Normal appearing white matter integrity is a predictor of outcome after ischemic stroke

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Abstract

Objective. To evaluate the relationship between normal appearing white matter (NAWM) integrity and post-ischemic stroke recovery in four main domains including, cognition, mood, gait, and dependency.

Methods. A prospective study was conducted, including patients diagnosed for an ischemic supratentorial stroke on a 3T-brain MRI performed 24-72 hours after symptoms onset. Clinical assessment one-year after stroke included a Montreal Cognitive Assessment, an Isaacs set test (IST), a Zazzo's cancellation task, a Hospital anxiety and depression scale, a 10-m walking test, a modified Rankin scale (mRS). DTI parameters in the NAWM were computed using FMRIB's Diffusion Toolbox. The relationships between mean NAWM DTI parameters and the clinical scores were assessed using linear and ordinal regression analyses, including the volumes of white matter hyperintensities (WMH), grey matter and ischemic stroke as radiological covariates.

Results. 207 subjects were included (66 ± 13 y.o, 67% men, median NIHSS 3, interquartile range 2-6). In the models including only radiological variables, NAWM fractional anisotropy (FA) was associated with the mRS and the cognitive scores. After adjusting for demographic confounders, NAWM FA remained a significant predictor of mRS ($\beta = -0.24$, $p = 0.04$). Additional path analysis showed that NAWM FA had a direct effect on mRS ($\beta = -0.241$, $p = 0.001$), and a less important indirect effect mediating WMH burden. Similar results were found with mean diffusivity, axial and radial diffusivity. In further subgroup analyses, a relationship between NAWM integrity in widespread white matter tracts, mRS and IST was found in right-hemispheric strokes.

Conclusion. NAWM DTI parameters measured early after an ischemic stroke are independent predictors of functional outcome and may be additional markers to include in studies evaluating post-stroke recovery.

Introduction

Stroke is a major source of cognitive impairment and functional disability. The severity of white matter hyperintensities (WMH) and brain atrophy are the main brain imaging markers reported to be associated with post-stroke outcome (1–6). Beside WMH, it is well known that normal appearing white matter (NAWM) can be affected by microstructural changes that might contribute to impair the normal brain functioning. However, the effect of NAWM has been sparsely investigated in post-stroke recovery studies (7–9), while NAWM might be a relevant area of cerebral plasticity. Indeed, the relationship between NAWM integrity, cognition and motor function has been largely reported during ageing (10–12). It has been described that altered NAWM integrity was associated with physical and leisure activities, together with better efficiency in information processing (10,11), and gait performances (13). The alteration of NAWM integrity can be investigated using diffusion tensor imaging (DTI), by the detection of a decrease fractional anisotropy (FA) and increase mean diffusivity (MD;14). Maillard et *al*. (15) reported that lower FA in NAWM was an independent marker for increased risk of conversion from normal white matter to WMH, suggesting a continuous process of white matter degradation including demyelination and axonal loss due to chronic ischemic vascular processes. In stroke patients, a relationship between diffusivity parameters of NAWM and 90-days functional recovery, along with cognitive recovery after one-year has been suggested (7–9). Similarly, in subjects with cerebral small vessel disease, a loss of NAWM integrity has been associated with lower gait performances (16). All this suggests a specific role of NAWM integrity in neuropsychological, gait and functional processes after stroke, but data remain scarce in the field of stroke.

The aim of the present study was to evaluate the predictive value of NAWM integrity, assessed on a brain MRI performed 24-72 hours after an ischemic stroke, on the main domains of post-stroke

recovery, ie. cognition, mood, gait and dependency, regardless of the other radiological markers of vascular and degenerative processes, along with the new ischemic lesion.

Materials and methods

Study population and ethics statement

Study population covered participants from the "Brain Before Stroke" study, a biomedical research protocol promoted by the Bordeaux University Hospital and aiming at evaluating the influence of the cerebral parenchyma surrounding the new ischemic lesion on outcome. All patients or their legal representative provided a written informed consent. The study was approved by the regional French Human Protection Committee (CPP 2012/19 2012-A00190-43). Patients were prospectively and consecutively recruited from June 2012 to February 2015 at the Bordeaux University Hospital. Inclusion criteria were an age > 18 years old, an ischemic supra-tentorial stroke diagnosed within 24-72 hours after symptoms onset (baseline), a National Institute of Health Stroke Score (NIHSS) comprised between 1 and 25, the absence of pre-stroke dementia or pre-stroke disability due to a neurological disease resulting in a modified Rankin scale (mRS) $\geq$ 1. Exclusion criteria are listed in supplemental materials.

Clinical assessment

Pre-stroke cognitive state was evaluated with the Informant Questionnaire in Cognitive Decline in the Elderly (IQCODE;17) submitted to a relative of the patient. Clinical assessment was achieved at one-year post-stroke during a medical visit. A Montreal Cognitive Assessment (MoCA) was performed to evaluate global cognition on 30 points (18). An Isaacs set test (IST) was performed for

the evaluation of executive functions (19), and a Zazzo's cancellation task (ZCT) for the evaluation of processing speed and attention (20). The time to perform the task (in seconds) and the number of errors were recorded. Mood was evaluated using the Hospital Anxiety and Depression (HAD) scale. Gait was evaluated by walking speed, using the 10-meter walk test (10-MWT;21). Contrary to MoCA and IST, where higher scores meant better performances, higher scores in ZCT, HAD and 10-MWT meant lower performances. Functional outcome at one-year was assessed by the mRS.

Imaging acquisition and processing

A 3 Tesla brain MRI was performed at baseline (General Electrics Medical Systems Discovery MR750W, Milwaukee, WI). The sequences acquired are detailed in supplemental materials, as imaging pre and post-processing. Briefly, a mask of ischemic stroke lesions and WMH was obtained for each subject using the 3D Slicer 4.3.1 software (Figure 1). Maps of grey matter (GM), white matter and cerebrospinal fluid were generated based on a voxel-by-voxel intensity analysis (SPM12, MATLAB R2012b). The sum of these three tissue classes provided the total intracranial volume (TIV). In the following analyses, GM, ischemic stroke lesion and WMH volumes were expressed as the ratio of TIV. Subsequently, the masks of ischemic stroke lesions and WMH were applied on the maps of white matter using the FMRIB Software Library (FSL) "maths" function, to get a mask of NAWM, free of ischemic stroke lesions and WMH. FA, MD, axial and radial diffusivity (AD and RD) maps were computed using FMRIB's Diffusion Toolbox from FSL (FSL 5.0.2, http://www.fmrib.ox.ac.uk/fsl). The NAWM masks were co-registered to the diffusion maps to extract mean DTI parameters values for each subject. NAWM microstructural alteration was defined by low FA values, and high MD, AD, RD values (22).

Statistical analysis

Regression analyses

To test the relationship between NAWM DTI parameters and the clinical scores, we performed either linear regressions (MoCA, IST, ZCT completion time and number of errors, HAD, 10-MWT) or ordinal logistic regressions (mRS). Each clinical score (ie. MoCA, IST, ZCT completion time and number of errors, HAD, 10-MWT and mRS) was inputted as dependent variable, while radiological markers, and demographic confounders (age, gender, educational level) were inputted as independent variables. Univariate analyses were first conducted. All variables having a p-value < 0.1 in the univariate analyses were included in multivariate analyses that were conducted in two-steps. First, we built a radiological model to evaluate the impact of mean NAWM DTI parameters against the other radiological markers (ie. WMH, GM and ischemic stroke volumes, and lacunar stroke defined according to the STRIVE recommendations;23). Second, these models were adjusted for demographic confounders in a clinicoradiological model. As the ischemic stroke lesion volume and the NIHSS at baseline were significantly correlated (supplemental Table I), we did not include the baseline NIHSS in the analyses, to avoid collinearity with the ischemic stroke lesion volume. Results were expressed as standardized regression coefficients β and SE, and were corrected for multiple comparisons using the Holm-Bonferroni method. As DTI parameters were highly correlated with each other (supplemental Table I), we included each NAWM DTI parameters in separate models.

Path analyses

Path analyses were performed to evaluate whether mean NAWM DTI parameters had a direct or indirect effect on outcome, passing through the other radiological variables. NAWM DTI parameters were included as predictors, and GM, WMH and ischemic stroke lesion volumes as mediators. A

direct path between NAWM DTI parameters and the clinical score measured the direct effect of the NAWM DTI parameter. Three indirect pathways passing through either GM, WMH or ischemic stroke volumes measured the indirect effect of the NAWM DTI parameter on the outcome variable. The "lavaan" package available on R software was used to perform the path analyses, and maximum likelihood estimators were produced. The adequacy of models fit was determined by the following parameters: low chi-squared (X^2) relative to degrees of freedom with p-value for X^2 goodness of fit statistic > 0.05, comparative fit index ≥ 0.95, root mean square error of approximation ≤ 0.06, and standardized root mean square residual ≤ 0.08 (24).

All statistical analyses were performed using the R software 3.5.1. Statistical significance was set at $p < 0.05$.

Tract-Based Spatial Statistics (TBSS) analyses

In order to identify the relevant white matter tracts implied in the association between NAWM microstructure and the outcome measures, the DTI maps were analyzed according to a conventional TBSS procedure (25) using linear regressions. In these TBSS models, each one-year clinical score was inputted as dependent variables, adjusting for age, gender, educational level, ischemic stroke volume, WMH volume, and GM volume. To overcome the potential influence of ischemic stroke location, the analyses were performed separately in the subgroups of right and left-hemispheric ischemic strokes, and left-handed patients were removed from the groups. Thus, we were able to analyze NAWM in lesional and contralesional hemispheres. Statistical threshold was set at $p < 0.05$ corrected for multiple comparisons (Threshold Free Cluster enhancement and 5000 permutations). The Johns Hopkins University white matter atlas implemented in FSL was used to labelize the significant white matter tracts.

Results

Subjects

Two hundred and seven patients were included in the analyses (Figure 2, mean age 66 ± SD 13, 67% men). Median NIHSS at baseline was 3 (IQR 2-6) and was correlated with the ischemic stroke volume ($r = 0.52$, $p < .001$). The other clinical scores are detailed in Table 1. The mRS was correlated with MoCA ($r = -0.25$, $p = 0.003$), HAD ($r = 0.26$, $p = 0.003$), and 10-MWT ($r = 0.31$, $p < .001$; supplemental Table II). Right and left-hemispheric stroke subgroups were comparable for demographic, clinical, and radiological data (supplemental Table III), including comparable NIHSS at baseline and infarct volume.

Relationship between NAWM DTI parameters and clinical scores at one-year

In univariate analyses, NAWM FA was associated with one-year MoCA ($\beta = 0.23$, $p = 0.001$), IST ($\beta = 0.27$, $p < .001$), ZCT completion time ($\beta = -0.34$, $p < .001$), ZCT number of errors ($\beta = -0.25$, $p < .001$), 10-MWT ($\beta = -0.31$, $p < .001$), and mRS ($\beta = -0.29$, $p < .001$). NAWM FA was not associated with HAD scores at one-year post-stroke (supplemental Table IV).

In multivariate analyses, the models including only radiological markers showed an association between NAWM FA and cognitive scores (Table 2), along with mRS ($\beta = -0.24$, $p = 0.005$). After controlling for age, gender and educational level, NAWM FA remained independently associated only with the mRS measured one-year after stroke ($\beta = -0.24$, $p = 0.04$). The models including the other DTI parameters showed a similar independent association between mRS and NAWM MD, AD and RD, regardless of the other radiological markers and demographic confounders (supplemental

Tables V, VI and VII). In our stroke sample, WMH and ischemic stroke volumes were also associated with functional outcome at one year (Table 2).

Path analyses

Path analyses were completed using WMH, GM and ischemic stroke volumes as mediators. The model including NAWM FA showed good fitting: $X^2 = 7.4$, degrees of freedom = 6, p = 0.286, comparative fit index = 0.993, root mean square error of approximation = 0.034, and standardized root mean square residual = 0.041. High NAWM FA value was associated with a good recovery directly (β = -0.241, p = 0.001), and indirectly with the mediation of WMH volume (Figure 3). To determine which pathways was more important in the prediction, we compared the β coefficient of the two pathways after computed the β coefficient of the indirect pathway as followed (-0.43 for pathway between NAWM FA and WMH volume x 0.181 for pathway between WMH volume and mRS). β coefficient of the indirect pathway was of -0.078, whereas the β coefficient of the direct pathway was of -0.241, highlighting the relevance of the direct pathway.

The model including NAWM MD ($X^2 = 11.2$, degrees of freedom = 6, p = 0.081, comparative fit index = 0.974, root mean square error of approximation = 0.06, and standardized root mean square residual = 0.048) showed similar results. NAWM MD had a direct effect on mRS (β = 0.247, p < .001), and an indirect effect mediated by WMH volume. The β coefficient of the direct pathway was more important than the β coefficient of the indirect one (β = 0.354 x 0.194 = 0.069). The models including NAWM AD and RD showed also similar results (supplemental Figure I).

TBSS analyses

In right-hemispheric strokes, high mRS (ie., poor prognosis) was associated with low FA, high MD, AD and RD, in widespread regions of white matter (supplemental Table VIII), regardless of ischemic stroke, WMH and GM volumes, age, gender and educational level (Figure 4). Lower performances in IST were associated with lower FA in the corpus callosum, and higher MD and RD in widespread white matter regions. No additional association was found with MoCA, ZCT, 10-MWT and HAD.

In the left-hemispheric strokes subgroup, no significant association was found.

Discussion

The main results of the present study are that *i)* NAWM integrity is an independent predictor of dependency state one year after an ischemic stroke; *ii)* NAWM integrity is an additional radiological marker associated with cognitive outcome; *iii)* the influence of NAWM integrity in the domain of executive functions is dependent of stroke location, being only observed in right-hemispheric strokes.

Similarly to these results, Etherton et *al.* (8) demonstrated that microstructural alterations of NAWM in the contralateral hemisphere of stroke was associated with a worse functional outcome at three months, whereas WMH volume was not, and Kliper et *al.* (7) demonstrated a relevant role of NAWM integrity on global cognitive outcome regardless of the ischemic lesion's volume. In the present study, we used a mean value of NAWM in both lesional and contralesional hemispheres. However, we can assume that the mean FA values extracted from the NAWM is related to the number and location of the voxels included in the NAWM masks, which are tightly related to the location and volume of the infarct and WMH. To overcome this issue, we added the NAWM volume in our models, which did not change the results, suggesting a predominant role played by the severity of the microstructural disorganization. Considering the association between NAWM integrity and mRS, we found an involvement of white matter tracts in widespread regions. The mRS is a global evaluation of

functional recovery, encompassing motor and cognitive functions. Thus, it was not surprising to identify white matter tracts reported to be involve in motor and cognitive outcome after stroke (26,27), as corpus callosum, corticospinal tract, superior longitudinal fasciculus, thalamic radiations, cingulum, or inferior fronto-occipital fasciculus.

Furthermore, TBSS analyses were based on the hemispheric side of the acute ischemic lesion, and these results were observed only for right-hemispheric lesions. Similarly, additional subgroup path analyses also identified a sustained effect of NAWM integrity on mRS only in right-hemispheric strokes (data not shown). On top of the infarct size, stroke location has been repeatedly identified as a major determinant of stroke outcome, with left-hemispheric lesions being associated with a worse prognosis (28,29). The absence of influence of NAWM integrity on functional and cognitive outcome following left-hemispheric strokes might reflect the influence of language disturbances, even when they do not seem to be clinically relevant. Indeed, language disturbances might impair the sensitivity of non-specific cognitive evaluations in the identification of cognitive disability, and worsen functional outcome. Overall, this result highlights the relevance of NAWM integrity in the recovery of some cognitive functions, especially executive domains, when strategic locations are spared.

Regarding mood scores, neither NAWM DTI parameters, nor other MRI markers were associated with HAD scores, suggesting that rather than the brain lesions, acute stress and difficulties to deal with the new handicap might be the main determinants of post-stroke mood disorders.

NAWM integrity and post-stroke outcome, the hypothesis of an "invisible" cerebrovascular disease

The role of NAWM integrity in outcome has been reported in large elderly populations (30–32). Vernooij et *al.* (32) reported an association between altered diffusivity parameters in NAWM and lower performances in processing speed, executive functions, global cognition, and motor speed. It

has been suggested that DTI parameters changes in NAWM were the early stage of a stepwise white matter disease, including degenerative and vascular processes (15,33). Supporting this hypothesis, the path analyses showed not only a direct effect of NAWM integrity on mRS, but also an indirect effect passing through the volume of WMH, that was associated with NAWM integrity. Therefore, the association between DTI parameters measured shortly after the ischemic stroke in NAWM might be related to the presence of an underlying and invisible cerebrovascular disease on conventional MRI sequences, reflecting the first step toward macrostructural white matter abnormalities.

Furthermore, although NAWM might be the location of early degenerative and vascular processes, the proposal of lower GM volume because of altered NAWM integrity is not clearly established. Our path analyses showed a direct effect of NAWM integrity on GM volume, suggesting a relationship between altered integrity in NAWM and cortical atrophy, but longitudinal studies are required to confirm a causal effect. Also, we found that NAWM FA was associated with mRS without being mediated by GM volume. This observation has already been raised in patients with subcortical and/or neurodegenerative cognitive impairment (4,34). Indeed, Kim et *al.* demonstrated an association between decreased FA in specific regions and gait performances (4) or executive functions (34), that was not mediated by brain atrophy, suggesting that white matter microstructural integrity explained a substantial part of clinical performances on top of brain atrophy.

Moreover, contrary to mRS, we observed that the association between NAWM DTI parameters in the whole population and cognitive scores did not remained after controlling for demographic factors. Aside from the potential influence of stroke location previously discussed, this might also be due to the role of age and educational level, which are known factors associated with white matter integrity in healthy adults (35). Thus, our results suggest that cognitive reserve and age-related microstructural white matter alterations could constitute a factor of vulnerability, impairing the cognitive recovery.

The hypothesis of altered NAWM integrity as a consequence of the acute ischemic stroke

Beside the hypothesis of an underlying "invisible" white matter pathology, it has been suggested that DTI parameters could be altered near and remote the ischemic lesion through the diaschisis (36). The disruption of white matter microstructural integrity remote from stroke has consequences on cognitive and motor performances (26,36,37). In line with this hypothesis, we observed similar results in both lesional and contralesional hemispheres for mRS and IST, suggesting an altered microstructural integrity near and remote from the lesion. Hence, the new post-stroke NAWM changes might inhibit compensatory mechanisms, impeding the reactivation of deafferented regions and brain plasticity, which contribute to a poorer outcome. However, to confirm the hypothesis of an association between altered NAWM integrity triggered by stroke and recovery, a longitudinal evaluation of NAWM and recovery scores is needed.

Limits

Several limitations of this study should be considered prior to the generalization of the results. First, although inclusion criteria allowed to include patients with various degree of stroke severity, our population study covered subjects with mild to moderate stroke due to the inability of more severe patients to perform the clinical assessment or MRI protocol. Second, our cognitive assessment was relatively short compared to existing neuropsychological battery of tests. However, we chose simple tasks which could be replicated in routine, and the addition of gait and mood assessment in the same time did not allow us to extend the time of the neuropsychological evaluation.

Conclusion

NAWM integrity is part of the early neuroimaging markers that could help to predict post-stroke functional outcome and could be added as potential target to follow in therapeutic trials aimed at developing neuroprotective agents. NAWM integrity is also a radiological marker of post-stroke cognitive recovery, but with a non-significant weight facing age, educational level, or stroke location. Further longitudinal studies are needed, to follow the changes occurring in NAWM after stroke, and the evolution of WMH.

Disclosure

None.

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Table 1. Characteristics of all participants

Demographic data and cardiovascular risk factors	**N = 207**
Age, mean ± SD	66 ± 13
Men, n (%)	138 (67)
Right-handed, n (%)	189 (91)
Educational level, n/184 (%)	
None	3 (1)
Primary	42 (23)
Junior high school	59 (32)
Secondary high school/baccalaureate	31 (17)
Superior	49 (27)
Cardiovascular risk factors, n (%)	
High blood pressure	100 (48)
Dyslipidemia	85 (41)
Current smoking	52 (25)
Diabetes mellitus	33 (16)
Atrial fibrillation	23 (11)
Clinical assessment	
IQCODE, median (IQR)	3 (3–3)
NIHSS at baseline, median (IQR)	3 (2-6)
MoCA at one-year, median (IQR)	25 (23-28)
IST at one-year, median (IQR)	32 (27–36)
ZCT at one-year: completion time (seconds), median (IQR)	79 (61–104)
ZCT at one-year: number of errors, median (IQR)	1 (0–4)
HAD at one-year, median (IQR)	9 (6–13)
10-MWT at one-year (seconds), median (IQR)	8.87 (7.75–10.56)
mRS at one-year: 0 – 1 – 2, n (%)	60 (29) – 65 (31) – 45 (22)
mRS at one-year: 3 – 4 – 5, n (%)	25 (12) – 11 (5) – 1 (< 1)

Radiological data	
Stroke hemispheric side, n (%)	
Left-side	98 (47)
Right-side	97 (47)
Left and right-sides	12 (6)
Lacunar strokes, n (%)	55 (27)
Stroke volume (mL), median (IQR)	8.5 (1.6-25.9)
GM volume (mL), median (IQR)	635 (581-688)
WMH volume (mL), median (IQR)	3.7 (1.4–10.1)
NAWM FA, median (IQR)	0.35 (0.33–0.37)
NAWM MD, median.10^{-3} mm^2/sec (IQR)	0.91 (0.87–0.98)
NAWM AD, median.10^{-3} mm^2/sec (IQR)	1.24 (1.2-1.31)
NAWM RD, median.10^{-3} mm^2/sec (IQR)	0.74 (0.7–0.81)

IQR is interquartile range.

Table 2. Predictors of clinical scores measured at one-year (multiple linear regressions)

	MoCA		IST		ZCT: time		ZCT: errors		10-MWT		mRS	
	β (SE)	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**
Radiological model												
NAWM FA	0.14 (0.11)	0.2	0.18 (0.16)	0.04	-0.26 (0.97)	0.002	-0.2 (0.12)	0.03	-0.18 (0.14)	0.1	-0.26 (0.05)	0.004
WMH volume	-0.22 (0.34)	0.01	-0.21 (0.49)	0.02	0.17 (3.08)	0.045	0.09 (0.37)	0.4	0.27 (0.48)	0.005	0.17 (0.15)	0.2
GM volume	0.11 (0.1)	0.2	0.06 (0.14)	0.7	-0.12 (0.91)	0.1	-0.1 (0.11)	0.4	-0.06 (0.12)	0.9	0.01 (0.04)	0.6
Stroke volume	-0.32 (0.12)	< .001	-0.23 (0.2)	0.005	0.18 (1.11)	0.03	0.22 (0.13)	0.01	0.06 (0.22)	0.9	0.37 (0.06)	< .001
Lacunar stroke	0.05 (0.74)	0.5	0.03 (1.06)	0.7	-0.01 (6.61)	0.8	-0.07 (0.8)	0.4	0.08 (0.87)	0.9	0.1 (0.31)	0.2
Clinicoradiological model												
NAWM FA	-0.05 (0.11)	1	-0.01 (0.16)	1	-0.09 (1.06)	0.5	-0.02 (0.13)	0.9	-0.1 (0.15)	1	-0.24 (0.05)	0.04
WMH volume	-0.29 (0.31)	< .001	-0.26 (0.46)	0.005	0.1 (3.04)	0.5	0.11 (0.38)	0.6	0.28 (0.53)	0.01	0.18 (0.16)	0.2
GM volume	0.02 (0.1)	1	-0.05 (0.15)	1	-0.02 (1.01)	0.8	-0.07 (0.13)	0.8	-0.05 (0.14)	1	-0.05 (0.05)	1
Stroke volume	-0.37 (0.1)	< .001	-0.2 (0.18)	0.02	0.13 (1.01)	0.3	0.22 (0.13)	0.01	-0.005 (0.22)	1	0.35 (0.06)	< .001
Age	-0.15 (0.03)	0.3	-0.19 (0.04)	0.1	0.3 (0.26)	0.003	0.1 (0.03)	0.8	0.08 (0.04)	1	-0.05 (0.01)	1
Gender: male	-0.05 (0.63)	1	-0.04 (0.95)	1	-0.13 (6.16)	0.3	-0.16 (0.76)	0.2	-0.07 (0.88)	1	-0.01 (0.31)	1
Educational level	0.21 (0.25)	0.01	0.19 (0.38)	0.04	-0.12 (2.47)	0.3	-0.17 (0.31)	0.1	-0.06 (0.35)	1	0.01 (0.12)	1

The results were corrected for multiple comparisons (Holm-Bonferroni method).

Figure 1. Example of tissue segmentation

Masks of NAWM (cyan) were obtained by subtracting the masks of ischemic stroke (yellow) and WMH (red) from the masks of white matter. Masks of grey matter (blue) were obtained using a voxel-based morphometry approach, segmenting ischemic stroke in an additional tissue class. The four different masks are represented on a FLAIR sequence.

Figure 2. Flow chart

Figure 3. Path analysis for the effect of NAWM FA and MD on one-year mRS

Numbers represent standardized β coefficient values. Continuous line arrows represent the statistically significant paths ($p < 0.05$), and dotted arrows represent non-significant paths. Age and gender were entered as covariates.

Figure 4. White matter tracts associated with mRS and IST measured at one-year in the subgroup of right-hemispheric stroke patients

TBSS analyses in the subgroup of right-side hemispheric strokes showed a negative association between mRS and FA, and a positive association between mRS, MD, AD and RD. A positive association was found between IST and FA in the forceps minor (corpus callosum), and a negative association was found between IST, MD and RD. The results were adjusted for ischemic stroke volume, WMH volume, GM volume, age, male gender and educational level ($p < 0.05$ corrected for multiple comparisons TFCE and 5000 permutations).