Cognitive recovery after stroke

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Cognitive recovery after stroke

Cognitief herstel na een beroerte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
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door

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te Capelle aan den IJssel

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1

General introduction

General introduction

Stroke is one of the leading causes of death and long-term disability worldwide.¹ The incidence of ischemic stroke in The Netherlands alone is 35.000 per year, translating to roughly 100 new patients with ischemic stroke every day.² Apart from the physical consequences, up to 75% of the patients have cognitive deficits after ischemic stroke.^{3,4} Even patients that have no or only mild physical impairment, can have serious cognitive deficits.⁵ Cognitive deficits after ischemic stroke are independently associated with lower quality of life, poorer functional outcome, and worse community reintegration.⁶⁻¹¹

Fortunately, roughly half of the patients with cognitive deficits after ischemic stroke show recovery over time.^{12,13} The other half, however, remains cognitively impaired or even deteriorates.^{13,14} Predicting cognitive recovery in patients with a cognitive disorder after ischemic stroke could have important consequences for daily practice: it could help in providing realistic psycho-education for patients and their families, and it could ultimately help in matching the goals in rehabilitation programs to the patient's potential for recovery. For example, recovery can be stimulated in patients that are likely to improve, while in patients with a low probability of improvement, the focus of rehabilitation treatment can be shifted from recovery to adaptation to deficits, by learning compensatory strategies or adapting the patient's environment.

However, prediction of cognitive recovery after ischemic stroke on clinical features alone is still inaccurate. Biomarkers that could increase predictive accuracy are greatly needed.¹⁵ Thus far, many predictors have been associated with presence of long-term cognitive impairment, while predicting cognitive recovery has received less attention. Emerging predictors of cognitive recovery include demographic characteristics (i.e. age, sex and level of education), pre-stroke condition (i.e. vascular risk factors, pre-stroke cognitive functioning, pre-stroke functional status), stroke severity, cognitive and emotional status (i.e. a post-stroke psychiatric disorder and post-stroke cognitive functioning in acute phase), and imaging characteristics (i.e. infarct size, infarct location, white matter hyperintensity severity).^{12,16-22}

In the past years, measures of brain connectivity have emerged in the literature as important markers of various types of brain injury that are relevant for cognition.²³⁻²⁶ Therefore, measures of brain connectivity may also be of value in prediction of cognitive recovery after ischemic stroke.²³⁻²⁶ The extent to which brain regions are structurally connected can be estimated with diffusion-weighted imaging (DWI). Properties of these brain networks can be described and calculated using graph theory, which describes the brain as a combination of nodes connected by edges

(i.e. brain regions connected by white matter tracts, **Figure 1**).²³ Nodes that are strongly connected to other nodes in the network are considered 'hubs'. The global integration of information within the network can be reflected in a single measure: global network efficiency.^{23,24} Research that has focused on the brain network after ischemic stroke, has shown that ischemic stroke does not only have local effects, but also disrupts the integrity of the global brain network.^{27,28} Moreover, changes can be even detected in the network of the contralateral hemisphere after ischemic stroke.²⁹ A study that simulated ischemic strokes at various locations in the brain network of healthy controls suggested that one's global network efficiency provides an indication of brain resilience, possibly reflecting one's potential of cognitive recovery.³⁰

Evidence of the prognostic value of measures of brain connectivity is accumulating in patients with cerebrovascular disease. For example, brain connectivity measures have already been shown to predict motor recovery after stroke,^{31,32} recovery from aphasia following language therapy, and cognitive impairment 3 and 6 months after stroke.³³⁻³⁵ In addition, there is also evidence that measures of brain connectivity can predict which patients will develop post-stroke apathy or depression.^{36,37} In patients with cerebral small vessel disease (CSVD), the predictive value is established of measures of brain connectivity on both cognitive performance and cognitive deterioration over time.³⁸⁻⁴² Moreover, it was shown in these CSVD patients that cognitive decline during follow-up was associated with a decrease in global network efficiency.⁴¹⁻⁴³ Furthermore, structural brain network measures appear to be superior in prediction of cognitive functioning compared to often used markers of vascular brain injury.⁴⁴ More broadly speaking, measures of brain connectivity seem to be a marker of brain health and resilience.^{30,45} As such, these measures can be seen as a valuable contribution to understanding the chronic consequences of stroke.

Figure 1: This figure shows an example of a network.

Nodes are depicted as circles and edges are depicted as lines. Nodes with a central position or with many connections to other nodes are often considered hubs. The shortest path is the number of edges that have to be traversed from a given node in the network to any of the other nodes in the network. The global network efficiency is calculated by taking the inverse of the average of all shortest paths in the network.

When looking more specifically at the cognitive deficits that are often seen after ischemic stroke, these can involve the ‘traditional’ cognitive domains memory, executive functioning, visuospatial functioning, language, and attention and processing speed.^{3,46,47} Another cognitive domain, social cognition, was only recently acknowledged as a cognitive domain in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).⁴⁸ It involves the psychological processes by which one perceives, processes and interprets social information, and it involves adequately responding to this social information.⁴⁹ There is emerging evidence that ischemic stroke is also associated with deficits in social cognition.^{50,51} Impairments in social cognition after ischemic stroke are independently negatively associated with quality of life and social participation, similar to impairments in traditional cognitive domains.^{52,53} However, it is not clear how often impairments in social cognition occur shortly after ischemic stroke, and how these impairments are related to performance in other cognitive domains.

The overarching aim of the work described in this thesis was to assess whether measures of brain connectivity can be implemented directly in daily practice to provide meaningful predictions of cognitive recovery for both clinicians and patients. Moreover, while preparing for the start of the work described in this thesis, it became apparent that little attention was paid to the relation of ischemic stroke with emotion recognition, while it is an important aspect of social and cognitive functioning. In the work described in this thesis we more specifically aimed to assess:

1. whether measures derived from the structural brain network predict cognitive recovery after ischemic stroke.
2. how often impairments in social cognition occur after ischemic stroke, and more precisely, emotion recognition.

These aims were addressed in the Prediction of Cognitive Recovery After Stroke (PROCRAS) study, a prospective mono-center cohort study that included 264 patients with ischemic stroke.

In **chapter 2** the study protocol of the PROCRAS study is described, providing the rationale, aims and study design of the study.

Chapters 3 and 4 address the first aim of this thesis. In **chapter 3**, we describe prediction of cognitive recovery with the lesion impact score. We devised this score to quantify the location of ischemic stroke within the brain network. It is a novel approach in which information of network topology is combined with lesion size into one single measure. We describe how the lesion impact score

relates to network efficiency and cognitive recovery. In **chapter 4**, describes the main objective of the PROCRAST study, where we investigated whether there is additional value of global network efficiency in predicting cognitive recovery one year after ischemic stroke.

During the study, we observed that a substantial amount of participants in the PROCRAST study did not have a visible lesion on the MRI, while all patients were included with a clinical diagnosis of ischemic stroke. **Chapter 5** describes the occurrence of a so called MRI-negative stroke. We discuss what may explain MRI negativity in patients in which we are highly certain that an ischemic stroke was the cause of the patient's complaints.

Chapters 6 and 7 concern the second aim of this thesis. **Chapter 6** first describes a case report and provides an overview of the literature on emotion recognition after ischemic stroke. In **chapter 7** the occurrence of impairments in emotion recognition after ischemic stroke is described, which is important because the relevance of addressing emotion recognition in daily practice depends on the frequency in which impairments in emotion recognition occur.

Lastly, in **chapter 8**, the main findings are summarized followed by a general discussion of the results, implications for clinical practice and recommendations for future research.

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2

A role for new brain MRI modalities in daily clinical practice: protocol of the Prediction of Cognitive Recovery After Stroke (PROCRAS) study

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Abstract

Background

Cognitive impairment is common after acute ischemic stroke, affecting up to 75% of patients. About half of them will show recovery, whereas the others will remain cognitively impaired or deteriorate. It is difficult to predict these different cognitive outcomes.

Objectives

The objective of this study is to investigate whether diffusion tensor imaging-based measures of brain connectivity predict cognitive recovery after 1 year in addition to patient characteristics and stroke severity. A specific premise of the PROCRAAS study is that it is conducted in a daily practice setting.

Methods

The PROCRAAS study is a prospective, mono-center cohort study, conducted in a large teaching hospital in the Netherlands. A total of 350 patients suffering from an ischemic stroke who screen positive for cognitive impairment on the Montreal Cognitive Assessment (MoCA < 26) in the acute stage, will undergo a 3T-MRI with a diffusion-weighted sequence and a neuropsychological assessment. Patients will be classified as being unimpaired, as having a mild vascular cognitive disorder or as having a major vascular cognitive disorder. One year after stroke patients will undergo follow-up neuropsychological assessment. The primary endpoint is recovery of cognitive function 1 year after stroke in patients with a confirmed poststroke cognitive disorder. The secondary endpoint is deterioration of cognitive function in the first year after stroke.

Results

The study is already ongoing for 1.5 years, and thus far 252 patients have provided written informed consent. Final results are expected in June 2019.

Conclusions

The PROCRAAS study will show the additional predictive value of diffusion tensor imaging-based measures of brain connectivity for cognitive outcome at 1 year in patients with a poststroke cognitive disorder in a daily clinical practice setting.

Introduction

Stroke has a high global incidence of 41-316 per 100 000 persons per year¹. Besides its physical consequences, cognitive deficits are common and occur in up to 75% of patients in the first weeks after stroke²⁻⁵. In half of them, cognition may improve^{3,6}. Yet, long-term cognitive consequences of stroke include a twofold increased risk of dementia⁷⁻⁹, and mild cognitive impairment⁶. Identification of those who will recover or who will have persistent cognitive impairment is important, since persistent cognitive dysfunction after stroke is independently correlated with worse long-term outcomes, such as independent living, community reintegration and quality of life¹⁰⁻¹⁴. Moreover, recovery may be stimulated further in patients who are prone to improvement. For example, rehabilitation programs could use this information in setting realistic and attainable therapeutic goals.

Prediction of long-term cognitive outcome after ischemic stroke is, however, still inaccurate. Evidence is emerging on predictors of poor outcome, including demographic variables (e.g. older age and lower level of education^{2,3}). Brain imaging measures such as size and location of a stroke, the degree of white matter disease and regional atrophy¹⁵⁻²¹ may also determine cognitive function and long term outcome after stroke. In contrast, fewer studies have addressed predictors of cognitive recovery among individuals with early poststroke impairment. Factors that have a positive effect on cognitive recovery are a stroke located in the right hemisphere and smoking^{22,23}, while neglect, depression and apathy have a negative influence on cognitive recovery²³⁻²⁵.

Measures of brain connectivity are of particular interest in this context. Stroke not only affects local connectivity, but can also cause remote brain changes, as shown by functional MRI and Diffusion Tensor Imaging (DTI) studies²⁶. The value of brain connectivity measures has already been established for the prediction of motor recovery^{27,28}. Conceivably, the relevance of measures of brain connectivity in vascular cognitive disorders is also increasingly recognized. For example, global network efficiency assessed with DTI, has been independently associated with cognitive performance in patients with cerebral small vessel disease²⁹⁻³². Moreover, brain connectivity measures are correlated with cognition and intelligence in healthy controls^{33,34}, and have been suggested to provide an indication of brain resilience³⁴. As such, it can be hypothesized that these measures could predict cognitive recovery after stroke. A recent study supporting this hypothesis, showed that brain connectivity measures predict applied cognitive functioning 6 months after stroke³⁵. Moreover, another study showed that an increased structural integrity of the contralesional hemisphere was associated with cognitive recovery after stroke³⁶.

The primary aim of the Prediction of Cognitive Recovery After Stroke (PROCRAS) study is to investigate whether DTI-based measures of brain connectivity predict cognitive recovery in the first year after stroke in patients with a confirmed poststroke cognitive disorder in addition to clinical, neuropsychological and conventional imaging variables. Secondary aims are to assess the relation of DTI-based measures of brain connectivity with other outcomes, including deterioration of cognitive function, cognitive complaints, quality of life, participation, global health and functional outcome will be determined. PROCRAS will also assess the feasibility of an extensive work-up including cognitive assessment and DTI in daily clinical practice.

Methods

Design

The PROCRAS study is a longitudinal, prospective, mono-center cohort study of cognition in patients with acute ischemic stroke, who will be followed for one year using five assessments.

Patient population

Patients will be recruited from the stroke unit of the Elisabeth-Tweesteden Hospital Tilburg, The Netherlands. This is a hospital with an admission rate of roughly 700 patients per year for the diagnosis of acute ischemic stroke. Figure 1 visualizes the anticipated patient flow, the numbers are estimated and based on unpublished pilot data and a feasibility study performed in Heidelberg³⁷. In all patients admitted with a clinical diagnosis of acute ischemic stroke, aged 50 or older the Montreal Cognitive Assessment (MoCA)³⁸ is administered as part of routine care. Patients with a score below 26 (screen positive) are eligible for inclusion (table 1). MoCA assessment will be re-attempted if at first patients are untestable. Exclusion criteria are pre-stroke dementia (known diagnosis of dementia or Informant Questionnaire on Cognitive Decline in the Elderly ((IQCODE)³⁹ ≥ 3.6); life expectancy of less than one year; severe stroke expected to require long term nursing care facilities, making patients not eligible for rehabilitation therapy; history of major neurological disease interfering with cognitive functioning; pre-stroke dependence in activities of daily living; insufficient command of the Dutch language; inability to participate in a neuropsychological assessment (e.g. due to poor vision, severe aphasia, or if the patient is deemed untestable); and an impossibility to undergo an MRI of the brain. If there is no information regarding the IQCODE, the researchers will discuss with the attending physician whether there are signs of pre-existing cognitive dysfunction. Only if there is no suspicion of pre-stroke dementia, patients are eligible for inclusion.

Table 1: Inclusion and Exclusion criteria.

Inclusion Criteria	Clinical diagnosis of ischemic stroke
	Age ≥ 50
	MoCA < 26 (MoCA ≥ 26 for the reference group)
Exclusion Criteria	Pre-stroke dementia: Known diagnosis of dementia or IQCODE ≥ 3.6
	Life expectancy < one year
	Severe stroke expected to require long term nursing care facilities
	History of major neurological disease interfering with cognitive functioning
	Pre-stroke dependence in activities of daily living (Barthel Index < 18)
	Insufficient command of the Dutch language in order to participate and understand questionnaires
	Impossibility to participate in a neuropsychological assessment
	An absolute contra-indication to undergo an MRI of the brain

Figure 1: The expected patient flow in the PROCAS study. The target is to include 300 screen positive patients at T2. Other numbers are estimated, based on this target.

Additionally, 60 patients with a MoCA score of 26 or higher (screen negative) will be included as a reference group, matched for age and gender to the screen positive patients (frequency matching). For this reference group the other inclusion and exclusion criteria and study procedures are identical to the screen positive patients.

It is expected that the inclusion target will be reached in 1.5 years. Patients are treated the same way as patients that do not participate in this study. This study does not interfere with treatment choices or rehabilitation therapy. To account for any confounding, it will be registered whether patients received rehabilitation therapy and what kind of therapy was provided. Moreover, basic demographic data will be collected on the source population to understand what patient population participates in the PROCRAAS.

Procedure

After informed consent, baseline characteristics will be assessed during hospital admission (T1). The second assessment takes place in an outpatient clinic 3-6 weeks after stroke (T2); the third assessment is a telephone interview 3 months after stroke (T3); the fourth assessment is another telephone interview 6 months after stroke (T4); and the fifth assessment is performed in an outpatient clinic one year after stroke (T5). The PROCRAAS study is ongoing for 18 months. From the first 100 patients at T2, 94 completed follow-up until T5.

Figure 2: An overview of the procedures to be performed on each time point.

Timeline					
Timing and setting	Demographics and pre-stroke condition	Neurological functioning and risk factors	Imaging	Cognitive status	Outcomes
T1 Acute stroke stage, during admission	Demographic factors Pre-stroke physical activities (IPAQ) Pre-stroke cognition (IQCODE) Pre-stroke ADL activities (BI) Pre-stroke comorbidity (CIRS)	Stroke characteristics Stroke severity (NIHSS) Current ADL activities (BI) Functional status (mRS) Vascular risk factors Laboratory findings		Cognitive screening (MoCA)	
T2 3-6 weeks after stroke, outpatient clinic		Motor functioning (MI)	MRI + DTI	Neuropsychological assessment	Emotional functioning (HADS)
T3 3 months after stroke, telephone interview		Functional status (mRS)			Cognitive complaints (CLICE-24) Quality of life (SSQOL) Participation (USER-P) Global health (PROMIS) Self-efficacy (SEsx)
T4 6 months after stroke, telephone interview		Functional status (mRS)			
T5 1 year after stroke, outpatient clinic		Motor functioning (MI) Functional status (mRS)		Neuropsychological assessment	Cognitive complaints (CLICE-24) Quality of life (SSQOL) Participation (USER-P) Global health (PROMIS) Self-efficacy (SEsx) Emotional functioning (HADS, NPI-Q)

Measures

Neuropsychological assessment

The neuropsychological assessment will be performed at T2 and T5. It is designed using the “60 minute protocol” as proposed in the vascular cognitive impairment harmonization standards⁶. Table 2 lists the domains and associated tests. Presence or absence of poststroke cognitive impairment is operationalized according to the criteria for vascular cognitive disorders (VCD)⁴⁰. Patients will be classified in three groups.

1. Unimpaired (performance on all domains better than 1 SD below appropriate norms)
2. Mild VCD (performance on ≥ 1 domains ≥ 1 but < 2 SDs below appropriate norms)
3. Major VCD (performance on ≥ 1 domains ≥ 2 SDs below appropriate norms).

The raw score for each test will be converted into a T-score, when possible corrected for age, gender and level of education. The score for a domain is calculated by averaging the T-scores of the tests constituting that domain. The T-score is standard score with a mean of 50 and a standard deviation of 10. For example, a T-score of 30 translates to 2 standard deviations below the mean, and a T-score of 60 corresponds to 1 standard deviation above the mean.

Only for the bells test no normative data are available. An abnormal score on this test will be defined based on a cut-off score of a difference of 5 or more omissions between columns 1-3 and columns 5-7⁴¹.

Table 2: An overview of neuropsychological tests to be performed.

Domain	Tests
Attention and processing speed	Reaction time test, Vienna Test System, S1, S2
	Symbol Digit Modalities Test
	Trailmaking test A
(Working) memory and learning	WAIS Digit Span forward and backward
	The Rey Auditory Verbal Learning Test
Frontal-Executive functions	Controlled Oral Word Association Test
	Hayling test
	Reaction time test Vienna Test System S3
	Trailmaking test B
Language	Boston naming test
	Semantic fluency
Visuospatial	Bells test
Social Cognition	Facial Expressions Emotions Stimuli-Test

MRI

MRI data will be acquired on a Philips 3 Tesla scanner (Intera, Philips, Best, the Netherlands) for each patient at T2 using a standardized scanning protocol. The protocol consists of a sagittal 3D T1-weighted, an axial T2-weighted, an axial fluid attenuated inversion recovery (FLAIR), an axial diffusion-weighted imaging (DWI), and a DTI sequence. Brain tissue volumes and white matter hyperintensity volumes will be automatically determined by brain segmentation, and infarct volumes will be determined by manual segmentation(42, 43).

DTI data will be analyzed and processed in ExploreDTI(44), as described earlier(45). First, whole brain fiber tracking will be performed. Second, the tract reconstructions are parcellated on 90 gray matter regions using the automated labeling atlas(46). Third, a weighted connectivity matrix is obtained by scaling each present connection between each brain region by the mean fractional anisotropy of that connection. Lastly, global network efficiency will be calculated by applying graph theory on the weighted connectivity matrix.

Other parameters

At T1, demographic factors will be ascertained, APOE genotyping will be performed, stroke severity will be assessed using the National Institutes of Health Stroke Scale(47), comorbidity using the Cumulative Illness Rating Scale(48), pre-existent cognitive functioning using the IQCODE(39), pre-existent physical activities using the short form of the International Physical Activities Questionnaire(49), and pre-existent and current activities of daily living using the Barthel Index(50). At T2 and T5, motor functioning will be assessed using the motricity index(51), and emotional functioning will be assessed using the Hospital Anxiety and Depression Scale(52) and the Neuropsychiatric Inventory-Questionnaire(53). At T3 and T5, self-efficacy will be assessed using the Self-Efficacy for symptom management scale(54); cognitive complaints using the CheckList for Cognitive and Emotional problems after stroke(55); quality of life using the short version of the Stroke Specific Quality of Life Scale(56); participation using the Utrecht Scale for Evaluation of Rehabilitation-Participation(57, 58); and global health using the Patient Reported Outcomes Measurement Information System(59, 60). Functional outcome will be assessed with the modified Rankin scale(61) at T1, T3-T5.

Aims, Determinants and Outcomes

Primary Aim

The primary aim is to investigate whether DTI-based measures of brain connectivity predict cognitive recovery after one year in addition to other determinants including patient characteristics and stroke severity.

The main DTI marker that will be used is global network efficiency. This measure reflects the integration as well as the micro structural integrity of the white matter.

The primary outcome measure is recovery of cognitive function in the first year after stroke. This measure will be dichotomized into cognitive recovery and no cognitive recovery (i.e. no change or deterioration). Cognitive recovery is operationalized as a transition from a mild VCD at 3-6 weeks (i.e. T2) to no disorder at one year (i.e. T5), or a transition from a major VCD at T2 to a mild or no VCD at T5. Hence, only patients with a confirmed VCD at T2 will be considered for this outcome. Patients that drop out will not be considered in the primary analyses. Their outcomes, obtained by telephone interview where possible, will be reported.

The secondary outcome measure is deterioration of cognitive function, operationalized as a transition from a mild VCD at T2 to a major VCD at T5 or a transition from no VCD at T2 to a mild or a major VCD at T5. For this outcome, only patients with no or a mild VCD at T2 will be considered .

In secondary analyses we will also address change in cognitive performance as a continuous measure, using domain T-scores. For neuropsychological tests that require writing or drawing, we will take motor functioning into account as a covariate in the analysis.

Secondary aims

A secondary aim is to assess the relation of DTI-based measures of brain connectivity with patient reported outcomes and functional outcome. For this aim the main DTI marker that will be used is again global network efficiency. The outcome measures are cognitive complaints, quality of life, participation, global health and functional outcome. The first four outcome measures will be assessed with questionnaires at 3 months after stroke (i.e. T3) and 1 year after stroke (i.e. T5). The questionnaires are repeated at T5 to assess whether a change in one of these measures occurs. Functional outcome is defined by the score on the modified Rankin Scale as assessed with a telephone interview by a trained researcher at T1, T3, T4 and T5. All patients with completed follow-up until at least T3 will be considered for this

analysis. Moreover, each of the outcome measures will be compared between the cognitive impaired group and the reference group.

Another secondary aim is to assess the feasibility of an extensive work-up including cognitive assessment and DTI in daily clinical practice. The outcome measure will be the proportion of patients that underwent an MRI scan and neuropsychological assessment within the timeframe of three to six weeks at T2.

Figure 3 visualizes the primary and other outcomes of the PROCRAST study and the population used in the analyses.

Figure 3: Outcomes of the PROCRAST study and the population used in the primary analysis.

VCD, vascular cognitive disorder.

Sample size calculation

Based on available literature, we estimate an area under the receiver operating characteristic (ROC) curve of 0.7 for the prediction model using clinical, neuropsychological and conventional imaging parameters, and that roughly half of the patients with a confirmed cognitive disorder will recover^{3,62}. When adding connectivity measures to this model, 200 participants are needed to detect an increase in the area under the ROC curve of 0.1 or more, with a power of 80% and an alpha of 0.05. As a rule of thumb, to reliably measure the weight of a predictor, at least 10 outcome events per predictor in a multivariate model are needed. This means that a maximum of 10 predictors can be used in these models. We estimate that 30% of the patients will not complete the full study procedures until T5, and

that 80% of the screen positive patients will have a confirmed cognitive disorder at T2. Therefore, we need to obtain around 300 screen positive patients with data at T2, to obtain 200 patients with a confirmed cognitive disorder at T2 and complete follow-up until T5. We will include one screen negative patient for every five included screen positive patients in the reference group.

Statistics

First, descriptive statistics will be used. Second, to assess the additional value of DTI-based measures of brain connectivity, the six strongest predictors from clinical and conventional imaging parameters will be selected using univariable logistic regression with cognitive recovery as a dichotomous outcome measure. The predictive value of the multivariate model including the strongest predictors from clinical parameters and conventional imaging markers will be assessed. ROC analyses will be used to assess whether this predictive value can be improved by adding network metrics achieved from DTI. The same procedure will be performed in the prediction of the outcome measures related to the secondary aim. In the model we will take the interval between the stroke and the assessment at T2 as co-variate.

Regulation Statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics Committee Approval

The PROCRAAS study was approved by the medical ethics committee of Brabant, based in Tilburg, The Netherlands. Written informed consent will be obtained from all participants.

Study organization and funding

Funding was obtained through ZonMW as part of the 'TopZorg' project in 2015 (grant # 842003011).

Results

At time of acceptance of this paper for publication, this study has been ongoing for 20 months. Thus far, 252 patients have provided written informed consent. Final results are expected in June 2019.

Discussion

The PROCRAAS study investigates whether DTI-based measures of brain connectivity predict cognitive recovery in a large stroke cohort in daily clinical

practice in addition to known predictors of cognitive outcome. It adds to the existing literature because of several reasons.

First, it specifically focusses on cognitive recovery, using a selection of relevant determinants of cognitive outcome after stroke. As the mechanisms of cognitive recovery or deterioration after stroke are complex involving multiple factors, a prediction model should incorporate each of the most important factors to provide reliable results. Moreover, by combining many of the known determinants in a large patient sample, the coherence between each of these factors can be better understood.

Second, this study combines the knowledge of different disciplines working in the stroke field, such as cognitive neuroscience, neuropsychology and cognitive rehabilitation. Approaching VCDs from different angles may help us better understand how VCDs develop, and how they continue to exist. Moreover, fundamental findings in cognitive neuroscience are not often translated in clinical practice⁶³. If the diagnostic work-up proves to be feasible, results from this study can be implemented into clinical practice, benefitting individual stroke patients.

The study design has several limitations. First, the study focusses on a relatively specific patient group, because of several exclusion criteria. For example, patients that cannot undergo a neuropsychological examination, for example due to a severe aphasia, are excluded. We have chosen to exclude patients with risk factors for a major VCD, since these patients have a low potential to show cognitive recovery. This would lower the sensitivity to find an effect. Second, this is a single center study, which can affect generalizability of the results. Third, the timeframe of three weeks at T2 is rather broad. This might result in more patient variation, since patients show most recovery in the first weeks after stroke⁶⁴⁻⁶⁶. However, this timeframe of three weeks has been chosen for pragmatic reasons. At this point in time, information on the potential of cognitive recovery would help to make decisions in stroke rehabilitation.

In summary, the results of the PROCRAAS study will support individualized prediction of cognitive recovery after stroke. The results of this study may help in the psychoeducation of patients, they may add value to rehabilitation programs in setting realistic and attainable therapeutic goals, and they may help to anticipate the need for support.

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Extent to which network hubs are affected by ischemic stroke predicts cognitive recovery

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Abstract

Background and Purpose

It is uncertain what determines the potential for cognitive recovery after ischemic stroke. The extent to which strategic areas of the brain network, so-called hubs, are affected by the infarct could be a key factor. We developed a lesion impact score, which estimates the damage to network hubs by integrating information on infarct size with healthy brain network topology. We verified whether the lesion impact score indeed reflects global network disturbances in patients, and assessed if it could predict cognitive recovery.

Methods

Seventy-five ischemic stroke patients without signs of a prestroke cognitive disorder were included, all with evidence of a cognitive disorder during hospitalization. A brain MRI and neuropsychological assessment were performed 5 weeks (± 1 week) after stroke. Neuropsychological testing was repeated after 1 year to assess cognitive recovery. Brain networks were reconstructed from diffusion-weighted data and consisted of 90 gray matter regions (i.e. network nodes).

A standard brain network map, indicating the hub-score of each node, was obtained from network data of 44 cognitively healthy adults. For each patient, we calculated the lesion impact score by multiplying the percentage of node volume affected by the infarct with the node's corresponding hub-score. The patients' maximum lesion impact score was used as outcome predictor.

Results

A higher lesion impact score in patients, indicating an increasing infarct size in nodes with a higher hub-score, was related to lower global brain network efficiency ($\beta = -0.528 [-0.776 \text{ to } -0.277]$; $P < 0.001$), independent of age, brain volume, infarct volume and white matter hyperintensity severity. A lower lesion impact score, however, was an independent predictor of cognitive recovery 1 year after stroke (odds ratio = 0.434 [0.193 to 0.978]; $P = 0.044$).

Conclusions

We introduced a lesion impact score that combines information on infarct size and network topology to predict long-term recovery after stroke. This score can potentially be used in a clinical setting, also without availability of high-resolution diffusion-weighted MRI.

Introduction

After acute ischemic stroke, up to 75% of patients suffer from a cognitive disorder.¹ Roughly half of them will show cognitive recovery.^{2,3} However, it remains unclear which of the patients will recover, and how exactly stroke affects cognitive functioning.^{4,5} An important determinant of a cognitive disorder after stroke may be the location of ischemic stroke.⁶ Small focal strokes in so-called 'strategic' locations can have severe consequences for cognitive functioning.^{7,8} One reason why certain brain regions are considered strategic is because they are highly connected with other regions, causing so-called disconnection syndromes when damaged (e.g. an infarct in the angular gyrus causing the Gerstmann syndrome).^{9,10}

The degree to which brain regions are functionally or structurally connected can be estimated with functional Magnetic Resonance Imaging (fMRI) or diffusion weighted imaging (DWI). The properties of these brain networks can be described using graph theory.^{11,12} With the use of graph theory, the brain network can be described as a combination of nodes (i.e. brain regions) connected by edges (i.e. white matter tracts). Organizational properties of the brain networks can be calculated, such as the global efficiency, a measure of global network integration. Certain brain regions have found to be critical for the integration of information within the network because of their central position and connectedness with other regions, also referred to as network hub'.¹³ Earlier work has shown that simulating a targeted lesion in these hubs decreases the global network efficiency of the network much more than random lesions in the network.¹⁴ These theoretical constructs have been confirmed in stroke patients using functional MRI, showing that strategic lesions in hubs are associated with widespread disruptions in functional connectivity, even in the contralesional hemisphere, and an overall decrease in global network efficiency.^{15,16}

Several small studies in stroke patients have shown that patients who have only little functional network disturbances after ischemic stroke have a higher chance of cognitive recovery.¹⁷⁻²⁰ The link between functional network disturbances and cognitive recovery may be largely driven by the location of the infarct in the brain network, that is, whether the infarct affects a network hub.

Therefore, we hypothesized that the degree to which an ischemic stroke affects network hubs determines the potential for cognitive recovery after stroke. To test this hypothesis, we overlaid each patient's infarct segmentation with a standard brain network topology map. The extent of ischemic damage to network hubs was summarized by a lesion impact score. We evaluated whether the lesion impact score was indeed related to a lower global efficiency of the structural brain network.

Secondly, we assessed whether the lesion impact score was a predictor of a cognitive disorder 5 weeks after stroke, and cognitive recovery 1 year after stroke.

Methods

Regulation Statement

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval

The PROCRAAS study was approved by the medical ethics committee of Brabant, based in Tilburg, the Netherlands. Written informed consent was obtained from all participants.

Study participants

Data were used from the ongoing longitudinal, prospective, Prediction of Cognitive Recovery after Stroke (PROCRAAS) study, at the Elisabeth Tweesteden Hospital, Tilburg, The Netherlands.²¹ The PROCRAAS study includes patients aged 50 and older, admitted with a clinical diagnosis of acute ischemic stroke and evidence of a cognitive disorder during hospitalization, indicated by a Montreal Cognitive Assessment (MoCA)²² score below 26. Exclusion criteria for PROCRAAS were prestroke evidence of a cognitive disorder (Informant Questionnaire on Cognitive Decline in the Elderly ≥ 3.6 ²³), prestroke dependence in activities of daily living, life expectancy of less than 1 year, severe stroke expected to require long-term nursing care facilities, impossibility to participate in a neuropsychological assessment (e.g. due to a severe aphasia or severe neglect), and having contraindications for brain MRI. At 5 weeks (± 1 week) after stroke, patients underwent a detailed neuropsychological assessment and brain MRI, including DWI sequences. The neuropsychological assessment was repeated 1 year after stroke. Patients who were included in the PROCRAAS study between July 2016 and May 2017, with a complete neuropsychological and MRI assessment 5 weeks after stroke were eligible for this study ($n=110$). Of these, 35 patients were excluded from the present analysis because no infarct was seen on the MRI ($n=24$), or because the infarct was only located in infratentorial regions or purely affected the white matter, and therefore did not affect any of the predefined network nodes ($n=11$). All the remaining 75 patients had data on cognition 5 weeks after stroke, and 70 patients had data on cognitive status after 1 year (5 patients were not reassessed

because of withdrawal of consent $n=3$, or death $n=2$). Five of the 75 patients had incomplete or low quality DWI data, and were therefore excluded from the network analyses.

Measures

MRI acquisition

MRI data of the patients were acquired on a Philips 3 tesla scanner (Intera, Philips, Best, the Netherlands). Patients were scanned 5 weeks after stroke according to a standardized scanning protocol as described earlier.²¹ The DWI sequence had the following parameters: 70 slices, voxel size $2.00 \times 2.00 \times 2.00$ mm³, repetition time/echo time: 7891/87 ms, 50 directions (b-value 1500 s/mm²) and 7 $b=0$ s/mm² images. DWI data of 44 cognitively healthy adults was used to construct a standard network topology map (see paragraph standard network topology map). These DWI data were also acquired on a Philips 3 tesla scanner with the following parameters: 48 contiguous slices, voxel size $1.72 \times 1.72 \times 2.50$ mm³, TR/TE 6638/73 ms, flip angle of 90 degrees, 45 directions (b value of 1,200 s/mm²) , and 1 $b=0$ s/mm² (three averages).

Infarct segmentation

Infarct volumes and locations were determined following previously described methods.²⁴ First, infarcts corresponding with the clinical symptoms were manually segmented on fluid-attenuated inversion recovery sequences by a trained rater, and reviewed by a second rater, with in-house developed software using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany). Both raters were blinded to the neuropsychological data, but had access to clinical data during hospitalization. Other structural sequences were used to support proper lesion identification, in accordance with the international STAndards for Reporting Vascular changes on nEuroimaging.²⁵ Next, infarct segmentations were transformed to the T1 1-mm MNI-152 (Montreal Neurological Institute) brain template, using an in-house developed image registration pipeline (RegLSM; available at www.metavcimap.org). The registration procedure consisted of linear registration followed by nonlinear registration, using the elastix toolbox.²⁶ As an intermediate step, registration to an age-specific brain template was performed,²⁷ which has shown to provide a more accurate registration in elderly subjects. These registration steps were combined into a single step in which the original lesion maps were registered directly to MNI-152 space, to prevent intermediate interpolations and thereby improve registration accuracy. Visual quality checks of all registration results were performed by one rater (N.A.W.), followed by manual adaptation when necessary. The resulting lesion maps were used to calculate total infarct volumes in milliliters.

Because infarct volumes were calculated in standard space, all volumes were normalized for differences in brain size and shape. In addition, the automated anatomical labeling atlas (AAL) was overlaid on the lesion maps to determine the infarct volume within each of the 90 cortical and subcortical gray matter regions (i.e. network nodes) (see figure 1, left panel).

Figure 1: The processing pipeline used to acquire the lesion impact score.

The lesion impact score was defined as the product of the percentage of node volume affected by the infarct (left panel) and the hub-score of the corresponding node (middle panel).

Left panel: The percentage of node volume affected by the infarct was acquired by overlaying the automated anatomical labeling atlas (AAL) on the lesion map. Nodes are depicted as spheres and indicate 90 cortical and subcortical brain regions.

Middle panel: A standard network topology map was created by averaging brain networks obtained from whole brain tractography data of 44 cognitively healthy adults. This standard topology map was used to calculate the hub-score of each node. In the figure, the size of the node is scaled according to the hub-score. Not all edges are visualized for clarity.

Right panel: The shortest path is calculated between each pair of nodes in the network. Nodes with a high hub-score (i.e. betweenness centrality, see methods) are nodes that are involved in a large number of shortest paths. In the example, hub nodes are visualized as larger circles in red.

Network construction and graph analysis

DWI data were processed and visualized using ExploreDTI.²⁸ First, signal drift and Gibbs ringing corrections were performed. The images were then warped to downsampled T1 volumes (2mm³), while correcting for subject motion, eddy currents and echo-planar imaging distortion. Whole brain deterministic fiber tractography was performed using the constrained spherical deconvolution (CSD) method with an L-max of 6, an angle threshold of 30 degrees, and a step length of 2 mm. A threshold of fractional anisotropy (FA) > 0.2 was applied to limit partial volume effects.

For each participant, the whole-brain fiber tractography maps were parcellated into 90 cortical and subcortical regions (i.e. network nodes) by affine registration of the automated anatomical labeling atlas (AAL) to patient space.²⁹ Two nodes were considered to be connected if a fiber bundle was present with two end points located in these nodes. Weighted connectivity matrices were obtained for each participant by multiplying each connection by the mean fractional anisotropy (FA) of that connection. To account for differences in network density across patients, networks were thresholded until all networks had a fixed density of 15%, while preserving the number of nodes participating in the network, using an in-house developed algorithm. Keeping the network density fixed ensures that potential differences in global network efficiency are not because of differences in the number of network connections, caused by, for example, brain size or infarct volume. Global network efficiency and betweenness centrality were calculated for each FA weighted connectivity matrix using the brain connectivity toolbox in MATLAB version 9.1.³⁰

Standard network topology map

To localize network hubs, we constructed a standard network topology map based on DWI data of 44 cognitively healthy adults (mean age 72 ± 4.6 years, 27 men (61.4%)). Participants had no history of disabling stroke or other known psychiatric or neurological disorder that could affect cognitive functioning, and an minimal state examination score of 27 or higher.

To determine whether a network node was considered a hub, we quantified the average betweenness centrality of each node within the cognitively healthy sample (Figure 1, middle panel). Nodes with a relatively high betweenness centrality are often considered network hubs.¹³ A high betweenness centrality indicates that the node participates in a large amount of shortest paths (Figure 1, right panel), meaning that a large part of the total information flow within the network is expected to travel through that node.³¹ Here, we refer to betweenness centrality as the hub-score.

Lesion impact score

To assess the potential impact of an infarct on the brain network, we calculated a lesion impact score for each node. The lesion impact score was defined as a product of (1) the percentage of node volume affected by the infarct and (2) the hub-score (Figure 1). Hence, a high lesion impact score indicates that the infarct affects a large proportion of a node with a relatively high hub-score. A low lesion impact score indicates either a very small infarct or an infarct affecting a node with a low hub-score (the hub-score ranges from 0 to 340,7). The highest lesion impact score of each patient's network was used in further analysis. Figure 2 visualizes how often nodes with a high hub-score were affected by an infarct in the current patient sample.

Figure 2: Axial (left) and lateral (right) view of the brain.

Nodes are depicted as spheres and indicate 90 cortical and subcortical brain regions. The color of the nodes indicate the frequency in which each node was affected by a lesion in the 75 ischemic stroke patients, and was included in the lesion impact score. The size of the node is scaled according to the hub-score. The hub-score of each node was obtained from a sample of cognitively healthy adults and was thus independent of the patient data³¹. Nodes with the highest hub-score included the left precuneus, the right superior parietal cortex, and the right superior frontal cortex.

Other imaging markers

The severity of white matter hyperintensities was assessed according to the Fazekas scale on the FLAIR sequences.³² Whole-brain volumetric data were obtained from the T1-weighted scans using Statistical Parametric Mapping (SPM8) software (<http://www.fil.ion.ucl.ac.uk/spm/>) in MATLAB. The CAT12 toolbox (<http://www.neuro.uni-jena.de/cat/>) was used to extract volumetric data for gray matter, white matter, and cerebrospinal fluid. Total intracranial volume was defined as the sum of gray matter, white matter, and cerebrospinal fluid volume. Brain volume was then normalized by dividing it by total intracranial volume.

Neuropsychological assessment

The neuropsychological assessment was performed at 5 weeks and 1 year after stroke. The cognitive domains that were assessed were attention and processing speed, working memory and learning, and frontal-executive functions. The domains and associated tests are presented in Supplemental Table I. Raw scores of each test were converted into standardized scores corrected for age, sex, and level of education, based on available normative data. Domain scores were calculated by averaging the standardized scores of each test in that domain. A poststroke *vascular cognitive disorder (VCD)* was defined according to the International Society of Vascular Behavioral and Cognitive Disorders (VASCOG) criteria as performance on ≥ 1 domains ≥ 1 standard deviations (SD) below appropriate norms, as previously reported.^{21,33} The presence of a VCD was further subdivided into a mild VCD (i.e. performance on ≥ 1 domains is ≥ 1 SD but < 2 SDs below appropriate norms), and a major VCD (i.e. performance on ≥ 1 domains is ≥ 2 SDs below appropriate norms).

Cognitive recovery was defined as a transition from a mild VCD at 5 weeks to no VCD at 1 year, or a transition from a major VCD at 5 weeks, to a mild or no VCD at 1 year. All other patients (i.e. those who remained cognitively stable and those who showed cognitive deterioration over time) were defined as *no cognitive recovery*.

Statistics

IBM SPSS version 24 was used. Since the lesion impact score had a strongly right skewed distribution, a log transformation was applied to obtain a normal distribution and a better fit to the data. First, to verify whether there was indeed an association between the lesion impact score and global network efficiency, a univariate regression analysis was performed with the lesion impact score as independent variable and global network efficiency as dependent variable. Next, we evaluated the association between the lesion impact score and cognitive outcome. A logistic regression analysis was performed with the lesion impact score as independent variable and presence of a VCD (yes/no) 5 weeks after stroke

as dependent variable. The same logistic regression analysis was repeated but with cognitive recovery after 1 year as dependent variable. In all of the analyses, age, sex, white matter hyperintensity severity, infarct volume, and brain volume were considered as covariates. First, univariate analyses were performed. Next, all possible confounders with a $P < 0.1$ were combined in a multivariate regression analysis.

Results

Of all the 75 included patients with a Montreal Cognitive Assessment < 26 during hospitalization, 60 (80%) had a VCD 5 weeks after stroke (at the moment that MRI scanning took place), and were included in the cross-sectional analysis, see Table 1 for the patient characteristics. Of the 70 (93%) patients with a cognitive assessment after 1 year, 55 (79%) had a VCD 5 weeks after stroke and could therefore show cognitive recovery. Cognitive recovery was seen in 22 (40%) of the 55 patients. Of the remaining 33 patients, 32 (58%) remained stable, and 1 (2%) showed cognitive deterioration. The distribution of the location of the strokes is shown in a summary map in Supplemental Figure I.

Table 1: Patient characteristics.

N	75
Age, years	70 (8.5)
Sex, men	50 (66.7%)
Level of education	5 (4-6)
NIHSS	2 (2-4)
Normalized infarct volume in mL	5.87 (1.97-21.8)
VCD 5 weeks after stroke	60 (80%)
WMH severity 0/1/2/3	7 (9.3%) /26 (34.7%) /34 (45.3%) /8 (10.7%)
Old infarcts or lacunes	21 (28%)

Data are presented as mean (SD), median (interquartile range), or N (%). Level of education is coded using Verhage's coding system (1-7), WMH severity is coded according to the Fazekas score. NIHSS = national institutes of health stroke scale at admission, VCD = vascular cognitive disorder, WMH = white matter hyperintensity.

Lesion impact score and global network efficiency

After log transformation, the lesion impact score ranged from -2 to 2. Thus, 1 point increase in the log transformed score, corresponds to a 10-fold increased impact of the infarct on the brain network. A higher lesion impact score was related to lower global network efficiency in patients (standardized β [95%CI]=-0.435 [-0.655 to -0.216], $P < 0.001$), see Figure 3. Higher age (β =-0.358 [-0.583 to -0.132]), white matter hyperintensity severity (β =-0.420 [-0.647 to -0.193]), normalized

infarct volume ($\beta=-0.211$ [-0.449 to 0.027]), and lower normalized brain volume ($\beta=0.432$ [0.213 to 0.652] all P -value <0.08) were all associated with lower global network efficiency, while sex was not related to global network efficiency. In the multivariate model including all possible confounders, the lesion impact score remained a significant predictor of global network efficiency ($\beta=-0.528$ [-0.776 to -0.277], $P<0.001$).

Lesion impact score and cognition

Figure 3: Scatterplot showing the relationship between the lesion impact score and global network efficiency in stroke patients.

The lesion impact score reflects the estimated impact of the infarct on the brain network, with higher scores indicating larger infarcts in more important network nodes. Logarithmic transformation of the lesion impact score was performed to obtain a better model fit. The log transformed score ranges from -2 to 2, meaning that with every 1 point increase in the transformed score, there is 10 times greater impact of the infarct on the brain network.

Figure 4: Logistic regression curve of cognitive recovery, showing that with an increasing lesion impact score, the probability of cognitive recovery decreases.

Logarithmic transformation of the lesion impact score was performed to obtain a better model fit. The log transformed score ranges from -2 to 2, meaning that with every 1 point increase in the transformed score, there is 10 times greater impact of the infarct on the brain network.

The lesion impact score was not significantly related to presence of a VCD 5 weeks after stroke (odds ratio=1.83; 95%CI[0.910 to 3.70], $P=0.090$). Moreover, none of the possible confounders (i.e. age, sex, white matter hyperintensity severity, and brain volume) were predictors of presence of a VCD (all $P>0.4$).

A lower lesion impact score was related to a higher chance of cognitive recovery after 1 year (odds ratio=0.282 [0.102 to 0.778], $P=0.014$, see Figure 4). Age, sex, white matter hyperintensity severity, and infarct volume were no significant predictors of cognitive recovery in univariate analyses ($P>0.2$). Only brain volume was positively related to cognitive recovery, and was therefore added to a multivariate model (odds ratio =1.86 [1.01 to 3.43], $P=0.048$). In the multivariate model, the lesion impact score remained a significant predictor of cognitive recovery (odds ratio=0.434 [0.193 to 0.978], $P=0.044$), whereas brain volume did not contribute significantly to the model.

Discussion

In this study, we developed the lesion impact score that estimates the extent of damage to strategic network locations in patients with ischemic stroke. We found that a higher lesion impact score was indeed a predictor of lower global network efficiency and that a lower lesion impact score predicted cognitive recovery 1 year after stroke. Importantly, these associations were independent of white matter hyperintensity severity and total infarct volume. The lesion impact score was no significant predictor of the presence of a VCD 5 weeks after stroke.

Our study adds 2 important new findings to the existing literature: we have demonstrated the feasibility of a lesion impact score - implemented on readily available structural MRI sequences (T1 and FLAIR) - to estimate brain network impairments in stroke patients, without the need for high-resolution DWI data; and secondly, we have demonstrated a relationship of the lesion impact score with long-term clinical outcome. The results are in line with a study showing that simulated lesions in network hubs result in significant reductions in global network efficiency, supporting the concept of hubs as strategic network locations.¹⁴ Moreover, our results are in line with previous research showing that damage to network hubs is associated with altered structural and functional network properties in stroke patients.^{15,16,34}

We found no significant cross-sectional association between the lesion impact score and cognition, although there was a trend in the expected direction. The fact that all included patients showed evidence of a cognitive disorder during hospitalization, may have reduced the contrast between the no VCD and VCD group.

To our knowledge, this study shows for the first time that there is an association between damage to a hub in the structural brain network and cognitive recovery after stroke. A previous study has primarily focused on the association between ischemic damage to functional network hubs and VCD after stroke.³⁵ A recent extensive review takes this a step further, arguing that hubs are generally affected in a wide range of neurological diseases.¹⁴ Many of these diseases result in a cognitive disorder, which strengthens the association between cognition and hub connectivity. Our results add to this that damage to hubs also negatively impacts the resilience of the brain and the ability to functionally recover after acute ischemic damage.

This study has several limitations. First, the methods and processing steps that are chosen to reconstruct the brain networks may affect the outcome parameters. For

example, it has been shown that different gray matter parcellation schemes,³⁶ or fiber tractography methods,^{37,38} can yield different estimates of hub connectivity and network efficiency. We therefore used an established method for network reconstruction, that has shown to be reproducible across different patient cohorts using diffusion data with a comparable resolution as in the current study.³⁹⁻⁴² This choice led to excluding cerebellar nodes from the network analysis. Results can therefore not be extrapolated to patients with infarcts located in the cerebellum or solely in the white matter. The organization of the cerebellar network and the location of cerebellar hubs is currently underexplored and remains to be investigated. Second, although damage to white matter connections (i.e. edges) is clearly also relevant for cognitive functioning, it was beyond the scope of this study to develop a score that integrates both damage to hubs and critical network edges. Third, there are many different ways to define hubs within a network based on graph theory. Here we used a measure of centrality (i.e. betweenness centrality) to define the hub-score of a node, in line with several other studies.^{43,44} An integrated approach of classifying hubs based on multiple nodal measures has been advocated in the literature.³¹ Importantly, regardless of the hub definition being used, largely the same brain regions are identified as network hubs.¹³ Fourth, manual segmentation of the infarct is required to calculate the lesion impact score, which is time consuming and complicates implementation of the score in clinical practice. However, the lesion impact score can be calculated without the need for high-resolution DWI data of the patients, which is often not part of the clinical MRI protocol, since the standard network topology map can be reconstructed from an independent reference dataset. When automated segmentation of lesions becomes available in daily practice, the lesion impact score could be more easily implemented. Fifth, a relatively small sample size of ischemic stroke patients was used in this analysis. Future research should address the reproducibility and validity of the lesion impact score in larger stroke cohorts.

In conclusion, we introduced a lesion impact score that combines information on lesion size and network topology to predict cognitive recovery after stroke. Since the score can be computed based on a patient's standard structural MRI scan, it is potentially applicable in a clinical setting. Future research should validate the lesion impact score in larger and independent cohorts.

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Supplemental Material

Supplemental Table 1: The domains and associated tests of the neuropsychological assessment.

Domain	Tests
Attention and processing speed	Reaction time test, Vienna Test System, S1, S2
	Symbol Digit Modalities Test
	Trailmaking test A
(Working) memory and learning	WAIS Digit Span forward and backward
	The Rey Auditory Verbal Learning Test
	Semantic Fluency
Frontal-Executive functions	Controlled Oral Word Association Test
	Trailmaking test B
	Reaction time test Vienna Test System S3

Supplemental Figure 1: A summary map showing the location of the strokes of the 75 patients in this study. The color bar indicates the frequency of the strokes, with purple meaning that only one patient had a stroke in this area, while red indicates that 5 patients had a stroke in this location. As is conventional for lesion maps, the left hemisphere is shown on the left and the right hemisphere is shown on the right.

4

Prediction of cognitive recovery after stroke (PROCRAS): the value of diffusion-weighted imaging-based measures of brain connectivity

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Abstract

Background and Purpose

Prediction of long-term recovery of a poststroke cognitive disorder (PSCD) is currently inaccurate. We assessed whether diffusion-weighted imaging (DWI)-based measures of brain connectivity predict cognitive recovery one year after stroke in patients with PSCD in addition to conventional clinical, neuropsychological, and imaging variables.

Methods

This prospective mono-center cohort study included 217 consecutive patients with a clinical diagnosis of ischemic stroke, aged ≥ 50 , and Montreal Cognitive Assessment score below 26 during hospitalization. Five weeks after stroke, patients underwent DWI-MRI. Neuropsychological assessment was performed five weeks and one year after stroke, and was used to classify PSCD as absent, modest or marked. Cognitive recovery was operationalized as a shift to a better PSCD category over time.

We evaluated four DWI-based measures of brain connectivity: global network efficiency and mean connectivity strength, both weighted for mean diffusivity and fractional anisotropy. Conventional predictors were age, sex, level of education, clinical stroke characteristics, neuropsychological variables and MRI findings (e.g. infarct size). DWI-based measures of brain connectivity were added to a multivariable model to assess additive predictive value.

Results

Of 135 patients (mean age, 71 years; 95 men [70%]) with PSCD 5 weeks after ischemic stroke, 41 (30%) showed cognitive recovery. Three out of four brain connectivity measures met the predefined threshold of $P < 0.1$ in univariable regression analysis. There was no added value of these measures to a multivariable model that included level of education and infarct size as significant predictors of cognitive recovery.

Conclusions

Current DWI-based measures of brain connectivity appear to predict recovery of PSCD, but at present have no added value over conventional predictors.

Introduction

Cognitive deficits after ischemic stroke occur in up to 75% of patients, and are independently associated with poor long-term outcome, including lower quality of life and disability.^{1,2} Although many patients with a cognitive disorder after ischemic stroke will show recovery over time, about half will not improve or may even deteriorate.³⁻⁵ Identifying patients with potential for cognitive recovery could help guiding patient's expectations and setting more realistic and attainable goals in rehabilitation programs.

Thus far, prediction of cognitive recovery after ischemic stroke is imprecise.⁶ Most studies focused on prediction of poor cognitive outcome, whereas predictors of recovery have received less attention. Emerging predictors of cognitive recovery from literature include demographic characteristics (i.e. age, sex and level of education [LoE]), stroke characteristics (i.e. stroke location and severity), vascular risk factors (i.e. diabetes mellitus and smoking), cognitive and emotional status (i.e. cognitive functioning in acute stage and poststroke depression or apathy), and imaging findings (i.e. infarct volume and white matter hyperintensity severity), although results vary between studies.^{4,7-13}

Measures of brain connectivity are emerging as important markers of brain injury after stroke, and thus might be of value in predicting cognitive recovery.^{14,15} Previous studies have shown that ischemic stroke does not only have local effects, but can also disrupt brain networks.¹⁵⁻¹⁷ The extent to which brain regions are functionally or structurally connected can be estimated with functional MRI or diffusion-weighted imaging (DWI). Global network efficiency, a measure of network integration,¹⁴ has been independently associated with cognitive performance and cognitive deterioration over time in patients with cerebral small vessel disease.¹⁸⁻²⁰ In addition, global efficiency is considered to reflect brain resilience in healthy controls.²¹ Recent studies also showed that global efficiency predicted cognitive functioning 6 months after stroke, and that it was related to recovery from aphasia following intensive therapy.^{22,23} We therefore hypothesized that global efficiency could predict recovery of cognitive deficits after ischemic stroke.

In this study, we assessed whether DWI-based measures of brain connectivity predict cognitive recovery one year after stroke in patients with PSCD in addition to clinical, neuropsychological, and conventional imaging variables.

Methods

Population

Data were used from the longitudinal, prospective, Prediction of Cognitive Recovery after Stroke (PROCRAS) study, at the Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands. The data that support the findings of this study are available from the corresponding author upon reasonable request. PROCRAS included patients ≥ 50 years, admitted with a clinical diagnosis of acute ischemic stroke and evidence of a cognitive disorder during hospitalization, indicated by a Montreal Cognitive Assessment (MoCA) score < 26 . In 90% of patients, the MoCA could be obtained in the first week after admission (median 3 days, interquartile range of 2-5 days). It should be emphasized that patients were included based on a clinical discharge diagnosis of ischemic stroke, established by an experienced neurologist, based on data collected in routine clinical care, with imaging being mostly limited to CT. Exclusion criteria for PROCRAS were indication of prestroke cognitive disorder (Informant Questionnaire on Cognitive Decline in the Elderly ≥ 3.6)²⁴, prestroke dependence in activities of daily living, life expectancy < 1 year, severe stroke expected to require long-term nursing care facilities, inability to participate in neuropsychological assessment (e.g. due to severe aphasia or severe neglect), and having contraindications for MRI. Patients with a history of stroke were not excluded.

Between July 1 2016 and May 10 2018, 386 eligible patients with MoCA score < 26 , 217 agreed to participate in the PROCRAS study (Figure 1). Five weeks after stroke, 143 patients had PSCD. Of these, 136 patients (95%) completed follow-up after 1 year, of which 5 only by phone (presence and severity of cognitive complaints, impact on daily functioning and social participation). Two independent senior neurologists were asked to determine whether the one year situation reflected either cognitive recovery or no cognitive recovery. No consensus was reached about the coding in one patient, resulting in exclusion from the final sample ($n=135$).

Figure 1: Flow diagram of patient flow.

Figure 2: Processing steps and study design.

Top: After pre-processing, whole brain tractography was performed on each patient's DWI data. These whole brain tractography maps were parcellated into 90 cortical and subcortical regions, by registering the automated anatomical labeling atlas to patient space. This resulted in two brain networks per patient, one with connections weighted by fractional anisotropy, the second weighted by mean diffusivity.

Middle: The figure shows a schematic network. Any network can be described by nodes (circles) connected by edges (lines). In case of the brain network, the nodes are (sub-)cortical regions and the edges white matter tracts. In the example, the shortest path between two nodes is highlighted in blue. This shortest path preferentially traverses edges that have a strong connection between nodes. Global efficiency is defined as the inverse of the average connectivity strength of all shortest paths in the network. The strength of a node is the average of all FA or MD values of the edges connecting to that node (see the edges that are highlighted in green for an example). The mean connectivity strength is a more generic measure of the network and is calculated by taking the average of the strength of all nodes in the network.

Middle and Bottom: In this study, we assessed whether DWI-based measures of brain connectivity predict cognitive recovery one year after stroke, and we assessed whether there was additional predictive value of DWI-based measures of brain connectivity on cognitive recovery.

Measures

Neuropsychological assessment

The neuropsychological assessment was performed 5 weeks (± 1 week) and 1 year (± 2 weeks) after stroke. Domains assessed were attention and processing speed, working memory and learning, and frontal-executive functions, based on the 60-minute protocol as proposed in vascular cognitive impairment harmonization standards (supplementary Table I).³ Raw test scores were converted into standardized z-scores corrected for age, sex, and LoE, based on available normative data. Mean test z-scores per domain constituted domain scores. PSCD was operationalized based on criteria from the International Society of Vascular Behavioral and Cognitive Disorders as performance on ≥ 1 domains ≥ 1 standard deviations (SD) below appropriate norms, as previously reported.^(25,26) Presence of PSCD was further subdivided into modest PSCD (i.e. performance on ≥ 1 domains is ≥ 1 SD but < 2 SDs below appropriate norms), and marked PSCD (i.e. performance on ≥ 1 domains is ≥ 2 SDs below appropriate norms).^{25,26}

MRI

Patients were scanned on a 3 tesla scanner (Intera, Philips, Best, the Netherlands) 5 weeks after stroke. The standardized scanning protocol consisted of sagittal 3D T1-weighted, axial T2-weighted, axial fluid attenuated inversion recovery (FLAIR), and DWI sequences.²⁶ DWI sequence parameters were: 70 slices, voxel size $2.00 \times 2.00 \times 2.00 \text{ mm}^3$, repetition time/echo time: 7891/87 ms, 50 directions (b-value 1500 s/mm^2) and 7 $b=0 \text{ s/mm}^2$ images. To calculate measures of brain connectivity, we reconstructed brain networks from DWI data of all patients (Figure 2).²⁷ After correction for subject motion and Gibbs ringing, eddy current and echo planar imaging distortions, whole-brain fiber tractography was performed. The resulting tractography maps were parcellated into 90 cortical and subcortical regions by affine registration of the automated anatomical labeling atlas to patient space. Two connectivity matrices were obtained for each patient: one weighted for fractional anisotropy (FA), and the other weighted for mean diffusivity (MD). To account for differences in network density across patients, networks were thresholded until a fixed density of 15%, while preserving the nodes participating in the network. Global efficiency - a measure of network integration -, and mean connectivity strength - a more generic measure of white matter tract integrity - were calculated for both MD and FA weighted brain networks. MD weighted edge weights were inverted, such that higher global efficiency and higher mean connectivity strength values indicate better white matter tract integrity. All four network measures were then transformed to z-scores with a mean of 0 and SD of 1 to facilitate interpretation. These z-scores were used as predictors in further

analysis. For three (2%) patients in the current analysis, these network measures could not be calculated because of missing data due to logistic issues.

Primary outcome measure

The primary outcome measure was cognitive recovery, defined as a transition from marked PSCD or modest PSCD at 5 weeks to modest/no or no PSCD at 1 year, respectively.

Conventional predictors

Conventional predictors of cognitive recovery were selected based on expert opinion and previous literature.^{4,7-13}

Demographic characteristics

Patient demographics were collected during hospitalization. LoE was scored ranging 1-7 covering the Dutch education system. In statistical models, LoE was divided into three categories: low ¹⁻³, intermediate ⁴⁻⁵, and high ⁶⁻⁷.

Stroke characteristics

Stroke severity was assessed at the emergency department using the National Institutes of Health Stroke Scale (NIHSS).²⁸ The Barthel Index was collected at day 4 or at discharge to assess functional status.²⁹ Stroke subtype and location were determined based on MRI and were classified as lacunar, non-lacunar supratentorial or infratentorial stroke. If there was no symptomatic lesion on MRI, we reclassified the clinical stroke syndrome according to the Oxfordshire criteria, in which PACS/TACS and POCS with only hemianopsia were defined as non-lacunar supratentorial, other POCS were defined as infratentorial and LACS was defined as lacunar.³⁰ Supratentorial strokes were classified as left or right.

Cognition and emotion

Indicators of cognitive functioning and emotion status were recorded in the first weeks after stroke, i.e. cognition during admission as measured with the MoCA; general cognitive functioning 5 weeks after stroke defined as the average z-score of cognitive domains from neuropsychological assessment; symptoms of depression or anxiety 5 weeks after stroke assessed with the Hospital Anxiety and Depression Scale (HADS)³¹, HADS-D or HADS-A subscale, respectively.

Cardiovascular disease and risk factors

We recorded: previous stroke or transient ischemic attack, hyperlipidemia (previous diagnosis or total cholesterol > 5 mmol/l), hypertension (previous diagnosis or blood pressure of >140/90), diabetes mellitus, atrial fibrillation, a history of

vascular disease (defined as ischemic heart disease or peripheral vascular disease), actual smoking status, symptomatic carotid stenosis, and a comorbidity sum score using the cumulative illness rating scale.³²

Other measures

We recorded treatment with either intravenous alteplase or intra-arterial thrombectomy in the acute phase, apolipoprotein E (APOE) $\epsilon 4$ allele carriership, recurrent stroke between admission for the first stroke and assessment after 5 weeks, and the number of days between stroke-onset and neuropsychological assessment.

MRI characteristics

The severity of white matter hyperintensities was assessed according to the Fazekas scale on FLAIR sequences.³³ The degree of medial temporal lobe atrophy was assessed with the MTA scale.³⁴ MRI abnormalities suggestive for old ischemic lesions or lacunes were recorded according to standards for reporting vascular changes on neuroimaging.³⁵ Brain tissue volumes were determined by brain segmentation as previously described.⁽²⁶⁾ We used brain parenchymal fraction as predictor in analyses, which is brain volume divided by total intracranial volume.³⁶ Because brain parenchymal fraction was intended to be a measure of atrophy, infarct volume was included in the brain volume.³⁵ Infarct volumes were determined by manual segmentation as reported earlier.^{26,27} Although a likely clinical diagnosis of ischemic stroke was established for all patients, some patients had no identifiable symptomatic infarct on MRI after 5 weeks. Infarct size was divided into three categories (i.e. no identifiable symptomatic infarct on MRI, infarct volume of 0-20 mL, and infarct volume of >20 mL), because the assumption of linearity with the logit was violated.

Statistics

Numerical continuous variables are presented as means (SDs), or medians (interquartile ranges), when appropriate. Discrete variables were summarized as counts (percentages).

We used a stepwise approach to construct a multivariable logistic regression model consisting of the strongest predictors of cognitive recovery, as outlined below. Results were reported as the odds ratio (OR), 95% confidence interval (CI), and *P*-value.

Step 1: All DWI-based measures of brain connectivity and conventional predictors were related to occurrence of cognitive recovery in univariable logistic regression

analysis. In this pre-selection step, only variables with $P < 0.1$ were eligible for entry in the multivariable logistic regression analysis³⁷ after checking for multicollinearity.

Step 2: Multivariable logistic regression analysis with backward stepwise selection was performed with selected conventional predictors from step 1 as independent variables and cognitive recovery as dependent variable. Variables were eliminated until the maximum amount of four degrees of freedom was reached, according to the general rule of 10 outcome events per variable.

Step 3: Selected DWI-based measures of brain connectivity from step 1 were added to the multivariable model from step 2 (i.e. model 1) in separate models to assess whether there was additional predictive value of one of these measures (i.e. models 2a, 2b and 2c). Different models were used because of high correlations between each of the network measures. Discrimination of models was reported with the area under the receiver operator curve (AUROC) and Nagelkerke's R^2 .³⁷

Imputation of missing data was not performed, because of a low amount of missing data (Table 2). All statistical analyses were performed using SPSS version 24.

Regulation Statement

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics Committee Approval

The PROCRAST study was approved by the medical ethics committee of Brabant, based in Tilburg, the Netherlands. Written informed consent was obtained from all participants.

Results

Of the 135 patients with a cognitive disorder 5 weeks after ischemic stroke, 41 (30%) showed cognitive recovery after one year, 9 (7%) showed cognitive deterioration, and the remaining 85 (63%) patients remained cognitively stable over time (Table 1).

Table 1: distribution of severity of PSCD after 5 weeks and after one year.

		PSCD after one year		
		No PSCD	Modest PSCD	Marked PSCD
PSCD after 5 weeks	Modest PSCD	28*	64	9
	Marked PSCD	1*	12*	21

*Patients that are defined as showing cognitive recovery.

DWI-based measures of brain connectivity

In the pre-selection of variables for the multivariable model, three of four network measures met the threshold of $P < 0.1$: global efficiency FA-weighted (OR recovery per SD=1.4[1.0-2.1]), mean connectivity strength FA-weighted (OR=1.4[1.0-2.1]), and mean connectivity strength MD-weighted (OR=1.5[1.0-2.2])(Table 2).

Conventional predictors

In the pre-selection of conventional predictors for the multivariable model, five of thirty-three variables met the threshold of $P < 0.1$: sex (men compared to women, OR=2.1 95%CI[0.9-5.1]); LoE (low LoE OR=4.4[1.6-12] or high LoE OR=3.3[1.3-8.0], both compared to intermediate LoE [reference]); comorbidity sum score (per point OR=0.9[0.8-1.0]); MoCA score (per point OR=1.1[1.0-1.3]); and infarct presence or size (no identifiable symptomatic infarct on MRI after 5 weeks, OR=0.3[0.1-0.9] and infarct volume of >20mL OR=0.3[0.1-0.8], both compared to infarct volume of 0-20 mL [reference]) (Table 2). Backward selection of these five predictors in multivariable analysis resulted in model 1 with two variables as strongest predictors of cognitive recovery 1 year after stroke: infarct presence or size and LoE (Table 3). Model performance was adequate with a Nagelkerke's R^2 of 0.19 and an AUROC of 0.73.

Additional prognostic value brain connectivity measures

In the last step of the analysis, DWI-based measures of brain connectivity were added to the multivariable model that consists of two conventional predictors. This did not significantly improve model performance: global efficiency FA weighted ($R^2=0.21$, AUROC=0.74, $\chi^2[1]=2.7$, $P=0.096$), mean strength FA weighted ($R^2=0.21$, AUROC=0.74, $\chi^2[1]=2.5$, $P=0.114$), and mean strength MD weighted ($R^2=0.21$, AUROC=0.75, $\chi^2[1]=2.8$, $P=0.096$)(Table 3).

Table 2: Relation between conventional predictors and cognitive recovery.

		Missings	Cognitive recovery	No cognitive recovery	OR	95%CI	P-value
	N		41	94			
Demographic characteristics	Age per decade	0	70(8)	72(9)	0.895	0.591-1.355	0.601
	Sex, male	0	33(81%)	62(66%)	2.129	0.881-5.145	0.093
	LoE						0.003
	Low ⁽¹⁻³⁾	0	11(27%)	10(11%)	4.400	1.606-12.055	0.004
	Intermediate ⁽⁴⁻⁵⁾	0	17(41%)	68(72%)	ref		
	High ⁽⁶⁻⁷⁾	0	13(32%)	16(17%)	3.250	1.315-8.029	0.011
Stroke characteristics	NIHSS	0	3(2-4)	3(2-6)	0.987	0.901-1.081	0.774
	Barthel index	0	20(17-20)	20(17-20)	0.988	0.906-1.079	0.792
	Lacunar stroke	0	14(34%)	32(34%)	1.005	0.463-2.178	0.991
	Non-lacunar supratentorial stroke	0	18(44%)	53(56%)	0.605	0.289-1.268	0.183
	Supratentorial left stroke	0	16(39%)	40(43%)	0.864	0.409-1.827	0.702
	Supratentorial right stroke	0	16(39%)	41(44%)	0.827	0.391-1.748	0.620
	Infratentorial stroke	0	11(27%)	21(22%)	1.275	0.548-2.965	0.625
Cardiovascular disease and risk factors	Diabetes mellitus	0	13(31%)	30(32%)	0.990	0.450-2.178	0.981
	Actual smoker	0	12(29%)	17(18%)	1.874	0.798-4.400	0.149
	History of myocardial infarction or peripheral vascular disease	0	11(27%)	34(36%)	0.647	0.288-1.453	0.292
	History of stroke or TIA	0	8(20%)	20(21%)	0.897	0.359-2.244	0.816
	Hypertension	0	32(78%)	69(73%)	1.288	0.540-3.074	0.568
	Hyperlipidemia	0	38(93%)	91(97%)	0.418	0.081-2.162	0.298
	Atrial fibrillation	0	7(17%)	18(19%)	0.869	0.332-2.275	0.775
	Symptomatic carotid stenosis	0	2(5%)	12(13%)	0.346	0.074-1.623	0.178
	Comorbidity score	0	10(8-11)	11(8-15)	0.921	0.844-1.005	0.065
Cognition and emotion	MoCA score	0	22(20-24)	21(19-23)	1.111	0.981-1.257	0.098
	Mean z-score of three cognitive domains	0	-1.01(0.50)	-1.14(0.55)	1.563	0.772-3.167	0.215
	HADS-A	17	5(2-6)	4(2-8)	0.969	0.873-1.075	0.546
	HADS-D	17	4(2-8)	5(1-9)	1.006	0.916-1.105	0.900
Other	Treated with i.v. alteplase and/or thrombectomy	0	8(20%)	21(22%)	0.843	0.338-2.098	0.713
	Carrier of at least 1 APOE ε4 allele	9	10(27%)	23(26%)	1.063	0.447-2.529	0.890
	Days from ischemic stroke till neuropsychological assessment	0	36(11)	38(10)	0.976	0.940-1.014	0.212
	Recurrent stroke between admission for stroke and assessment	0	0(0%)	1(1%)	NA		
DWI-based measures of brain connectivity	Global efficiency FA weighted	3	0.25(0.91)	-0.10(1.02)	1.448	0.983-2.133	0.061
	Global efficiency MD weighted	3	0.21(0.88)	-0.09(1.04)	1.361	0.930-1.991	0.113
	Mean strength FA weighted	3	0.25(0.97)	-0.10(1.00)	1.429	0.971-2.101	0.070
	Mean strength MD weighted	3	0.26(0.91)	-0.11(1.03)	1.462	0.991-2.157	0.055

Table 2: Continued.

	Missings	Cognitive recovery	No cognitive recovery	OR	95%CI	P-value
MRI characteristics						
Fazekas score	0	2(1-2)	2(1-2)	1.155	0.770-1.730	0.486
Medial temporal lobe atrophy	0	1(1-2)	2(1-2)	0.816	0.504-1.321	0.409
Old infarcts	0	15(37%)	30(32%)	1.231	0.570-2.656	0.597
Brain parenchymal fraction	0	0.21(1.06)	-0.09(0.96)	1.369	0.939-1.997	0.102
Infarct volume (mL)	32*	4(1-11)	10(2-30)	0.985	0.966-1.004	0.127
Infarct size						0.013
No symptomatic infarct on MRI	0	6(15%)	26(28%)	0.318	0.116-0.872	0.026
Infarct volume 0-20mL	0	29(70%)	40(42%)	ref		
Infarct volume >20mL	0	6(15%)	28(30%)	0.296	0.108-0.806	0.017

Data are presented as mean (standard deviation), median (interquartile range), count (percentage). The odds ratio's for brain parenchymal fraction and DWI-based measures of brain connectivity are per SD.

*The amount of missings in the variable infarct volume are the patients with no symptomatic infarct on MRI, thus having no infarct volume.

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; N, number; NA, not applicable; Ref, Reference; NIHSS, National Institutes of Health Stroke Scale; TIA, Transient ischemic attack; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; APOE, apolipoprotein E; FA, fractional anisotropy; MD, mean diffusivity.

Table 3: Multivariable analysis for prediction of cognitive recovery 1 year after stroke, maximum 4 d^* in model 1 (n=132).

	Model 1		Model 2a		Model 2b		Model 2c	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
No symptomatic infarct on MRI	0.363	0.125-1.057	0.347	0.118-1.023	0.347	0.118-1.025	0.355	0.120-1.051
Infarct volume 0-20mL	ref		ref		ref		ref	
Infarct volume >20mL	0.296	0.104-0.841	0.322	0.112-0.922	0.323	0.112-0.926	0.330	0.115-0.949
LoE Low ⁽¹⁻³⁾	4.494	1.516-13.327	4.387	1.475-13.045	4.427	1.492-13.138	4.538	1.520-13.549
LoE Intermediate ⁽⁴⁻⁵⁾	ref		ref		ref		ref	
LoE High ⁽⁶⁻⁷⁾	2.936	1.144-7.536	2.922	1.120-7.626	2.915	1.119-7.592	2.897	1.110-7.562
Global efficiency FA weighted per SD			1.417	0.933-2.153				
Mean strength FA weighted per SD					1.392	0.917-2.112		
Mean strength MD weighted per SD							1.424	0.931-2.179
Model performance								
Nagelkerke R ²	0.187		0.212		0.210		0.212	
AUROC	0.731		0.744		0.743		0.749	
Likelihood-ratio test			$\chi^2(1)=2.774, P=0.096$		$\chi^2(1)=2.497, P=0.114$		$\chi^2(1)=2.774, P=0.096$	

*Comorbidity sum score and MoCA score were eliminated from this model, because of the restriction of 4 degrees of freedom.

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; ref, reference; LoE, Level of Education FA, fractional anisotropy; MD, mean diffusivity; AUROC, area under the receiver operator curve.

Discussion

We show that DWI-based measures of brain connectivity predict cognitive recovery one year after stroke in patients with PSCD. However, they did not add prognostic value over a multivariable model derived from conventional predictors, in particular infarct size and LoE.

Our selection of candidate clinical predictors was derived from literature.²⁶ Because there were few previous studies on predictors of recovery of PSCD with variable results,^{4,7-9,13} we chose to also include predictors that were previously consistently linked to poor long-term cognitive outcome after ischemic stroke.²⁶ This ultimately resulted in a substantial set of thirty-three candidate predictors, of which only five predicted cognitive recovery in univariable analyses. This shows that it is difficult to predict cognitive recovery one year after stroke.

Large infarcts were associated with lower chances of cognitive recovery than small infarcts, as is generally reported in the literature,^{4,12} but not invariably.³⁸ Furthermore, higher educational level was associated with higher chances of recovery than intermediate LoE.^{4,21} Some variables in this study that did not predict cognitive recovery stood out. First, age has been quite consistently associated with poor cognitive outcome after stroke,³⁹ but was not associated with recovery in this study. Second, while most studies observed stroke severity to be associated with poor cognitive outcome, some studies, as well as this study, did not find this association.³⁹ Third, low LoE was associated with higher odds of recovery than intermediate LoE. This may be a chance finding, because relatively few patients had low LoE. An explanation may also be that educational level not always adequately reflects prestroke cognitive capacity, because of historical variation in educational opportunities. Alternatively, lower cognitive reserve in patients with lower LoE may affect the temporal dynamics of cognitive recovery.⁴⁰ Another unexpected finding was that patients without a symptomatic infarct on MRI were less likely to recover than those with a visible small infarct. Although the proportion of 24% MRI negative patients may seem substantial, it is similar to the 29% reported in a study in which patients were scanned shortly after stroke onset.⁴¹ In our setting, absence of an infarct on MRI may have several explanations. First, the MRI was performed 5 weeks after stroke. At this time, most lesions were DWI negative, making it more difficult, for example, to differentiate the symptomatic lesions from white matter hyperintensities. We have previously reported that over 20% of these MR negative patients received acute treatment at admission, which may have prevented occurrence of a lesion⁴². We also reported that an expert panel adjudicated 60% of MRI negative patients as having a likely diagnosis of ischemic stroke and that these patients, apart from having a lower acute NIHSS and shorter

duration of admission, had similar clinical features compared to MRI positive patients, including similar initial MoCA.⁴² Nevertheless, it is likely that some of the MRI negative patients had alternative diagnoses, that may have contributed to lower odds of cognitive recovery. Yet, including such patients in this study also reflects daily practice, where the discharge diagnosis of ischemic stroke is based on the symptomatology and acute CT scanning, often without MRI confirmation.

Our finding that DWI-based measures of brain connectivity predict cognitive recovery is in accordance with an earlier study that showed that response on intensive language therapy could be predicted using DWI-based global efficiency.²³ However, that study included fewer, and a more selected group of patients, and operationalized recovery in cognition differently. To our knowledge, our study is the first to evaluate the value of DWI-based measures of brain connectivity in predicting cognitive recovery one year after stroke in such a large sample of stroke patients. Our hypothesis of the added value of DWI-based measures of brain connectivity over conventional predictors was not confirmed, but in previous work using a subsample of the participants in this study, we showed that a score that combines information on infarct size and network topology does independently predict cognitive recovery.²⁷ Possibly, further evolution of network measures and analyses may increase their clinical and prognostic value in the near future.

A strength of our study is that we included consecutive patients with PSCD 5 weeks after stroke. Better prognostication of recovery at this stage is relevant for daily practice. Moreover, nearly all patients in this study completed follow-up, which limits risk of bias. Limitations of our study are that despite the substantial cohort size for a single center study, sample size was still modest for the purpose of predictive modelling and demonstrating added value for connectivity measures.⁴³ Our prediction model could possibly be further improved by including more precise white matter hyperintensity volume and hippocampal volume estimates using existing segmentation techniques. In addition, new diffusion-based connectivity methods have been developed, such as fixel based analysis, that can estimate bundle-specific microstructure in voxels with complex white matter architecture.⁴⁴ Furthermore, Single-Shell 3-Tissue Constrained Spherical Deconvolution is a method that can better differentiate between different tissue compartments, which may also provide additional information on white matter integrity.⁴⁵ Future studies need to investigate whether such techniques can improve the accuracy of the connectivity measures compared to using FA/MD. Moreover, although definitions of PSCD and cognitive recovery are relevant for daily practice, we may have missed more subtle cognitive improvement. Also, the group of patients in this study was selected from a large sample of patients admitted with a diagnosis

of ischemic stroke. Many patients met one or more exclusion criteria or could not be included because of a missing MoCA score, possibly creating selection bias, although there were no differences in demographic and stroke characteristics between patients included in this study and patients that were not. It should also be noted that preselection using the MoCA cutoff of 26 may have led to excluding patients with higher LoE that would have had a cognitive disorder in formal neuropsychological testing. However, this cut-off is often used in daily practice, and the distribution of educational levels was as expected.

Conclusion

DWI-based measures of brain connectivity predicted long-term cognitive recovery in patients with PSCD, but did not contribute to better prediction over clinical, neuropsychological and conventional imaging variables. The field of brain connectivity measures is evolving rapidly. Given the promise of these measures shown in our study, it may well be that these measures will evolve into useful predictors of cognitive outcome after stroke in the near future.

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Supplemental Materials

Supplemental Table 1: The domains and associated tests of the neuropsychological assessment.

Domain	Tests
Attention and processing speed	Reaction time test, Vienna Test System, S1, S2
	Symbol Digit Modalities Test
	Trailmaking test A
(Working) memory and learning	WAIS Digit Span forward and backward
	The Rey Auditory Verbal Learning Test
	Semantic Fluency
Frontal-Executive functions	Controlled Oral Word Association Test
	Trailmaking test B
	Reaction time test Vienna Test System S3

5

Absence of an infarct on MRI is not uncommon after clinical diagnosis of ischemic stroke

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Abstract

Introduction

An infarct on brain MRI is often seen as gold standard when diagnosing ischemic stroke. Although MRI has high sensitivity in detecting a lesion shortly after ischemic stroke, this rapidly declines when time progresses. We assessed the occurrence of a negative MRI 4-6 weeks after a discharge diagnosis of ischemic stroke, and compared the clinical characteristics of patients with a positive or negative MRI.

Patients and methods

The first 125 patients from a prospective longitudinal study of cognitive recovery after ischemic stroke were included in this study. Clinical characteristics were collected during admission. Per protocol, 4-6 weeks after stroke a brain MRI was performed. We operationalized different levels of certainty of the clinical diagnosis of ischemic stroke of a panel of 3 expert vascular neurologists.

Results

Thirty patients (24%) were MRI negative. Patients that were MRI negative had lower stroke severity at admission, shorter duration of hospital-stay, and better functional status at discharge. The panel judged that 18/30 (60%) MRI negative patients and 27/30 (90%) MRI positive patients had a likely diagnosis of ischemic stroke. Compared to MRI negative patients with a less likely diagnosis, those with a likely diagnosis had higher admission stroke severity and more often received an acute intervention.

Discussion and Conclusion

Absence of an infarct on MRI is not uncommon 4-6 weeks after a clinical diagnosis of ischemic stroke. The relatively high proportion of MRI negative strokes with a likely clinical diagnosis of ischemic stroke indicates that neurologists should be cautious ruling out the diagnosis based on MRI beyond the acute stroke stage.

Introduction

A clinical diagnosis of ischemic stroke can often be made with high certainty.^{1,2} However, there are also many cases in which the diagnosis is less certain, and misdiagnosis of stroke is not uncommon.^{2,3} Magnetic resonance imaging (MRI) is an established method to detect a lesion shortly after ischemic stroke.⁴ In daily practice, MRI is often used to increase diagnostic certainty and even to guide decision making in providing therapy.⁵ However, in up to one third of patients with a diagnosis of ischemic stroke no corresponding lesion is found on MRI performed within 2 weeks of onset of complaints (i.e. MRI negative stroke).^{6,7}

Several determinants of MRI negative stroke have been established in earlier work. Stroke characteristics, such as stroke location (e.g. lacunar or infratentorial strokes) and lower stroke severity have been associated with MRI negative stroke in the acute phase.⁷ Moreover, the timing of the MRI scan in relation to onset of complaints is essential. An increased duration between symptom onset and scanning has been associated with MRI negative stroke in a large study of 300 patients imaged in the acute phase.⁶ Furthermore, an increased duration between symptom onset and scanning has been associated with fogging of a lesion, reversal of a lesion after recanalization (e.g. as a consequence of acute treatment), and small lacunar strokes being not distinguishable from white matter hyperintensities.⁸⁻¹³

This indicates that with an increasing duration between symptom onset and scanning, there should be more caution when interpreting results of MRI. However, thus far, it is unclear how often patients with a clinical diagnosis of ischemic stroke at discharge have a negative MRI several weeks after stroke. This information would be relevant in daily practice, especially in patients presenting late after onset of symptoms or patients in which doubt about the diagnosis arises later in the diagnostic process.

Therefore, we aimed to describe the occurrence of MRI negative stroke, and to compare the characteristics of MRI positive and negative patients 4-6 weeks after stroke. Moreover, we compared clinician's certainty of the diagnosis between patients who were MRI positive and negative.

Methods

Population

Data were used from an ongoing longitudinal, prospective, mono-center cohort study, concerning the Prediction of Cognitive Recovery after Stroke (PROCRAS).¹⁴ The PROCRAS study includes patients aged 50 and older, with the clinical

diagnosis of acute ischemic stroke and evidence of cognitive dysfunction during hospitalization, indicated by a Montreal Cognitive Assessment (MoCA)¹⁵ score below 26. In addition, a reference group with a MoCA score of 26 or higher is included matched for age and sex to the patients with cognitive dysfunction. Exclusion criteria for PROCRAAS were pre-stroke evidence of a severe cognitive disorder, pre-stroke dependence in activities of daily living, life expectancy of less than one year, severe stroke expected to require long-term nursing care facilities, impossibility to participate in a neuropsychological assessment, and an absolute contraindication to undergo an MRI-scan of the brain. On average 4-6 weeks (± 1 week) after stroke, patients underwent a brain MRI. The first 125 patients in the PROCRAAS study that underwent MRI scanning were included in this analysis. These 125 patients (20 with MoCA ≥ 26 and 105 with MoCA < 26) came from the first 141 patients that provided informed consent for participation in the PROCRAAS study. Most drop-outs before scanning were because of withdrawal of consent ($n=15$), 1 participant died. There were no statistical significant differences between drop-outs and patients in this study.

Diagnosis

Clinical diagnosis of ischemic stroke was operationalized in this study as the diagnosis at discharge, which was established by at least a resident neurology and a stroke trained neurologist. Patients with suspected stroke (i.e. acute onset of focal neurological symptoms) are examined at the emergency department following the Dutch national guidelines and are admitted to the stroke unit when there is no definite other diagnosis explaining the symptoms. If during admission evidence for a stroke mimic arises (e.g. a tumor or functional neurological disorder better explains the current symptoms), the diagnosis is revised and the patient is treated accordingly. In cases of doubt about the diagnosis, the patients are discussed in a panel of at least 2 stroke neurologists and at least 2 residents neurology to reach final consensus. In all other cases in which ischemic stroke is the most likely diagnosis, patients are discharged with a diagnosis of ischemic stroke, and they are treated with secondary preventive medication.

Measures

Imaging

All patients underwent a Computed Tomography (CT) scan of the brain at the emergency department as part of standard care. In addition, MRI data of the patients was acquired on a Philips 3 tesla scanner (Intera, Philips, Best, the Netherlands). Patients were scanned on average 4-6 weeks after stroke according to a standardized scanning protocol as described earlier,¹⁴ and included sagittal 3D

T1-weighted (160 slices, voxel size: 1.00x1.00x1.00 mm³, repetition time (TR)/echo time (TE): 8.3/3.8 ms), axial T2-weighted (34 slices, voxel size: 0.45x0.45x4.00 mm³, TR/TE 3000/80ms), axial fluid attenuated inversion recovery (FLAIR) (34 slices, voxel size: 0.45x0.45x4.00 mm³, TR/TE/inversion time: 11000/125/2800 ms), and axial diffusion weighted imaging (DWI) sequence (EPI sequence, 28 slices, voxel size 1.20x1.20x4.00 mm³, TR/TE: 2738/59 ms, 3 orthogonal directions (b-value: 1000 s/mm²) and one b=0 s/mm² image).

All scans were assessed by a neuroradiologist and one rater from the research team (MRI negativity rates were 30% and 23%, respectively). When there was disagreement on whether there was a lesion or whether there was a lesion corresponding to the clinical symptoms, a panel of two neuroradiologists and a vascular neurologist were consulted to make a final decision.

Data collection

Patient demographics such as age and sex were collected during hospitalization. Level of education was coded according to Verhage's coding system, which is a score ranging from 1-7 and covers the Dutch education system. We further categorized it into a low level of education¹⁻³, middle level of education⁴⁻⁵, and high level of education⁶⁻⁷. Stroke classification was assessed using the Oxfordshire Community Stroke Project classification (OCSP).¹⁶ Stroke severity was assessed at the emergency department using the National Institutes of Health Stroke Scale (NIHSS).¹⁷ We recorded whether patients received an acute intervention (i.e. received intravenous alteplase or intra-arterial thrombectomy). Imaging of the carotid arteries was performed according to local and national guidelines using either duplex ultrasound, CT-angiography, or both. A symptomatic carotid stenosis was defined as a stenosis of >50% at the same side as the location of ischemic strokes located in the anterior circulation. Cognitive screening was performed using the MoCA on average 3 days after stroke during hospitalization. We recorded the following vascular risk factors: previous stroke or transient ischemic attack, hyperlipidemia (previous diagnosis or total cholesterol > 5 mmol/l), hypertension (previous diagnosis or blood pressure of >140/90) diabetes mellitus, atrial fibrillation, a history of vascular disease (defined as ischemic heart disease or peripheral vascular disease), and smoking status. The Barthel Index was collected at day 4 or at discharge when patients were discharged earlier to assess functional status.¹⁸ This scale ranges from 0-20 and higher scores indicate more functional independence. The severity of white matter hyperintensities was assessed according to the Fazekas scale on the FLAIR sequences.¹⁹

Certainty of clinical diagnosis

Sixty case descriptions were made containing all information collected during hospitalization for all MRI negative patients (n=30) and a sample of randomly selected MRI positive patients (n=30). A panel of 3 expert vascular neurologists judged these case descriptions in randomized order, blinded for the results of the study MRI and the proportions of patients that were classified as MRI negative or positive. They were aware that the case descriptions were of patients with a discharge diagnosis of ischemic stroke. Of note, 12 out of the 60 (20%) patients underwent additional imaging (either repeat CT or MRI of the brain) during hospitalization (this was 40 out of 125 [32%] for the entire group). This showed an infarct in 9 out of 12 (75%; for the entire group this was 36 out of 40 [90%]). The results of additional imaging during hospitalization were reported in the case descriptions. The panel indicated for each case 1) whether they thought an ischemic stroke was the most likely diagnosis, and 2) how certain they were of this answer on a continuous scale that ranges from 0-100. We then defined 7 mutually exclusive categories that reflect different levels of agreement and certainty of the panel, see Table 1.

Table 1: Criteria of agreement and certainty levels for a clinical diagnosis of ischemic stroke. If there was no unanimous decision whether ischemic stroke was most likely, the mean level of certainty was calculated by averaging the level of certainty of the 2 neurologists that agreed.

	Ischemic stroke most likely	Mean level of certainty
Highly certain diagnosis of ischemic stroke	3x yes	≥75
Certain diagnosis of ischemic stroke	3x yes	≥50 and <75
Moderately certain diagnosis of ischemic stroke	2x yes	≥50
Unclear	2x yes or 2x no	<50
Moderately certain that ischemic stroke is not most likely	2x no	≥50
Certain that ischemic stroke is not most likely	3x no	≥50 and <75
Highly certain that ischemic stroke is not most likely	3x no	≥75

Statistics

Variables were summarized in a table using means (standard deviations), medians (interquartile ranges), and counts (percentages), where appropriate. Characteristics of patients were compared using independent t-tests for continuous and normally distributed variables, Mann-Whitney U tests and Kruskal Wallis tests for nonparametric continuous variables, and χ^2 tests for categorical variables. To help interpreting the size of differences between the 2 groups, point estimates of effect size are reported (i.e. using Cohen's d for parametric and nonparametric

continuous variables and Cramér's V for categorical variables). For all the analyses SPSS version 24 was used.

Regulation Statement

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval

The PROCRAST study was approved by the medical ethics committee of Brabant, based in Tilburg, the Netherlands. Written informed consent was obtained from all participants.

Results

Of the 125 patients in this study, 30 (24%) were classified as MRI negative. In 109 of the 125 (87%) patients, there was agreement on the presence or absence of a symptomatic lesion between the rater from the research team and the neuroradiologist. For the remaining 16 patients (7 MRI negative and 9 MRI positive) a final unanimous decision was made by the consulted panel of 2 neuroradiologists and 1 vascular neurologist.

Patients that were MRI negative had a lower NIHSS (mdn 1, IQR 0-3) at admission than patients that were MRI positive (mdn 2, IQR 2-4), this difference had a moderate effect size (Cohen's $d=0.50$), see Table 2. MRI negative patients had a higher Barthel Index (mdn 20, IQR 20-20) than MRI positive patients (mdn 20, IQR 13.5-20), with a small effect size ($d=0.36$). MRI negative patients had a shorter duration of admission (mdn 2, IQR 2-3) than MRI positive patients (mdn 4, IQR 2-10), with a moderate effect size ($d=0.71$). Of note, 2 (7%) patients in the MRI negative group and 38 patients (40%) in the MRI positive group underwent additional imaging (either repeat CT or MRI of the brain) during hospitalization. There was one patient in the MRI negative group in whom additional imaging during hospitalization did show a lesion. There were no statistically significant differences between the two groups for other variables; of note, there was no difference in days from symptom onset to imaging between both groups (mean difference = 4 days, Cohen's $d=0.34$, $P=0.105$)

Table 2: Patient characteristics compared between patients with a positive and negative MRI 4-6 weeks after stroke.

	MRI positive	MRI negative	Effect size	P-value
N	95	30		
Demographic characteristics				
Age	69.6 (9.0)	73.1 (8.5)	0.40*	0.058
Sex, male	67 (71%)	20 (67%)	0.04#	0.689
Level of Education				
Low	13 (14%)	5 (17%)	0.08#	0.648
Middle	55 (58%)	19 (63%)		
High	27 (28%)	6 (20%)		
Clinical diagnosis and functional impact				
LACS	33 (35%)	10 (33%)	0.06#	0.787
POCS	27 (28%)	7 (23%)		
PACS or TACS	35 (37%)	13 (43%)		
NIHSS at admission	2 (2-4)	1 (0-3)	0.50*	0.006
Barthel Index at day 4	20 (13.5-20)	20 (20-20)	0.36*	0.022
Vascular risk factors				
Symptomatic carotid stenosis	7 (7%)	4 (13%)	0.09#	0.315
Atrial fibrillation	14 (15%)	2 (7%)	0.10#	0.249
Previous TIA or ischemic stroke	24 (25%)	10 (33%)	0.08#	0.387
Hypertension	75 (79%)	22 (73%)	0.06#	0.520
Diabetes mellitus	31 (33%)	11 (37%)	0.04#	0.683
Hyperlipidemia	88 (93%)	29 (97%)	0.07#	0.431
Active smoker at stroke	22 (23%)	5 (17%)	0.07#	0.451
Vascular history	28 (30%)	11 (37%)	0.07#	0.459
Cognition				
MoCA score	22 (19-25)	23 (21-25)	0.16*	0.366
Other				
Duration of admission in days	4 (2-10)	2 (2-3)	0.71*	<0.001
Day from onset until scan	36 (10)	40 (13)	0.34*	0.105
Received acute intervention	19 (20%)	7 (23%)	0.04#	0.695
Intravenous alteplase	19 (20%)	7 (23%)		
Intra-arterial thrombectomy	3 (3%)	1 (3%)		
Imaging				
Fazekas grade				
0	9 (9%)	5 (17%)	0.24#	0.067
1	34 (26%)	9 (30%)		
2	37 (39%)	6 (20%)		
3	15 (16%)	10 (33%)		

Data are presented as mean (SD), median (IQR) or N (%). LACS, lacunar syndrome; POCS, posterior circulation syndrome; PACS, partial anterior circulation syndrome; TACS, total anterior circulation syndrome; NIHSS, National institute of health stroke scale; TIA, transient ischemic attack; MoCA, montreal cognitive assessment. * Cohen's d; # Cramér's V.

Out of the 30 patients that were MRI negative, 13 (43%) patients were judged to have a highly certain clinical diagnosis of ischemic stroke, see Table 3. When adding a certain clinical diagnosis of ischemic stroke to this group, the number increased to 18/30 (60%) with a likely diagnosis of stroke. For the subsample of 30 MRI positive patients, 25 (83%) were judged to have a highly certain clinical diagnosis of ischemic stroke. This increased to 27 (90%), when adding patients with a certain diagnosis of ischemic stroke. We further explored the characteristics of MRI negative patients according to the certainty of their diagnosis, see Table 4. MRI negative patients with a more likely clinical diagnosis of ischemic stroke received an acute intervention more often ($\chi^2[3]=9.65$, $P=0.022$) and had a higher NIHSS ($\chi^2[3]=14.15$, $P=0.003$) than patients with a less likely clinical diagnosis of ischemic stroke.

There were no patients in which the panel indicated that ischemic stroke was not the most likely diagnosis.

Table 3: The certainty of the clinical diagnosis of ischemic stroke compared between patients with MRI negative and MRI positive stroke.

	MRI positive	MRI negative
N	30	30
Highly certain diagnosis of ischemic stroke	25 (83%)	13 (43%)
Certain diagnosis of ischemic stroke	2 (7%)	5 (17%)
Moderately certain diagnosis of ischemic stroke	3 (10%)	8 (27%)
Unclear	0 (0%)	4 (13%)
Moderately certain that ischemic stroke is not most likely	0 (0%)	0 (0%)
Certain that ischemic stroke is not most likely	0 (0%)	0 (0%)
Highly certain that ischemic stroke is not most likely	0 (0%)	0 (0%)

Table 4: MRI negative patients divided by different levels of certainty of the clinical diagnosis.

	Highly certain	Certain	Moderately certain	Unclear
N	13	5	8	4
Demographic characteristics				
Age	74 (71-79)	75 (70-75)	73 (68-81.5)	75.5 (67.5-78.5)
Sex, male	7 (54%)	3 (60%)	7 (88%)	3 (75%)
Level of Education				
Low	2 (15%)	0 (0%)	1 (12.5%)	2 (50%)
Middle	9 (69%)	5 (100%)	3 (37.5%)	2 (50%)
High	2 (15%)	0 (0%)	4 (50%)	0 (0%)
Clinical diagnosis and functional impact				
LACS	5 (38%)	0 (0%)	3 (37.5%)	2 (50%)
POCS	1 (8%)	3 (60%)	2 (25%)	1 (25%)
PACS or TACS	7 (54%)	2 (40%)	3 (37.5%)	1 (25%)
NIHSS at admission	4 (2-4)	2 (0-2)	0.5 (0-1)	0 (0-0)
Barthel Index at day 4	20 (20-20)	20 (18-20)	20 (19.5-20)	20 (19-20)
Vascular risk factors				
Symptomatic carotid stenosis	1 (8%)	0 (0%)	2 (25%)	1 (25%)
Atrial fibrillation	1 (8%)	0 (0%)	1 (12.5%)	0 (0%)
Previous TIA or ischemic stroke	3 (23%)	2 (40%)	4 (50%)	1 (25%)
Hypertension	9 (69%)	5 (100%)	6 (75%)	2 (50%)
Diabetes mellitus	6 (46%)	2 (40%)	3 (37.5%)	0 (0%)
Hyperlipidemia	12 (92%)	5 (100%)	8 (100%)	4 (100%)
Active smoker at stroke	3 (23%)	1 (20%)	1 (12.5%)	0 (0%)
Vascular history	6 (46%)	2 (40%)	3 (38%)	0 (0%)
Cognition				
MoCA score	23 (22-24)	21 (21-22)	25 (21-25)	22.5 (22-23.5)
Other				
Duration of admission in days	2 (2-3)	2 (2-2)	2 (1.5-4)	2 (1-2)
Day from onset until scan	38 (33-48)	32 (26-37)	39 (30-58.5)	43.5 (31-54.5)
Received acute intervention	6 (46%)	1 (20%)	0 (0%)	0 (0%)
Intravenous alteplase	6 (46%)	1 (20%)	0 (0%)	0 (0%)
Intra-arterial thrombectomy	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Imaging				
Fazekas grade				
0	1 (8%)	1 (20%)	2 (25%)	1 (25%)
1	4 (31%)	1 (20%)	2 (25%)	2 (50%)
2	2 (15%)	1 (20%)	2 (25%)	1 (25%)
3	6 (46%)	2 (40%)	2 (25%)	0 (0%)

Data are presented as median (IQR) or N (%). LACS, lacunar syndrome; POCS, posterior circulation syndrome; PACS, partial anterior circulation syndrome; TACS, total anterior circulation syndrome; NIHSS, National institute of health stroke scale; TIA, transient ischemic attack; MoCA, montreal cognitive assessment.

Discussion

In this study, we found that 24% of patients was MRI negative 4-6 weeks after stroke. MRI negative patients were less affected at admission than MRI positive patients. Remarkably, clinicians judged that 43% of MRI negative patients were highly likely to have had an ischemic stroke. This percentage increased to 60% for a likely diagnosis of ischemic stroke.

These findings add to the growing body of literature about MRI negative strokes in the acute phase, in establishing a similar rate of MRI negative stroke 4-6 weeks after stroke.^{7,20,21}

We found that in many patients with a certain clinical diagnosis of ischemic stroke, there is no corresponding lesion on MRI. In daily practice, MRI is often used to aid in decision making, especially in patients in which there is doubt about the diagnosis.^{5,22} Our data do not provide support for using the MRI to exclude ischemic stroke 4-6 weeks after onset of complaints, because even in patients with a likely clinical diagnosis of ischemic stroke, there is often no corresponding lesion on MRI. Clinicians should therefore be cautious when interpreting a negative MRI 4-6 weeks after stroke. Moreover, MRI negative stroke patients have previously been noted to have a similar long term outcome and a similar probability of recurrent stroke as patients with MRI positive stroke.⁷ This underlines that it is just as important to provide secondary stroke prevention for MRI negative stroke patients as it is for MRI positive stroke patients. It should be noted that these results cannot be extrapolated to patients that visit the neurologist for the first time after having experienced stroke symptoms 4-6 weeks ago.

MRI negativity after ischemic stroke can have many causes. One cause may be that there was in fact no ischemic stroke, and a stroke mimic might have explained the symptoms. In our study, this was supported by the difference in levels of certainty of the clinical diagnosis between patients that were MRI positive and patients that were MRI negative. The prevalence of stroke mimics presenting at the emergency department and the stroke unit is estimated to be 25-30%.^{22,23} However, the patients in the present study were already preselected through our protocol, that only included patients with a clinical diagnosis of ischemic stroke at discharge, leaving out patients with other discharge diagnoses. Literature on the accuracy of discharge diagnoses of ischemic stroke is sparse. One paper suggests high concordance between admission diagnosis and discharge diagnosis, while another shows that the accuracy of discharge diagnoses may vary among tertiary-care and community hospitals.^{24,25} With the increasing use of additional imaging at the emergency department and during admission in the last 2 decades, we believe that the accuracy of a discharge

diagnosis of ischemic stroke is likely to be high. Therefore, the prevalence of stroke mimics in this study is likely to be much lower than the estimated 25-30% in the emergency department. Moreover, patients in which there was more doubt about the diagnosis did not seem to be similar to the typical population of stroke mimics, that is more often described by younger female patients with no vascular risk factors.²³ Another cause for MRI negativity after ischemic stroke, may be that MRI negative stroke has a different underlying pathophysiology from MRI positive stroke.⁷ Experimental studies have shown that mild to moderate cerebral ischemia can cause isolated persistent synaptic failure, without neuronal death.²⁶ It may very well be possible that MRI cannot detect this mild ischemia, because damage limited to the synapses does not result in MRI positivity. A third possibility is that after several weeks, small lacunar strokes might not be distinguishable from white matter hyperintensities.¹¹⁻¹³ Lastly, it may have been possible that there was reversal of a potential lesion as a consequence of therapy.⁹

This study has several limitations. First, it is difficult to distinguish stroke mimics from MRI negative stroke, especially when time progresses after onset of complaints and sensitivity of MRI to detect a lesion decreases.²⁷⁻²⁹ This is mainly because there is no gold standard in assessing ischemic stroke. We propose that the clinician's certainty of the clinical diagnosis should be valued more after several weeks of symptom onset. Second, patients that were MRI negative may have actually had a visible lesion when a more detailed MRI was performed. For example, both imaging with slices of 3 mm instead of 5 mm, and repeat MRI imaging have shown to be more sensitive in detecting small ischemic lesions.^{30,31} However, the MRI imaging protocol in this study is equivalent to the protocol used in daily practice, making results better generalizable to the general stroke population. Furthermore, all patients in this study were scanned on the same MRI scanner to ensure that differences in the detection of ischemic lesions were not due to scanner type. Third, the inclusion criteria of the PROCRAST study have led to an oversampling of patients with ischemic stroke and signs of cognitive impairment during admission. It is unclear whether this may have led to an increase or decrease of MRI negative strokes. There is evidence that presence of pre-existing cognitive impairment is associated with higher occurrence stroke mimics.³² However, we excluded patients with signs of pre-stroke cognitive impairment from this study.

In conclusion, patients with a clinical diagnosis of ischemic stroke frequently have a negative MRI scan 4-6 weeks after stroke. A large proportion of patients with MRI negative stroke have a highly certain clinical diagnosis of ischemic stroke, suggesting that clinicians should be cautious ruling out the diagnosis based on MRI beyond the acute stroke stage.

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Impaired emotion recognition after left hemispheric stroke - a case report and brief review of the literature

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Abstract

Impaired recognition of emotion after stroke can have important implications for social competency, social participation, and consequently quality of life. We describe a case of left hemispheric ischemic stroke with impaired recognition of specifically faces expressing fear. Three months later, the patient's spouse reports that the patient was irritable and slow in communication, which may be caused by the impaired emotion recognition. The case is discussed in relation to the literature concerning emotion recognition and its neural correlates. Our case supports the notion that emotion recognition, including fear recognition, is regulated by a network of interconnected brain regions located in both hemispheres. We conclude that impaired emotion recognition is not uncommon after stroke, and can be caused by dysfunction of this emotion-network.

Introduction

Social cognition concerns the psychological processes by which we perceive, process and interpret social information¹. Nowadays, neurologists are increasingly aware of the importance of screening for deficits in social cognition². For example, screening for impaired social cognition has become more common in patients with traumatic brain injury^{2,3}. After stroke, impaired social cognition is prevalent, with a reported prevalence rate of 49%⁴. Despite the high prevalence, deficits in social cognition after stroke are often overlooked by the neurologist, and it is generally not spontaneously mentioned by the patient or his caregiver.

After stroke, impaired social cognition is partly reflected by worse emotion recognition in studies that compared patients to healthy controls in tasks examining facial, prosodic and lexical emotional stimuli^{5,6}. These studies show that impaired emotion recognition after stroke is not limited to one modality: a stroke affects general processing of emotion for different modalities.

Impaired emotion recognition after stroke has a negative influence on social participation, and it can have important implications for a patient's quality of life⁷. Moreover, it can affect social competence⁸, it predicts social behavior disorders⁹, and it is negatively correlated with maintenance of personal and professional relations^{10,11}.

We present a case with a profound difficulty in the recognition of faces expressing fear after insular stroke. Furthermore, the case is discussed in relation to the literature concerning emotion recognition and its neural correlates.

Case Description

A sixty-five-year-old, right-handed man, who had just retired from his work as a detective, presented with a global aphasia, agitation and a mild paresis of his right arm, which started acutely 5 hours before admission. He had no known vascular risk factors, and he had a degree in higher vocational education. The admission CT-scan of his brain revealed no signs of ischemia or hemorrhage. One day after admission, the total score on the Montreal Cognitive Assessment (MoCA) was 20 out of a maximum of 30 points, mainly failing the subdomains language (0/3), delayed recall (2/5) and visuospatial function (2/5). The patient correctly copied the cube and made no mistake in the contour of the clock. However, he did not add numbers to the clock and placed the hands at ten to eleven, instead of ten past eleven. Two days after admission, the patient did not report any complaints. The aphasia, paresis and agitation had resolved quickly, and the patient was discharged home. As part of an observational study – the PROCRAST study, see box 1 for more

information –, the patient underwent a detailed neuropsychological assessment and MRI-scan of his brain 4 weeks after the stroke. Apart from complaining of being tired more quickly, he had no other complaints at that point. As part of the neuropsychological assessment, the 'Ekman 60 faces test', part of the Facial Expressions of Emotion: Stimuli and Tests (FEEST) was performed¹². Interestingly, out of 10 presented fearful faces, he recognized only 1 facial expression correctly. For his performance on other emotions, see table 1. His total score on the FEEST was nearly 3 standard deviations below the norm. There were no symptoms of depression or anxiety on the Hospital Anxiety and Depression Scale (HADS). Moreover, there were no signs of prosopagnosia, and the bells test revealed no visuospatial dysfunction. Further extensive neuropsychological testing revealed problems with naming objects on the Boston Naming Test, but no impaired performance on the verbal fluency test. In table 2 the T-scores for each domain and the subtests that constitute these domains are presented. The MRI showed a lesion of the posterior part of the left insula, but also of a part of the left temporal cortex and the left parietal cortex as can be seen in figure 1. In order to investigate potential impairments in brain connectivity, the brain network of the patient was reconstructed from the diffusion weighted MR images as described in Reijmer, et al¹³. The mean fractional anisotropy of the white matter tracts connected to each of the 90 cortical and subcortical brain regions was calculated. The brain networks of 25 age-matched healthy control participants served as a reference group. Results showed that the connectivity strength of the patient was markedly reduced (> 1.5 SD lower compared to the reference sample) in several parietal, temporal, and subcortical regions, primarily in the left hemisphere (Figure 2), indicating disconnection of a network of brain regions.

Three months after the stroke, the patient felt no restrictions in his ability to perform hobbies such as gardening and reading, and he experienced no difficulties in social contact. However, his wife reported that he has been slower in communication and manifests slight irritability ever since the stroke.

Box 1:

In the Prediction Of Cognitive Recovery After Stroke (PROCRASt) study, we aim to investigate the additional value of measures of structural connectivity derived from diffusion tensor imaging (DTI)-MRI in the prediction of cognitive recovery after stroke. Patients with the clinical diagnosis of a stroke with a MoCA total score below 26, undergo a neuropsychological assessment and DTI-MRI 3-6 weeks after stroke. 1 year after stroke the neuropsychological assessment is repeated to assess the primary endpoint.

Table 1: The patient's results for the 'Ekman 60 faces test'.

Emotion	Nr correct answers*	Mean scores reference sample (SD)	Cutoff values
Anger	8 / 10	7.33 (1.90)	4
Disgust	6 / 10	9.00 (1.62)	6
Fear	1 / 10*	6.47 (2.03)	3
Happiness	10 / 10	9.93 (0.42)	9
Sadness	5 / 10	8.03 (1.66)	5
Surprise	5 / 10*	8.66 (1.44)	6
Total	35 / 60*	49.41 (4.88)	41

The mean scores, standard deviations and cutoff values for the reference sample (aged 61-70) are derived from the FEEST manual. This sample consisted of 58 healthy participants with an IQ > 90. Cutoff values have been calculated by using the nearest integer value to a z-value of 1.65 below average¹².

* Scores below the cutoff.

Table 2: Neuropsychological assessment of the patient.

Domain	T-score	Tests	T-scores
Attention and processing speed	46.6	Reaction time test, Vienna Test System, S1, S2	50.5
		Symbol Digit Modalities Test	44.2
		Trailmaking test A	41.0
(Working) memory and learning	39.2	WAIS Digit Span forward and backward	41,7
		The Rey Auditory Verbal Learning Test	38.0
Frontal-Executive functions	39.8	Controlled Oral Word Association Test	30.0*
		Hayling test	40.0
		Reaction time test Vienna Test System S3	47.0
		Trailmaking test B	44.0
Language	31.6*	Boston naming test	23.1*
		Semantic fluency	40.0
Visuospatial function	NA	Bells test, no T-score available, 1 omission	NA

This table shows the T-scores of the patient for each of the tested domains in the neuropsychological assessment. * Scores below 1.5 standard deviation.

Figure 1: Transversal Fluid attenuated inversion recovery (FLAIR) images of the patient, revealing a lesion to the posterior part of the insula, and part of the left temporal cortex and left parietal cortex.

Figure 2: Axial (left) and lateral (right) view of the disconnectivity profile of the patient (obtained from analyzing the DTI-MRI data). Nodes represent 90 cortical and subcortical brain regions⁴⁵. The red nodes indicate regions with more than 1.5 standard deviations decreased connectivity strength compared to 25 age-matched healthy controls. Note that nodes surrounding the ischemic zone are affected, but also nodes in the contralesional hemisphere and a frontal node, suggesting the stroke affected a network of brain regions.

Discussion

In this article we present a case with a profound deficit in the recognition of facial emotions expressing fear after enduring a stroke of the posterior part of the left insula and parts of the left temporal and parietal cortex. There was no evidence of depressive or anxious symptoms on follow-up, suggesting the difficulty in recognition of fearful faces was not caused by a depressive or anxiety disorder. It has not been ruled out that visuospatial dysfunction caused the impaired recognition of facial emotions. However, the score of 2/5 for the MoCA's visuospatial subdomain might have been caused by a language disorder rather than a visuospatial disorder. Moreover, the bells test revealed no abnormalities at the neuropsychological examination 4 weeks after stroke, making a neglect very unlikely. It was not clear whether our patient had difficulties in emotion recognition before the stroke, for example due to an autism spectrum disorder or traumatic brain injury in the past. However, we think that his higher education level and his work as a detective require at least adequate social cognitive skills. Therefore, it is plausible to attribute the profound deficit in fear recognition to the stroke. This case stood out because of two reasons. First, the stroke involved the left hemisphere, while emotion recognition is generally attributed to the right hemisphere⁵. Secondly, the deficit in recognition of fearful faces after ischemia of the posterior part of the insula seems to contradict earlier findings in the literature¹⁴⁻¹⁶. Recognition of fear has been strongly linked to activity in the amygdala¹⁶, whereas the insula is thought to be specifically engaged in the recognition of disgust^{14,15}. We will discuss the literature in relation to the case and these two findings.

Laterality in emotion recognition

Researchers have still not reached consensus on the specific contribution of the right and left hemisphere to emotion recognition. A recent review of many studies examining emotion recognition after stroke found more support for the hypothesis that emotion recognition seems to be largely lateralized to the right hemisphere, independent of valence^{5,17}. Several studies report that left hemispheric stroke patients perform as good as healthy controls in the recognition of emotions¹⁸⁻²¹. However, other studies do reveal differences in emotion recognition between patients with a left hemispheric stroke and healthy controls²²⁻²⁴. The left hemispheric stroke of our patient is in line with these studies, and adds to the theory that the left hemisphere also contributes to the process of emotion recognition. According to the motoric direction theory, the left hemisphere is specialized in 'approach' emotions (i.e. happiness, anger and surprise), whereas the right hemisphere is responsible for recognizing 'withdrawal' emotions (i.e. sadness, fear and disgust)²⁵. The patient had relative ease in recognizing anger and happiness, although

he scored below the cutoff score for surprise. He scored relatively low for the withdrawal emotions: fear, sadness and disgust. Although the patient does partly fit the pattern of this hypothesis, the location of the stroke would suggest that the specialization of both hemispheres is just the opposite of what the motoric direction theory suggests. Possibly, disconnectivity between both hemispheres (Figure 2) could explain this mismatch. *Neural correlates of emotion recognition*

Several brain structures have been suggested to be involved in emotion recognition. For example, lesions to left or right temporal cortex lead to impaired emotion recognition²⁶. However, lesions to the basal ganglia^{27,28}, the cerebellum²⁹, the thalamus³⁰, the right inferior parietal cortex and the anterior intracalcarine cortex¹⁸ can have the same consequence. It is well known that activity in the amygdala has been strongly linked to recognition of fear¹⁶, and a lesion of the amygdala causes an impairment in fear recognition³¹⁻³³. However, this does not imply that lesions of the amygdala are the unique cause of impaired fear recognition. For example, a study reported that a lesion to the right intracalcarine cortex also seems to lead to a specific impairment in the recognition of fear¹⁸. This suggests that even the recognition of one single emotion, in this case the emotion fear, is a process that involves, like all cognitive functions³⁴, a network of brain structures.

A meta-analysis of fMRI and PET-studies¹⁶ in healthy controls concluded that the neural network involved in recognition of emotion consists of three important structures. The first is the medial prefrontal cortex (MPFC), which has a general role in emotional processing. The other two are the anterior cingulate cortex (ACC) and the insula, which are more specifically involved in emotion recognition, especially in more cognitive demanding tasks¹⁶.

The insula and emotion recognition

Because our patient had a stroke involving, among others, the posterior part of the left insula, this specific lesion might have caused the difficulty in recognition of emotion. In behavioral and imaging studies, the insula is found to be engaged in the recognition of disgust^{14,15}. However, less is known about the consequences of a lesion to the insula. Several case studies describe different responses to an acute lesion of the left insula. In one study a patient had impairments in global cognitive functioning as reflected by cognitive screening with the MoCA³⁵, comparable with the case we described. In a double case report, one patient with insular stroke had only slightly slower response times but no impaired emotion recognition³⁶. The second case that is described had a subcortical stroke, disconnecting the connections from the insula to the frontal cortex. In this case an impaired recognition of all negative emotions was found. Another study reported on a

patient with behavioral changes after an isolated stroke of the anterior part of the right insula³⁷. Although emotion perception was not assessed, an additional SPECT scan showed hypoperfusion in several right anterior brain structures, most of which are thought to be involved in an emotion-network.

A matter of (dis-)connection?

As stated earlier, the left insula plays a role in a network of structures involved in emotion recognition. This can be supported by a recent study in which direct electrical stimulation was applied to the left insula during awake surgery in thirteen patients causing a decreased recognition of all negative emotions³⁸. Another study found that impaired emotion recognition was associated with dysfunction of a bilateral fronto-temporal-limbic network in 180 patients with traumatic brain injury (TBI)³⁹. A different study found that damage anywhere to the inferior fronto-occipital fasciculus or the inferior longitudinal fasciculus is associated with impaired emotion recognition⁴⁰. The seemingly contradicting evidence of different presentations after insular stroke can be better interpreted as the consequence of disconnection to frontal or a variety of contralateral regions⁴¹. This implies that the process of emotion recognition is not confined to a specific location, a lesion anywhere in this 'emotion-network' may lead to a deficit in emotion recognition⁴².

We hypothesize that in our patient the stroke caused damage to the network involved in emotion recognition, which is supported by the analysis of the DTI-MRI data (figure 2). Although this analysis does not provide direct evidence for emotion recognition being a network-function, it does support this theory by showing disconnection in more brain structures than those directly affected by the stroke. We propose that the profound impairment of recognition of fear can be explained by a disconnection of fibers to this emotion-network.

Impact of impaired emotion recognition after stroke

Impaired emotion recognition has been found to negatively impact social participation and quality of life after stroke⁴³. For deficits in emotion regulation, the same consequences have been established⁴⁴. The patient's spouse reported that the patient showed slight irritability and slowness in communication after the stroke, although the patient himself stated having no difficulties in social interaction. We hypothesize that the deficit in emotion recognition could partly contribute to these symptoms, and this deficit could consequently lead to restrictions in social participation.

Conclusions

Impaired emotion recognition is prevalent after stroke. However, it is not often reported by the patient or the caregiver, it is not easily recognized, and it is not routinely investigated in clinical practice. This is unfortunate, since impaired emotion recognition negatively impacts social participation. Detection of impaired emotion recognition may help in guidance of the patient and his caregiver. In turn, this should help people better reintegrate into daily life and increase quality of life.

Emotion recognition is a complex process involving many neural structures. A lesion anywhere in this emotion-network can lead to dysfunction. Further research on emotion recognition should shift its focus from the specific localization of emotion recognition to identifying the brain regions, and the functional and structural connections that form part of this emotion-network.

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High occurrence of impaired emotion recognition after ischemic stroke

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Abstract

Introduction

Deficits of emotion recognition after ischemic stroke are often overlooked by clinicians, and are mostly not spontaneously reported by patients. However, impaired emotion recognition after stroke negatively affects the ability to return to work and the quality of life. It is still unknown how often impairments of emotion recognition occur shortly after ischemic stroke. We aimed to estimate the occurrence of impaired emotion recognition after ischemic stroke and to characterize these patients with impaired emotion recognition.

Patients and methods

Two hundred thirty patients were included, derived from a prospective study of cognitive recovery. Five weeks after ischemic stroke a neuropsychological assessment was performed, including an emotion recognition task (i.e. Ekman 60-faces test). Emotion recognition was regarded as impaired if the total score was below the fifth percentile for a large independent reference sample.

Results

Emotion recognition was impaired in 33.5% of patients. Patients with impaired emotion recognition were more likely to have an abnormal Montreal Cognitive Assessment during hospitalisation, and 5 weeks after their stroke, a higher proportion of them had a vascular cognitive disorder (VCD). Even 20% of patients without VCD had impaired emotion recognition.

Discussion

Emotion recognition was often impaired after ischemic stroke. This is clinically relevant, since impaired emotion recognition negatively impacts social functioning.

Conclusion

Even when there was no cognitive disorder in traditional cognitive domains, emotion recognition was impaired in 1 out of 5 patients. Clinicians should systematically ask patients and their caregivers about deficits in emotion recognition, and, if needed, test for these deficits.

Introduction

Social cognition entails the psychological processes by which one perceives, processes and interprets social information.¹ It is recognized that impairments of social cognition can be seen in a wide range of neurological and psychiatric illnesses,¹⁻³ and this cognitive domain is now therefore acknowledged in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).⁴ Emotion recognition is one of the subdomains of social cognition, and involves the ability to extract emotion-relevant information from sensory cues (e.g. a facial expression) to classify and recognize emotions.⁵ This information is necessary to better understand the intentions of others and to regulate one's own behavior.¹ Impairments of emotion recognition have been found to negatively affect social participation, quality of life, and maintenance of personal and professional relations.⁶⁻⁹

In the context of emotion recognition, patients with ischemic stroke have been of particular interest, to study the influence of stroke localization on the performance of emotion recognition tasks.¹⁰⁻¹³ Debate is ongoing about whether the right hemisphere is dominant in recognizing emotion compared to the left hemisphere.^{13,14} However, studies in the last decade have shown that it is a network of brain structures in both hemispheres that enables us to recognize emotions.¹⁵⁻¹⁷ This network consists of the medial prefrontal cortex, the anterior cingulate cortex and the insula.¹⁷

After ischemic stroke, there are frequently impairments of 'traditional' cognitive domains, such as impairments of executive functioning, visuospatial functioning and attention and processing speed.¹⁸⁻²⁰ It is therefore possible that impairments of emotion recognition occur frequently as well.¹⁸⁻²⁰ Nevertheless, these impairments after ischemic stroke are often not detected by clinicians.¹ Several factors may contribute to this, the first being that impairments may be too subtle to notice during a consultation. Second, clinicians may not be aware of the importance of investigating emotion recognition, and even when they are aware of the importance, they might not know how to investigate it. Lastly, patients typically do not mention difficulties of recognizing emotions, because of impaired self-awareness.^{1,21}

To increase awareness in both clinicians and patients, it is relevant to assess how often impairments of emotion recognition occur after ischemic stroke. Establishing that a patient has impaired emotion recognition can have clinical consequences. For example, it may lead to psycho-education being provided to the patient and their partner, and to patients being trained to better recognize emotions.^{22,23} Therefore,

investigating whether impaired emotion recognition indeed occurs frequently after ischemic stroke could support existing recommendations to systematically test for impairments of social cognition after ischemic stroke.¹⁸

Moreover, little is known about the way emotion recognition is related to general cognitive functioning shortly after ischemic stroke. One recent study of social cognition in the long term after ischemic stroke showed only weak associations between other aspects of cognitive functioning and social cognition,²⁴ but whether these associations are present in the subacute phase is unclear. It is important to study the association between emotion recognition and general cognitive functioning, because impairments of emotion recognition might be explained by general cognitive impairments.^{24,25}

We aimed to establish the occurrence of impaired emotion recognition after ischemic stroke. In addition, we aimed to describe the differences between patients with and without impaired emotion recognition. Lastly, we aimed to investigate the association of emotion recognition with cognitive functioning after ischemic stroke.

Methods

Population

Data were derived from a longitudinal, prospective, mono-center cohort study, concerning the Prediction of Cognitive Recovery after Stroke (PROCRAS).²⁶ The PROCRAS study included patients aged 50 and older, with a clinical diagnosis of acute ischemic stroke and evidence of cognitive dysfunction during hospitalization, as indicated by a Montreal Cognitive Assessment (MoCA)²⁷ score below 26. In addition, a selection of patients with ischemic stroke and a MoCA score of 26 or higher was included in PROCRAS matched for age and sex with the patients with cognitive dysfunction, in a 1:5 ratio. This means that for every 5 included patients with a MoCA <26, one patient was included with a MoCA ≥26. Exclusion criteria for PROCRAS were pre-stroke evidence of a severe cognitive disorder, pre-stroke dependence in activities of daily living, life expectancy of less than one year, severe stroke expected to require long-term nursing care facilities, impossibility to participate in a neuropsychological assessment, and an absolute contraindication to undergo an MRI-scan of the brain. On average 5 weeks (±1 week) after ischemic stroke, patients underwent a detailed neuropsychological assessment, including a test for emotion recognition: the Ekman 60-faces test (EFT). During the inclusion period between July 2016 and May 2018, 386 patients were eligible for inclusion (see figure 1 for a flowchart of the patient flow). Of these, 217 provided written informed consent to

participate in the study. In addition, all patients that were included in the PROCRAST study with a MoCA ≥ 26 were also considered for the present analysis ($n=47$). Of the 264 inclusions at baseline, 34 patients were excluded from the present analysis. Reasons for exclusion were withdrawal of consent ($n=20$), inclusion failure ($n=4$), death ($n=1$), the patient's condition precluding the completion of all the tests in the neuropsychological test battery ($n=3$), and failure to perform the EFT for logistic reasons or due to technical issues ($n=6$).

Figure 1: flowchart of patients in the study.

Measurements

Neuropsychological assessment

Patients underwent cognitive testing 5 weeks (± 1 week) after ischemic stroke. The cognitive domains that were assessed were attention and processing speed, frontal-executive functioning, working memory and learning, and visuospatial functioning. The domain of attention and processing speed consists of reaction time tests S1 and S2 of the Vienna test system, the symbol digit modalities test (SDMT), and the trail making test part A; the domain frontal-executive functioning consists of the controlled oral word association test (COWAT), the trail making test part B, and reaction time test S3 of the Vienna test system; the domain of working memory and learning consists of the Wechsler Adult Intelligence Scale digit span forward and backward, the Rey auditory verbal learning test (RAVLT), and a semantic fluency test; and the domain of visuospatial functioning consists of the Bells test.²⁸ See Table 1 for an overview of the cognitive domains and associated tests. The Bells test was used to screen for signs of visuospatial neglect, which might influence facial emotion recognition. The SDMT²⁹ is a test of processing speed in which participants are required to substitute as many symbols with digits

as they can within 90 seconds. A higher score indicates better processing speed. The RAVLT³⁰ is a test of memory in which participants are asked to immediately recall as many of the 15 words that are read to them out loud by the examiner. This process is repeated four times, and the total score is the total number of words they can recall in all five sessions (i.e. immediate recall condition). After 10-15 minutes they are asked which words they recall to have heard in the first five sessions (i.e. delayed recall condition). Higher scores in both conditions indicate better memory. The COWAT³¹ is a word fluency task, in which participants name as many words as they can that start with a specific letter within 60 seconds. A higher score indicates better executive functioning.

Apart from the Bells test, raw scores of each test were converted into standardized scores corrected for age, sex, and level of education, based on available normative data. Domain scores were calculated by averaging the standardized scores of each test in that domain. A post-stroke vascular cognitive disorder (VCD) was operationalized according to VASCOG criteria as a performance on ≥ 1 domains ≥ 1 standard deviations (SD) below appropriate norms, as previously reported.^{18,26} The presence of a VCD was further subdivided into modest VCD (i.e. performance on ≥ 1 domains being ≥ 1 SD but < 2 SDs below appropriate norms), and marked VCD (i.e. performance on ≥ 1 domains being ≥ 2 SDs below appropriate norms). It should be noted that these categories are based on the neuropsychological test data, whereas the VASCOG criteria for major VCD also require the cognitive disorder to have significant impact on activities of daily living.

Table 1: Neuropsychological tests and the associated cognitive domains.

Domain	Tests
Attention and processing speed	Reaction time test, Vienna Test System, S1, S2
	Symbol Digit Modalities Test
	Trailmaking test A
(Working) memory and learning	WAIS Digit Span forward and backward
	The Rey Auditory Verbal Learning Test
	Semantic Fluency
Frontal-Executive functions	Controlled Oral Word Association Test
	Trailmaking test B
	Reaction time test Vienna Test System S3
Visuospatial functioning	Bells test
Emotion recognition	Ekman 60-faces test

Ekman 60-faces test (EFT)

The EFT consists of 60 black-and-white photographs of faces of 10 actors (4 male, 6 female) and measures emotion recognition. In each photograph, an actor portrays one of the 6 basic emotions: happiness, surprise, anger, fear, sadness or disgust. The test uses one photograph of each of the 6 basic emotions of each actor, resulting in 60 stimuli. Photographs were shown in a random order, one by one on a computer screen each for 5 seconds. Participants were asked to verbally indicate which basic emotion best described the picture being shown, and the examiner then recorded this answer. The 6 basic emotions that participants could choose from were shown below each stimulus during the entire test. The next stimulus was only provided after the participant had provided an answer for the previous stimulus, without time restriction. Administration of the test took roughly 15 minutes, and took place in an outpatient clinic setting. Participants could score up to 10 correct answers per basic emotion, resulting in a maximum total score of 60 correct answers. Raw scores of the EFT were then corrected for age, sex, and level of education using a Dutch reference group, consisting of 639 healthy controls (43.5% male) with a mean age of 47 years (± 18.5 , range 16-92).³² Emotion recognition was judged to be impaired if the total score was below the 5th percentile.

Other measures

Patient demographics such as age and sex were collected during hospitalization. Level of education was coded according to Verhage's coding system, which is a score ranging from 1-7 that covers the Dutch education system. We assessed whether the ischemic stroke was localized in the cortex, and coded whether an ischemic lesion was located in the right hemisphere, the left hemisphere, or infratentorial. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) at presentation in the emergency department.³³ Cognitive screening was performed using the MoCA during hospitalization a median of 3 days (interquartile range 3 days) after the ischemic stroke. Furthermore, the Hospital Anxiety and Depression Scale (HADS)³⁴ was completed by the patients a median of 5 weeks (IQR 2 weeks) after the ischemic stroke, to test for symptoms of a depression (i.e. HADS-D) or anxiety (i.e. HADS-A) at the time when the neuropsychological assessment took place, as anxiety and depression can also underlie impairments in emotion recognition.³⁵

Statistics

The occurrence of impaired emotion recognition was calculated for all participants, and also separately for the group with a MoCA <26 and the group with a MoCA ≥ 26 , by dividing the number of patients with impaired emotion recognition by the total number of patients per group. The presence of statistical differences between the characteristics of patients with impaired and normal emotion recognition was assessed with independent samples t-tests, Mann-Whitney-U tests or chi-

square tests, where appropriate, after testing whether the data conformed to the assumptions. To study the relation between the total score on emotion recognition and the scores on other cognitive domains, Pearson correlation analyses were performed with raw scores of the SDMT, the COWAT, the immediate and delayed recall conditions of the RAVLT, and the raw score of the EFT. These tests were chosen as each of them represents a different cognitive domain. Furthermore, partial correlations were carried out, controlling for age, sex and level of education, for each of these analyses. IBM SPSS version 24 was used for all of the analyses.

Results

Out of the total of 230 patients in our analysis, 77 had impaired emotion recognition (33.5%). In the patient group with a MoCA <26, impaired emotion recognition was found in 37%, compared to 17% of the patients with a MoCA $\geq$ 26. Correcting for the relative undersampling of patients with a MoCA $\geq$ 26, we estimated the occurrence of impaired emotion recognition by using the MoCA performance scores of patients screened for eligibility (Figure 1). Based on this, we estimated that the overall occurrence of impaired emotion recognition was roughly 30%.

Patients with impaired emotion recognition did not differ in age, sex or level of education from those without impaired emotion recognition (see Table 2). Moreover, these two groups did not differ in stroke severity at presentation in the emergency department, and in both groups there was an equal distribution of cortical localization and lateralization of ischemic stroke. Patients with impaired recognition were more likely to have a MoCA <26 during hospitalization than the patients that had no impaired emotion recognition ($\chi^2(1)=6.5$, $P=0.011$).

Five weeks after their ischemic stroke, these two patient groups did not report different levels of symptoms of anxiety or depression (see Table 3). However, modest and marked VCD were more common among patients with impaired emotion recognition ($\chi^2(2)=13.1$, $P=0.001$). Of note, out of the 84 patients with no VCD in this cohort, 17 (20%) had an impaired emotion recognition.

As regards the continuous scores, higher scores on the SDMT ($r=0.396$, $P<0.001$), immediate recall condition of the RAVLT ($r=0.317$, $P<0.001$), delayed recall condition of the RAVLT ($r=0.272$, $P<0.001$) and the COWAT ($r=0.329$, $P<0.001$), correlated significantly with higher scores on the EFT. These relationships weakened in partial correlations controlling for age, sex and level of education, but remained statistically significant (SDMT $r=0.246$, $P<0.001$; immediate recall condition of the RAVLT $r=0.172$, $P=0.010$; delayed recall condition of the RAVLT $r=0.186$, $P=0.005$; COWAT $r=0.235$, $P<0.001$).

Table 2: Patient characteristics at baseline, comparing between patients with impaired and with normal emotion recognition.

		Impaired emotion recognition	Normal emotion recognition	Test statistic (df)	P-value
	N	77	153		-
Demographics	Age	69.9 (8.7)	70.4 (9.1)	$t(228)=0.35$	0.724
	Sex, males	56 (73%)	98 (64%)	$\chi^2(1)=1.74$	0.187
	Level of Education	4 (4-5)	5 (4-5)	$U=5812$	0.863
	Handedness (right/left/ambidextrous)	73(95%)/3(4%)/1(1%)	142(93%)/6(4%)/5(3%)	$\chi^2(2)=0.78$	0.676
Stroke characteristics	NIHSS at admission	3 (2-4)	2 (1-4)	$U=6590$	0.173
	Cortical localization	30 (39%)	52 (34%)	$\chi^2(1)=0.55$	0.457
	Supratentorial right localization	30 (39%)	60 (39%)	$\chi^2(1)=0.00$	0.970
	Supratentorial left localization	33 (43%)	66 (43%)	$\chi^2(1)=0.00$	0.968
	Infratentorial localization	18 (23%)	33 (22%)	$\chi^2(1)=0.09$	0.755
Cognition	MoCA <26 during hospitalization	70 (91%)	118 (77%)	$\chi^2(1)=6.52$	0.011

Data are presented as N (%), mean (standard deviation) or median (interquartile range), where applicable. Level of education is coded according to Verhage's coding scale. MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale.

Table 3: Patient characteristics 5 weeks after ischemic stroke, comparing between patients with impaired and with normal emotion recognition.

		Impaired emotion recognition	Normal emotion recognition	Test statistic (df)	P-value
	N	77	153		-
Emotional complaints	HADS-A	3 (2-8)	4 (2-7)	$U=4534$	0.475
	HADS-D	4 (1-7)	3 (2-7)	$U=4929$	0.796
Cognition	No VCD	17 (22%)	67 (44%)	$\chi^2(2)=13.08$	0.001
	Modest VCD	43 (56%)	71 (46%)		
	Marked VCD	17 (22%)	15 (10%)		
Bells test	Signs of neglect	3 (4%)	9 (6%)	$\chi^2(1)=0.41$	0.523

The categorization of VCD is based on the neuropsychological assessment and was defined according to VASCOG criteria.¹⁰ Data are presented as N (%), or median (interquartile range), where applicable. HADS, Hospital Anxiety and Depression Scale; VCD, vascular cognitive disorder.

Discussion

In this study, impaired emotion recognition occurred in 1 out of 3 patients after ischemic stroke. Patients with impaired emotion recognition after ischemic stroke were characterized by showing more cognitive impairment during hospitalization and 5 weeks after ischemic stroke than patients with normal emotion recognition. However, emotion recognition and measures of traditional cognitive domains were only weakly correlated, which may explain that 1 in every 5 patients with no cognitive disorder in the traditional cognitive domains still had impaired emotion recognition.

To our knowledge, this is the first study investigating the occurrence of impaired facial emotion recognition after ischemic stroke. One earlier study of 59 patients with acute ischemic stroke found that 49% had impaired perception of emotion prosody.³⁶ Facial emotion recognition has been studied in other patient groups, such as patients with moderate to severe traumatic brain injury (TBI).³⁷ The authors estimated that impaired emotion recognition occurs in 13-39% of these patients, which is in line with our findings.³⁷

Furthermore, we found that impaired emotion recognition was weakly associated with impairments in other cognitive domains. This finding is in line with recent research of social cognition in the long term after stroke, which also showed weak associations between emotion recognition and general cognitive functioning.²⁴ This association being weak is further supported by the finding that 20% of our patients with no VCD 5 weeks after stroke had impaired emotion recognition. Again, this weak association has also been found in patients with moderate to severe TBI.³⁸ In addition, there were no differences between our patients with and without impaired emotion recognition as regards signs of visuospatial neglect. Whether visuospatial dysfunction of another cause may have led to worse performance on the EFT cannot be ascertained, because visuospatial functioning was only assessed with the Bells test.

There was no association between impaired emotion recognition and symptoms of depression or anxiety. Previous literature shows that emotion recognition is impaired in patients with major depression and anxiety.³⁵ The severity of symptoms of anxiety and depression in this cohort was low, however. We conclude that we did not find an association between symptoms of depression and anxiety, because most of these patients would not have had an established diagnosis of depression or anxiety according to the DSM.

Previous studies of emotion recognition and ischemic stroke mainly focused on the neurobiology of emotion recognition, to improve our understanding of the influence of lesion location on emotion recognition.^{12,13} Somewhat in contrast with previous literature, stroke location was not associated with emotion recognition in our study. Results from earlier studies have been conflicting, with several studies suggesting that patients with right hemisphere stroke perform worse than patients with left hemisphere stroke.^{13,39,40} However, other studies did not confirm these findings, but found that patients with stroke generally perform worse than healthy controls, regardless of stroke location.^{12,24,41} This is in agreement with our results. The ischemic stroke population in our cohort was quite heterogeneous, consisting of patients with the distribution of stroke locations and stroke severities that one would expect in daily practice. We believe that our findings can therefore be generalized to the ischemic stroke population.

Our evidence indicates a high occurrence of impaired emotion recognition after ischemic stroke. We therefore recommend clinicians to be more aware of possible deficits, and if there is any doubt, they should test for impairments of social cognition. Furthermore, the weak association between emotion recognition and traditional cognitive domains suggests that emotion recognition is a separate entity that should be incorporated in the neuropsychological evaluation of patients with ischemic stroke.³⁸ Deficits of social cognition underlie most of the behavioral changes following stroke, and these deficits are associated with an increased caregiver burden and distress.⁴²⁻⁴⁵ Addressing behavioral changes and establishing social cognitive deficits following stroke may therefore also benefit caregivers, enabling them to better cope with their changed partner, for example with the help of psycho-education.^{23,46}

This study has several limitations. First, it included a relatively large group of patients that showed signs of a cognitive disorder during hospitalization, due to the inclusion criteria. Therefore, we may have overestimated the occurrence of impaired emotion recognition after ischemic stroke. Moreover, due to its design, this study did not include a cohort of consecutive patients, which means we could only make an estimation of the occurrence of impaired emotion recognition after ischemic stroke. However, even among the patients without a VCD, a substantial amount number was found to have impaired emotion recognition. Second, it could be questioned whether worse performance on the Ekman 60-faces test could be due to other factors than impaired emotion recognition. For example, the weak correlations with tests of attention and processing speed imply that patients may in fact have had an impaired processing speed, instead of impaired emotion recognition. Furthermore, visuospatial functioning was not extensively assessed,

which raises the question whether - in some patients - a visuospatial deficit could have played a role, although the Bells test showed no differences in signs of visuospatial neglect between patients with impaired emotion recognition and those with normal emotion recognition. In addition, we found only weak correlations between traditional cognitive domains and emotion recognition, which suggests that only a minor part of the variance of emotion recognition can be explained by impairments in traditional cognitive domains. Moreover, the severity of the stroke may in fact have influenced the impairment of both traditional cognitive domains and emotion recognition. Third, the ecological validity of measuring emotion recognition using the EFT can be questioned, as emotion is portrayed using still images. However, literature regarding both patients with TBI and stroke shows that there is a high correlation between the performance on the EFT and other tests of social cognition.^{21,24} Moreover, the EFT has been shown to be an indicator of behavioral change and impaired self-awareness.^{21,45}

In conclusion, impaired emotion recognition occurs frequently after ischemic stroke, even in patients without a disorder in the traditional cognitive domains. Therefore, clinicians should routinely ask patients and their caregivers about possible deficits in emotion recognition after ischemic stroke. If impairments in emotion recognition are present, clinicians should consider treatment and provide psycho-education, since deficits of emotion recognition can have negative consequences for the social functioning of patients.

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8

Summary and general discussion

With an ageing population, it is expected that the incidence of stroke will increase.^{1,2} As a result of the development of new acute treatment options, more patients will survive after ischemic stroke, also resulting in many patients that will have to live with the consequences of stroke.³ Among the chronic consequences of stroke, cognitive impairment occurs frequently.^{4,5} It has a negative impact on the quality of life and social participation.⁶⁻¹⁰ Although many patients show recovery to some extent, it remains difficult to predict an individual's cognitive outcome.¹¹⁻¹³

The overarching aim in this thesis was to assess whether measures of brain connectivity could be directly implemented in daily practice to provide meaningful predictions of cognitive recovery after ischemic stroke for both clinicians and patients. This thesis presents studies in which we assessed whether measures derived from the structural brain network predict cognitive recovery after ischemic stroke, and assessed how often impairments in social cognition occur after ischemic stroke, and more precisely, emotion recognition.

Measures of Brain Connectivity

Main findings

As described in the introduction of my thesis, measures of brain connectivity show potential as predictors of cognitive outcome in patients with cerebrovascular disease. The work described in this thesis adds that the lesion impact score, a score that we developed combining information of lesion size with network topology, was an independent predictor of cognitive recovery after ischemic stroke (**chapter 3**). By contrast, in **chapter 4**, we could not show there was additional value of brain connectivity measures in predicting cognitive recovery over other conventional predictors. Therefore, measures of brain connectivity do not appear to be ready for implementation in daily practice yet, although our findings do show promise. It can be debated whether the brain connectivity measures described in **chapter 4** are specific enough for predicting cognitive recovery after ischemic stroke. The results described in these chapters call for a more detailed assessment of the questions: why is there a discrepancy between the results of **chapters 3 and 4**; and what are the implications of the results described in **chapters 3 and 4** for future research? What would a model that actually can make meaningful predictions of cognitive recovery after ischemic stroke look like? To answer these questions, using 4 cases from the PROCAS study as examples, I will reflect on the determinant, domain and outcome used in the PROCAS study, to set the stage for further work on this topic.

The determinant of PROCRAAS: Measures of brain connectivity

Case 1. This patient, aged 63 years, suffered a large ischemic stroke of the right hemisphere (infarct volume of 74 milliliters). The global efficiency of his structural brain network was +1.2 standard deviations above the average of all patients in the study. His MRI showed relatively little abnormalities other than the ischemic stroke, which could indicate that his brain health was good before suffering from stroke. His z-scores at the neuropsychological assessments are shown in Table 1, indicating that one year after stroke he did not show cognitive recovery. 3 months after stroke, the patient reported that he was not satisfied with his recovery and he noticed quite some restrictions on a social and societal level. He rated his quality of life as poor. Unfortunately, this remained unchanged after 1 year. He could not resume working, but did not experience restrictions in daily life. He frequently practices sports and went on trips.

Table 1:

	Attention	Memory	Executive functioning
5 weeks	-1.08	-0.89	-0.60
1 year	-0.46	-1.39	-0.73

Case 2. This patient, aged 85 years, also suffered a large ischemic stroke of the right hemisphere (infarct volume of 73 milliliters). The global efficiency of his brain network was -1.6 standard deviations below the average of all patients in the study. His MRI showed severe white matter disease and an old ischemic stroke in the left occipital region. These abnormalities could indicate that his brain health was showing decline before suffering from stroke. His z-scores at the neuropsychological assessments are shown in Table 1, indicating that one year after stroke he did not show cognitive recovery. 3 months after stroke, the patient reported that he was not satisfied with his recovery and he noticed quite some restrictions in daily living. Apart from being very satisfied about his relation with his wife and children, he rated his quality of life as poor. Unfortunately, his functioning deteriorated after one year. He had a urinary tract infection several times complicated by a delirium, and he required help in most daily activities. He went to a nursing home for 2 days per week for daytime activities.

Table 2:

	Attention	Memory	Executive functioning
5 weeks	-1.16	-0.79	-1.80
1 year	-1.45	-0.90	-1.39

The two patients described above both suffered from a similarly large stroke in the right hemisphere. Their global network efficiency, however, was markedly different. Why is this the case? It may be that apart from the infarct, this can be explained by more global parameters, such as their different age and degree of

white matter disease. More broadly speaking, by a difference in brain health and resilience before they suffered from a stroke.

In the primary analysis of the PROCAS study described in **chapter 4**, we defined four measures of brain connectivity. These four measures were closely related to each other, as they reflected the integrity of the brain network as a whole in slightly different ways, using related diffusion metrics. The choice for these measures was based on earlier associations with cognitive outcome (i.e. cognitive functioning on a specific time point, not considering change over time) or cognitive deterioration in patients with stroke, cerebral small vessel disease and amyloid angiopathy.¹⁴⁻¹⁸ Of course, one explanation for not finding additional prognostic value may be that measures of brain connectivity are not suited for predicting cognitive recovery and are only related to cognitive outcome or deterioration. However, as described earlier, research suggests that these measures provide an indication of brain resilience, which could mean that it is associated with one's potential of recovery.¹⁹ Then why did we find no additional prognostic value? It seems that global properties of the brain network are best suited to describe the overall health of one's brain. Therefore it may be a very useful determinant in patients with a brain disease that affects large parts of the brain, such as neurodegenerative disease, cerebral small vessel disease and patients with diabetes, and possibly the patient presented in case 2.^{18,20-24} In patients with ischemic stroke, there is a *localized* lesion in a brain that may otherwise have been mostly healthy or unhealthy. It might be that by using *global* measures of network integrity as predictor for cognitive recovery, information was lost on more subtle differences between patients' brain networks, particularly related to the stroke itself. Global network efficiency is a variable with quite some variance between patients. Since an ischemic stroke only affects a relatively small portion of one's network, it may be that the effects of this stroke on one's brain network are lost in the large variance that already exists between patients for this global network metric. In hindsight, individual differences in cognitive recovery may be better explained by combining information on organization of one's brain network with information about the infarct.²⁵ In **chapter 3** we describe such a multimodal measure that combines the topology of the brain network derived from a reference group with infarct location and infarct size (i.e. the lesion impact score). This measure did have added value in predicting cognitive recovery, even independent of infarct size. This suggests that when looking at one's potential of cognitive recovery, it can be useful to consider organizational properties of the brain network, if combined with other measures that provide information on the nature of the injury. This would also mean that it can be helpful to look at specific subnetworks in specific patient groups (i.e. language network in aphasic patients), or to combine different weights to stroke

location such as the recently developed location impact score that was developed in multiple ischemic stroke cohorts.²⁶

Other researchers have already shown some promising results in different patient groups with cerebral small vessel disease (CSVD) and Mild Cognitive Impairment (MCI) using multimodal measures that combine information on connectivity and injury.²⁷⁻³⁰ In the last few years there has been increasing attention for lesion-network-symptom-mapping.³¹ In this type of analysis, the location of ischemic stroke is transposed onto a standardized functional brain network, and is then associated with specific symptoms.³¹ Using this approach, it has been shown that the disability to recognize faces (i.e. prosopagnosia) can be traced back to a lesion in a specific functional brain network.³² Instead of relating a symptom to a location within a functional brain network, one could relate the potential of cognitive recovery to the brain network using this approach as well. A study that did just that in a small sample of ischemic stroke patients looks promising, by providing structural brain maps that are related to complex behaviors and aspects of cognition.³³ In fundamental research, the predictive value of multimodal measures such as these have been shown to be related to brain ageing and the potential of learning a motor skill.^{34,35}

In the research described in **chapter 4**, adding more measures of brain connectivity would have increased the required sample size for statistical modeling. An alternative possibility to overcome part of this problem is using a pattern classifier, for which is promising literature on predicting a cognitive state using a combination of graph theoretical measures and functional MRI.²⁵ A pattern classifier is an example of machine learning, which can be helpful in developing a prognostic model using measures of brain connectivity.³⁶ The advantage of machine learning is that it can help finding the most optimal predictive model, in which it can deal with complex input.³⁷ Sometimes, this can come at the cost of interpretability of the model. This means that a prediction that is done using machine learning, cannot always be theoretically understood based on the data that is used to create the model. It is therefore important that interpretability is necessary when creating a model using machine learning.³⁸ Taking this into account, machine learning makes it possible to better assess relations or patterns between variables in relation with the outcome than standard statistical modeling. It seems that especially measures of brain connectivity and cognitive functioning are suited for this type of modeling as it can better account for the complex relations and interactions between each of these variables. If these techniques are further developed, they can even be tested on the PROCRA dataset.

The ultimate goal of the PROCRAAS study was to be able to more accurately predict cognitive recovery for an individual patient. This would mean that the properties of a patient's brain network in combination with other variables provide enough meaning to be able to educate and inform a patient about his or her chances of recovery, and provide an indication of how rehabilitation therapy would have the most effect. At this moment, this is clearly a bridge too far. Nevertheless, application of the technique in a single subject is shown in **chapter 6**, in which we describe a case that had impaired facial emotion recognition after ischemic stroke. We showed that the stroke may have caused a more widespread disruption of the brain network. I will further discuss this in the paragraph *emotion recognition*.

The outcome of PROCRAAS: cognitive recovery

Case 3. This patient, aged 75 years, had a left occipital infarct and a small infarct in the left thalamus (21 milliliters). His z-scores at the neuropsychological assessments are shown in Table 3. According to the predefined criteria, this patient had a modest post-stroke cognitive disorder (PSCD) 5 weeks after stroke and 1 year after stroke. This patient showed a large improvement in the attention and executive functioning domain. Only because there was not enough recovery in the memory domain, this patient was defined as showing *no cognitive recovery*. 3 months after stroke he reported to be active in daily life, and reported to experience only very little restrictions. He frequently met with friends and family and went on trips. He rated his quality of life as good. One year after stroke, he did not experience any restrictions at all and he rated his quality of life as very good.

Table 3:

	Attention	Memory	Executive functioning
5 weeks	-1.15	-1.24	-1.5
1 year	-0.56	-1.1	0

Case 4. This patient, aged 80 years, also had a left occipital stroke (4 milliliters). His z-scores at the neuropsychological assessments are shown in Table 4. According to the predefined criteria, this patient had a modest PSCD 5 weeks after stroke. One year after stroke he had a minimal improvement in the memory domain, which led to classifying his results as no PSCD. Therefore, this patient was defined as showing *cognitive recovery*. Conversely, this patient actually mostly declined on most cognitive domains. 3 months after stroke he reported to be active in daily life, he regularly met with friends and family, he practiced sports once a week. He did notice some restrictions in daily life, but was still able to enjoy practicing his hobbies. He rated his quality of life as good. One year after stroke, he experienced more restrictions in daily life and he could not practice sports anymore. He required help in different activities of daily living. He was not satisfied with this need for help, but was still very satisfied about the relations with his wife and children. He still rated his quality of life as good.

Table 4:

	Attention	Memory	Executive functioning
5 weeks	0.98	-1.04	-0.37
1 year	-0.02	-0.98	-0.87

Similar to losing information about one's brain network by using only measures that describe global network integrity, information was also lost about one's cognitive status at 5 weeks and after one year by defining cognitive recovery as a dichotomous outcome measure (Table 5). The choice to dichotomize cognitive recovery was made to make a robust and clinically relevant distinction. However, this inherently made this outcome measure less sensitive to more subtle forms of recovery (case 3). To complicate this further, recovery was defined as a change from cognitive performance after 5 weeks to better performance after one year. This means that both the assessment at 5 weeks and the assessment at one year influence the final judgement whether a patient showed cognitive recovery or not, as is illustrated by cases 3 and 4. Furthermore, it may be that the measurement of cognitive functioning 5 weeks after stroke was relatively late for establishing cognitive functioning shortly after stroke.^{4,11,12,39} Some patients may already have shown recovery before this measurement, and were incorrectly classified later as showing no cognitive recovery over time. Other patients may not even have been considered in the analysis because no cognitive disorder could be ascertained after 5 weeks, while they still showed recovery of cognitive functioning. Yet other patients may have taken more time to show cognitive recovery than one year. Moreover, since cognitive recovery is a measure of *change over time*, the actual endpoint (i.e. the cognitive outcome) can still be different between 2 patients that both show cognitive recovery (Table 5). One patient with cognitive recovery can still be greatly impaired in daily life (case 4), while another patient that did recover may not experience any restrictions in daily life.

Table 5: Operationalization of cognitive recovery in the PROCRAAS study.

	VCD 1 year after stroke			
		No VCD	Modest VCD	Marked VCD
VCD 5 weeks after stroke	Modest VCD	Recovery	No recovery	No recovery
	Marked VCD	Recovery	Recovery	No recovery

Box 1.

A post-stroke cognitive disorder is defined as performance on ≥ 1 cognitive domain ≥ 1 standard deviation (SD) below appropriate norms. This is further subdivided into modest PSCD (i.e. performance on ≥ 1 cognitive domain is ≥ 1 SD but < 2 SDs below appropriate norms) and marked PSCD (i.e. performance on ≥ 1 cognitive domains is ≥ 2 SDs below appropriate norms).

Furthermore, in the PROCRAAS study a post-stroke cognitive disorder was defined as impairment in any of the cognitive domains, according to VASCOG criteria (Box

1).⁴⁰ However, each of these cognitive domains can be impaired to a different degree.⁴⁰ Every time one carries out activities in daily life, it requires an interplay of different cognitive domains.⁴¹ This leads one to question whether impairment of a certain cognitive domain may have more impact on one person's life than impairment of another cognitive domain. For example, before even considering more complex cognitive functioning, a prerequisite is that a patient is awake, has sufficient attention and can adequately process the information that is provided.⁴² This suggests that lumping cognitive domains together into one construct may lead to losing valuable information. All these issues may also question the validity of cognitive recovery as an outcome measure. Future studies should consider cognitive recovery to be a non-linear and dynamic process. Advanced modelling techniques are required that can account for recovery occurring at a different pace and to a different extent for each individual. A possibly more realistic prediction for an individual would not be whether a patient recovers or not, but what the most probable *trajectory* of recovery would be.⁴³ In earlier work, it was shown that this is possible for individual patients with aphasia, by showing probability plots of the predicted trajectory of recovery including confidence intervals to account for the accuracy of each prediction.⁴³ As discussed earlier, it may be that machine learning can help dealing with more complex input by looking at the relation between performance in different cognitive domains using, for example, a pattern classifier.^{25,36} Moreover, machine learning is better suited for predictions of recovery trajectories while considering complex input at the same time.^{37,43}

In the light of predicting stroke outcome, considering patient reported outcome measures (PROMs) is also important.⁴⁴ A patient that successfully recovers after stroke, does not necessarily have to have regained function of his arm and leg. At the other hand, a patient that has fully regained function of his arm and leg (the walking and talking patient), is not necessarily satisfied with his recovery. Other factors, apart from factors related with the stroke and cognitive recovery, may play a role here, such as a patient's coping style, level of optimism, resilience and a patient's social network.^{45,46} PROMs measure different aspects of, for example, social participation, health or quality of life, and are exclusively reported by the patient.⁴⁴ In addition, family reported outcome measures (FROMs) can be used to help interpreting the patient reported measures. This is especially useful in patients with diminished self-awareness.⁴⁷ When considering PROMs as outcome measure, patients can be guided using a patient centered perspective.

The domain of PROCRAAS: ischemic stroke

The PROCRAAS study included 264 patients with a clinical diagnosis of ischemic stroke and signs of a cognitive disorder during admission, excluding patients with

signs of pre-existing cognitive impairment. This is a group in which it would be valuable in daily practice to be able to predict whether a patient will show cognitive recovery. However, it is inevitable that some patients in this study did have pre-existing cognitive impairment or subclinical brain disease that may have interacted with the potential of recovery. The questionnaire that was used for assessing pre-existing cognitive impairment was the IQCODE, which has an estimated sensitivity and specificity of around 80% at the cutoff that was used in this study (i.e. 3.6).⁴⁸ Although this seems good, it means that quite some patients may have scored below this threshold and still have had pre-existing cognitive impairment.

Another important issue is generalizability. Quite some patients have been excluded from the PROCRAST study, for example, patients with aphasia. This means that the results of the PROCRAST study cannot be generalized to patients with aphasia after stroke. Generalization is also an issue that needs to be addressed for the calculation of the lesion impact score (**chapter 3**). This score could only be calculated for patients that 1) had a visible lesion on brain MRI, that 2) was located in one of the 90 brain regions defined by an often used brain atlas (i.e. the AAL atlas). In future research, the score would most probably benefit from expanding this brain coverage by including the cerebellum and brain stem. Moreover, it may also benefit from incorporating damage to edges, changing the way the score is calculated.⁴⁹ Methods have already been developed to analyze the network structure of edges within a network, which could be helpful to implement damage to edges in one score.⁴⁹ By addressing these points, the lesion impact score can be calculated for more patients improving its generalizability.

PROCRAST, looking back and ahead

The overarching aim of this thesis was to assess whether measures of brain connectivity could be directly implemented in daily practice to provide meaningful predictions of cognitive recovery after ischemic stroke for both clinicians and patients. When considering implementation, the additional MRI scan proved to be no issue for most patients. Patients were happy to have participated as the MRI provided them with extra insight in their ischemic stroke, and as is also evident from the fact that most patients completed follow-up. Moreover, there were not much problems to arrange a scan within the 5 weeks after stroke for the participants in this study. Although patients and planning seem to be ready for implementation in daily practice, this is, however, still a bridge too far. Apart from developing a reliable model that can provide accurate predictions for an individual as discussed earlier, the time needed for the processing of the scans should be shortened. Therefore, it is important that future research concentrates on developing reliable ways of automating labor expensive techniques such as the

processing of DWI, and segmentation of lesions and brain tissue volumes.^{50,51} This will enable complex parameters to be used for models that can be implemented in daily practice. Therefore, if the lesion impact score (**chapter 3**) is proven valid in future research, a goal will be to develop a script that will generate the lesion impact score after inputting a patient's lesion maps.

An answer to the question I asked at the beginning of this paragraph: "What would a model that actually can make meaningful predictions of cognitive recovery after ischemic stroke look like?" also remains difficult to answer. As of now, it seems that a model needs several parameters that can be classified into roughly 3 categories to make a meaningful prediction. These categories are pre-existing brain health (e.g. age, level of education, severity of white matter disease, amyloid burden), current brain health and functioning (e.g. cognitive screening, neuropsychological assessment, global network efficiency) and information on lesion impact (e.g. stroke severity, infarct volume, lesion impact score). As discussed above, future studies may further our knowledge of cognitive recovery after stroke by including a broader patient group, by making use of multimodal determinants (e.g. measures that combine information on lesion size and the topology of the brain network) and by designing models that can account for complex input and output. Several issues may help enabling this goal.

First, future prognostic studies on cognitive recovery should include greater numbers of patients to be able to develop reliable prognostic models that better generalize to new individuals. An example is an impressive meta-analysis of a large number of studies on cognition and ischemic stroke, for which data from the PROCRAST study was also used.^{26,52} To achieve this, data sharing between different research groups should be encouraged and it should become a standard in research. On the other hand, smaller studies are also needed to be able to study certain cognitive functions or certain imaging techniques at a higher level of detail than is possible in large meta-analyses.

Second, there are many ways to develop models and many ways to come to a prediction. However, the models that are to be used in daily practice, should be the best that are available, and also account at the design step for how it can be implemented in daily practice. To accomplish this, researchers should be challenged to develop the best model, for example, by means of a competition.⁵³ This would not only result in the strongest model for patients, but it also prevents an abundance of prognostic models in the literature.⁵³

Lastly, measures of brain connectivity should also be incorporated in different research designs. These measures may help in selecting patients for an intervention or for psychoeducation. Unfortunately, thus far there is no evidence for any effect of cognitive training on recovery of cognitive function after stroke.⁵⁴ Luckily, there is evidence of adaptive or compensatory strategy training programs.^{55,56} However, these training programs only help patients to cope with their cognitive impairment, instead of regaining (part of) their pre-existing cognitive functioning.^{55,56} It may be that a small group of patients may actually have benefit of a cognitive training program, and that measures of brain connectivity could help selecting these patients. One study already applied this to patients with aphasia, by showing that patients that benefit from intensive language therapy had higher global efficiency.¹⁴

Measures of brain connectivity may ultimately also help in selecting patients that could benefit from influencing their brain network using non-invasive brain stimulation, using transcranial magnetic stimulation (TMS).^{57,58} In the last 30 years, there is quite some evidence for the positive effects of TMS on various neurological and psychiatric disorders.^{57,58} When it is possible to directly measure the effect of TMS on the brain network, it will be possible to directly apply different therapeutic schemes based on its effect on the brain network. Measures of brain connectivity can also be used in psychoeducation. For example, the brain can be seen as a train network, in which the brain regions are train stations and the connections between brain regions are the tracks connecting the stations. When an ischemic stroke damages a brain region (e.g. a power outage occurs in a train station), processing of information slows, because this information has to take a detour to arrive at the next train station. This can replace the more traditional way of looking at the location and size of the stroke, mostly ignoring the brain in which this stroke has occurred.

Emotion Recognition

Emotion recognition is one of the subdomains of social cognition.⁵⁹ Emotion recognition is a prerequisite for other aspects of social cognition, such as theory of mind and empathy, and at this moment emotion recognition can be assessed most reliably of all domains of social cognition.⁵⁹ It involves extracting emotion-relevant information from cues, such as facial or vocal expressions, to correctly classify and recognize emotions.⁵⁹ Emotion recognition is vital to understand others and to appropriately adjust one's behavior to the situation.⁶⁰

Main findings

In this thesis, we described a case report of a patient that had impaired facial emotion recognition after ischemic stroke located in the left insula (**chapter 6**). This seemingly contrasts with earlier literature that states that the right hemisphere is responsible for the process of emotion recognition.⁶¹ An analysis of the structural brain network of this case showed that the stroke may have caused a more widespread disruption of his brain network, which may explain why he had more difficulties recognizing facial emotions. Based on a brief literature review, we conclude in **chapter 6** that it is in fact a bihemispherical network of neural structures that is involved in correctly recognizing emotions. It may not come as a surprise that when an ischemic stroke causes dysfunction anywhere in this network of structures, emotion recognition may get impaired. In **chapter 7** we showed that emotion recognition is in fact impaired in 1 out of 3 patients after ischemic stroke. These patients were actually rather similar to the patients that did not have impaired emotion recognition. This means that in contrast with what was previously thought, impairment in recognizing emotions occurs regardless of the size of stroke and lateralization of stroke. Again, it may be that considering location of ischemic stroke within the specific subnetwork of emotion recognition may further our understanding of occurrence of impaired emotion recognition.

Recently, it was shown that impairments in social cognition remain present in the long term after ischemic stroke.⁶² This suggests that patients may show only little recovery in their ability to recognize emotions after stroke. As discussed earlier, impairment in each cognitive domain may have a different and unique impact on functioning in daily life. It may be helpful to also consider emotion recognition recovery in future studies of cognitive recovery after stroke. We conclude that because of the high occurrence of impaired emotion recognition after stroke, it is important for clinicians to evaluate social cognition in daily practice, since it can have negative consequences on social participation and quality of life.⁶³⁻⁶⁶ We propose that routinely asking patients and their caregivers about post-stroke changes in social behavior or empathy can help selecting patients that need further neuropsychological examination of their social cognitive capacities. Moreover, psychoeducation can be provided, as it is an important first step in cognitive rehabilitation.⁵⁵ It is important that patients with deficits in social cognition are recognized, because there is evidence in patients with traumatic brain injury that a strategy training for impairments in social cognition can have long-lasting beneficial effects.⁶⁷ The effect of this training program is going to be studied in patients with ischemic stroke.

Clinical implications

In the work described in this thesis, we have shown that measures of global brain connectivity look promising, but at this moment do not add prognostic value in predicting cognitive recovery after stroke in a way that can be applied in current clinical practice. However, when combining information on network topology with other modalities (i.e. multimodal measures), this may help better predicting a patient's chances of cognitive recovery. Before a multimodal measure such as the lesion impact score (**chapter 3**), can be implemented in daily practice, more research is needed. In the next few years, several hurdles have to be taken to get brain networks in daily practice. First, reliable and strong prognostic models need to be developed. This means that models do not only need to explain a large amount of variance, but also that findings are reproducible across and within different cohorts. Next, it is important to invest resources in automation of most of the post-processing of MRI scans of patients. This would also enable a different output of brain imaging results, where not only a qualitative description of the radiologist, but also quantitative results of, for example, a patient's brain volume, infarct volume and network properties could be reported in relation to reference values. There is already a substantial amount of published data on the application of this so-called 'radiomics' (i.e. quantitative imaging) in cancer research.⁶⁸ When it is possible to introduce quantitative imaging results into daily practice, this can be the next step to more individualized tailored care.

The research that was described in **chapters 6 and 7** can have implications for daily practice directly. We found that impairments in emotion recognition occur frequently after ischemic stroke. As we know from earlier research, patients with ischemic stroke are not unique in having impairments in emotion recognition: it can be seen in all kinds of neurological and psychiatric diseases.⁶⁰ This implies that clinicians should more actively ask their patients and their caregivers about post-stroke changes in social behavior or empathy. Psychoeducation should be provided to patients with signs of impairment in their social cognitive capacities, and a referral to a neuropsychologist should be considered. The best way to achieve this, is to increase awareness by educating all involved caregivers in stroke care on the cognitive and emotion consequences following stroke, such as neurologists, rehabilitation physicians, neuropsychologists, residents neurology, physician assistants, physical and occupational therapists and (specialized) nurses. In the following years, it seems to be important that the patient and their caregiver take as much control over the patient's complaints as possible. This would mean that it is possible for a patient to get easy access to information and if needed he would, for example, receive screening questions regarding cognition and social cognition

through a patient portal. If the patient screens positive, then this would lead to an invitation to the outpatient clinic where the complaint can be studied further.

In the work described in **chapter 5**, we showed that 5 weeks after stroke patients often do not have a corresponding lesion on MRI. Although a negative MRI should prompt the question whether the patient did suffer from ischemic stroke, we showed that a large proportion of these patients still had a likely clinical diagnosis of ischemic stroke. Patients with a negative MRI were rather similar to patients that had a corresponding lesion on MRI. For MRI negative patients it is just as important to have information on prognosis as for MRI positive patients. When looking at prognosis, patients with MRI negative stroke do not differ much from patients that had a nonspecific transient ischemic attack (TIA), which has been coined as a transient neurological attack (TNA).⁶⁹ The similarity between MRI positive stroke as compared to MRI negative stroke and TIA compared to TNA is actually rather striking. Patients with TNA also have a higher risk of recurrent stroke, similar to MRI negative stroke patients.⁷⁰⁻⁷² In patients with TIA and TNA, diagnosis is based on the judgement of the clinician, as there is no gold standard diagnostic test. If an urgent MRI is made, abnormalities can be seen in approximately 20-30% of patients in both groups.^{69,72} Understandably, there is an ongoing discussion as to how to treat patients with TNA, should they be treated likewise to patients with TIA?⁷² In my opinion, this discussion could be extended to patients with MRI negative stroke. In absence of a better explanation for the symptoms of a patient with MRI negative stroke, the patient should be treated the same way as patients with MRI positive stroke would be treated. This indicates that clinicians should be aware that a negative MRI is not unusual in patients that suffered from an ischemic stroke, especially in patients with less severe strokes, and less specific symptoms. This finding can have direct consequences for daily practice, as physicians tend to use the MRI to rule-in or rule-out the diagnosis of ischemic stroke. This can lead to patients with MRI negative stroke being undertreated and this would leave them at higher risk of a recurrent stroke. Again, it seems important to increase awareness and to educate physicians on the existence of an MRI negative stroke.

Conclusions

Cognitive impairment occurs often after ischemic stroke. Establishing which patient has the potential to recover, could help in adjusting rehabilitation programs to the patient's needs and capabilities. We showed that DWI based measures of brain connectivity are promising in determining a patient's potential to recover. However, further research is needed to assess how these measures can add value in daily practice.

We also showed that emotion recognition is impaired in one out of three patients, while it is often not recognized by the clinician or the patient. Clinicians should be aware that these impairments occur often and should routinely inform patients about changes in social behavior or empathy. If there are signs of changes in a patient's social behavior or empathy, patients or their caregivers should be provided with psychoeducation and referral to a neuropsychologist should be considered.

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Appendices

**Nederlandse Samenvatting
Dankwoord
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Nederlandse Samenvatting

Een herseninfarct is een van de meest voorkomende oorzaken van overlijden en langdurige handicap. In Nederland zijn er dagelijks ongeveer 100 nieuwe patiënten met een herseninfarct. Door groei van de bevolking en doordat de levensverwachting stijgt, zal dit aantal de komende jaren verder toenemen. Naast de fysieke gevolgen, ervaren de meeste patiënten (naar schatting 75%) ook stoornissen in de informatieverwerking: *cognitieve stoornissen*. Deze cognitieve stoornissen zijn geassocieerd met verminderde kwaliteit van leven en leiden tot slechter fysiek en sociaal functioneren.

Gelukkig herstellen cognitieve stoornissen bij ongeveer de helft van de patiënten met een herseninfarct spontaan over de tijd. Bij de overige patiënten blijven deze echter (gedeeltelijk) bestaan of kunnen ze zelfs verslechteren. Bij wie herstel op zal treden en bij wie niet blijkt erg lastig te voorspellen. Bij een betere voorspelling zouden we patiënten en hun naasten beter kunnen voorlichten over de vooruitzichten en wellicht zouden beter haalbare revalidatiedoelen kunnen worden bepaald.

Vroeger dacht men dat bepaalde functies op bepaalde plaatsen in de hersenen waren gelokaliseerd. Tegenwoordig denken we dat de diverse functies worden geregeld vanuit netwerken van structuren binnen de hersenen: hersennetwerken. Hersennetwerken kunnen in kaart worden gebracht door te kijken naar de samenhang tussen verschillende hersenfuncties, maar ook door te kijken naar hoe de *structurele* verbindingen lopen tussen hersengebieden. De hersenfuncties kunnen bijvoorbeeld in kaart worden gebracht met een hersenfilmpje (EEG) of met bepaalde MRI technieken (functionele MRI: fMRI). Een structureel hersennetwerk kan met behulp van weer andere MRI technieken in kaart worden gebracht, waarbij diffusie gewogen MRI (DWI) het meest gebruikt wordt.

Netwerken kunnen op zijn eenvoudigst weergegeven worden als punten en lijnen tussen die punten (figuur 1). In dit geval stellen de punten hersengebieden voor en de lijnen de verbindingen tussen die hersengebieden. Je kunt op basis van deze figuren al zien dat sommige punten belangrijker zijn voor het netwerk dan andere punten. Deze belangrijke punten worden ook wel hubs genoemd. Je kunt ook kijken hoe veel stappen het kost om van een willekeurig punt in het netwerk naar een willekeurig ander punt te komen in het netwerk. Hoe minder stappen het kost om van A naar B te komen, hoe efficiënter het netwerk. Zo zijn er nog vele eigenschappen van netwerken, welke kunnen worden beschreven met behulp van getallen, zogenaamde *netwerkmaten*. Een netwerkmaat die al veel werd gebruikt in eerder onderzoek is de efficiëntie van het globale hersennetwerk. Zo werd bij patiënten met onder andere een herseninfarct al vastgesteld dat de efficiëntie

van het globale hersennetwerk geassocieerd is met cognitieve stoornissen na enkele maanden en ook met cognitieve achteruitgang over de tijd.

Figure 1: In dit figuur wordt een voorbeeld gegeven van een netwerk. Een punt met veel verbindingen naar andere punten in het netwerk wordt ook wel een hub genoemd. Ook wordt er een kortste pad weergegeven dat kan worden afgelegd van een willekeurig punt naar een willekeurig ander punt. Niet geheel toevallig loopt dit kortste pad vaak via hubs.

Legend

○ Node	— Edge
● Hub node	— Shortest path

Op basis van de eerdere literatuur, hypothetiseerden wij dat netwerkmaten iets zouden kunnen zeggen over de *weerbaarheid* van de hersenen. Oftewel, een patiënt met een weerbaar hersennetwerk heeft een grotere potentie te herstellen, dan een patiënt met een minder weerbaar hersennetwerk. In dit proefschrift is daarbij het overkoepelende doel om te onderzoeken of hersennetwerkmaten direct kunnen worden geïmplementeerd in de dagelijkse praktijk om betekenisvolle voorspellingen te doen van cognitief herstel na een herseninfarct. Meer specifiek onderzochten we of deze netwerkmaten, verkregen vanuit een structureel hersennetwerk, cognitief herstel 1 jaar na een herseninfarct kunnen voorspellen. Dit hebben wij onderzocht in de PROCRAAS studie, waarvan het protocol in **hoofdstuk 2** is beschreven.

In de zoektocht naar een betere manier om cognitief herstel na een herseninfarct te voorspellen, bespreken we in **hoofdstuk 3** de ontwikkeling van een nieuwe score, de 'lesion impact score'. De achterliggende gedachte is dat de mate waarin een herseninfarct de hubs binnen het hersennetwerk beschadigt een essentiële rol speelt wanneer het gaat om cognitief functioneren. Eerst ontwikkelden wij een hersennetwerkk kaart op basis van de hersennetwerken van gezonde controles. Vervolgens hebben we voor elk van de patiënten bekeken waar dit infarct precies was gelokaliseerd in deze standaard hersennetwerkk kaart. Vervolgens

vermenigvuldigden we de grootte van het herseninfarct met een getal dat aangaf hoe belangrijk het beschadigde hersengebied was voor het hersennetwerk (de Hub-score). De uitkomst noemden we de ‘*lesion impact score*’, omdat we hiermee de *impact* van het infarct op het netwerk wilden weergeven. Allereerst vonden we dat naar mate de *lesion impact score* groter was, en het herseninfarct dus een grotere impact had op het hersennetwerk, de efficiëntie van het globale hersennetwerk van de patiënten kleiner was. Vervolgens vonden we dat hoe groter de *lesion impact score* was, hoe kleiner de kans was voor patiënten om cognitief herstel te vertonen. Hiervoor gebruik ik graag een metafoor, waarbij de hersenen kunnen worden gezien als een treinnetwerk, bestaande uit stations (hersengebieden) en verbindingen tussen die stations (het spoor). Wanneer een herseninfarct in Utrecht centraal is gelokaliseerd (een hersengebied met een hoge hubwaarde), heeft dit een grotere impact op de loop der treinen in Nederland (potentie van een patiënt om cognitief te herstellen), dan wanneer een herseninfarct in Lunteren is gelokaliseerd (een hersengebied met een lage hubwaarde). In dit hoofdstuk bleek dus dat niet alleen de grootte van het infarct van belang is als het gaat om de kans een goed cognitief herstel te vertonen, maar ook de locatie van het infarct binnen het hersennetwerk.

In **hoofdstuk 4** onderzochten we of de efficiëntie van het hersennetwerk een aanvullende voorspellende waarde had in het voorspellen van cognitief herstel na een herseninfarct. Er bleek wel een duidelijk verband te bestaan tussen efficiëntie van het hersennetwerk en cognitief herstel. Helaas bleek echter de voorspelling niet beter dan met behulp van reeds bekende voorspellers mogelijk is. Zo bleek al sprake van een redelijke voorspelling van het cognitief herstel met behulp van het opleidingsniveau en de infarctgrootte. Wanneer de efficiëntie van het globale hersennetwerk werd toegevoegd als voorspeller, bleek dit geen toegevoegde waarde te hebben in de betrouwbaarheid van de voorspellingen. In dit hoofdstuk wordt duidelijk dat cognitief herstel na een herseninfarct zich lastig laat voorspellen. Dit blijkt doordat veel van de onderzochte voorspellers geen verband hadden met cognitief herstel. Ook blijkt dit doordat de nauwkeurigheid van voorspellingen zelfs door het beste model beperkt was. We concluderen in dit hoofdstuk dat hersennetwerkmaten veelbelovend zijn. Zoals al in **hoofdstuk 3** werd beschreven, is er bij een combinatie van hersennetwerkmaten met andere maten (multimodale maten) wel een verband met cognitief herstel te vinden. De waarde van de *lesion impact score* zal dan ook in vervolgonderzoek in een grotere groep worden onderzocht.

Terwijl het PROCRAAS onderzoek in volle gang was, viel het ons op dat een substantieel aantal deelnemers geen zichtbaar herseninfarct had op de MRI

scan, terwijl alle deelnemers wel de diagnose herseninfarct hadden gekregen. In **hoofdstuk 5** beschrijven we dat maar liefst 1 op de 4 patiënten een zogenaamd MRI-negatief herseninfarct heeft. In eerste instantie roept dit uiteraard de vraag op of deze patiënten wel een herseninfarct hebben gehad? Om die reden hebben we 3 verschillende ervaren neurologen onafhankelijk van elkaar laten beoordelen hoe waarschijnlijk zij de diagnose herseninfarct vonden op basis van de informatie die de onderzoekers hadden op het moment dat de patiënt met de studie mee ging doen. Zij wisten hierbij niet wat de uitkomst was van de MRI scan die voor het onderzoek werd gemaakt. Hieruit bleek dat 6 op de 10 patiënten met een MRI-negatief herseninfarct een waarschijnlijke klinische diagnose had. Opvallend was dat patiënten met een MRI-negatief herseninfarct weinig verschilden van patiënten die wel een zichtbaar infarct op de MRI scan hadden. Omdat uit eerder onderzoek blijkt dat patiënten met een MRI-negatief herseninfarct ook een soortgelijke prognose hebben als patiënten met een zichtbaar infarct op de MRI scan, stel ik voor dat patiënten met een MRI-negatief herseninfarct ook op dezelfde manier worden behandeld. Dit voorstel kan directe consequenties hebben voor de dagelijkse praktijk, waar de MRI vaak wordt gebruikt om een diagnose herseninfarct aan te tonen of uit te sluiten.

De cognitieve functies kunnen onderverdeeld worden in verschillende domeinen. Het meest bekende domein is het geheugen, maar daarnaast kennen we onder andere de domeinen aandacht en verwerkingssnelheid, ruimtelijk inzicht en executieve functies. Dit laatste domein behelst onder andere het plannen, het uitvoeren van dubbeltaken en het hebben van overzicht. Naast deze traditionele cognitieve domeinen is er ook een domein dat pas recent ook formeel als zodanig wordt erkend: sociale cognitie. Dit domein behelst alle psychologische processen waarmee iemand sociale informatie waarneemt, verwerkt, interpreteert en erop reageert. Eerder onderzoek toonde al aan dat patiënten met een herseninfarct ook stoornissen in sociale cognitie vertonen en deze stoornissen zijn op hun beurt geassocieerd met een slechtere kwaliteit van leven en deelname aan het sociale leven. Sociale cognitie is weer onder te verdelen in subdomeinen, waarvan emotieherkenning er één is. In **hoofdstuk 6** is een patiënt beschreven die moeite had emoties te herkennen nadat hij een infarct had in de linker hersenhelft. In eerdere literatuur is terug te vinden dat vooral de rechter hemisfeer belangrijk is voor het herkennen van emoties. Uit een samenvatting van eerdere literatuur wordt in **hoofdstuk 6** duidelijk dat men emoties herkent middels een netwerk van met elkaar verbonden hersenstructuren in beide hersenhelften. Het is dan ook niet verwonderlijk dat een herseninfarct ergens in dit netwerk kan leiden tot een gestoorde emotieherkenning. In **hoofdstuk 7** wordt vervolgens beschreven dat maar liefst 1 op de 3 patiënten een gestoorde emotieherkenning heeft na een

herseneninfarct. Stoornissen in emotieherkenning worden vaak niet opgemerkt door klinici of patiënten zelf. Daarnaast rapporteren naasten het vaak niet uit zichzelf. Dit maakt het extra uitdagend om stoornissen in emotieherkenning te herkennen in de dagelijkse praktijk. Het is daarom belangrijk dat klinici hiervoor aandacht hebben door routinematig patiënten en hun naasten gericht te vragen naar veranderingen in sociaal gedrag of empathie. Bij verdenking op een dergelijke stoornis kunnen patiënten worden doorverwezen naar een neuropsycholoog voor verdere diagnostiek en eventuele behandeling.

Het overkoepelende doel van dit proefschrift was om te onderzoeken of hersennetwerkmaten direct kunnen worden geïmplementeerd in de dagelijkse praktijk om betekenisvolle voorspellingen te doen van cognitief herstel na een herseneninfarct. In deze vraag zijn er twee subvragen te onderscheiden:

1. Kunnen hersennetwerkmaten worden geïmplementeerd in de dagelijkse praktijk?
2. Kunnen hersennetwerkmaten betekenisvolle voorspellingen doen van cognitief herstel na een herseneninfarct?

Voor wat betreft implementatie, deden de patiënten graag mee aan het onderzoek, zoals ook blijkt uit het grote percentage deelnemers dat de hele studie heeft doorlopen. De MRI scan bleek ook zeker geen horde, waarbij vele deelnemers het juist zelfs fijn vonden, omdat de MRI scan hen extra inzicht gaf over wat hen was overkomen. Ook logistiek waren er geen grote problemen om het neuropsychologisch onderzoek en de MRI scan binnen enkele weken na het herseneninfarct te organiseren. Hoewel de dagelijkse praktijk er dus klaar voor lijkt te zijn, zijn er echter nog andere hordes die moet worden genomen. Zoals eerder besproken is het tot dusver nog niet gelukt een betrouwbaar model te ontwikkelen dat nauwkeurige voorspellingen kan doen van cognitief herstel na een herseneninfarct. Naast het ontwikkelen van een betrouwbaar model, is het ook van belang dat de verwerkingsduur korter wordt van de stappen die moeten worden genomen om van een MRI scan op hersennetwerkmaten te komen. Zo zou het erg zinvol kunnen zijn als er betrouwbare methodes worden ontwikkeld die arbeidsintensieve technieken automatiseren, zoals het verwerken van DWI en het 'uittekenen' (segmenteren) van herseneninfarcten. Pas dan zal de stap naar de dagelijkse praktijk écht gemaakt kunnen worden. Zo zal bijvoorbeeld voor de lesion impact score (**hoofdstuk 3**) worden onderzocht of het ook in een grotere groep patiënten uit verschillende landen voorspellingen kan doen van cognitief functioneren na een herseneninfarct. Hierbij is een extra doel om een programma

te ontwikkelen dat automatisch de score berekent wanneer de gesegmenteerde herseninfarcten worden ingevoerd.

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Curriculum Vitae

Hugo Paul Aben was born the 9th of March 1989, in Capelle aan den IJssel, the Netherlands. After graduating from secondary school (Rotterdams Montessori Lyceum), he started studying medicine in the Erasmus University in Rotterdam. He obtained his medical degree at the end of 2012 and started working as a resident neurology in the Elisabeth Tweesteden Hospital in Tilburg in 2013. He started his neurology training in 2014 and in 2016 he started his PhD project on prediction of cognitive recovery after stroke (supervised by prof. dr. G.J. Biessels, dr. P.L.M. de Kort, prof. dr. J.M. Spikman and prof dr J.M.A. Visser-Meily).

Currently, Hugo is continuing his training to become a neurologist in the Elisabeth Tweesteden Hospital in Tilburg, which he hopes to complete in the spring of 2023. He is interested in the interface between neurology, psychiatry and psychology and wants to subspecialize as a behavioral neurologist.

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