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Esther M. Boot, Mijntje M. I. Schellekens, Hao Li, Merel S. Ekker, Jamie I. Verhoeven, E. Verburgt, M. Immens, Nina A. Hilkens, F. J. A. Meijer, R. P. C. Kessels, Frank-Erik Leeuw, Anil M. Tuladhar & the ODYSSEY Investigators

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Structural connectome and cognitive performance in young stroke survivors

E.M. Boot MD[1], M.M.I. Schellekens MD[1], MD, Hao Li[1], M.S. Ekker MD[1], J.I. Verhoeven MD[1], E. Verburgt MD[1], M. Immens MD[1], N. Hilkens MD[1], F.J.A. Meijer MD[3], R.P.C. Kessels[2,4,5], F.E. de Leeuw MD[1], A.M. Tuladhar MD[1*] on behalf of the ODYSSEY Investigators**

1. Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour; Department of Neurology, Nijmegen; The Netherlands
2. Radboud University, Donders Institute for Brain, Cognition and Behaviour, Center for Cognition, Postbus 9104, 6500 HE, Nijmegen, the Netherlands
3. Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour; Department of Radiology, Nijmegen; The Netherlands
4. Vincent van Gogh Institute for Psychiatry, Postbus 5, 5800 AA, Venray, the Netherlands
5. Radboud University Medical Center, Department of Medical Psychology and Radboudumc Alzheimer Center, PO box 9101, 6500 HB, Nijmegen, The Netherlands

*Corresponding author: A.M. Tuladhar, Department of Neurology, Radboud University Medical Center, Reinier Postlaan 4, PO-box 9101, 6500 HB Nijmegen, The Netherlands. E-mail:Anil.Tuladhar@radboudumc.nl

**A list of authors and their affiliations appears at the end of the paper.

Abstract

Background: We aimed to study the relationship between brain network measures and cognitive performance in this population, focusing on hub regions.

Methods: A sub-cohort of young stroke survivors (ages 18-49) with confirmed cerebral ischemia from the ODYSSEY study underwent MRI and neuropsychological assessments at baseline (n=60) and follow-up (n=46) up to 2 years, the discovery cohort. Additionally, a validation cohort of young stroke survivors with confirmed cerebral ischemia who had baseline standard MRI protocol and neuropsychological assessment (n=423), as well as follow-up neuropsychological assessment (n=288), was included for validation analysis. We used Diffusion Tensor Imaging (DTI) based connectivity matrices for graph analysis. Lesion impact scores (combining affected voxel percentage and mean betweenness centrality) and rich club scores (quantifying affected voxels in rich club areas) were calculated using a normative brain atlas derived from DTI data from 23 stroke-free controls. Participants were categorized having no/mild or major vascular cognitive disorder (VCD) and group differences were examined.

Results: Among 60 participants (median age: 39.2 years (IQR 27.9-46.2) and 52% women), 20 were classified as having major VCD. The major VCD group exhibited larger lesion volumes (p=0.01), lower global efficiency (p=0.03) and local efficiency (p=0.05) compared to the no/mild VCD group at baseline and follow-up. However, after adjusting for network density in sensitivity analyses, these differences in global and local efficiency were no longer statistically significant. Univariable logistic regression analyses revealed that the Lesion Impact Score were a significant predictor for VCD at follow-up and the Rich Club Score predicted VCD at baseline and follow-up. However, in multivariable logistic regression, both the Lesion Impact Score and the Rich Club Score did not retain predictive significance. Following validation analysis, no predictive values were observed for any of these scores.

Conclusions: Our findings indicate a significant association between brain network measures and cognitive function in young stroke survivors, indicating a role of network disruption in post-stroke cognitive impairment. However, our study did not reveal specific associations with hub regions.

Introduction

Stroke in young adults, aged 18-50 years, constitutes approximately 10% of all stroke cases and shows an increasing incidence.[1,2] While these patients often show good motor recovery,[3,4] one-third of young stroke patients experience mild vascular cognitive impairment, and another third experiences major vascular cognitive impairment up to six months post-stroke.[5] Notably, during the chronic phase, post-stroke cognitive impairment (PSCI) is present in up to 40%, which may persists even decades after the initial event.[3,6,7] These young individuals require robust cognitive abilities to establish families, advance their careers, and maintain active social lives.[3] Consequently, PSCI may significantly impact their quality of life.[3,6,8] Several studies have examined the mechanisms underlying PSCI and found associations with stroke severity, stroke recurrence and lesion characteristics (e.g. volume and location).[6,9] However, these relationships do not entirely account for the variation in cognitive outcomes observed among stroke patients.

Increasing evidence suggests that the impact of the stroke lesion on a certain location of the brain network may explain the disproportional effects on PSCI, especially when the hub regions, highly connected to other brain regions, are damaged.[10,11] The brain's network can be characterized through graph theory, a mathematical framework reliant upon delineating edges (connections) between nodes (brain regions) predicated on structural associations.[12] Focal lesions can disrupt the intricate brain circuits, consequently impairing the brain's capacity to efficiently integrate neural processes.[13-15] Strategically located stroke lesions may diminish the overall network efficiency by disrupting the connectivity of regions linked to the lesion.[15] The hub regions play a pivotal role in the integration of information across different brain networks, which is an important prerequisite for optimal cognitive function.[16,17]

Accumulating evidence suggests that a less efficient brain network is linked with cognitive impairment across various neurological diseases[18-20] and has the capacity to predict cognitive performance longitudinally.[21,22] Furthermore, several studies have shown that stroke patients with a less efficient brain network have lower chance of cognitive recovery.[23-26] Moreover, various studies focused particularly on specific brain networks (i.e. default mode network), while others analyzed overall brain connectivity or measures involving ipsilesional, contralesional, or interhemispheric connections. Specifically, hub regions appear to play a critical role in cognitive recovery, examined through various approaches, including evaluating the effect of the degree of affected hub regions (lesion impact score) and assessing the influence of rich-club regions on cognitive function.[27-29] However, the majority of these studies have been conducted on stroke patients aged over 50, many of whom have concurrent comorbidities, including neurodegenerative diseases and prestroke brain lesions. Furthermore, limited information is available regarding the relation between brain network metrics and cognitive performance in younger stroke patients.

Given the association between reduced network efficiency, hub disruption and cognitive deficits, as well as poorer recovery in older stroke populations, we hypothesized that less efficient brain networks would be associated with worse cognitive performance in young stroke patients compared to controls and that the network alterations would predict a lower likelihood of cognitive recovery. Furthermore, greater lesion impact on hub regions would be related to poorer cognitive outcomes at both baseline and follow-up.

Therefore, we aimed 1) to investigate the relation of brain network measures, derived from structural brain networks, and cognitive performance in young adults with a first-ever ischemic stroke, in comparison to age-matched stroke-free controls, with a specific focus on hub regions, and 2) to investigate whether the impact of stroke lesions on hub regions is associated with cognitive outcomes and recovery after one year.

Methods

Participants

This study is a part of the *'Observational Dutch Young Symptomatic StrokE studY'* (ODYSSEY), a multicenter prospective cohort study examining risk factors and prognosis of stroke at young age.[30] This study focused on young stroke patients aged 18 to 49 years who had experienced a first-ever ischemic stroke with radiological evidence of cerebral ischemia. Exclusion criteria were a history of stroke, retinal infarction, and cerebral venous sinus thrombosis. Detailed information regarding data collection can be found in the study protocol.[30] From this study, we derived two distinct cohorts: the discovery cohort and the validation cohort. The discovery cohort comprised participants who were all enrolled at the RadboudUMC, Nijmegen, The Netherlands and underwent a diffusion tensor imaging (DTI) protocol at the baseline. Participants were included between December 2016 and July 2021. The validation cohort consisted of participants in who underwent a standard MRI protocol, without DTI, at baseline. Inclusion of participants in this cohort took place in all participating centers and occurred between May 2013 and July 2021. For the purposes of this study, only participants with supratentorial infarctions, a complete neuropsychological assessment, and available MRI data were considered for inclusion. The flowchart of the study population is presented in Figure 1. Controls were recruited among the participants' spouses, relatives or social environment. Inclusion criteria for controls were: age between 18 and 50 years old without a history of any transient ischemic attack (TIA) or stroke at the moment of inclusion.

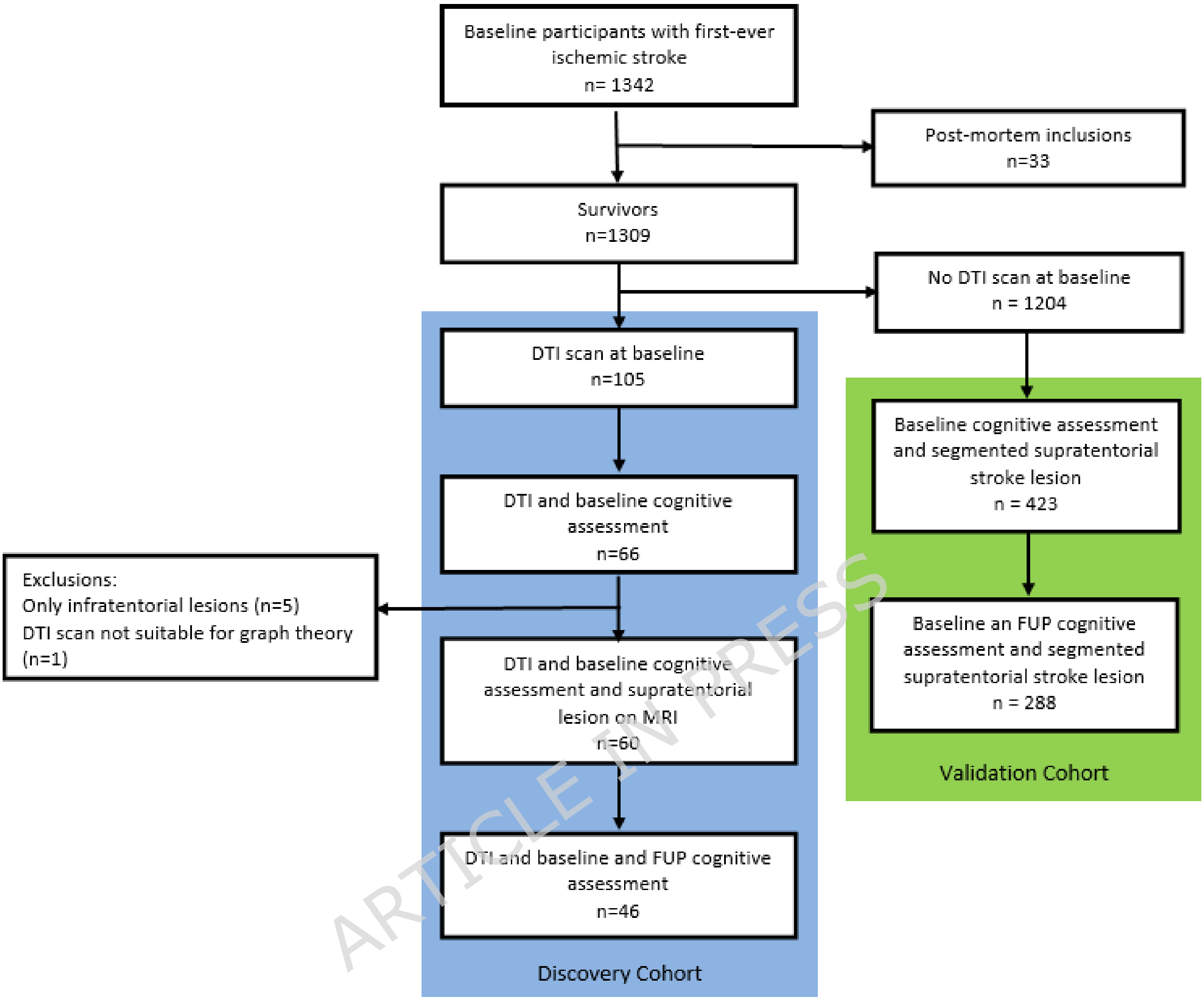

Figure 1 Flowchart of the study population

Standard protocol approvals, registrations, and patient consent

All participants gave written informed consent according to the Declaration of Helsinki. The Medical Review Ethics Committee region Oost-Nederland approved the study (NL41531.091.12).

Neuropsychological screening at baseline and follow-up.

Patients underwent comprehensive neuropsychological assessments at two time points: baseline (median 86 days (IQR: 50.8-139.5) post-stroke) and follow-up (median 536.0 days (IQR: 436.8-588.8) post-stroke). The evaluation covered seven key cognitive domains, employing various tests: (i) episodic memory, (ii) processing speed, (iii) visuoconstruction, (iv) executive functioning, (v) visual neglect, (vi) language, and (vii) attention/working memory. Global cognitive function was assessed using the Mini Mental State Examination. Age-, education, and sex-adjusted Z-scores were computed using normative data, except for the Star Cancellation test, where a cutoff value (<44) was employed to signify visuospatial neglect. Further details on data collection can be found elsewhere.[5]

Cognitive performance was defined according to the diagnostic criteria for vascular cognitive disorder (VCD) of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG). Mild VCD was defined of a composite Z-score between -1.5 and -2 0 below the age, education and sex-adjusted normative mean, and major VCD as a Z-score of <-2.0, in one or more cognitive domains.[31] Mild VCD is sometimes defined as a Z-score between -1.0 and -2.0 in one or more cognitive domains,[32] but this represents 13.6% of the normal population. By adjusting the cut-off criteria to -1.5 instead of -1.0 (representing 2.3% of the normal population) we attain a higher specificity and, consequently, a lower probability of false positive diagnoses.

Cognitive recovery was defined as a shift from mild VCD in the subacute phase to no VCD in the chronic phase or from major VCD in the subacute phase to mild or no VCD in the chronic phase.[33]

MRI data acquisition in the discovery cohort.

MRI scans were performed on a 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany). The imaging protocol included: (i) 3D T1 magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE 2300/2.3 ms; flip angle 8; voxel size 0.9×0.9×0.9mm), (ii) 3D fluid attenuated inversion recovery (FLAIR) (TR/TE 5000/394 ms; voxel size 1.0×1.0×1.0mm), (iii) diffusion-weighted imaging (TR/TE 8700/67 ms; voxel size 2×2×2mm; 3 unweighted scans, 100 diffusion-weighted scans, with non-co-linear orientation of the diffusion-weighting gradient, and b value 0,50(3×)/150(7×)/350(30×)/1000(60×) s/ mm^2).

MRI data acquisition in the validation cohort.

MRI scans were performed on clinical MR scanners available at the participating centers, with each center using its own clinical imaging protocol.

Lesion segmentation

All stroke lesions were semi-automatically segmented using ITK-SNAP. Lesions occurring within two weeks of the index event were segmented from DWI sequences (discovery cohort: n=26, validation cohort: n=367), while lesions observed beyond this two-week period were segmented based on FLAIR sequences (discovery cohort: n=33, validation cohort: n=54) or if not available on T1 sequences (discovery cohort: n=1, validation cohort: n=1) or T2 sequences (discovery cohort: n=0, validation cohort: n=1). Subsequently, thorough visual inspection of the segmented lesions was conducted, with manual adjustments being made when deemed necessary. For the discovery cohort, we firstly registered the FLAIR and DWI to the brain-extracted T1-weighted images using Functional Magnetic Resonance Imaging of the Brain Software Library (FSL). Next, we registered the T1-weighted images to Montreal Neurological Institute (MNI) 152 template using the Functional MRI of the Brain nonlinear registration tool (FLIRT) for linear registration followed by the Functional MRI of the brain linear image registration tool (FNIRT). For the validation cohort, in which clinical MRI scans were performed, we spatially normalized both the segmented lesions directly to Montreal Neurological Institute (MNI) 152 template employing Elastix,[34] a software application that offers intensity based medical image registration based on the Insight Segmentation and Registration Toolkit (ITK). Following normalization, we visually inspected the normalized images and excluded MRI scans that could not be normalized due to anatomical constraints. We calculated the lesion volumes using FSLstats.[35] Lesion overlay maps of each cohort can be found in the S*upplementary* in *Figure 1*.

Brain network and network measures

We established network nodes, represented as brain regions, using the Automated Anatomical Labelling (AAL) template,[36] which encompassed 90 regions (45 in each hemisphere, excluding the cerebellum). Registration of the AAL template to individual diffusion image spaces was achieved through the application of previously obtained transformation matrices. The diffusion data was pre-processed according to the following steps 1. removing noise and Gibbs artifacts, 2. correcting for head motion, 3. addressing eddy currents-induced distortion, 4. correcting susceptibility-induced distortion (using 'topup'), and 5. addressing intensity bias. We used MRtrix 3.0 software,[37] Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; v6.0.3),[35] Synb0-DISCO,[38] and Advanced Normalization Tools (ANTs, v 2.1.0)[39] for these preprocessing steps. In cases where a b0-image with reversed phase encoding was unavailable in our Diffusion Weighted Imaging (DWI) scans, we utilized 'topup' based on a synthesized b0 image generated from the T1 image using Synb0-DISCO.[38] Subsequently, calculation of diffusion tensor and mean fractional anisotropy (FA) was performed using FSL's DTIFit. Third, fiber assignment by continuous tracking (FACT) was used to generate whole-brain WM tracks for each participant, starting from voxels with FA > 0.2 and ending upon exiting the brain mask, encountering voxels with FA < 0.2, or when the turning angle exceeded 60°. Connectivity between two regions was established if the endpoints of the reconstructed streamlines intersected both regions. Fourth, the connection weight (e.g. connection strength) was determined as the mean FA of the reconstructed streamlines multiplied by the number of reconstructed streamlines linking the two regions.[40] Finally, we corrected for the differences in the AAL regions size[41], resulting in an undirected, weighted 90 × 90 matrix for each participant. Subsequently, we applied graph theory analysis to calculate various network measures using the Brain Connectivity Toolbox: [42] 1) network strength, 2) global efficiency, 3) local efficiency, 4) density,

5) clustering coefficient and 6) betweenness centrality. Network strength is a weighted version of degree, representing the sum of neighbouring link weights. Global efficiency is the average inverse of the shortest path length within the network. Local efficiency denotes the efficacy of communication between adjacent nodes. Density indicates the level of interconnectedness among nodes in the network. The clustering coefficient signifies the extent to which neighbouring nodes exhibit connections amongst themselves. Betweenness centrality is the frequency in which a node is involved in shortest paths.

Lesion Impact Score and Rich Club score

To identify the hub regions, we used DTI data of age- and sex-matched stroke-free controls (n=23).[43] After constructing the structural brain networks and applying graph theory analysis, the average betweenness centrality was computed for each brain region across all controls. Higher betweenness centrality values indicate that a substantial portion of the overall information flow within the network is likely to pass through that particular brain region[44] and can be classified as a brain network hub.[17] The Lesion Impact Score represents the potential impact of a lesion on the brain network.[33,45] We used the previously established nodes, as outlined above, to define the brain regions. The Lesion Impact Score for each participant was calculated by multiplying the percentage of node volume affected by the lesion with the average betweenness centrality of that node. For further analysis, the highest Lesion Impact Score per participant was used. For each participant, the highest score across all brain regions was used, based on the assumption that the region with the greatest impact would most strongly influence cognitive outcomes. This calculation included all regions, not only predefined hubs. This atlas-based approach ensured consistency across cohorts, including the validation sample without diffusion MRI, but does not account for patient-specific connectivity or hub variability and may underestimate lesion impact.

Additionally, we assessed the presence of affected voxels within 12 predefined rich club regions. The selection of these regions was informed by previous work,[16] in which rich club regions in healthy participants were studied and six bilateral regions were identified that were characterized by high interconnections. These regions include the superior parietal and frontal lobules, precuneus, thalamus, putamen, and hippocampus. The Rich Club score was defined as the cumulative number of affected voxels within these regions and was employed for subsequent analyses.

Statistical analysis

Baseline characteristics were reported as mean ± standard deviation (SD) for normally distributed data and median and interquartile ranges (IQR) for the skewed parameters. We analysed group differences by using χ^2-tests or Fishers' exact tests for categorical variables and two-sample t-tests or

Mann-Whitney U tests for the continuous variables, where appropriate. Furthermore, we performed an analysis of covariance (ANCOVA), adjusted for age and sex, to explore differences in global network measures between participants with no/mild VCD and with major VCD and participants with or without cognitive recovery. Additionally, all groups were compared to stroke-free controls. Post hoc pairwise group comparisons were performed using Tukey's honestly significant difference (HSD) test to account for multiple comparisons. Significant variables were additionally adjusted for lesion volume.

The Lesion Impact Score and Rich Club Score were skewed, thus necessitating a logarithmic transformation prior to analysis. Linear regression analysis was conducted to assess the relationship between global efficiency and both scores. Additionally, logistic regression was employed to investigate the relation between the Lesion Impact Score and Rich Club score among participants with no/mild VCD compared to those with major VCD, while were additionally adjusted for age, sex and lesion volume. We performed the same analysis for cognitive recovery. To validate these findings, we assessed the associations between the Lesion Impact Score and/or the Rich Club score and VCD in validation cohort (n=288) and/or cognitive recovery in a validation cohort (n=288), adjusted for age, sex and lesion volume.

Results

Baseline characteristics

In this study, a total of 60 participants and 23 controls were included in the discovery dataset. Baseline characteristics can be found in Table 1. For the validation cohort (n=423), baseline characteristics are detailed in the *supplementary Table 1*. Within the discovery cohort, we observed a significantly higher proportion of males in participants with no/mild VCD than those with major VCD (p=0.003), while no significant difference was found between educational level between males and females (p=0.64). Furthermore, we found a significantly higher proportion participants with a high National Institutes of Health Stroke Scale (NIHSS) at discharge in the major VCD group as compared to the no/mild VCD group (p=0.03) and modified Ranking Scale (mRS0 scores at baseline (p<0.001). Cognitive recovery from baseline to follow-up assessment was found in seven (15.2%) participants. No significant difference in cognitive recovery was present between the group with no or mild VCD and the group with major VCD (p=0.66). Participants with major VCD exhibited larger lesion volumes compared to the no/mild VCD group (p=0.02).

Table 1: Baseline Characteristics

	All participants (n=60)			Controls (n=23)	p-value[1]
	No/mild VCD n=40	Major VCD n=20	p-value[1]		
Mean age at index event, years (SD)	40.3 (31.6-46.3)	38.8 (25.-44.4)	0.67	34.5 (27.0-47.0)	0.85
Men, n (%)	25 (62.5%)	4 (20%)	**0.003**	12 (52.2%)	0.75
Median time to baseline assessment, days (IQR)	90.5 (49.8-138.0)	76.5 (53.3-142.0))	1.0	NA	NA
Mean time to follow-up assessment, days (SD)*	523.5 (105.8)	505.0 (97.0)	0.58	NA	NA
Mean interval baseline and follow-up, days (SD)*	406.3 (96.0)	394.2 (87.3)	0.68	NA	NA
Median education level (IQR)	5 (5-6)	5 (5-5)	0.07	6 (5-6.5)	0.09
Median NIHSS score at discharge (IQR) **	0 (0-1.25)	1 (0-3.5)	**0.03**	NA	NA
Median mRS at baseline (IQR)	1 (0-1)	2 (1-2)	**<0.001**	NA	NA
Median MMSE at baseline (IQR)	28.0 (27.0-29.0)	26.0 (24.8-27.0)	**0.001**	28.0 (27.0-29.0)	0.16
MINI symptoms of depression at baseline, n (%)***	3 (7.7%)	2 (10%)	1.0	1 (4.4%)	1.0
TOAST, n (%)			0.66	NA	NA
Atherothrombotic	0 (0)	1 (5)			
Likely atherothrombotic	2 (5)	1 (5)			
Small vessel disease	6 (15)	2 (10)			
Cardioembolic	13 (32.5)	4 (20)			
Rare causes	5 (12.5)	4 (20)			
Multiple causes	3 (7.5)	3 (15)			
Cryptogenic	11 (27.5)	5 (25)			
Cognitive recovery, N (%)*	4 (12.5)	3 (21.4)	0.66	NA	NA
Mean time to MRI, days (IQR)	28.5 (4.8-80)	12.5 (4.5-94.8)	0.90	NA	NA
Lesion location, N (%)			0.90	NA	NA
Right supratentorial	19 (47.5)	9 (45.0)			
Left supratentorial	14 (35.0)	7 (35.0)			
Bilateral supratentorial	2 (5)	1 (5.0)			
Unilateral supratentorial and infratentorial	2 (5)	0			
Bilateral supratentorial and infratentorial	3 (7.5)	3 (15.0)			
Lesion volume on MRI, mL (IQR)	0.91 (0.4-2.6)	3.99 (0.8-16.8)	**0.01**	NA	NA
Lesion Impact Score (IQR)	726.4 (167.5-3500.2)	3144.3 (411.4-9280.2)	**0.04**	NA	NA
Rich Club Score (IQR)	0 (0-67)	41 (1.75-165)	**0.03**		

Education category 5, i.e. middle school / secondary vocational training. IQR: interquartile range. NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; MMSE: Mini-Mental State Examination; MINI: Mini International Neuropsychiatric Interview; CIS-20R: Checklist Individual Strength; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

*46 completed second neuropsychological assessment, ** 2 missing, *** 1 missing, **** 14 missing
[1] χ²-tests or Fishers' exact tests for categorical variables and two-sample t-tests or Mann-Whitney U tests for the continuous variables.

Associations between structural network measures, and VCD and cognitive recovery

The group with major VCD demonstrated a lower global efficiency (p=0.026), lower local efficiency (p=0.047) and lower density (p=0.027) in comparison to the no/mild VCD group at baseline (Figure 2). The observed differences remained statistically significant at follow-up. Network strength in the major VCD group was significantly lower than in the no/mild VCD group at follow-up (p = 0.02) (Supplementary Figure 2). All these differences remained statistically significant after additionally adjusting for lesion volume. Controls displayed higher global efficiency (p<0.001), higher local efficiency (p<0.001), higher density (p<0.001), higher strength (p=0.001), and higher clustering coefficient (p=0.001) compared to the major VCD group, adjusted for age and sex (Figure 2). Of all network measures, only a lower betweenness centrality in participants who showed cognitive recovery was observed compared to those who did not experience cognitive recovery (p=0.024) (Supplementary Figure 3). In univariable logistic regression models, none of the baseline network measures, including betweenness centrality, were associated with cognitive recovery.

To rule of the effect of density, we performed sensitivity analyses. Due to high correlations between density and the network measures (r > 0.5-0.9), we first regressed out the effect of density from the network measures using linear regression. The sensitivity analyses showed no significant differences anymore between the groups for each of the network measures.

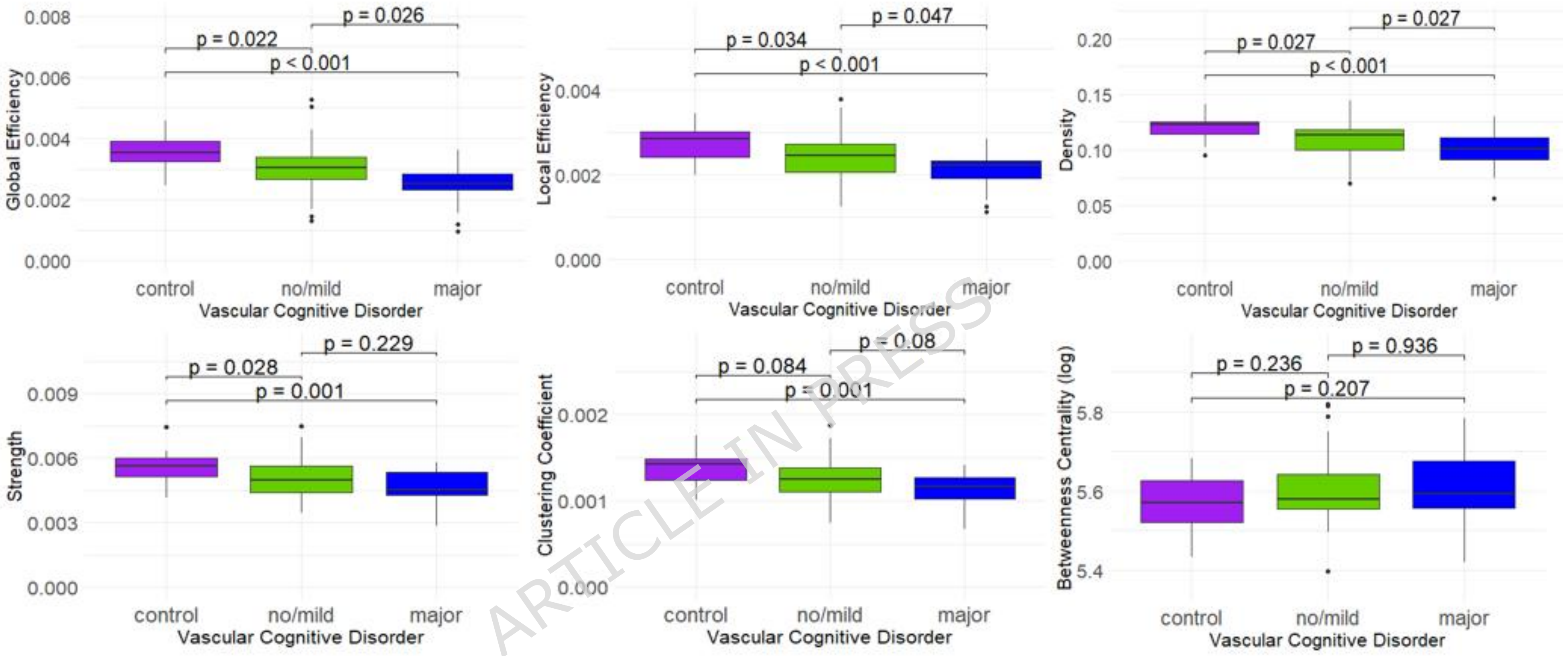

Figure 2. Boxplots of the structural network properties, showing the differences at baseline stratified by different groups (controls, n=23, participants with major VCD n=20, and participants with no/mild VCD, n=40), adjusted for age and sex. Correction for multiple comparisons was performed by the Tukey Test.

Associations between Lesion Impact Score and Rich Club score, and VCD and cognitive recovery

A higher Lesion Impact Score was related to a lower global effiency (standardized β -0.27, p=0.04) (*Supplementary Figure 4*). The Lesion Impact Score was higher in patients with major VCD at the baseline as compared to those with no/mild VCD (p=0.04) (table 1). Table 2 shows the univariate and multivariable logistic regression models. The univariate model showed that the Lesion Impact Score (OR: 1.72, 95% CI: 1.12-2.63, p=0.01) was a significant predictor for major VCD at follow-up. However, in the multivariable model, adjusted for age, sex and lesion volume, the Lesion Impact Score did not predict VCD at follow-up.

A higher Rich Club score was associated with a diminished global efficiency (standardized β -0.27, p=0.03) (*Supplementary Figure 5*). Patients with major VCD at baseline displayed a higher Rich Club score when compared to those with no/mild VCD (p=0.03) (table 1). The univariate model showed that the Rich Club Score was a significant predictor for major VCD at baseline (OR: 1.26, 95% CI: 1.00-1.59, p=0.049) and follow-up (OR: 1.33, 95% CI:1.01-1.74, p=0.04). In the multivariable model, adjusted for sex and age, the Rich Club Score was not associated with major VCD at baseline nor at follow-up.

Within the validation cohort (baseline n=423 and follow-up n=288), 34.8% of the participants experienced major VCD at baseline and 20.8% at follow-up (*Supplementary table 1*). Univariate logistic regression models showed that neither the Lesion Impact Score nor the Rich Club score were significant predictors for VCD at baseline or follow-up, or for cognitive recovery.

Table 2. Association between Lesion Impact Score and Rich Club score, and vascular cognitive disorder (VCD) at baseline and follow-up. At baseline, 59 participants were included and at follow-up 45 participants. In the multivariable model, age, sex and lesion volume were additionally adjusted for. OR: odds ratio, CI: confidence interval, NA: not applicable.

Discussion

In this study consisting of participant with an ischemic stroke at young age, we showed that participants with major VCD exhibited a structural network that was less integrated (indicated by lower global efficiency) and less segregated (indicated by lower local efficiency) compared to both participants with no/mild VCD and to stroke-free controls. Furthermore, we observed that Lesion

Logistic regression models predicting major VCD at baseline						
	Univariate model		Multivariable model Lesions Impact score		Multivariable model Rich Club Score	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Lesion Impact Score	1.24 (0.96-1.59)	0.10	1.08 (0.8-1.44)	0.63	NA	NA
Rich Club Score	**1.26 (1-1.59)**	**0.049**	NA	NA	1.18 (0.87-1.59)	0.30
Age at event	0.99 (0.94-1.04)	0.66	0.97 (0.92-1.04)	0.42	0.97 (0.91-1.04)	0.37
Sex	**6.4 (1.79-22.82)**	**0.004**	**7.76 (1.86-32.44)**	**0.002**	**8.22 (1.93-35.02)**	**0.001**
Lesion Volume	1.06 (1-1.13)	0.06	**1.05 (0.98,1.13)**	**0.04**	1.04 (0.98,1.11)	0.07
Logistic regression models: predicting major VCD at follow-up						
	Univariate model		Multivariable model Lesions Impact score		Multivariable model Rich Club Score	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Lesion Impact Score	**1.72 (1.12-2.63)**	**0.01**	1.45 (0.84-2.5)	0.13	NA	NA
Rich Club Score	**1.33 (1.01-1.74)**	**0.04**	NA	NA	1.07 (0.72-1.58)	0.75
Age at event	1.00 (0.94-1.06)	0.87	0.96 (0.88-1.05)	0.37	0.97 (0.89-1.05)	0.46
Sex	**5.81 (1.34-25.17)**	**0.02**	**8.8 (1.4-55.36)**	**0.01**	**7.46 (1.26-44.13)**	**0.01**
Lesion Volume	**1.09 (1.01-1.18)**	**0.03**	1.04 (0.96-1.12)	0.17	**1.08 (0.97-1.21)**	**0.02**
Logistic regression models: predicting Cognitive Recovery						
	Univariate model		Multivariable model Lesions Impact score		Multivariable model Rich Club Score	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Lesion Impact Score	0.96 (0.72-1.28)	0.79	1.16 (0.74,1.81)	0.50	NA	NA
Rich Club Score	0.9 (0.64-1.27)	0.55	NA	NA	1.04 (0.67-1.63)	0.85
Age at event	1.00 (0.92-1.08)	0.98	1.01 (0.93-1.10)	0.81	1.01 (0.93-1.09)	0.89
Sex	0.68 (0.13-3.43)	0.64	0.78 (0.15,4.16)	0.78	0.76 (0.15-4.01)	0.75
Lesion Volume	0.94 (0.81-1.08)	0.38	0.9 (0.74,1.11)	0.15	0.93 (0.78-1.11)	0.24

Impact Score and Rich Club Score were no significant predictors for major VCD during follow-up at one-year after stroke. These findings were consistent in a larger subset of participants.

In the current study, we found that young stroke patients have a less efficient brain network compared to stroke-free controls, which is consistent with a previous study in a young stroke population.[46] More importantly, we showed that the degree of network disruption was associated with cognitive performance. Patients with major VCD had more network damage (e.g. less efficient brain networks characterized by lower global and local efficiency) than patients with no/mild VCD, independently of lesion volume. These findings add to the previous literature on older stroke populations showing that focal brain lesions can results in less integrated structural networks explaining at least in part the cognitive performance.[20,23,26,47]

Moreover, we investigated the impact of hub regions on cognitive outcome using two metrics: the lesion impact score and the rich-club score. The latter metric is derived from literature indicating the correlation between rich-club organization and cognitive function.[27-29] In our study, hub regions were defined as nodes with high betweenness centrality, indicating their central role in facilitating information flow within the network. In contrast, rich club regions refers to a subset of highly interconnected hubs that exhibit stronger internal connections compared to random networks, supporting efficient global communication. Both the Lesion Impact Score and the Rich Club score are methods for assessing the impact of lesions on these hubs. The advantage of using these scores is that it can be derived using clinical imaging scanners (CT or MRI) that may be used for early identification of cognitive impairment. While a previous study suggested the utility of the lesion impact score as a biomarker for predicting cognitive outcomes in stroke patients, our study did not find a significant association between the lesion impact score and cognitive performance in either the discovery or validation cohort.[45] Discrepancies between studies, including variations in VCD definition and the inclusion of larger infarct volumes in previous studies, may have influenced the significance of hub region-affected lesions. These variations underscore the complexity of assessing the relationship between lesion impact on hub regions and cognitive outcomes after stroke. Another possible explanation is that cognitive deficits in young ischemic stroke patients arise from strategic lesion network localizations, rather than specifically affecting the hubs.[48] Together, our findings could not confirm that lesion impact scores and rich club scores as a biomarker for predicting cognitive outcome may be useful in our study cohort.

Prior studies observed a link between network properties and cognitive recovery.[23,25,49-51] Notably, these studies used a variety of approaches, while some focused solely on specific networks such as the default mode network whereas others targeted particular patient subgroups, such as those with right hemispheric stroke. In our cohort, comprising a heterogeneous group of stroke patients, none of the baseline network metrics exhibited significance as predictors for cognitive recovery. In contrast to the study by Aben et al.,[33] which exclusively enrolled patients with lesions in predefined hub regions characterized by larger lesions, we did not found evidence for an association between the impact of stroke lesion on hub regions and cognitive recovery in our validation dataset consisting of a larger sample size. One possibility is that we included smaller lesions that may not necessarily affect the hub regions, thereby potentially resulting in underestimation of the impact of the Lesion Impact Score. This suggests that these imaging-based scores are not able to predict cognitive recovery in our study population, implying that there are other factors related to brain plasticity at play that determine cognitive recovery in young individuals who have experienced a stroke. Additionally, their study included a higher percentage of participants with VCD (80%) at baseline compared to ours (58%), indicating that a significant proportion of our participants may not undergo cognitive recovery. This discrepancy is partly due to our stricter definition of VCD, ensuring greater specificity. Together, our findings did not confirm that lesion impact scores and rich club scores as a biomarker for predicting cognitive outcome may be useful in our study cohort.

Interestingly, we found a higher proportion of female patients in the major VCD group. As educational level did not differ between sexes, we could not explain this finding by variation in cognitive reserve. However, our sample size is relatively small and therefore this result should be interpreted with caution. The underlying mechanisms remain unclear and may relate to sex-specific vascular risk factors. Future research is needed to confirm this observation in larger young stroke cohorts

There are several notable strengths worth highlighting in our study. Firstly, the prospective study design employed in this investigation facilitated robust data collection, resulting in reliable information. Although, the design of our study precludes making causal inferences, these findings provide valuable insights into enhancing our comprehension of the underlying pathophysiological processes. Secondly, patients with confirmed diffusion restriction were selectively included, ensuring the absence of misdiagnosed individuals within our cohort. Thirdly, our study conducted comprehensive neuropsychological testing both at baseline and at follow-up, enabling a thorough examination of cognitive performance and thus enhancing the robustness of our findings. Fourthly, in this study, Lesion Impact and Rich Club scores were derived by overlaying patient lesions onto a normative connectome from 23 healthy controls. This atlas-based approach does not account for patient-specific connectivity or individual hub variability. In young stroke patients, where plasticity and network reorganization may play a role, this method may underestimate hub disruption. Therefore, our validation findings should be interpreted with caution, as they may partly reflect methodological limitations rather than absence of hub involvement. Furthermore, it is important to note that, because diffusion MRI data were not available in this sample, we could not replicate the full network analyses performed in the discovery cohort. .

There are several limitations that should be acknowledged in our study. The inclusion of the patients may potentially introduce a form of selection bias, given that our sample predominantly comprises patients from a tertiary care setting. Additionally, it is worth noting that the stroke severity, as measured by NIHSS and MRS, was relatively mild within our cohort. This observation might be attributed to the absence of follow-up assessments for all participants in the ODYSSEY study, potentially due to the inability of the most severely impaired individuals to attend follow-up visits. As a result, our findings may not represent the full range of stroke cases typically encountered in clinical practice. Secondly, it is plausible that betweenness centrality may not be the most suitable metric for delineating these hub regions in a normative atlas. Alternative network measures for hub regions have been proposed in the literature, such as degree, betweenness, and closeness centrality, or ranking nodes based on all the previously mentioned network properties, [17] warranting further investigation to determine which measure is the most sensitive for this specific stroke population. We addressed this through the use of the Rich Club score, which also exhibited no significant association with VCD in a larger cohort. Fourthly, it is worth noting that our study encompassed lesions in both the acute phase (within the first few days) and the subacute phase (within the first 6 months) of stroke onset. This temporal inclusion range can introduce variability into the results, as it is well-established that lesions evolve over time, with some diffusion lesions extending beyond the eventual stroke lesion observable on the T2 FLAIR sequence. However, subgroup analysis with narrower time windows was not feasible due to small sample sizes, which would limit statistical power. Additionally, recovery of the altered network measures may altogether take place in the first months after stroke.[23,26] Fifthly, a methodological consideration is the relatively low network density observed, which is inherent to the deterministic tractography approach used but consistent with previous connectomics studies.[52] The lower density in the major VCD group likely reflects disease-related structural changes rather than methodological bias. To account for the potential influence of density, we performed additional analyses in which all network metrics were corrected for density using linear regression. These analyses showed that the network measures were strongly correlated with density, and that the originally observed significant differences between no/mild VCD and major VCD did not persist after correction. This suggests that part of these initially observed differences may have been driven by differences in density rather than reflecting actual differences in network organization. Moreover, correcting for density reduced variability in the network measures, which may have lowered statistical power. Future work should further investigate alternative normalization approaches and examine how different thresholding or binarization methods influence graph-theoretical measures in clinical datasets. Sixthly, in this study, as in several other brain network studies, we excluded patients with infratentorial lesions because the constraints of our selected analytical methods prevented us from conducting tractography and network analysis on infratentorial brain regions. Consequently, we were unable to provide information regarding the direct impact of infratentorial stroke lesions. Nonetheless, it is noteworthy that the importance of infratentorial lesions in relation to cognitive performance is gaining greater recognition and is emerging as more substantial than previously understood.[53-55] Seventhly, rich-club regions were defined according to van den Heuvel and Sporns.[16] Since the original hubs were identified using the Desikan–Killiany atlas, we mapped these regions to their corresponding AAL regions (e.g., precuneus, superior frontal, superior parietal, thalamus, and putamen). Although atlas definitions differ slightly, these hub regions are robust across parcellations, and such mapping is commonly applied in rich-club analyses.[16,17,56,57]Eightly, our research exclusively relied on baseline imaging data. While this provided valuable insights into the initial impact of stroke lesions on cognitive function, the utilization of longitudinal imaging data may offer a more comprehensive understanding of the structural changes and their potential relationships with cognitive outcomes over time. Another limitation to consider is the possibility that cognitive recovery defined as changes in the VCD classification might serve as a relatively coarse measure that does not detecting subtle cognitive recovery. It is conceivable that a more sensitive measure could provide a more refined assessment, however, our method reveals clinically relevant discoveries. Furthermore, the sample size of the discovery cohort provides limited power for multivariable logistic regression, particularly given the number of events per predictor. Although we used a sparse model with only five covariates, non-significant results may reflect type II error. Nevertheless, for young stroke, this sample represents a relatively large and well-characterized cohort, reflecting the rarity of this condition. Lastly, we lacked information on pre-stroke cognitive functioning. Nonetheless, given the relatively young age of our participants and the limited influence of other comorbidities, such as pre-existing vascular of degenerative disorder in this age group, pre-stroke cognitive functioning will have minimal effects on post-stroke cognitive functioning.

Conclusions

Our study demonstrated a less efficient brain network in young stroke survivors with worse cognitive performance in both the subacute and chronic phases following stroke. However, specific associations with the impact of stroke lesions on hub regions were not found. It is imperative for future research to prioritize longitudinal imaging data, expand the participant pool, and explore the development of predictive models for cognitive outcomes and cognitive recovery in young ischemic stroke patients. These efforts may better enable us to identify at-risk individuals for cognitive disorder following stroke and facilitate targeted interventions to support their cognitive recovery.

Data Availability

The data are available from the corresponding author, upon reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the author(s) utilized ChatGPT to enhance the language. Following the use of this tool, the author(s) reviewed and edited the content as necessary and assume full responsibility for the content of the published article.

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Potential Conflicts of Interest

Nothing to report.

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ODYSSEY study – Investigators.

Esther M. Boot[1], MD, Mijntje M. I. Schellekens[1], MD,PhD Jamie I. Verhoeven[1], MD,PhD, Merel S. Ekker[1], MD, PhD, E. Verburgt[1], MD, M. Immens[1], MD, Nina A. Hilkens[1], MD, PhD, Mayte E. van Alebeek[6], MD, PhD, Paul J.A.M. Brouwers[7], MD, PhD, Renate M. Arntz[7], MD, PhD, Gert W. van Dijk[8], MD, PhD, Rob A.R. Gons[9], MD, PhD, Inge W.M. van Uden[9], MD, PhD, Tom den Heijer[10], MD, PhD, Julia H. van Tuijl[11], MD, Karlijn F. de Laat[12], MD, PhD, Anouk G. W. van Norden[13], MD, PhD, Sarah E. Vermeer[14], MD, PhD, Marian S.G. van Zagten[15], MD, PhD, Robert J. van Oostenbrugge[16], MD, PhD, Marieke J.H. Wermer[17], MD, PhD, Paul J. Nederkoorn[18], PhD, MD, Frank G. van Rooij[19], MD, PhD, Ido R. van den Wijngaard[20], MD, PhD, Paul L.M. de Kort[11], MD, PhD, Frank-Erik de Leeuw[1], MD, PhD, Anil M. Tuladhar[1], MD, PhD

1. Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands

6. Department of Neurology, Gelre Hospitals, Apeldoorn, the Netherlands

7. Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands

8. Department of Neurology, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands

9. Department of Neurology, Catharina Hospital, Eindhoven, the Netherlands

10. Department of Neurology, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands

11. Department of Neurology, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands

12. Department of Neurology, Haga Hospital, Den Haag, Netherlands

13. Department of Neurology, Amphia Hospital, Breda, the Netherlands

14. Department of Neurology, Rijnstate Hospital, Arnhem, the Netherlands

15. Department of Neurology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

16. Department of Neurology, School for Mental Health and Neuroscience (MHeNs), Maastricht University Medical Centre, Maastricht, the Netherlands

17. Department of Neurology, University Medical Centre Groningen, Groningen, the Netherlands

18. Department of Neurology, Amsterdam University Medical Centre, location AMC, Amsterdam, the Netherlands

19. Department of Neurology, Frisius Medical Centre, Leeuwarden, the Netherlands

20. Department of Neurology, Haaglanden Medical Center, Den Haag, The Netherlands