was used to manually trace lesions, with the aid of corresponding slices on the FLAIR image. One experienced investigator traced all the lesions and was blinded for baseline characteristics and outcome measures. Normalized lesion volumes (ml) were calculated with the same formula used to normalize hippocampal volume. Next, the T1-weighted images were brain-extracted (FSL-BET: Brain Extraction Tool)[241] and subsequently, along with the lesion mask, registered to the Montreal Neurological Institute (MNI) standard space by an affine transformation with 12 degrees of freedom using FSL-FLIRT (FMRIB's Linear Image Registration Tool; Software Library release 5.0, http://www.fmrib.ox.ac.uk/fsl), followed by non-linear registration using FNIRT (FMRIB's Non-linear Image Registration Tool). Next, for each patient group all lesion masks were merged and averaged, which resulted in a lesion probability map for left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke patients.

Statistical analyses

Baseline characteristics were presented as means (±SD), median (Q1-Q3), or number of cases (%). To investigate whether participants in the present DTI study differed from non-participants on basic demographical and clinical characteristics we used a t-test in case of normal distributed data (age at event and follow-up), a Mann-Whitney U test in case of ordinal data (NIHSS at admission), and Pearson's chi-square test in case of categorical data (sex, TOAST, lesion location). For the participants, group differences between the three groups of patients (left/right/infratentorial stroke) on basic demographical and clinical characteristics were investigated using a t-test, Kruskal-Wallis test (three groups), or Pearson's chi-square test when appropriate. Since the explanatory nature of this study, two-tailed p-values <0.05 were considered significant.

We investigated whether different lesion locations (left hemisphere/right hemisphere/infratentorial) were associated with differences in left and right hippocampal integrity compared with a non-stroke population. We therefore calculated mean FA and MD for the left and right hippocampus separately, stratified by stroke location (left hemisphere/right hemisphere/infratentorial) and were compared with controls by means of ANCOVA, adjusted for age at follow-up and sex.

We investigated whether lesion volume was associated with lower ipsilateral hippocampal integrity in hemispheric stroke, independent from hippocampal volume. Linear regression was used for this purpose adjusting for age, sex, follow-up duration, lesion location (left/right), and ipsilateral hippocampal volume. To investigate the relation between ipsilateral hippocampal volume and ipsilateral hippocampal integrity, the same linear regression model was used as to investigate the relation between lesion volume and hippocampal integrity and we subsequently reported whether there was an independent association between ipsilateral hippocampal volume and ipsilateral hippocampal integrity.

Finally, we investigated whether there were patients with normal ipsilateral hippocampal volume and lower ipsilateral hippocampal integrity and possibly already an attendant worse memory performance compared with patients with normal volume and high hippocampal integrity. We used controls as a reference for normal hippocampal volume. To account for the effects of aging on hippocampal volume[262] we divided the control group into two equal groups based on the median age of the control group. Next, we used the mean hippocampal volume and SD of these two age groups to calculate an age-adjusted Z-score of hippocampal volume for each participant. Hippocampal atrophy was defined as more than 1.5 below the mean volume of controls.[263, 264] Normal hippocampal volume was defined as less than or equal to 1.5 SD below mean volume of controls. Next, we excluded patients with thalamic stroke from the analysis to investigate the independent effect of the hippocampus. For left and right-hemispheric stroke patients separately, patients with normal ipsilateral hippocampal volume were split into two equal groups based on the

median of ipsilateral hippocampal MD: low ipsilateral hippocampal MD (lowest 50%) and high ipsilateral hippocampal MD (highest 50%). We investigated whether these two patient groups with normal volume and low versus high hippocampal MD significantly differed in hippocampal MD, using an ANCOVA model, adjusted for age, sex, follow-up duration, and ipsilateral hippocampal volume. Next, we investigated whether hippocampal volume significantly differed between these patients with high or low hippocampal MD, using an ANCOVA model, adjusted for age, sex, and follow-up duration. Last, we investigated in patients with normal volume whether there was a difference in memory performance between patients with low hippocampal MD and high hippocampal MD. In this way, we investigated the additional effect of higher hippocampal MD on memory performance in stroke patients. An ANCOVA model was used for this purpose adjusted for age, sex, education, follow-up duration, and ipsilateral hippocampal volume.
The described analyses on memory performance were also performed for patients with normal thalamic volume and low or high ipsilateral thalamic integrity (thalamic stroke excluded), to investigate whether present results were specific for the hippocampus.

Results

T1-weighted whole-brain imaging, DTI-scanning (no artefacts), and memory performance was available from 146 ischemic stroke patients and 84 stroke-free controls. Baseline characteristics between participants and those who refused or were lost to follow-up were not significantly different. Those who participated in the FUTURE study, but did not participate in the present study had lower education (p=0.03) and a higher mRS at follow-up (p=0.0001) compared with participants who did participate in the present DTI study.
Table 1 shows the baseline characteristics of the study population and group comparisons between the three groups of patients. Mean follow-up duration was 10.4 years (SD 8.0) and mean age at follow-up was 50.0 years (SD 9.8). Mean age of controls was 48.9 years (SD 11.9). Infratentorial stroke patients had a significant higher proportion of men compared with left-hemispheric stroke patients (p=0.002) and right-hemispheric stroke patients (p=0.003) (Table 1). Left-hemispheric stroke patients reported more depressive symptoms compared with infratentorial stroke patients (p=0.02). Based on the NIHSS at admission, right-hemispheric stroke patients had a more severe stroke compared with left-hemispheric stroke patients (p=0.008). Infratentorial stroke patients had a more severe stroke compared with left-hemispheric stroke patients (p=0.03), but did not differ in stroke severity compared with right-hemispheric stroke patients (p=0.6).

Right-hemispheric stroke patients had a significant higher mean lesion volume compared with left-hemispheric stroke patients (p=0.01) and infratentorial stroke patients (p=0.0004). Whereas, left-hemispheric stroke patients had a significant higher mean lesion volume compared with infratentorial stroke patients (p=0.02). Left-hemispheric stroke patients and right-hemispheric stroke patients showed the highest lesion probability in the Medial Cerebral Artery (MCA) territory (Figure 1). Infratentorial stroke patients had the highest lesion probability in right cerebellum and pons (Figure 1).

We observed higher mean right hippocampal MD in right-hemispheric stroke patients compared with controls (p=0.007), with a trend towards significance for higher left hippocampal MD in left-hemispheric stroke patients compared with controls (p=0.059) (Figure 2). Right-hemispheric stroke patients showed lower mean right hippocampal FA compared with controls (p=0.007). There were no differences in mean left and right hippocampal MD or FA between patients with infratentorial stroke and controls (Figure 2). We did not observe a relationship between ipsilateral hippocampal volume and ipsilateral hippocampal FA or MD in hemispheric stroke patients after adjusting for age, sex, follow-up duration, lesion location (left/right), and normalized lesion volume (p>0.05).

Relationship between lesion volume and ipsilateral hippocampal integrity

After adjusting for age, sex, follow-up duration, lesion location (left/right), and ipsilateral hippocampal volume, larger hemispheric stroke volumes were associated with lower values of ipsilateral hippocampal FA (β=-0.38, p=0.0002) and higher values of ipsilateral hippocampal MD (β=0.26, p=0.01).

Patients with normal ipsilateral hippocampal volume and high versus low ipsilateral hippocampal MD

In left-hemispheric stroke patients with normal left hippocampal volume (less than or equal to 1.5 SD below the mean volume of controls) and significantly higher values of left hippocampal MD ($F(1,36)=38.28$, $p<0.0001$), we did not observe a worse immediate verbal recall score ($F(1,34)=0.05$, p=0.8) or a worse delayed verbal recall score ($F(1,33)=0.35$, p=0.6) compared with patients with normal volume and lower hippocampal MD (Table 2). These two groups did not significantly differ in mean left hippocampal volume (p=0.6) (Table 2).

Right-hemispheric stroke patients with normal right hippocampal volume and significantly higher values of right hippocampal MD ($F(1,25)=27.07$, $p<0.0001$) did not show a worse immediate verbal recall score ($F(1,24)=0.27$, p=0.6) or a worse delayed verbal recall score ($F(1,24)=0.56$, p=0.5) compared with patients with normal volume and lower hippocampal MD values (Table 2). These two groups did not significantly differ in mean right hippocampal volume (p=0.4).

Table 1 | Demographic and clinical characteristics of ischemic stroke patients and controls

Characteristics	Total ischemic stroke population	Hemispheric stroke		Infratentorial stroke	Controls	p-value[b]
		Left	Right			
No.	146	60	52	34	84	
Age at event, mean (SD), y	39.6 (8.2)	39.7 (8.1)	39.0 (8.4)	40.4 (8.1)		0.7
Follow-up duration, mean (SD), y	10.4 (8.0)	10.6 (8.1)	10.0 (7.9)	10.7 (8.3)		0.9
Age at follow-up, mean (SD), y	50.0 (9.8)	50.3 (9.4)	49.0 (9.5)	51.2 (11.1)	48.9 (11.9)	0.6
Men, No. (%)	67 (45.9)	21 (35.0)	23 (44.2)	23 (67.6)	38 (45.2)	0.01
Education, median (Q1-Q3)	5 (4-6)	5 (4-6)	5 (4-5.75)	5 (5-6)	5 (5-6)	0.3
NIHSS at stroke onset, median (Q1-Q3)	4 (2-8)	3 (2-5)	5 (3-10)	5 (2.5-8)		0.01
Normalized total brain volume, mean (SD), ml	1127.4 (59.4)	1130.8 (61.4)	1107.3 (64.6)	1152.2 (31.9)	1156.6 (32.9)	
Normalized lesion volume, mean (SD), ml	20.2 (42.0)	15.4 (33.3)	37.7 (56.2)	2.1 (5.1)		0.0002
MRS at follow-up, median (Q1-Q3)	1 (0-1)	1 (0-1.75)	1 (0-2)	1 (0-1)	0 (0-0)	0.5
HADS - depressive symptoms, mean (SD)		4.1 (3.9)	3.2 (3.2)	2.3 (2.8)	2.5 (2.8)	0.04
CIS-20R - subjective fatigue, mean (SD)		30.9 (14.3)	27.6 (11.9)	24.2 (15.0)	23.05 (12.7)	0.08
TOAST, No. (%)						0.5
Atherothrombotic stroke	34 (23.3)	11 (18.3)	14 (26.9)	9 (26.5)		
Cardioembolic stroke	10 (6.8)	7 (11.7)	1 (1.9)	2 (5.9)		
Lacunar stroke	17 (11.6)	10 (16.7)	4 (7.7)	3 (8.8)		
Rare causes	28 (19.2)	9 (15.0)	12 (23.1)	7 (20.6)		
Multiple causes	2 (1.4)	0 (0.0)	1 (1.9)	1 (2.9)		
Unknown cause	55 (37.7)	23 (38.3)	20 (38.5)	12 (35.3)		

Lesion location, No. (%)						
Left supratentorial stroke	60 (41.1)					
Right supratentorial stroke	52 (35.6)					
Infratentorial stroke	34 (23.3)					
Cortical stroke[a]						
Frontal lobe		35 (58.3)	33 (63.5)			
Parietal lobe		24 (40.0)	26 (50.0)			
Temporal lobe		21 (35.0)	28 (53.8)			
Occipital lobe		14 (23.3)	8 (15.4)			
Subcortical stroke[a]						
Basal ganglia		22 (36.7)	27 (51.9)			
Thalamus		7 (11.7)	13 (25.0)			
Brainstem stroke[a]				24 (70.6)		
Cerebellar stroke[a]				15 (44.1)		

NIHSS=National Institutes of Health Stroke Scale, mRS= modified Rankin Scale. HADS=Hospital Anxiety and Depression Scale, CIS-20R=Checklist Individual Strength. TOAST=Trial of Org 10172 in Acute Stroke Treatment. Missing data in patients: education=0.7%, NIHSS at admission=1.4%, HADS-depressive symptoms=0.7%, CIS-20R=0.7%. [a]Stroke could be located in more than one region in a patient. [b]Group comparison between the three groups of patients (left/right/infratentorial stroke).

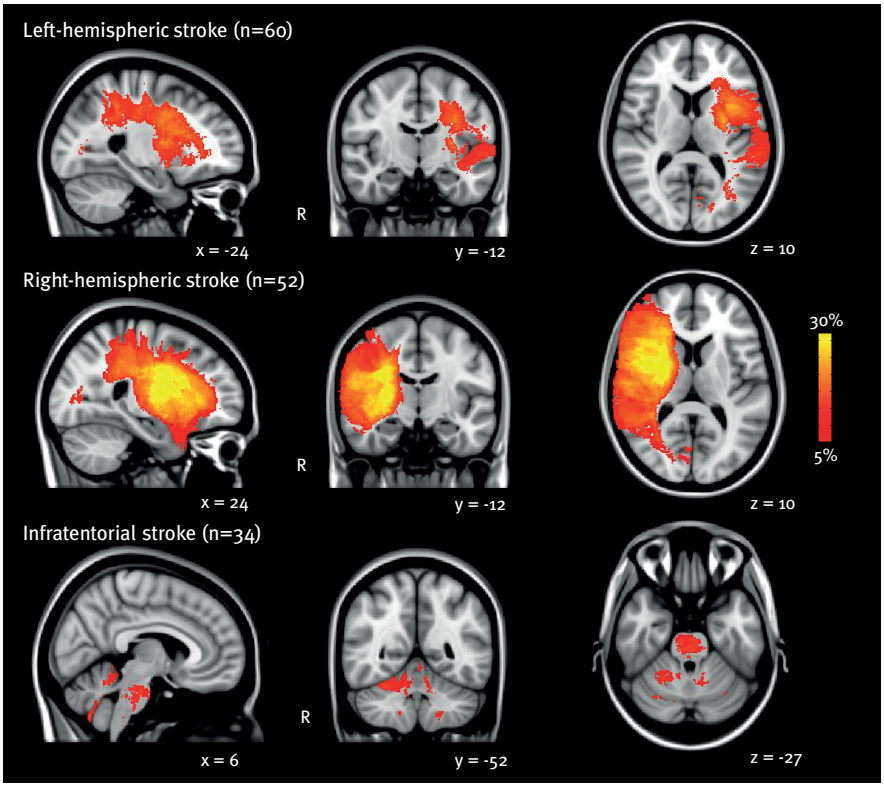

Figure 1 | Lesion probability maps in patients with left-hemispheric stroke, right-hemispheric stroke, and infratentorial stroke

The color overlay created on top of the Montreal Neurologic Institute (MNI) standard brain template shows the probability of each voxel containing a lesion in each patient group. The color bar denotes the probability range.

Thalamic integrity after ischemic stroke in young adults

We used the thalamus as a control region to investigate whether the results were specific for hippocampal integrity or also apply to other ipsilateral structures.

After adjusting for age and sex, we observed a significant higher mean left thalamic MD after left-hemispheric stroke (0.087×10^{-2} mm²/s, SD 0.06×10^{-3}) compared with controls (0.083×10^{-2} mm²/s, SD 0.05×10^{-3}) ($F(1,133)=20.2$, $p<0.0001$). We observed a higher mean right thalamic MD after right-hemispheric stroke (0.088×10^{-2} mm²/s, SD 0.06×10^{-3}) compared with controls (0.084×10^{-2} mm²/s, SD 0.05×10^{-3}) ($F(1,119)=22.7$, $p<0.0001$). No significant differences between hemispheric stroke patients and

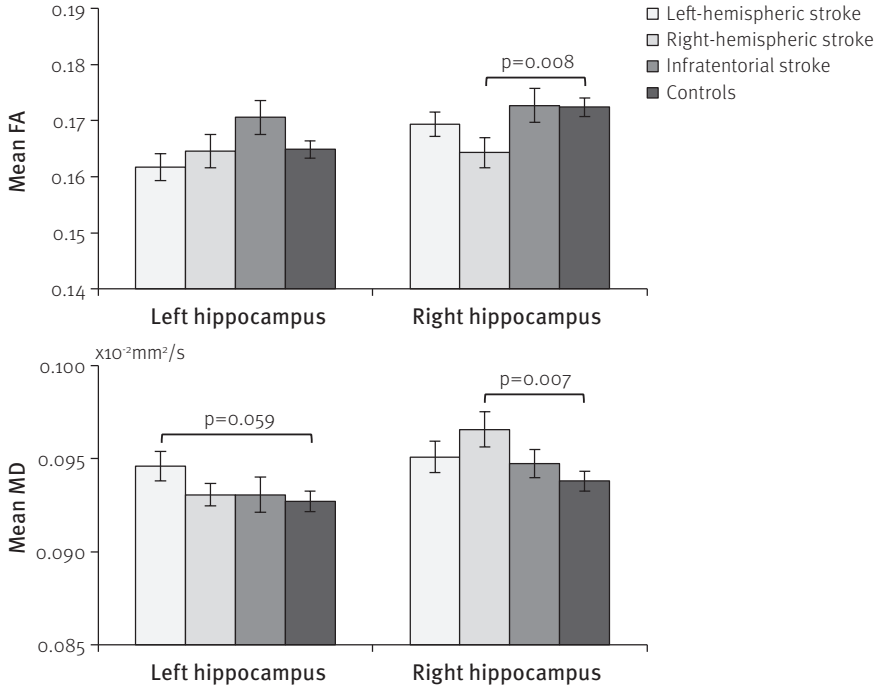

Figure 2 | Unadjusted mean fractional anisotropy (FA) and mean diffusivity (MD) in the left and right hippocampus about 10 years after ischemic stroke in young adults compared with controls

P-values are adjusted for age at follow-up and sex.

controls were found for the contralateral hippocampal FA and MD. Infratentorial stroke patients did not differ from controls in mean left and right thalamic MD or FA (p>0.05). In left-hemispheric stroke patients with normal left thalamic volume and significantly higher left thalamic MD ($F(1,30)=41.69$, p<0.0001) no difference in mean immediate recall score (p=0.2) and delayed recall score (p=0.6) was observed compared with patients with normal left thalamic volume and lower thalamic MD. These two groups did not significantly differ in mean left thalamic volume (p=0.3).

In right-hemispheric stroke patients with normal right thalamic volume and significantly higher right thalamic MD ($F(1,15)=14.87$, p=0.002) no difference was observed in mean immediate recall score (p=0.4) and delayed recall score (p=0.8) compared with patients with normal thalamic volume and lower right hippocampal MD. No difference between these two groups in mean right hippocampal volume was observed (p=0.2).

Table 2 | Comparisons between hemispheric stroke patients with normal ipsilateral hippocampal volume and high versus low ipsilateral hippocampal MD

	Left-hemispheric stroke patients with normal left hippocampal volume			Right-hemispheric stroke patients with normal right hippocampal volume		
	Low hippocampal MD	High hippocampal MD	p-value[a]	Low hippocampal MD	High hippocampal MD	p-value[b]
No.	21	20		15	16	
Ipsilateral hippocampal MD (mm2/sec)	$8.9x10^{-4}$ ($0.1 x10^{-4}$)	$9.9x10^{-4}$ ($0.1 x10^{-4}$)	<0.0001	$9.1x10^{-4}$($0.1 x10^{-4}$)	$9.9x10^{-4}$ ($0.1 x10^{-4}$)	<0.0001
Ipsilateral hippocampal volume (ml)	3.2 (0.1)	3.1 (0.1)	0.6	3.2 (0.1)	3.3 (0.1)	0.4
Immediate verbal recall (Z-score)	-0.6 (0.2)	-0.6 (0.2)	0.8	-0.3 (0.2)	-0.1 (0.2)	0.6
Delayed verbal recall (Z-score)	-0.4 (0.2)	-0.6 (0.2)	0.6	-0.1 (0.3)	-0.4 (0.3)	0.5

Data are presented as number or adjusted mean (±SEM). [a] Comparison between left-hemispheric stroke patients with low left hippocampal MD versus high left hippocampal MD. [b] Comparison between right-hemispheric stroke patients with low right hippocampal MD versus high right hippocampal MD. For the analyses on hippocampal volume we adjusted for age, sex, and follow-up duration. For the analyses on ipsilateral hippocampal MD we additionally adjusted for ipsilateral hippocampal volume. For the analyses on immediate and delayed verbal recall we adjusted for age, sex, education, follow-up duration, and ipsilateral hippocampal volume. MD = Mean Diffusivity.

Discussion

We showed that after a mean follow-up of ten years, a first-ever hemispheric stroke at young age (18 through 50 years) is associated with a lower ipsilateral hippocampal integrity compared with a non-stroke population. Larger lesion volume was associated with a lower ipsilateral hippocampal integrity independent of ipsilateral hippocampal volume. In a subset of hemispheric stroke patients with normal ipsilateral hippocampal volume and a significantly higher mean ipsilateral hippocampal MD no worse memory performance was found compared with patients normal hippocampal volume and lower hippocampal MD.

The strengths of our study include its large sample size and the long follow-up. We collected baseline and follow-up information according to identical procedures in all patients with high inter-rater and intra-rater agreement for hippocampal volumes. We used strict protocols for memory assessment and researchers were trained, in order to reduce the risk of information bias.

Some methodological issues of our study need to be considered.[255] Although the FUTURE study has a prospective design, the current analysis is cross-sectional and we therefore can only report on lower hippocampal integrity after stroke compared with a non-stroke population. While this may be due to post-stroke microstructural degradation of the hippocampus, a longitudinal design is required to further support causality. However, our data demonstrate a relation between the stroke and a reduced ipsilateral hippocampal integrity, since we did not observe a lower microstructural integrity of the contralateral hippocampus. Furthermore, larger hemispheric stroke volume was associated with lower ipsilateral hippocampal integrity independent of ipsilateral hippocampal volume. Therefore, it is highly unlikely that these patients already had a lower microstructural integrity of the ipsilateral hippocampus before stroke onset.

Also, selection bias might have occurred, since patients who participated in the FUTURE study, but could not participate in de present DTI study had a poorer outcome compared with participants. However, selection would only have occurred when the relation between the stroke and microstructural integrity of the hippocampus would be selectively different in non-participants and this does seem unlikely.[255]

The observed associations in the present study do not apply to all measures of microstructural integrity. The value of FA reflects the directionality of molecular displacement by diffusion and is influenced by crossing fibers.[265] These crossing fibers are present in the hippocampus[266] and thalamus[267] and influence the FA. Due to the intrahippocampal and thalamic fiber incoherence, low FA may not necessarily reflect underlying lower structural integrity.[268] Thus, crossing fibers in the hippocampus and thalamus might be an explanation for a lack of finding with FA but not with MD. MD reflects the magnitude of water diffusion which is less influenced by direction of fibers

and therefore MD remains relatively constant and is more reliable for assessing microstructural integrity of brain structures with crossing fibers.[233, 268, 269]
Another limitation of our study was that the DTI voxel size at MRI acquisition was relatively large. This could have caused cerebrospinal fluid partial volume effects in the hippocampal and thalamic region of interest.[268] This is especially the case in patients with hippocampal or thalamic atrophy, which could induce higher MD values. We used eroded hippocampal and thalamic masks for our analyses and therefore it seems unlikely that partial volume effects had an influence on our results.
A limitation of the current approach is the cut-off of Z≤-1.5SD as "normal hippocampal volume"[263, 264] since older subjects with smaller volumes might still have normal volumes for their age.[262] However, we have tried to reduce this effect by dividing the controls into two equal groups based on the median age of the control group and subsequently determined "normal volume" per age category.
Our data clearly demonstrate a relationship between hemispheric stroke volume and remote effects on the microscopic level in the ipsilateral hippocampus. This relationship has also been found on macroscopic level of the ipsilateral hippocampus.[221, 255] However, the results on lower ipsilateral hippocampal integrity in left-hemispheric stroke patients were somewhat less convincing, showing a trend towards significance. This might be explained by our finding on the association between larger stroke volume and remote lower ipsilateral hippocampal integrity. As we observed larger stroke volumes in right-hemispheric stroke patients it might be that this resulted in larger reductions of ipsilateral hippocampal integrity in right-hemispheric stroke patients compared with left-hemispheric stroke patients. Interestingly, we did observe lower left thalamic integrity in left-hemispheric stroke patients compared with controls. Although thalamic stroke was excluded, this difference might be due to the location of the thalamus as it lies closer to the most common stroke location in our stroke cohort (MCA territory) compared with the hippocampus and therefore possibly disconnection due to stroke is more likely. Thus, our finding highlights that stroke volume is an important risk factor for remote effects on the ipsilateral hippocampus. A possible explanation for these remote effects may be the occurrence of spreading depression (SD).[221] SD is the pervasive failure of brain ion homeostasis that transiently interrupts function of intact brain regions, which causes secondary neuronal damage and infarct expansion.[221] Another possibility could be disconnection of the hippocampus due to stroke in the connecting fiber tracts.[219]
Another important finding of our study is that patients with preserved hippocampal volume and low hippocampal integrity at present do not show a worse memory performance compared with patients with normal volume and higher hippocampal integrity. Thus, the addition of low ipsilateral hippocampal integrity in stroke patients with normal hippocampal volume is not associated with a worse memory performance. Other studies in a non-demented elderly did observe an association between lower

hippocampal integrity and verbal memory performance, independent of hippocampal volume.[232, 233] In healthy elderly individuals a low hippocampal integrity before volume loss might reflect an early marker of underlying neurodegenerative disease, such as Alzheimer's Disease.[232, 233] However, in young stroke patients the co-occurrence of Alzheimer pathology is very unlikely given their young age (about 10%).[19, 20] Possibly, the variance in hippocampal MD values found in our young stroke population is smaller due to a different underlying mechanism and therefore no difference in memory performance was found. The course and extent of hippocampal damage might differ due to different underlying mechanisms and needs further investigation. Nevertheless, our results put forward the idea of a lower reserve in patients with a normal hippocampal volume on conventional MRI, but with lower microstructural integrity. They still might be at risk to develop MCI/dementia earlier, compared with a non-stroke population, especially when these patients come to an age where aging-related neurodegenerative pathology (amyloid pathology) occurs. Future longitudinal research should further investigate whether these young patients with higher hippocampal MD eventually develop MCI/dementia earlier compared with a non-stroke population.[270]

Finally, our results suggest that hemispheric stroke has a generalized effect on ipsilateral brain structures remote from the infarction, such as a lower ipsilateral hippocampal and thalamic integrity. This is further confirmed by previous studies on hippocampal and thalamic volume after ischemic stroke.[221, 227, 228, 255] Lower microstructural integrity in remote structures has also been found in subjects with cerebral small vessel disease.[271-273] Thus, these results in subjects with cerebral small vessel disease and stroke patients provide evidence that beyond the area of infarction, remote effects of subcortical damage occur.

In conclusion, our data suggest that vascular lesions are associated with remote lower ipsilateral hippocampal integrity. At present, patients with normal volume and lower hippocampal integrity do not show a worse memory performance compared with patients with normal volume and higher hippocampal integrity. Possibly, a history of stroke, combined with brain changes associated with normal ageing, might eventually lead to exacerbated memory decline. Our findings add to the increasing awareness of stroke not only being an acute disease with immediate consequences, but also results in lifelong consequences.

7

Chapter

Remote lower white matter integrity increases the risk of long-term cognitive impairment after ischemic stroke in young adults

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Remote lower white matter integrity increases the risk of long-term cognitive impairment after ischemic stroke in young adults.

Stroke. 2016; 47(10): 2517-2525

Abstract

Background and objective:

Post-stroke cognitive impairment occurs frequently in young patients with ischemic stroke (18 through 50 years of age). Accumulating data suggest that stroke is associated with lower white matter integrity remote from the stroke impact area, which might explain why some patients have good long-term cognitive outcome and others do not. Given the life expectancy of decades in young patients we therefore investigated remote white matter in relation to long-term cognitive function.

Methods

We included all consecutive first-ever ischemic stroke patients, left/right hemisphere, without recurrent stroke or TIA during follow-up, aged 18 through 50 years, admitted to our university medical center between 1980 and 2010. One hundred and seventeen patients underwent MRI scanning including a T1-weighted scan, a diffusion tensor imaging scan, and completed a neuropsychological assessment. Patients were compared to a matched stroke-free control group (age, sex, and education matched). Cognitive impairment was defined as >1.5SD below the mean cognitive index score of controls and no cognitive impairment as ≤1SD. Tract-Based-Spatial Statistics was used to assess the white matter integrity (FA and MD).

Results

About 11 years after ischemic stroke lower remote white matter integrity was associated with a worse long-term cognitive performance. A lower remote white matter integrity, even in the contralateral hemisphere, was observed in cognitively impaired patients (n=25) compared with cognitively unimpaired patients (n=71).

Conclusion

These findings indicate that although stroke has an acute onset, it might have long lasting effects on remote white matter integrity and thereby increases the risk of long-term cognitive impairment.

Introduction

Cognitive impairments are common after stroke in young adults (18 through 50 years of age).[15, 163, 274] Stroke severity at admission,[275] stroke volume, and stroke location[4] are related to post-stroke cognitive impairment. These factors however do not fully explain why some patients show good cognitive outcome after stroke and others do not.[2]
Accumulating data suggest that, apart from temporary remote neurophysiological changes after stroke (i.e., diaschisis),[276] a focal (ischemic) lesion could potentially affect long-term remote *structural* integrity (e.g., of the hippocampus and thalamus) in the ipsilateral hemisphere after stroke,[163, 221, 227, 277, 278] which has been associated with a worse post-stroke memory performance.[221, 255] Besides remote structural changes in the ipsilateral hemisphere, a few small neuroimaging studies (6 to 16 patients) in older stroke patients (60 years and over) found loss of white matter integrity as remote as the contralesional hemisphere[279] and this was associated with motor impairment up to six months after stroke[280, 281] and poorer cognitive recovery three months after right middle cerebral artery stroke.[282] It is unknown whether lower microstructural integrity in areas remote from the initial stroke, including as remote as the contralateral hemisphere, is related to long-term (i.e., years) cognitive dysfunction after stroke. In addition, the presence of pre-existing (subclinical) cerebral small vessel disease, such as diffuse white-matter hyperintensities or subclinical infarcts may also contribute to the post-stroke spectrum of cognitive impairment,[2] however, this has never been investigated in young stroke patients. A better understanding of the etiology of post-stroke cognitive impairment and its possible recovery is especially important in young stroke survivors, as they are in a demanding phase of their lives with respect to educational, vocational, and family-related functioning.
We hypothesized that patients with cognitive impairment years after their index stroke show a lower white matter structural integrity remote from the initial stroke and more co-existing cerebrovascular disease compared with cognitively unimpaired patients. Conversely, patients with a higher structural integrity in remote brain structures were expected to have an average post-stroke cognitive performance compared with stroke-free controls.

Patients and methods

Study design

This study is part of the *FUTURE* study, a prospective cohort study of prognosis after transient ischemic attack (TIA), ischemic stroke, or hemorrhagic stroke in adults aged 18 through 50 years admitted to the Radboud university medical centre, the Netherlands, between January 1, 1980, and November 1, 2010.[25, 163] The Medical Review Ethics

Committee region Arnhem-Nijmegen approved the study and written informed consent was obtained from all participants.
Patients were identified through a prospective registry of all consecutive young stroke/ TIA patients that has been kept at the department since the 1970s with a standardized collection of baseline and clinical characteristics. Ischemic stroke was defined as focal neurologic deficit persisting more than 24 hours. Patients had the opportunity to undergo an extensive neuropsychological examination together with subsequent MRI scanning during the follow-up between November 2009 and December 2011.[163]
The present study comprises all consecutive patients with a first-ever ischemic stroke in one of the hemispheres. Exclusion criteria in the present study were a previous stroke or TIA, cerebral venous sinus thrombosis, retinal infarction,[25] recurrent stroke/ TIA during the follow-up period, and severe aphasia. Lesion location was based on neuroimaging findings at follow-up, which was related to the stroke location at the time of the event described in medical records and radiological findings.
Controls were recruited among the patients' spouses, relatives, or social environment. Inclusion criteria were 18 years or older, without a history of stroke or TIA. The control group and patient group were matched for age (p=0.5) , sex (p=0.6), and education (p=0.1). Controls were used to define cognitive impairment and no impairment in stroke patients. Controls were all living independently, none fulfilling the clinical criteria of dementia.

Cognitive performance

The neuropsychological tests used in the FUTURE study covered the main cognitive domains and detailed information on these cognitive tests has been described extensively elsewhere.[25, 163] A z-score per test was calculated for each participant based on the mean and the SD of the controls (n=84). Next, averaging z-scores of cognitive tests that mainly reflected the same cognitive domain resulted in a composite z-score per cognitive domain. The seven cognitive domains were: processing speed (Symbol-Digit Modalities Test, Abbreviated Stroop Color Word Test parts I and II), visuoconstruction (Rey-Osterrieth Complex Figure-copy trial, ROCF), working memory (Paper and Pencil Memory Scanning Test, PPMST), immediate memory (ROCF-immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test, RAVLT), delayed memory (delayed recall of the ROCF and the RAVLT), attention (Verbal Series Attention Test, VSAT), and executive functioning (Verbal fluency and Stroop interference).
The cognitive index score is a composite score defined as the average of the seven cognitive domains. Cognitive impairment was defined as a cognitive index score > 1.5 SD below the mean of controls, which has often been used as a cut-off for vascular cognitive impairment in stroke patients.[5] No cognitive impairment was defined as a cognitive index score less than or equal to 1 SD below the mean of controls.[163, 283]

Other measurements

Level of education was classified with a widely-used Dutch scoring system (1=less than primary school; 7=university degree).[284] Functional outcome during follow-up visit was evaluated using the modified Rankin Scale (mRS).[237] Assessment of stroke etiology (TOAST)[7] and severity (National Institutes of Health Stroke Scale, NIHSS) was done retrospectively for all cases by a validated approach,[33, 202] as these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event. Depressive symptoms were assessed using the depression subscale of the Hospital Anxiety and Depression Scale[55] and fatigue by the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[61]

Neuroimaging data acquisition

Participants underwent a 1.5-T MRI scanning on the Siemens, Magnetom Avanto. A T1-weighted whole-brain MPRAGE scan was collected, TI 1000 ms, repetition time [TR] 2730 ms, echo time [TE] 2.95ms, flip angle 7°, field of view [FOV] = 256mm, voxel size 1.0×1.0×1.0mm^3) as well as a set of whole-brain diffusion-weighted images (TR 9100ms, TE 98ms, diffusion directions 61, with non-collinear orientation of the diffusion-weighting gradient and a b-value of 1000 s/mm^2. Seven unweighted images, FOV = 220mm, voxel size 2.2×2.2×2.2mm^3), a FLAIR pulse sequence (TI /TR/TE 2200ms/12220ms/85ms; interslice gap: 0.6mm; voxel size 1.2×1.0×3.0mm^3), and a gradient echo susceptibility weighted imaging (SWI) sequence (TR/TE 49/40ms; voxel size 0.8×0.7×1.0mm^3).[25]

Neuroimaging data processing

Ischemic stroke volume and lesion probability map

Ischemic stroke was defined as a hypointense area on a T1-weighted MPRAGE whole-brain scan with corresponding gliotic rim on the FLAIR image. One experienced investigator, blinded for baseline characteristics and outcome measures traced all ischemic strokes manually using a T1-weighted image (in the coronal plane). Stroke volumes (ml) were normalized using the following formula: average intracranial volume of the total population × (stroke volume of the participant/intracranial volume of the participant).[260] Intracranial volume was calculated as the sum of gray matter, white matter, and CSF using VBM8.[255] Next, brain-extracted images[238] were registered, along with the lesion mask, to the Montreal Neurological Institute (MNI) standard space by an affine transformation (12 degrees of freedom) using FSL-FLIRT,[238] followed by non-linear registration using FNIRT.[238] Next, all stroke masks were merged and averaged, which resulted in a lesion probability map.

Diffusion tensor imaging (DTI) preprocessing

The raw DTI data were denoised using a local PCA filter, which reduces random noise by locally shrinking less significant Principal Components using an overcomplete approach.[285] Next, misalignments from eddy-currents and subject motion were corrected by a mutual information-based co-registration technique (SPM; affine transformation). An average bo-image mask was constructed and was used to mask the results. Magnetic susceptibility induced EPI distortions in the diffusion tensor images were unwarped along the phase-encode direction by mapping the mean unweighted image onto the T1 reference image.[286] The diffusion tensors and their indices (fractional anisotropy; FA, and mean diffusivity; MD) were robustly estimated using the in-house developed iteratively re-weighted-least-squares algorithm named 'PATCH'.[261]

Tract-Based Spatial Statistics (TBSS)

In short, TBSS projects all FA and MD images onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics.[287] The TBSS non-linear registration of a large (cortical) stroke failed in some cases and therefore, a FNIRT configuration file optimized for FA data was used[238] where the stroke lesions were masked out. The FA skeleton was thresholded at 0.3 to include the major white matter tracts and exclude brain parts with low inter-subject reliability. For all TBSS analyses the FA and MD white matter skeleton were first symmetrized for all subjects[287] and flipped (right to left) for right-hemispheric stroke patients.

Vascular risk factors and treatment at follow-up assessment

Blood pressure readings in the left and right arm were performed three times in supine position. Next, the mean blood pressure was calculated for the left and right arm separately. The highest mean blood pressure was used to identify hypertension. Hypertension was defined as a systolic blood pressure ≥135 mmHg, or a diastolic blood pressure of ≥85 mmHg, or the use of antihypertensive medication. Diabetes mellitus was defined as random blood glucose level >11.1 mmol/L, or two consecutive fasting venous plasma glucose levels ≥7.0 mmol/L,[288] or the use of antidiabetics (oral or insulin). Dyslipidemia was defined as total cholesterol ≥5.0 mmol/L or LDL ≥2.5 mmol/L, or triglycerides ≥2.0 mmol/L,[24] or the use of statins. Information on smoking was collected by a structured questionnaire. Current smoking was defined as smoking ≥1 cigarette per day in the year prior to follow-up. The Body Mass Index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Cerebral small vessel disease

White Matter Hyperintensities (WMH) of presumed vascular origin were defined as hyperintense signal on FLAIR, without cavitation.[18] We used an in-house developed validated semi-automatic approach to define WMH. All scans were inspected for segmentation errors and gliosis surrounding lacunes or surrounding the ischemic stroke were excluded. WMH-volumes were normalized to intracranial volume.[260] Microbleeds were defined as small areas of signal void with associated blooming seen on SWI with a diameter of less than 10 mm in diameter, excluding signal voids in the area of the ischemic stroke.[18, 289] Lacunes of presumed vascular origin were defined as round or ovoid, subcortical, fluid-filled cavities in the territory of one perforating arteriole on the FLAIR image with a diameter of 3mm to about 15mm.[18] One experienced researcher analyzed all MRI data and was blinded for baseline characteristics and outcome measures. Interrater and intrarater reliability for the presence of microbleeds yielded a kappa of 1.0 and 0.92 respectively. In a random sample of 10% the interrater reliability for the presence of lacunes yielded a kappa of 0.76 and intrarater reliability a kappa of 0.80.

Statistical analyses

Group differences in baseline characteristics between those who participated and those who did participate in the FUTURE study, but not in the present DTI study were tested with a Mann-Whitney *U* test, ANOVA, or Pearson's chi-square test, when appropriate. Two-tailed p-values$<$0.05 were considered statistically significant.

Normalized WMH-volume and normalized stroke volume showed a right skewed distribution and therefore a base-10 logarithm transformation was used. As the WMH-volume data contained zero's, a constant number of 0.001 was added to all data points before log transformation.

For each TBSS analysis 5000 permutations were used and significant associations were determined using the threshold-free cluster-enhancement with a threshold of p$<$0.05 corrected for multiple comparisons.[287, 290, 291] All TBSS analyses were adjusted for age, sex, follow-up duration, education, lesion location (left/right hemisphere), normalized WMH-volume, depressive symptoms, and fatigue unless otherwise stated. In case of missing values for these covariates (always $<$1.7%) the mean of the whole group was taken.

First, voxel-wise statistical analysis using TBSS was carried out to investigate the relationship between remote white matter integrity (FA and MD of the ipsilateral and contralateral hemisphere) in stroke patients (n=117) and the cognitive index score, additionally adjusted for normalized stroke volume. Subsequently, this TBSS analysis was repeated for the performance on each of the seven cognitive domains. In addition, to investigate the strength of the association between white matter integrity in the contralateral hemisphere (skeletal DTI parameters FA and MD) and the cognitive index

score a linear regression model was used with the cognitive index score as dependent variable and the mean FA/MD as independent variable, adjusted for age, sex, education, follow-up duration, depressive symptoms, fatigue, lesion location, normalized lesion volume, and normalized WMH-volume.
Next, we investigated whether low remote white matter integrity increased the risk of long-term cognitive impairment and whether a higher remote white matter integrity was associated with no post-stroke cognitive impairment. Therefore, FA and MD white matter of the ipsilateral and contralateral hemisphere of patients with cognitive impairment were compared with cognitively unimpaired patients, additionally adjusted for normalized stroke volume.
Finally, we expected stroke volume and pre-existing cerebral small vessel disease to be associated with remote lower white matter integrity and consequently account for post-stroke cognitive performance itself. Therefore, the relation between stroke volume and ipsilateral and contralateral FA and MD of the white matter was assessed, adjusting for age, sex, follow-up duration, lesion location (left/right), WMH-volume, depressive symptoms, and fatigue. The prevalence of microbleeds, lacunes, vascular risk factors, and treatment were compared between cognitively impaired and unimpaired patients using a Chi-square test. Log-transformed WMH-volume and stroke volume were compared between these two groups with AN(C)OVA, adjusted for age in case of WMH-volume.

Results

T1-weighted whole-brain imaging, DTI, and FLAIR, SWI, and overall cognitive performance was available from 117 ischemic stroke patients and 84 stroke-free controls (Figure 1). Of the 195 patients with first-ever ischemic stroke in one hemisphere and no recurrent stroke/TIA who participated in the FUTURE study, 117 were included in the present study (Figure 1). Non-participants had a higher mRS at follow-up, a higher NIHSS score at admission, were significantly older at the qualifying event, and less often had an unknown cause according to the TOAST criteria compared with participants (Table 1).
Mean follow-up duration of the stroke population was 10.7 years (SD 8.1), mean age at follow-up was 49.8 years (SD 9.4), and the most frequent lesion location was in the middle cerebral artery (MCA) territory (Table 2 and Figure 2).
About 11 years after stroke the FA of the white matter both in the ipsilateral and contralateral hemisphere was positively related with the cognitive index score, whereas white matter MD of the ipsilateral and contralateral hemisphere was negatively associated with the cognitive index score (n=117) (Figure 2). These associations were independent of WMH-volume, stroke volume, and other confounding variables.

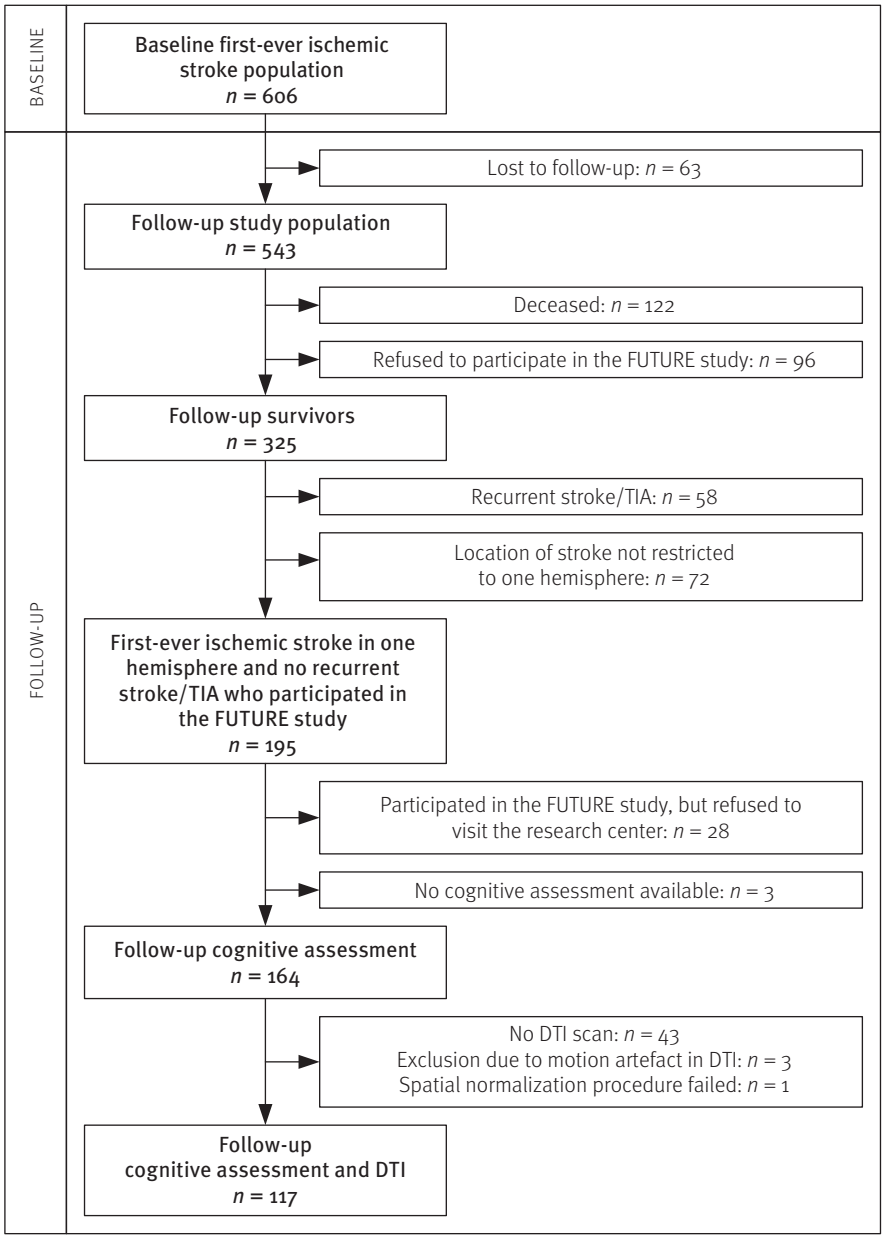


Figure 1 | Flowchart op the study population

Table 1 | Demographic and clinical characteristics between participants and patients who did not participate in the present sub study

Characteristics	Participants	Non-participants	p-value
No.	117	78	
Age at event, mean (SD), y	39.0 (8.2)	41.5 (7.2)	0.03
Follow-up duration, mean (SD), y	10.7 (8.1)	10.2 (9.3)	0.70
Age at follow-up, mean (SD), y	49.8 (9.4)	51.8 (10.4)	0.16
Men, No. (%)	47 (40.2)	23 (29.5)	0.13
Education, median (Q1-Q3)	5 (4-6)	5 (4-5)	0.08
NIHSS at stroke onset, median (Q1-Q3)	4 (2-8)	6 (2-12)	0.02
mRS at follow-up, median (Q1-Q3)	1 (0-2)	2 (1-3)	<0.0001
Lesion location			0.56
Left hemisphere, No. (%)	62 (53.0)	38 (48.7)	
Right hemisphere, No. (%)	55 (47.0)	40 (51.3)	
TOAST			
Atherothrombotic stroke, No. (%)	24 (20.5)	24 (30.8)	0.10
Cardioembolic stroke, No. (%)	9 (7.7)	11 (14.1)	0.15
Lacunar stroke, No. (%)	14 (12.0)	11 (14.1)	0.66
Rare causes, No. (%)	23 (19.6)	17 (21.8)	0.72
Multiple causes, No. (%)	1 (0.9)	3 (3.8)	0.15
Unknown cause, No. (%)	46 (39.3)	12 (15.4)	0.0003

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment. Missing data in participants: education=1.7%, NIHSS at admission=0.9%. Missing data in non-participants: education=2.6%.

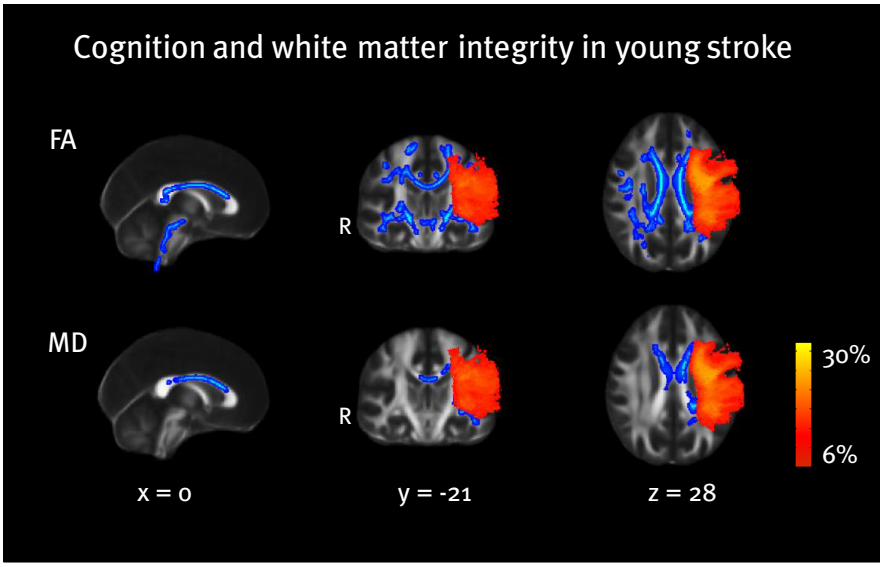
Subsequent analyses showed that a lower remote white matter integrity was associated with a lower performance on the domains of processing speed, attention, working memory, and executive functioning (Figure 3).

A higher mean FA value of the white matter skeleton in the contralateral hemisphere was related to a higher cognitive index score (β=0.24, p=0.008). A higher mean MD value of the white matter in the contralateral hemisphere was related to a worse cognitive index score (β=-0.18, p=0.03).

Table 2 | Demographic and clinical characteristics of ischemic stroke patients and controls

Characteristics	Ischemic stroke patients	Controls
No.	117	84
Age at event, mean (SD), y	39.0 (8.2)	
Year of stroke event, No. (%)		
1980-1989	18 (15.4)	
1990-1999	34 (29.1)	
2000-2010	65 (55.6)	
Follow-up duration, mean (SD), y	10.7 (8.1)	
Age at follow-up, mean (SD), y	49.8 (9.4)	48.9 (11.9)
Men, No. (%)	47 (40.2)	38 (45.2)
Education, median (Q1-Q3)	5 (4-6)	5 (5-6)
NIHSS at stroke onset, median (Q1-Q3)	4 (2-8)	
Normalized stroke volume, median (Q1-Q3), ml	5.5 (0.2-32.8)	
Normalized WMH-volume, median (Q1-Q3), ml	1.4 (0.7-3.3)	0.4 (0.03-1.04)
mRS at follow-up, median (Q1-Q3)	1 (0-2)	0 (0-0)
HADS - depressive symptoms, mean (SD)	3.7 (3.6)	2.5 (2.8)
CIS-20R - subjective fatigue, mean (SD)	29.1 (13.4)	23.0 (12.7)
Lesion location		
Left hemisphere, No. (%)	62 (53.0)	
Right hemisphere, No. (%)	55 (47.0)	
TOAST		
Atherothrombotic stroke, No. (%)	24 (20.5)	
Cardioembolic stroke, No. (%)	9 (7.7)	
Lacunar stroke, No. (%)	14 (12.0)	
Rare causes, No. (%)	23 (19.7)	
Multiple causes, No. (%)	1 (0.9)	
Unknown cause, No. (%)	46 (39.3)	

Data are expressed as mean (SD), number (%), or median (Q1- Q3). NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; HADS, Hospital Anxiety and Depression Scale; CIS-20R, Checklist Individual Strength; TOAST, Trial of Org 10172 in Acute Stroke Treatment. Missing data in patients: education = 1.7%, NIHSS at admission = 0.9%, HADS-depressive symptoms = 1.7%, CIS-20R = 1.7%. No missing data in controls.



White matter tracts in the contralesional hemisphere with lower microstructural integrity in patients with lower cognitive performance

FA analysis	
Corpus callosum	Anterior commissure
Genu	Inferior longitudinal fasciculus (ILF)
Body	Inferior fronto-occipital fasciculus (IFOF)
Splenium	Arcuate fasciculus
Cingulum	Superior longitudinal fasciculus
Internal capsula	Superior and inferior cerebellar peduncle
Cortico-spinal tract	Cortico-ponto-cerebellar tract
MD analysis	
Corpus callosum	
Body	
Splenium	

Figure 2 | The relation between the cognitive index score en white matter integrity

Voxel-wise analysis of the FA, positively related with the cognitive index score, and MD negatively related with the cognitive index score in the population with stroke (n=117). The analyses were adjusted for age, sex, education, follow-up duration, WMH-volume, stroke volume, lesion location, depressive symptoms, and fatigue. The analysis was thresholded at $p<0.05$ and corrected for multiple comparisons (in blue). The color bar denotes the lesion probability map (in red).

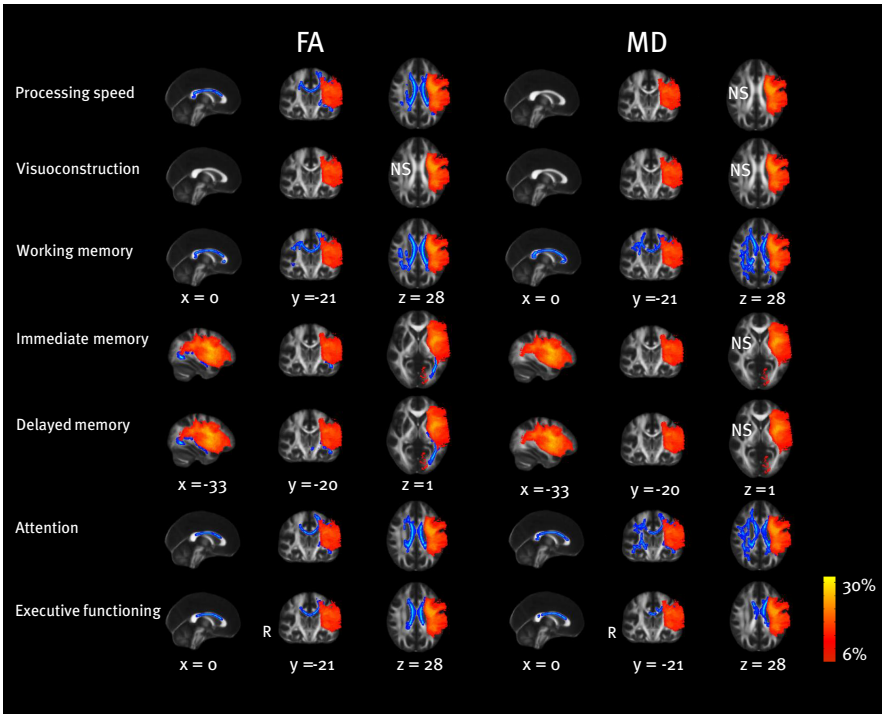


Figure 3 | The relation between cognitive domain scores and white matter integrity

Voxel-wise analysis of the FA, positively related with processing speed, working memory, immediate memory, delayed memory, attention, and executive functioning, and MD negatively related with working memory, attention, and executive functioning in the stroke population (n=117). The analyses were adjusted for age, sex, education, follow-up duration, WMH-volume, stroke volume, lesion location, depressive symptoms, and fatigue. The analysis was thresholded at p<0.05 and corrected for multiple comparisons (in blue). The color bar denotes the lesion probability map (in red). NS= no significant association found.

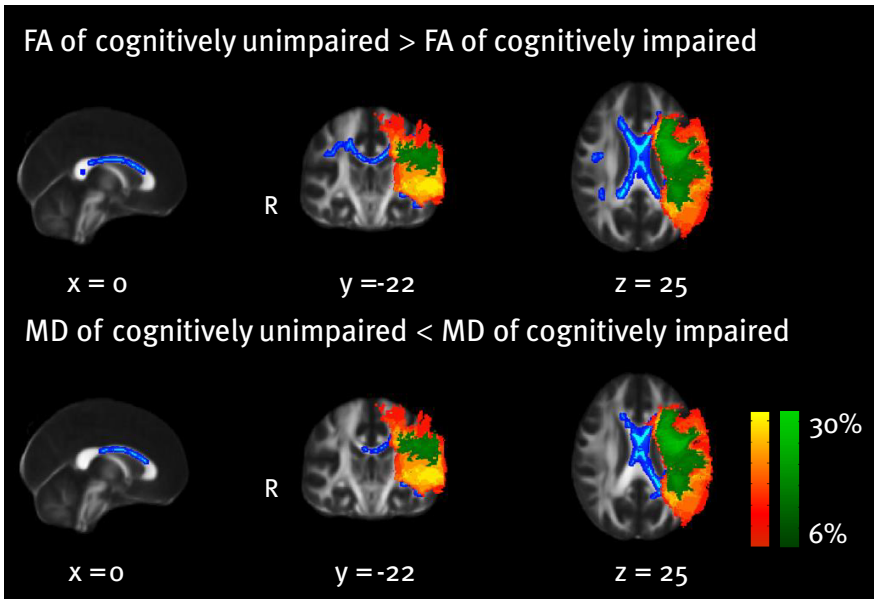
Cognitively impaired patients more often had a stroke in the frontal lobe (p=0.02) and parietal lobe (p=0.004) compared with cognitively unimpaired patients (Table 3).
Even almost 11 years after stroke, a significant lower ipsilateral and contralateral white matter FA and a higher MD was observed in cognitively impaired patients compared with cognitively unimpaired patients (Figure 4).
Stroke volume was associated with lower white matter FA and higher MD values in the ipsilateral and contralateral hemisphere, especially involving the corpus callosum (Figure 5). Cognitively impaired patients showed a significant higher median WMH-volume, a larger stroke volume, had a higher prevalence of ≥1 microbleed(s), not of

Table 3 | Demographic and clinical characteristics, prevalence of cerebral small vessel disease, and medication use in patients with cognitive impairment and no cognitive impairment

Characteristics	Ischemic stroke		p-value[b]
	Cognitively impaired	Cognitively unimpaired	
No.	25	71	
Age at follow-up, mean (SD), y	53.3 (9.7)	48.3 (9.0)	0.25[c]
Normalized stroke volume, median (Q1-Q3), ml	11.1 (0.4-51.3)	1.7 (0.1-15.8)	0.04
Lesion location, No. (%)			0.17
Left hemisphere	16 (64.0)	34 (47.9)	
Right hemisphere	9 (36.0)	37 (52.1)	
Cortical stroke, No. (%)[a]			
Frontal lobe	18 (72.0)	32 (45.1)	0.02
Prefrontal cortex			
Anterior cingulate cortex	2 (8.0)	1 (1.4)	0.10
Medial prefrontal cortex	2 (8.0)	1 (1.4)	0.10
Dorsolateral prefrontal cortex	4 (16.0)	6 (8.5)	0.01
Ventrolateral prefrontal cortex	8 (32.0)	15 (21.1)	0.27
Parietal lobe	16 (64.0)	23 (32.4)	0.01
Precuneus	1 (4.0)	2 (2.8)	0.77
Intraparietal sulcus	8 (32.0)	9 (12.7)	0.03
Temporal lobe	10 (40.0)	30 (42.3)	0.84
Occipital lobe	7 (28.0)	11 (15.5)	0.17
Subcortical stroke, No. (%)[a]			
Basal ganglia	10 (40.0)	29 (40.9)	0.94
Thalamus	4 (16.0)	11 (15.5)	0.95

Cerebral small vessel disease at follow-up			
Normalized WMH-volume, median (Q1-Q3), ml	2.8 (1.7-4.0)	1.2 (0.6-2.3)	0.01
Prevalence of ≥1 microbleed(s), No. (%)	9 (36.0)	5 (7.0)	0.0001
1 microbleed	4 (16.0)	2 (2.8)	
2 microbleeds	3 (12.0)	3 (4.2)	
3 microbleeds	0 (0.0)	0 (0.0)	
≥4 microbleeds	2 (8.0)	0 (0.0)	
Prevalence of ≥1 lacune(s), No. (%)	7 (28.0)	11 (15.5)	0.17
1 lacune	4 (16.0)	8 (11.3)	
2 lacunes	3 (12.0)	1 (1.4)	
3 lacunes	0 (0.0)	2 (2.8)	
Vascular risk factors at follow-up			
Smoking ever, No. (%)	21 (84.0)	49 (69.0)	0.17
Smoking current, No. (%)	11 (44.0)	17 (23.9)	0.06
Hypertension, No. (%)	16 (64.0)	38 (53.5)	0.36
Dyslipidemia, No. (%)	23 (92.0)	64 (90.1)	0.78
Diabetes mellitus, No. (%)	3 (12.0)	5 (7.0)	0.44
BMI, mean (SD)	26.7 (6.4)	25.3 (3.9)	0.92
Medication at follow-up			
Oral antidiabetic medication, No. (%)	3 (12.0)	2 (2.8)	0.08
Blood pressure-lowering agents, No. (%)	9 (36.0)	18 (25.4)	0.31
Insulin, No. (%)	0 (0.0)	3 (4.2)	0.30
Statin, No. (%)	16 (64.0)	28 (39.4)	0.03
Antiplatelet drugs, No. (%)	17 (68.0)	54 (76.1)	0.43

WMH, white matter hyperintensities; BMI, Body Mass Index; Data on smoking of one patient without cognitive impairment was missing.
[a] Stroke could be located in more than one region in a patient.
[b] Statistical comparison between cognitively impaired and unimpaired patients.
[c] The analysis was adjusted for follow-up duration.

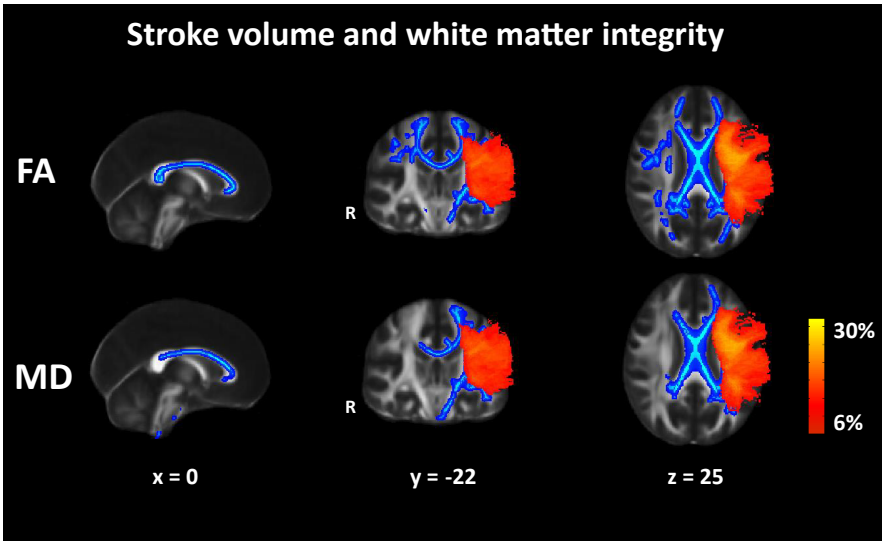


White matter tracts in the contralesional hemisphere with lower microstructural integrity in cognitively impaired patients compared with unimpaired patients

FA analysis	
Corpus callosum	Superior longitudinal fasciculus
Genu	Arcuate fasciculus
Body	
Splenium	
MD analysis	
Corpus callosum	
Body	

Figure 4 | White matter integrity in cognitively impaired patients compared with cognitively unimpaired patients

Voxel-wise analysis of significant higher FA in cognitively unimpaired patients compared with impaired patients, and lower MD in cognitively unimpaired patients compared with impaired patients. The analyses were adjusted for age, sex, education, follow-up duration, stroke volume, WMH- volume, lesion location, depressive symptoms, and fatigue. The analysis was thresholded at $p<0.05$ and corrected for multiple comparisons (in blue). The color bars denote the lesion probability maps of cognitively impaired patients (in red) and cognitively unimpaired patients (in green).



White matter tracts in the contralesional hemisphere with lower microstructural integrity in stroke patients with a larger stroke volume

FA analysis	
Corpus callosum	Internal capsula
Genu	Cortico-spinal tract
Body	Anterior commissure
Splenium	Arcuate fasciculus
Cingulum	Superior longitudinal fasciculus
Inferior fronto-occipital fasciculus (IFOF)	Cortico-ponto-cerebellar tract
MD analysis	
Corpus callosum	
Genu	
Body	

Figure 5 | The association between stroke volume and white matter integrity

Voxel-wise analysis of the FA, negatively related with normalized stroke volume, and MD positively related with stroke volume. The analyses were adjusted for age, sex, follow-up duration, WMH-volume, lesion location, depressive symptoms, and fatigue. The TBSS analysis was thresholded at $p<0.05$ and corrected for multiple comparisons (in blue). The color bar denotes the lesion probability map (in red).

lacunes compared with cognitively unimpaired patients (Table 3). Cognitively impaired patients did not have a higher proportion of patients with vascular risk factors and treatment (except for statins) compared with unimpaired patients (Table 3).

Discussion

This study showed that almost 11 years after ischemic stroke in young adults a lower white matter integrity remote from the index stroke area, which could be as remote as the contralateral hemisphere, was associated with an increased risk of long-term cognitive impairment. Conversely, higher remote white matter integrity was associated with a low risk of long-term cognitive impairment. A larger stroke volume was associated with lower remote white matter integrity, even in the contralateral hemisphere. The presence of concomitant cerebral small vessel disease was more frequently observed in cognitive impaired patients compared with unimpaired patients, however, after controlling for WMH-volume in the TBSS analysis this did not change the results on lower remote white matter integrity after stroke.

Although stroke has been associated with remote neurophysiological effects, termed as diaschisis, which tends to normalize over time,[276] we now showed that about 11 years after stroke a lower *structural* integrity of remote white matter is associated with long-term cognitive impairment.

There are some potential underlying mechanisms for lower remote white matter integrity and worse concomitant cognitive performance. As we adjusted for stroke volume in the analyses, stroke volume is not the only predictor for difference in remote white matter integrity and concomitant differences in long-term cognitive outcome. An alternative explanation could be the higher prevalence of cerebral small vessel disease in cognitively impaired patients compared with cognitively unimpaired patients. Lower white matter integrity, as measured by diffusion tensor imaging, could be an early marker of the pathogenic cerebral small vessel disease related mechanism before WMH, lacunes, and microbleeds occur on conventional MRI.[292] However, the absolute number of microbleeds, lacunes, or WMH-volume was relatively low in both groups, as expected in these relatively young patients, and after adjustment for WMH-volume we still observed a lower remote white matter integrity in cognitively impaired patients compared with unimpaired patients. Therefore, it seems less likely that cerebral small vessel disease largely explained our results on remote white matter integrity and the concomitant worse cognitive performance.

Another explanation might be that lower remote microstructural integrity is caused by vascular damage caused by being exposed to the same vascular risk factors that caused the initial stroke event. Furthermore, based on studies in rats, stroke itself might cause spreading depression in the *ipsilateral* hemisphere,[221, 293] which may allow the onset of secondary (Wallerian) degeneration of remote white matter after ischemic stroke.[294] However, the extent of this phenomenon should be further investigated to whether it also could explain the lower microstructural integrity in *contralateral* white matter as we observed in cognitively impaired patients. For instance, a lower white matter integrity of the corpus callosum in the contralateral hemisphere was associated

with cognitive impairment. It seems that beside cognitive outcome, microstructural integrity of the corpus callosum has been found to predict the degree of motor function after stroke,[295] and therefore seems to be an important white matter structure for outcome after stroke.

Another important clinical finding is the higher remote white matter integrity in patients with preserved cognitive performance, which might be due to a different underlying mechanism compared with lower remote white matter integrity. Plasticity and vicariation (intact brain areas take over the functions of the stroke area) might have occurred in cognitively unimpaired patients.[276] This idea is possibly supported by our findings that FA correlated better with remote white matter integrity compared with MD, as lower FA may not necessarily reflect lower underlying structural integrity since FA reflects the directionality of molecular displacement by diffusion and is influenced by crossing fibers.[268] MD reflects the magnitude of water diffusion which is less influenced by direction of fibers and therefore MD remains relatively constant.[268, 269] Therefore, lower FA, but not higher MD in stroke patients may reflect plasticity, resulting into a reorganization of white matter and subsequently into more (new) crossing fibers.[296] Caution must be taken in interpreting these findings as different pathologies, different stages of disease, or the rate of degeneration can lead to different tensor behaviors (FA and MD).[269] Another possible explanation might be that no secondary neurodegeneration occurred in cognitively unimpaired patients as opposed to cognitively impaired patients.

Strengths of our study include its large sample size and the long follow-up duration. We collected baseline and follow-up information according to identical procedures in all patients, used strict protocols for cognitive assessment, and researchers were trained, in order to reduce the risk of information bias.

However, some methodological issues of the present study need to be considered. Although the FUTURE study has a prospective design, the current analysis is cross-sectional and we therefore can only report on lower microstructural integrity after stroke in cognitively impaired patients. While this lower integrity may be caused by post-stroke microstructural degradation of white matter, a longitudinal design is required to further support causality. However, our data clearly demonstrate a relation between stroke volume and reduced white matter integrity.

Although we have tried to statistically correct for differences in stroke characteristics (volume and location) as thoroughly as possible between cognitively impaired patients and unimpaired patients, there still might be some residual confounding between these two groups. For instance, we observed a higher proportion of cognitively impaired patients with a stroke in the dorsolateral prefrontal cortex and intraparietal sulcus compared with unimpaired patients. These areas have been found to be "connector hubs",[297] which play a central role in integrating information from multiple networks.[298] A stroke in these areas is considered as a strategic lesion, as it hampers

the communication between different networks important for multiple cognitive components. Consequently, this may result into deterioration of multiple remote white matter fibers, which in turn more severely affects post-stroke cognitive functioning.
Also, selection might have occurred, since patients who participated in the FUTURE study, but could not participate in the present DTI study, had a poorer outcome compared with participants. However, selection bias seems unlikely as both the direction and magnitude of the association between white matter integrity and cognitive performance will not be selectively different in participants and non-participants.
Another limitation of the present study is the exclusion of patients with severe aphasia from cognitive testing. This might have potentially limited the generalizability of our present results on cognitive tests to a young first-ever ischemic stroke population in general. However, our previous work on long-term cognitive outcome in these young ischemic stroke patients showed a low number of patients with aphasia.[255] Therefore, it seems unlikely that excluding these small number of patients largely influenced the generalizability of present results to young patients with ischemic stroke.
In conclusion, our results implicate that remote structural integrity of the white matter is associated with cognitive performance 11 years after stroke. Longitudinal studies are needed to investigate the course of remote lower white matter integrity and concomitant cognitive performance after onset of stroke, which might reveal early individual treatment opportunities after stroke.

IV

Part

Summary and discussion

8

Chapter

Summary, general discussion and future perspectives

Summary

The aim of the present thesis was to describe the spectrum and severity of long-term cognitive impairments after first-ever ischemic stroke in young adults, using MRI biomarkers to understand the underlying mechanisms of cognitive impairments that cannot always be explained by lesion characteristics itself. Stroke frequently occurs in older adults [299], but up to 14% of all ischemic strokes occur in young adults (18 through 50 years of age). This thesis is part of the FUTURE study, a prospective cohort study on causes and long-term consequences of a young stroke (**chapter 2**). Data on long-term cognitive outcome and underlying MRI biomarkers are lacking in these young adults. A better understanding of the etiology of post-stroke cognitive impairment and its possible recovery is especially important in young stroke survivors, as they are in a demanding phase of their lives with respect to educational, vocational, and family-related functioning.

Chapter 3 provides a critical overview on the etiology and long-term perspective of stroke in young adults. Although stroke in young adults often is associated with rare causes, we postulated that the traditional vascular risk factors, often observed in older stroke patients, may explain a considerable proportion of stroke in young adults as well. Furthermore, the long-term prognosis with respect to cardiovascular disease, mortality, and psychosocial consequences is less favorable than previously thought.

Long-term cognitive impairment after a young ischemic stroke

In **chapter 4** the cognitive performance of young-stroke patients about 11 years after first-ever ischemic stroke is compared with a stroke-free population. Up to 50% of the patients (dependent on the cognitive domain examined) showed a below-average performance (>1 SD below the average of the performance of controls) or a cognitive impairment (>1.5 SD). Deficits in processing speed, working memory, and attention were most commonly observed. A negative relation was found between longer follow-up duration and the performance in the domains immediate memory, delayed memory, and executive functioning.

Remote structural changes underlying a worse post-stroke cognitive performance

We focused on structural changes in the brain remote from the ischemic stroke that might explain cognitive impairments that frequently cannot solely (if at all) be explained by the stroke volume and location itself. In **chapter 5** we demonstrated that the ipsilateral, and not the contralateral hippocampal volume was smaller compared with controls. In the patients with smaller ipsilateral hippocampal volume, we observed a worse memory performance compared with controls, although still within the clinically unimpaired range (i.e., less than 1.5 standard deviations below the mean of the

controls). A larger stroke volume was associated with a lower ipsilateral hippocampal volume. In left-hemispheric stroke patients a positive association was found between left hippocampal volume and lower immediate and delayed visual memory performance. **Chapter 6** describes hippocampal integrity after ischemic stroke. Using Diffusion Tensor Imaging (DTI), a lower ipsilateral hippocampal integrity (Fractional Anisotropy [FA] and Mean Diffusivity [MD]), not contralateral hippocampal integrity was found in hemispheric stroke patients compared with a non-stroke population. A larger stroke volume was associated with a lower ipsilateral hippocampal integrity after ischemic stroke in one of the hemispheres. We did not observe a reduced verbal and visual memory performance in patients with "normal" ipsilateral hippocampal volume but a reduced hippocampal integrity compared with controls.
Chapter 7 describes the white matter integrity remote from the ischemic lesion which could contribute to a better understanding of long-term cognitive impairments, but perhaps also of recovery after ischemic stroke in young adults. Even on average 11 years after ischemic stroke we found that a higher remote white matter integrity was associated with a better cognitive outcome. This relation was independent of stroke volume, WMH-volume, and other confounders. We found a lower white matter integrity in areas remote from the stroke area in cognitively impaired patients compared with cognitively unimpaired patients, after adjustment for cerebral small vessel disease, stroke volume, and other confounders. Areas involved white matter in the ipsilateral hemisphere, but also the contralateral stroke-free hemisphere. Stroke volume was negatively associated with remote white matter integrity, also in white matter areas in the contralateral hemisphere (corpus callosum). In addition, we showed that the prevalence of cerebral small vessels disease was higher in cognitively impaired patients compared with cognitively unimpaired patients, but the severity was low. Based on the findings of this study it seems less likely that cerebral small vessel disease largely explained the worse cognitive outcome and concomitant lower remote white matter integrity.

General discussion

This thesis is embedded within the FUTURE study, which is a large prospective cohort study on etiology and long-term prognosis of stroke in young adults (aged 18 through 50 years). This chapter provides the most important methodological considerations and discussion of the main findings presented in this thesis. Thereafter, the clinical implications and suggestions are described for future research.

Methodological considerations

Study design

The studies presented in this thesis had a prospective design, which means that cognitive performance and neuroimaging data of all patients and controls were measured at one time point after stroke. Due to this design we were not able to determine the exact course of the cognitive prognosis after ischemic stroke in young adults and the relation with the associated imaging biomarkers over time. However, the follow-up duration between stroke onset and long-term outcome measures varied from less than a year to up to 30 years. As a result, we were able to gain important insights into the time course of the outcome after stroke. The present design also has a major advantage, as it enabled the collection of all the data in a standardized way within a relatively short period of time. Furthermore, cross-sectional data are also essential for generating hypotheses for future studies.

Internal validity

The internal validity of the present cohort study is determined by our understanding and inclusion of relevant predictors and confounding variables (confounding), the validity of the measurements (information bias) and sampling (selection bias). There are ways to minimize their impact before the start of the study or due to adjustment in the analyses or even by choosing proper measurements.

A *selection bias* may have been present.[300] For instance, we consistently observed that non-participants had a more severe stroke according to the NIHSS score, had a lower mRS at follow-up, were older at the time of the stroke, and less often had an unknown cause according to the TOAST etiology criteria compared with participants. Although it seems unlikely that observed associations in participants were different from those in non-participants, it is possible that we have missed the patients with an even worse cognitive outcome after stroke, which might have underestimated the strength of present associations.

Information bias occurs when there is a flaw in measuring the exposure, covariate, or outcome variables that subsequently results in different quality (accuracy) of information.[300] Misclassification can be divided into differential and non-differential misclassification. Differential misclassification arises when the degree of misclassifi-

cation differs between groups, which results into an over- or underestimation of the true association. Non-differential misclassification arises when categories of a variable have the same error rate of being misclassified, which often leads to an underestimation of the true association.

The FUTURE study consisted of a long-term follow-up, which inevitably leads to differences in diagnostic work-up and acute treatments due to improvements over the last decades, which is an example of non-differential misclassification. However, with respect to mortality, the etiology of the stroke, and recurrent vascular events no cohort effects were found in the FUTURE study.[23] Still, differences in treatment methods over time might have had an influence on cognitive outcome after ischemic stroke. For instance, since the beginning of the year 2000 intravenous recombinant tissue plasminogen activator (rt-PA) has been the first choice of acute stroke treatment in Europe (treatment < 4.5 hours arriving at the hospital after stroke) and is associated with a reduction of lesion volume.[301] Although this treatment has been associated with a better functional outcome at follow-up,[301] a favorable basic and instrumental ADL outcome,[302] improvement of aphasia and neglect symptoms,[2, 303-305] no beneficial effect of this treatment has been found with respect to memory, speed of information processing, executive functioning, and attention six months after stroke.[302] However, it should be mentioned that patients treated in the study of Nys et al. (2006) had more severe stroke symptoms after stroke onset than patients not treated with rt-PA.[302] After repeating the analyses with comparable groups with regard to stroke severity Nys et al. (2006) obtained essentially the same results, suggesting that the bias in stroke severity cannot fully explain their results. Nys et al. (2006) suggests that their still might be some residual confounding of baseline differences between the two patient groups and therefore the authors suggest that future studies on cognitive outcome after rt-PA treatment should include more representative patients who are typically enrolled in acute stroke trials.[303] Thus, at present the exact impact of this treatment on neuropsychological functioning remains unknown, and to what extent this may have affected the prevalence of long-term cognitive impairment in young adults is yet unclear. However, it should be noted that in 2004 this treatment was introduced in our center, which resulted in only 16 ischemic stroke patients (2.7% of total ischemic stroke population in the FUTURE study) who received thrombolytic therapy.[23] It seems unlikely, that these few cases largely influenced the prevalence of cognitive impairment in our cohort if there is an effect of rt-PA on cognitive outcome at all. Future large cohort studies should unravel whether rt-PA benefits cognitive function, especially in young adults.

In most human beings the left hemisphere of the brain is dominant for language. Therefore, decrements in expression or comprehension of language due to stroke (aphasia) might hamper the performance on the neuropsychological tests, more in left-hemispheric stroke patients compared with right-hemispheric stroke patients. For

this reason, differential misclassification might have occurred in left-hemispheric stroke patients compared with right-hemispheric stroke patients with respect to cognitive outcome. However, we re-ran our analyses on (verbal and visual) memory performance and hippocampal volume and integrity after excluding the patients with aphasia at discharge, which did not alter our conclusions. Furthermore, researchers indicated during the neuropsychological screening whether the test administration was valid or not and severe aphasia was an exclusion for verbal tests.

Another example of differential misclassification in cognitive functioning might have been caused by the fact that researchers who assessed cognitive functioning could not be blinded for stroke or a non-stroke subject, as stroke is often associated with visible physical impairments. However, we used strict administration protocols for the cognitive tests and all researchers were trained to reduce the risk of information bias.

As for the neuroimaging data, manual segmentation of the hippocampus, stroke volume, but also small vessel disease characteristics could not have been done blindly to the side of the stroke. However, researchers were blinded for other demographical data, clinical outcome measures, and cognitive performance. Furthermore, the intra-rater and inter-rater reliability of a random set of hippocampal manual segmentations and small vessel disease segmentations were high, therefore differential misclassification does not seem likely.

Smaller hippocampal volumes have a higher risk of partial volume effects when investigating hippocampal integrity, especially increasing the risk of including CSF in the hippocampal mask. This might have influenced the reliability of the hippocampal integrity index observed in smaller hippocampal volumes. We have minimized this risk of differential misclassification by eroding the hippocampal mask by one voxel in all directions.

Also, one can argue that the associations we observed were the result of confounding variables.

Confounding occurs when the association between the determinant and outcome is caused by a third variable that is not an intermediate factor between the determinant and the outcome.[300] In our analyses we adjusted for major confounding factors (such as age, sex, education, depressive symptoms, fatigue), which might have influenced cognitive outcome, hippocampal volume, hippocampal integrity, and white matter integrity.

Another potential confounding factor is that we do not have data on the patients' pre-stroke cognitive performance, which could have influenced post-stroke cognitive performance. Thus, some people can tolerate more of these brain changes than others and maintain function.[306] In addition, it is possible that young stroke patients also have other diseases or for example vascular risk factors, which may also affect both cognitive performance and white matter integrity prior and after stroke. We have tried

to overcome these problems by using an age, sex, and education matched stroke-free control group, which were recruited among patients' spouses, relatives, or social environment. We have therefore included a control group with approximately the same environmental exposure as the patients. It was our intention not to include completely healthy controls as this would have resulted in an overestimation of the between group differences.
Also, when measuring post-stroke cognitive performance the performance on cognitive domains may influence one another. For instance, a worse memory performance could be influenced by decrements in attention and/or processing speed. Due to an inability to concentrate or a slower processing speed the to be remembered information is not well encoded in the first place. Moreover, a lower executive functioning might cause an inability to organize the to be encoded and remembered information efficiently, which also could hamper memory functioning. Still, despite cognitive decrements in multiple cognitive domains, an actual memory impairment may also exist. Also, a larger stroke volume is likely to cause cognitive impairments in multiple cognitive domains, beside the cognitive domain of memory for instance. Adjusting in the statistical analyses for other cognitive domains and thereby adjusting indirectly for the severity of the stroke may be less appropriate, as stroke severity is also part of the cause of post-stroke memory impairment. For these reasons, we intentionally did not adjust for other cognitive domains in the analyses between memory performance and hippocampal volume and integrity.

Neuropsychological assessment

The neuropsychological tests used in the present thesis covered the main cognitive domains and all tests have been previously applied in large-scale epidemiological studies of cerebrovascular disease, producing reliable findings.[42, 43] The neuropsychological assessment in total was feasible and the length was about 45 minutes. In order to keep the administration duration feasible and to be able to examine as much patients as possible (e.g., patients with fatigue or limited motivation), not all aspects of cognitive function could be assessed in detail. For instance, the domain of executive functioning was investigated by a fluency test and the abbreviated Stroop test, but did not include tests that measure planning (e.g., subtests of the Behavioural Assessment of the Dysexecutive Syndrome battery) or mental flexibility (such as the Trail Making Test). This might have led to an underestimation of patients with impairments in executive functioning. Also, language comprehension was not objectively assessed in our neuropsychological assessment, which might have underestimated the number of patients with subtle language problems. However, we have tried to identify patients during neuropsychological assessment that were not able to complete neuropsychological tests due to language problems. We then excluded these patients with post-stroke language disorders from verbal testing. Future studies on cognitive

outcome after ischemic stroke in young adults are encouraged to incorporate language as an outcome measure.

External validity

External validity is the extent to whether present results obtained in our sample population can be generalized to make predictions about the Dutch young stroke population in general.[300] The studies presented in this thesis were academic-hospital based, not community-based. Consequently, our sample may not represent all cases of young stroke in our catchment area. However, those who survive usually visit a university medical center during the course of their disease and we included all consecutive cases admitted to our hospital in the FUTURE study. Moreover, the age- and sex- standardized prevalence of stroke in the catchment area equals that of the age- and sex- standardized prevalence of stroke in the Netherlands.[205] Therefore, for the FUTURE study in general (N = 606 first-ever ischemic stroke patients) it seems that the stroke population is representative to the wider Dutch stroke population. However, we showed that patients not participating in the present MRI studies were somewhat older at stroke onset, had a higher NIHSS score at event, a lower education, and less frequently had an unknown cause according to the TOAST criteria. It does not seem likely that present observed associations in participants were different in non-participants, but it might have underestimated the strength of the real associations.

Precision

Precision reflects the repeatability of a measure, but in essence does not need to reflect accuracy.[300] Flaws in precision of a measure are caused by random error. Random error may result into high sampling variance and underestimation of the effects. We have tried to reduce the sampling variability by investigating a large sample size, using a single scanner with the same hard- and software during our inclusion period, and showed high inter- and intrarater reliability of hippocampal volumes and cerebral small vessel disease markers. Possibly, in some subanalyses with smaller sample sizes a reduction in power might have occurred, which resulted in an underestimation true association.

Underestimation of the effects might be caused by within-person variability, for example in cognitive performance due to random error (i.e., bad night's sleep). Patients and controls were measured once, but we used compound scores instead of neuropsychological test scores, which was an average of a larger number of observations, that mainly measured the same cognitive domain. In this way, we have tried to reduce the risk of random error.

Pathogenesis of long-term post-stroke cognitive impairment

Based on the studies presented in this thesis, some potential underlying neuroimaging biomarkers have been identified that could account for long-term cognitive impairment in these young stroke patients. We have clearly demonstrated that stroke volume is associated with a smaller ipsilateral hippocampal volume, lower ipsilateral hippocampal and thalamic integrity, and remote white matter integrity.

As we adjusted for stroke volume in the analyses, stroke volume is not the only predictor for differences in remote white matter integrity and concomitant differences in long-term cognitive outcome. An alternative explanation could be the higher prevalence of cerebral small vessel disease in cognitively impaired patients compared with cognitively unimpaired patients. Lower white matter integrity could be part of the pathogenic cerebral small vessel disease related mechanism even before WMH, lacunes, and microbleeds occur.[292] However, the absolute number of microbleeds, lacunes, or WMH-volume was relatively low in the cognitively impaired and cognitive unimpaired patient groups, as expected in these relatively young patients. Furthermore, we still observed a lower remote white matter integrity in cognitively impaired patients after adjustment for WMH-volume. Therefore, it seems less likely that cerebral small vessel disease largely explained the results on remote white matter integrity and a concomitant worse memory performance.

Another explanation might be that lower remote microstructural integrity is caused by vascular damage by being exposed to the same vascular risk factors that caused the initial stroke event. Furthermore, based on studies in rats, stroke itself might cause spreading depression in the *ipsilateral* hemisphere,[221, 293] which may allow the onset of secondary (Wallerian) degeneration of remote white matter after ischemic stroke.[294, 307] However, the extent of this phenomenon should be further investigated to whether it also could explain the lower white matter integrity in the *contralateral* hemisphere as we observed in cognitively impaired patients. Lastly, cognitively impaired patients might have had pre-existing lower white matter integrity before stroke onset due to a genetic predisposition,[308] which may influence post-stroke cognitive recovery. This needs further investigation.

Clinical relevance

Our results contribute to the understanding of the spectrum of cognitive impairments in young ischemic stroke patients. We further identified imaging biomarkers that were associated with a lower long-term post-stroke cognitive performance. In clinical practice this information could be used by doctors and neuropsychologists to inform their patients on the long-term cognitive prognosis.

Future directions

Although the studies described in this thesis yielded important findings, some recommendations for future research can be made. First, a longitudinal design can provide valuable insights into changes in cognitive function over time after stroke in young adults, as well as their relation with the course of structural brain changes. For instance, at present it remains unknown whether the ischemic stroke itself induced remote structural changes or whether these remote structural effects develop over a longer period of time.

Second, more research should focus on a personalized approach. That is, it is unknown which patients exactly are at risk for remote structural changes with an attendant worse cognitive performance. For instance, it might be interesting to investigate whether patients with similar stroke volumes and location show differences in cognitive decline over time after ischemic stroke and subsequent remote lower white matter integrity. Some patients might be more vulnerable for cognitive decline than others. Also, the concept of cognitive reserve may explain the large individual differences in cognitive (dys)function after stroke, as patients with better cognitive reserve may be able to successfully compensate for cognitive decrements, resulting in better outcome. Ideally, a large community-based cohort is followed over time with cognitive assessment, incorporating information on pre-stroke cognitive functioning, neuroimaging data (DTI, T1, FLAIR, SWI) and incident ischemic stroke patients are compared with stroke-free individuals.

Finally, another important target for future research is to investigate whether these young ischemic stroke patients become demented earlier in life than their stroke-free peers. Interestingly, stroke in older individuals often co-occurs with Alzheimer pathology,[309] but in our young stroke patients (about 50 years at follow-up assessment) the co-occurrence of Alzheimer pathology is very unlikely given their young age (about 10%).[19, 20] Dementia possibly occurs after a much longer interval after ischemic stroke in these young adults compared with ischemic stroke in older individuals. This might therefore contribute to the understanding of stroke as a risk factor itself for developing dementia. Longitudinal studies may also be able to identify additional risk factors for developing dementia after a stroke at young age.

Appendices

References

Summary in Dutch | Nederlandse samenvatting

Acknowledgements | Dankwoord

Curriculum Vitae

List of publications

Dissertations of the disorders of
movement research group, Nijmegen

Donders Graduate School for
Cognitive Neuroscience Series

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Dutch summary | Nederlandse samenvatting

Het doel van dit proefschrift is inzicht te verschaffen in het spectrum en de ernst van de cognitieve stoornissen, die gemiddeld 11 jaar na een herseninfarct op jonge leeftijd op kunnen treden. In dit proefschrift zijn MRI-biomarkers onderzocht om cognitieve problemen te begrijpen, aangezien deze niet altijd goed verklaard kunnen worden door de karakteristieken van het herseninfarct zelf, zoals de grootte en de locatie. De incidentie van een herseninfarct neemt toe met leeftijd. Uit epidemiologisch onderzoek blijkt echter dat ongeveer 14% van alle patiënten met een herseninfarct tussen de 18 en 50 jaar is. In de Engelse wetenschappelijke literatuur wordt dit ook wel een "young stroke" genoemd. Dit proefschrift is een onderdeel van de FUTURE-studie, een prospectieve cohortstudie naar de oorzaken en gevolgen van een herseninfarct bij volwassenen van 18 tot en met 50 jaar (**hoofstuk 2**).

Onderzoeken naar gevolgen wat betreft cognitief functioneren na het doormaken van een herseninfarct in deze leeftijdsgroep waren beperkt tot één jaar follow-up. Echter, deze volwassenen hebben gezien hun jonge leeftijd een relatief lange levensverwachting. Het herseninfarct treedt op in een periode van hun leven waarin een groot beroep gedaan wordt op hun cognitieve vermogens; studie, werk, gezin en een sociaal leven. De bevindingen van dit proefschrift dragen daarom bij aan een beter begrip van deze lange termijn cognitieve prognose.

Hoofdstuk 3 bestaat uit een kritische review die een overzicht geeft van de etiologie en langetermijnprognose van een herseninfarct op volwassen leeftijd. Een herseninfarct op jonge leeftijd wordt vaak geassocieerd met een zeldzamere oorzaak, maar het blijkt echter dat een substantieel deel van deze jonge patiënten (tenminste 50%) toch één of meer veel voorkomende vasculaire risicofactoren heeft, zoals hypertensie en diabetes. Daarnaast is de langetermijnprognose met betrekking tot cardiovasculaire ziekten, sterfte, en psychosociale gevolgen minder gunstig dan eerder werd aangenomen.

Cognitieve stoornissen jaren na een herseninfarct op volwassen leeftijd

In **hoofdstuk 4** wordt de cognitieve prestatie ongeveer 11 jaar na een herseninfarct beschreven en vergeleken met een controlegroep. De resultaten laten zien dat ongeveer de helft van de patiënten een beneden gemiddelde prestatie of zelfs een cognitieve stoornis heeft op tenminste één van de cognitieve domeinen. Stoornissen in snelheid van informatieverwerking, werkgeheugen en aandacht komen het meeste voor. We hebben vastgesteld dat een langere follow-up-duur (in jaren) gerelateerd is aan een verminderde prestatie op neuropsychologische testen die een beroep doen op de geheugenfunctie en executieve functies. Deze resultaten laten zien dat bij deze nog relatief jonge patiënten -met een over het algemeen goed motorisch herstel -

verminderde cognitieve prestaties aanwezig zijn op de langere termijn ten opzichte van een controlegroep zonder herseninfarct.

Structurele veranderingen op afstand van het herseninfarct en de relatie met cognitie

In **deel III** ligt de focus op structurele veranderingen in hersengebieden op afstand van het gebied waar het herseninfarct zich bevindt. De cognitieve stoornissen na een herseninfarct kunnen immers vaak niet helemaal verklaard worden door het volume of locatie van het infarct zelf.

In **hoofdstuk 5** wordt beschreven dat het volume van de ipsilaterale hippocampus kleiner is na een herseninfarct in één van de hemisferen vergeleken met een controlegroep. Er is echter geen verschil gevonden in het volume van de contralaterale hippocampus van deze patiënten vergeleken met een controlegroep. We laten zien dat deze patiënten ook een verminderde geheugenprestatie hebben ten opzichte van een controlegroep zonder herseninfarct. Echter, deze verminderde geheugenprestatie is op groepsniveau niet dermate afwijkend dat er sprake is van een stoornis.

Een groter herseninfarct wordt geassocieerd met een kleiner volume van de ipsilaterale hippocampus na een herseninfarct in de linker of rechter hemisfeer. Bij patiënten met een herseninfarct in de linker hemisfeer is een positieve relatie tussen de het volume van de linker hippocampus en een onmiddellijke en uitgestelde herinnering van visuele informatie aangetoond.

In **hoofdstuk 6** wordt de microstructurele integriteit van de hippocampus beschreven gemiddeld 10 jaar na een herseninfarct. Na een herseninfarct in de linker of rechter hemisfeer is er een verminderde integriteit van de ipsilaterale hippocampus aangetoond ten opzichte van de controlegroep. Ook hier is er echter geen sprake van een verschil in de integriteit van de contralaterale hippocampus tussen patiënten en de controlegroep. Ook hier is er een negatieve relatie aangetoond tussen de grootte van het herseninfarct en de integriteit van de ipsilaterale hippocampus. Opvallend is ook dat patiënten met een “normaal” volume van de ipsilaterale hippocampus, maar een verminderde integriteit van de ipsilaterale hippocampus geen significant verminderde verbale en visuele geheugenprestatie laten zien.

In **hoofdstuk 7** zijn de veranderingen in de integriteit van de witte stof op afstand van het herseninfarct onderzocht. We hebben daarbij de prevalentie en ernst van ‘cerebral small vessel disease’ onderzocht (schade aan de kleine bloedvaten in de hersenen die zich uit in microbloedingen, lacunes en wittestofafwijkingen). Ongeveer 10 jaar na een herseninfarct op volwassen leeftijd blijkt dat patiënten met cognitieve stoornissen een verminderde integriteit van de witte stof hebben op afstand van het gebied waarin het herseninfarct is opgestreden in vergelijking met patiënten zonder cognitieve stoornissen. Dit is zelfs zichtbaar in witte stofbanen in de contralaterale hemisfeer, mogelijk ontstaan via het corpus callosum. De resultaten zijn onafhankelijk van het

volume van het herseninfarct, het volume van de wittestofafwijkingen en andere verstorende factoren. Wel blijkt, dat hoe groter het herseninfarct is, des te groter zijn de afwijkingen in de integriteit van de witte stof op afstand, zelfs in de contralaterale hemisfeer. Patiënten met cognitieve stoornissen na een herseninfarct hebben vaker microbloedingen en wittestofafwijkingen dan patiënten zonder cognitieve stoornissen, maar de ernst van deze afwijkingen is gering.

Conclusie

De studies beschreven in dit proefschrift laten zien dat cognitieve stoornissen op de lange termijn na een herseninfarct op volwassen leeftijd (18 tot en met 50 jaar) frequent voorkomen, waarbij over het algemeen een goed motorisch herstel plaatsvindt. Er zijn verminderde cognitieve prestaties gevonden in bijna alle cognitieve domeinen en vooral op het gebied van tempo van informatieverwerking, werkgeheugen en aandacht. We hebben verder aangetoond dat er structurele veranderingen plaatsvinden op afstand van het herseninfarct die gerelateerd zijn aan een verminderde cognitieve prestatie op de lange termijn, zelfs na het corrigeren voor het volume van het herseninfarct, het volume van de wittestofafwijkingen en andere verstorende factoren. Het infarctvolume is een consistente voorspeller voor structurele veranderingen op afstand van het herseninfarct. De ernst van schade aan de kleine vaten is gering in patiënten met stoornissen in meerdere cognitieve domeinen. Hierdoor lijkt het minder waarschijnlijk dat schade aan de kleine vaten een belangrijke rol speelt bij het gevonden resultaat van verminderde wittestofintegriteit op afstand van het hersen-infarct.

Toekomstige studies met een longitudinaal design kunnen onderzoeken of patiënten met een verminderde integriteit van de witte stof op afstand van het herseninfarct een verhoogd risico lopen op vervroegd ontstaan van dementie vergeleken met een controlegroep zonder herseninfarct. Het is verder interessant om te onderzoeken of en welke patiënten met een vergelijkbare grootte van het herseninfarct en dezelfde lokalisatie verschillende cognitieve uitkomsten laten zien, met mogelijk daarbij verschillen in wittestofintegriteit op afstand. Mogelijk zijn sommige patiënten extra kwetsbaar voor cognitieve achteruitgang en structurele veranderingen op afstand van het herseninfarct. Dit kan implicaties hebben voor individuele preventie en behandeling van cognitieve achteruitgang na een hersen-infarct op jonge leeftijd.

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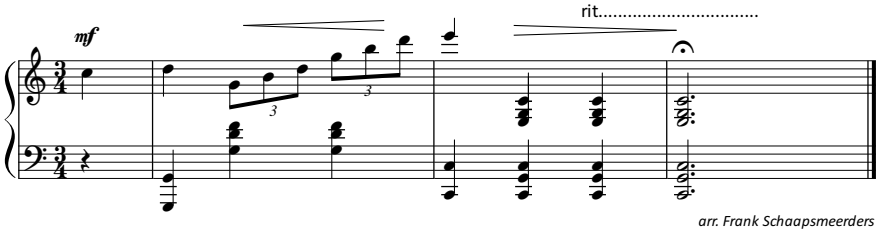
Rest mij alleen nog:



Curriculum Vitae

Pauline Schaapsmeerders was born on March 19, 1988 in Nijmegen, the Netherlands. After completing secondary school she started studying Psychology at the Radboud University, with a special interest in neuropsychology. She completed her Masters's degree cum laude in 2011 after four years of studying. During that time she followed the Radboud disciplinary honours programme, which included three research internships. The first internship was on the underlying neural mechanisms of the placebo effect at the Radboud University (prof. dr. M. Kompier). The second internship was at the department of Biological Psychology at the Radboud University, where she studied the behavioral consequences of chronic ethosuximide treatment on the anti-epileptogenesis in WAG/Rij rats (prof. dr. G. van Luijtelaar). During this internship the enthusiasm for conducting research on the diseased brain with clinical correlates began to grow. Afterwards, the third research internship was at the department of Neurology on cerebrovascular disease in young patients, at the Radboudumc collaborating with prof. dr. F-E de Leeuw and prof. dr. R. Kessels. The result of this internship was the start of a PhD project in 2011 with a main focus on neuroimaging biomarkers for long-term cognitive impairments after a stroke at young age. In July 2013 she won a research award for the best abstract at the International Neuropsychological Society meeting in Amsterdam.

In 2015 she already started working as a researcher at the department of Neurosurgery at the Elisabeth-TweeSteden hospital (dr. G-J Rutten) studying neuroimaging data of glioma patients with different clinical outcomes.

Besides a special interest in research in the field of neuropsychology, she is working as a psychologist for several years now with a special interest in cerebrovascular disease and dementia.

List of publications

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Dissertations of the disorders of movement research group, Nijmegen

Vascular disorders of movement – The Radboud Stroke centre

- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
- Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011
- Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012
- Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, 14 April 2014
- Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, 12 June 2015
- Nathalie E. Synhaeve. Determinants of long-term functional prognosis after stroke in young adults. Radboud University Nijmegen, 28 September 2016
- Anil M. Tuladhar. The disconnected brain: mechanisms of clinical symptoms in small vessel disease. Radboud University Nijmegen, 4 October 2016

Parkinson Center Nijmegen (ParC)

- Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, 17 June 2008
- Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, 27 May 2009
- W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, 7 October 2009
- Samyra H.J. Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, 29 April 2010
- Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, 29 November 2010
- Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, 29 November 2010
- Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, 24 May 2011
- Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, 6 December 2011
- Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, 22 December 2011
- Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, 4 June 2012
- Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, 22 November 2012
- Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 13 February 2013

- Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 6 March 2013
- Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, 6 March 2013
- Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, 6 June 2013
- Marjolein A van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, 10 January 2014
- Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, 21 May 2014
- Marjolein B. Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, 27 June 2014
- Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, 13 February 2015
- Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, 23 June 2015
- Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, 2 September 2015
- Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, 1 December 2015
- Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, 11 February 2016
- Merel M. van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, 13 April 2016
- Arno M. Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, 2 June 2016

Non-Parkinsonian disorders of movement

- Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, 5 April 2012
- Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, 20 December 2013
- Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, 7 January 2014
- Ella M.R. Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias. Radboud University Nijmegen, 29 June 2016

Neuromuscular disorders of movement

- Mireille van Beekvelt. Quantitative near infrared spectroscopy (NIRS) in human skeletal muscle. Radboud University Nijmegen, 24 April 2002
- Johan Hiel. Ataxia telangiectasia and Nijmegen Breakage syndrome, neurological, immunological and genetic aspects. Radboud University Nijmegen, 23 April 2004
- Gerald JD Hengstman. Myositis specific autoantibodies, specificity and clinical applications. Radboud University Nijmegen, 21 September 2005
- M. Schillings. Fatigue in neuromuscular disorders and chronic fatigue syndrome, a neurophysiological approach. Radboud University Nijmegen, 23 November 2005
- Bert de Swart. Speech therapy in patients with neuromuscular disorders and Parkinson's disease. Diagnosis and treatment of dysarthria and dysphagia. Radboud University Nijmegen, 24 march 2006

- J. Kalkman. From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model. Radboud University Nijmegen, 31 October 2006
- Nens van Alfen. Neuralgicamyotrophy. Radboud University Nijmegen, 1 November 2006
- Gea Drost. High-density surface EMG, pathophysiological insights and clinical applications. Radboud University Nijmegen, 9 March 2007
- Maria Helena van der Linden. Pertubations of gait and balance: a new experimental setup applied to patients with CMT type 1a. Radboud University Nijmegen, 6 October 2009
- Jeroen Trip. Redefining the non-dystrophic myotonic syndromes. Radboud University Nijmegen, 22 January 2010
- Corinne G.C. Horlings. A weak balance: balance and falls in patients with neuromuscular disorders. Radboud University Nijmegen, 1 April 2010
- E. Cup. Occupational therapy, physical therapy and speech therapy for persons with neuromuscular diseases, an evidence based orientation. Radboud University Nijmegen, 5 July 2011
- Alide Tieleman. Myotonic dystrophy type 2, a newly diagnosed disease in the Netherlands. Radboud University Nijmegen, 15 July 2011
- Nicol Voermans. Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome. Radboud University Nijmegen, 2 September 2011
- Allan Pieterse. Referral and indication for occupational therapy, physical therapy and speech-language therapy for persons with neuromuscular disorders. Radboud University Nijmegen, 13 February 2012
- Bart Smits. Chronic Progressive External Ophthalmoplegia more than meets the eye. Radboud University Nijmegen, 5 June 2012
- Ilse Arts. Muscle ultrasonography in ALS. Radboud University Nijmegen, 31 October 2012
- Willemijn Leen. Glucose transporter – 1 deficiency syndrome. Radboud University Nijmegen, 26 June 2014
- M. Minis. Sustainability of work for persons with neuromuscular diseases. Radboud University Nijmegen, 13 November 2013
- Femke Seesing. Shared Medical appointments for neuromuscular patients and their partners. Radboud University Nijmegen, 2 September 2016
- Nicole Voet. Aerobic exercise and cognitive behavioral therapy in fascioscapulohumeral dystrophy: a model based approach. Radboud University Nijmegen , 14 October 2016

Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuro-psychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit: http://www.ru.nl/donders/graduate-school/phd/