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Prediction of Cognitive Recovery After Stroke

The Value of Diffusion-Weighted Imaging–Based Measures of Brain Connectivity

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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 1 year after stroke in patients with PSCD in addition to conventional clinical, neuropsychological, and imaging variables.

METHODS: This prospective monocenter cohort study included 217 consecutive patients with a clinical diagnosis of ischemic stroke, aged ≥50 years, and Montreal Cognitive Assessment score below 26 during hospitalization. Five weeks after stroke, patients underwent DWI magnetic resonance imaging. Neuropsychological assessment was performed 5 weeks and 1 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 4 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 magnetic resonance imaging findings (eg, 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 of 4 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.

Key Words: brain infarction ■ cognition ■ cognitive dysfunction ■ hospitalization ■ magnetic resonance imaging

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.

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Thus far, prediction of cognitive recovery after ischemic stroke is imprecise.[6] Most studies focused

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Nonstandard Abbreviations and Acronyms

APOE	apolipoprotein E
AUROC	area under the receiver operator curve
DWI	diffusion-weighted imaging
FA	fractional anisotropy
LoE	level of education
MD	mean diffusivity
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
OR	odds ratio
PROCRAS	Prediction of Cognitive Recovery After Stroke
PSCD	poststroke cognitive disorder

on prediction of poor cognitive outcome, whereas predictors of recovery have received less attention. Emerging predictors of cognitive recovery from literature include demographic characteristics (ie, age, sex, and level of education [LoE]), stroke characteristics (ie, stroke location and severity), vascular risk factors (ie, diabetes and smoking), cognitive and emotional status (ie, cognitive functioning in acute stage and poststroke depression or apathy), and imaging findings (ie, 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 magnetic resonance imaging (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 1 year after stroke in patients with poststroke cognitive disorder (PSCD) in addition to clinical, neuropsychological, and conventional imaging variables.

METHODS

Population

Data were used from the longitudinal, prospective, PROCRAS study (Prediction of Cognitive Recovery After Stroke), 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 of age, 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, 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 computed tomography. 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 (eg, 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, of 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 whom 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 1-year situation reflected either cognitive recovery or no cognitive recovery. No consensus was reached about the coding in 1 patient, resulting in exclusion from the final sample (n=135).

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 (Table I in the Data Supplement).[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 SD below appropriate norms, as reported previously.[25,26] The presence of PSCD was further subdivided into modest PSCD (ie, performance on ≥1 domain is ≥1 SD but <2 SDs below appropriate norms) and marked PSCD (ie, performance on ≥1 domain is ≥2 SDs below appropriate norms).[25,26]

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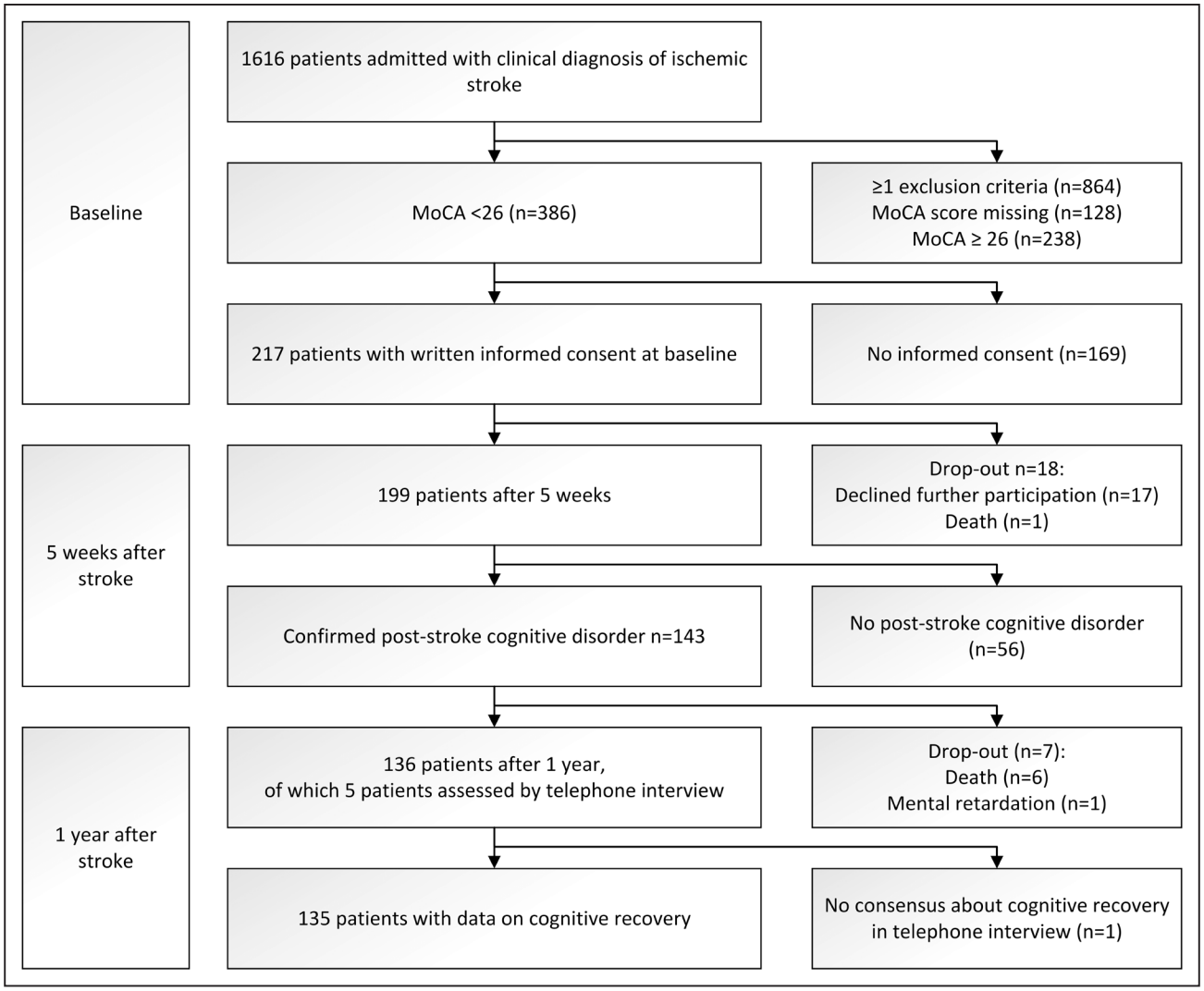

Figure 1. Flowchart of patient flow.

MRI

Patients were scanned on a 3T 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, and DWI sequences.[26] DWI sequence parameters were as follows: 70 slices; voxel size, 2.00×2.00×2.00 mm^3; repetition time/echo time, 7891/87 ms; 50 directions (*b* value, 1500 s/mm^2); and 7 b=0 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 anatomic labeling atlas to patient space. Two connectivity matrices were obtained for each patient: 1 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 4 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 3 (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 from 1 to 7 covering the Dutch

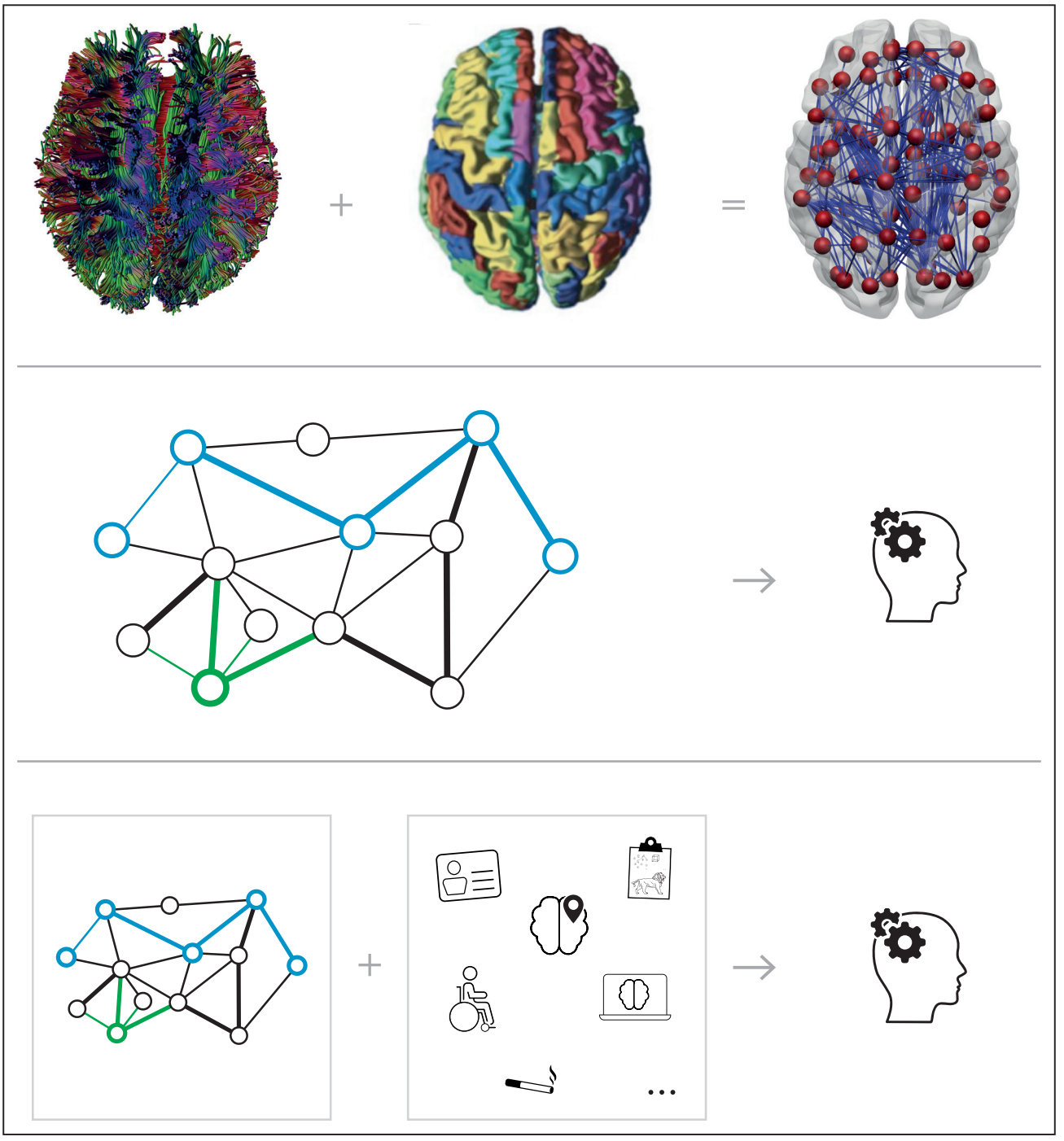

Figure 2. Processing steps and study design.
Top, After preprocessing, whole-brain tractography was performed on each patient's DWI data. These whole-brain tractography maps were parcelated into 90 cortical and subcortical regions, by registering the automated anatomic labeling atlas to patient space. This resulted in 2 brain networks per patient, one with connections weighted by fractional anisotropy and 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 either cortical or subcortical regions and the edges white matter tracts. In the example, the shortest path between 2 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 the 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 1 y after stroke, and we assessed whether there was additional predictive value of DWI-based measures of brain connectivity on cognitive recovery.

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education system. In statistical models, LoE was divided into 3 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.[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, nonlacunar 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 nonlacunar supratentorial, other POCS was 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, that is, 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,[31] D or 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, 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, APOE (apolipoprotein E) ε4 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 fluid-attenuated inversion recovery 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 described previously.[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 3 categories (ie, 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% CI, and *P*.

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 preselection step, only variables with $P<0.1$ were eligible for entry in the multivariable logistic regression analysis[37] 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 a dependent variable. Variables were eliminated until the maximum amount of 4 *df* 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 (ie, model 1) in separate models to assess whether there was additional predictive value of one of these measures (ie, 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 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.

Ethics Committee Approval

The PROCRAS 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 1 year, 9 (7%) showed cognitive deterioration, and the remaining 85 (63%) patients remained cognitively stable over time (Table 1).

DWI-Based Measures of Brain Connectivity

In the preselection of variables for the multivariable model, 3 of 4 network measures met the threshold of

Table 1. Distribution of Severity of PSCD After 5 Weeks and After 1 Year

	PSCD after 1 y			
PSCD after 5 wk		No PSCD	Modest PSCD	Marked PSCD
	Modest PSCD	28*	64	9
	Marked PSCD	1*	12*	21

PSCD indicates poststroke cognitive disorder.
*Patients that were defined as showing cognitive recovery.

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 preselection of conventional predictors for the multivariable model, 5 of 33 variables met the threshold of *P*<0.1: sex (men compared with 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 with 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 size (no identifiable symptomatic infarct on MRI after 5 weeks OR, 0.3 [0.1–0.9] and infarct volume of >20 mL OR, 0.3 [0.1–0.8], both compared with infarct volume of 0–20 mL [reference]; Table 2). Backward selection of these 5 predictors in multivariable analysis resulted in model 1 with 2 variables as the strongest predictors of cognitive recovery 1 year after stroke: infarct size and LoE (Table 3). Model performance was adequate with a Nagelkerke 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 2 conventional predictors. This did not significantly improve model performance: global efficiency FA weighted (R^2, 0.21; AUROC, 0.74; χ^2[1], 2.7; *P*=0.096), mean strength FA weighted (R^2, 0.21; AUROC, 0.74; χ^2[1], 2.5; *P*=0.114), and mean strength MD weighted (R^2, 0.21; AUROC, 0.75; χ^2[1], 2.8; *P*=0.096; Table 3).

DISCUSSION

We show that DWI-based measures of brain connectivity predict cognitive recovery 1 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 33 candidate predictors, of which only 5 predicted cognitive recovery in univariable analyses. This shows that it is difficult to predict cognitive recovery 1 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 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 the occurrence of a lesion.[42] 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 National Institutes of Health Stroke Scale and shorter duration of admission, had similar clinical features compared with 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

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, y	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
Nonlacunar 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	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 3 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 intravenous alteplase 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		
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, 0–20 mL	0	29 (70%)	40 (42%)	Ref		
Infarct volume, >20 mL	0	6 (15%)	28 (30%)	0.296	0.108–0.806	0.017

(*Continued*)

Table 2. Continued

	Missings	Cognitive recovery	No cognitive recovery	OR	95% CI	*P* value
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

Data are presented as mean (SD), median (interquartile range), and count (percentage). The ORs for brain parenchymal fraction and DWI-based measures of brain connectivity are per SD. APOE indicates apolipoprotein E; DWI, diffusion-weighted imaging; FA, fractional anisotropy; HADS, Hospital Anxiety and Depression Scale; LoE, level of education; MD, mean diffusivity; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; Ref, reference; and TIA, transient ischemic attack.

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

and acute computed tomography 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 1 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 modeling 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

Table 3. Multivariable Analysis for Prediction of Cognitive Recovery 1 Year After Stroke, Maximum 4 *df 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
Infarct size								
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
Intermediate (4–5)	Ref		Ref		Ref		Ref	
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	

AUROC indicates area under the receiver operator curve; FA, fractional anisotropy; LoE, level of education; MD, mean diffusivity; MRI, magnetic resonance imaging; OR, odds ratio; and Ref, reference.

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

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 with 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 ≥1 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 who 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 cutoff is often used in daily practice, and the distribution of educational levels was as expected.

CONCLUSIONS

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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Disclosures

None.

Supplemental Materials

Online Table I

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