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Normal-Appearing White Matter Deteriorates over the Year After an Ischemic Stroke and Is Associated with Global Cognition

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Abstract

Normal-appearing white matter (NAWM) is a hub of plasticity, but data relating to its influence on post-ischemic stroke (IS) outcome remain scarce. The aim of this study was to evaluate the relationship between NAWM integrity and cognitive outcome after an IS. A longitudinal study was conducted including supra-tentorial IS patients. A 3-Tesla brain MRI was performed at baseline and 1 year, allowing the analyses of mean fractional anisotropy (FA) and mean diffusivity (MD) in NAWM masks, along with the volume of white matter hyperintensities (WMH) and IS. A Montreal Cognitive Assessment (MoCA), an Isaacs set test, and a Zazzo's cancellation task were performed at baseline, 3 months and 1 year. Mixed models were built, followed by Tract-based Spatial Statistics (TBSS) analyses. Ninety-five patients were included in the analyses (38% women, median age 69 ± 20). FA significantly decreased, and MD significantly increased between baseline and 1 year, while cognitive scores improved. Patients who decreased their NAWM FA more over the year had a slower cognitive improvement on MoCA ($\beta = -0.11$, $p = 0.05$). The TBSS analyses showed that patients who presented the highest decrease of FA in various tracts of white matter less improved their MoCA performances, regardless of WMH and IS volumes, demographic confounders, and clinical severity. NAWM integrity deteriorates over the year after an IS, and is associated with a cognitive recovery slowdown. The diffusion changes recorded here in patients starting with an early preserved white matter structure could have long term impact on cognition.

Keywords Stroke · Diffusion tensor imaging · Prognosis · Longitudinal

Abbreviations

DTI Diffusion tensor imaging
DWI Diffusion weighted imaging

ET Echo time
FA Fractional anisotropy
FLAIR Fluid attenuated inversion recovery
FOV Field of view
FSL FMRIB software library
GM Grey matter
HAD Hospital Anxiety and Depression Scale
IQCODE Informant Questionnaire in Cognitive Decline in the Elderly
IS Ischemic stroke
IST Isaacs set test
MD Mean diffusivity
MoCA Montreal Cognitive Assessment
NAWM Normal-appearing white matter
NIHSS National Institute of Health Stroke Score
Ns Not significant
RT Repetition time
TBSS Tract-based spatial statistics
TFCE Threshold free cluster enhancement

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WMH White matter hyperintensities
ZCT Zazzo's cancellation task

Introduction

Stroke is one of the leading causes of disability-adjusted life-years [1], suggesting the need in identification of modifiable prognostic markers to develop prevention policy. Aside from the stroke lesion, white matter hyperintensities (WMH) is the main radiological biomarkers associated with post-stroke outcome [2–4]. More recently, normal-appearing white matter (NAWM) has emerged as a research topic, and has been reported as a new radiological predictive factor of functional, cognitive, and motor recovery after an ischemic stroke (IS: [5–9]. However, data remains scarce and prolonged longitudinal follow-up is needed to investigate the impact of NAWM integrity on long-term outcome, and to include it as a new target for interventional studies. The analysis of NAWM integrity is of interest as it might be a surrogate of white matter plasticity that still occurs in adulthood [10], and can be modified by factors as cardiovascular risk factors, psychosocial factors, and health behaviors [11, 12], before the occurrence of macrostructural white matter abnormalities. In the present study, we aimed at evaluating the evolution of NAWM integrity over the year following an IS using diffusion tensor imaging (DTI), and its relationship with outcome using longitudinal data.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

A prospective consecutive study was conducted at the Bordeaux University Hospital between 2012 and 2015. The study was approved by the regional French Human Protection Committee (CPP 2012/19 2012-A00190-43). The inclusion criteria were men and women > 18 years old with a clinical diagnosis of minor to severe supra-tentorial IS (National Institute of Health Stroke Score [NIHSS] 1–25). The exclusion criteria were a severe neurological deficit, including aphasia, hindering the clinical and radiological assessments; MRI contraindication; history of psychiatric disorder matching to axis 1 DSM-IV criteria; chronic disease compromising the patient's follow-up throughout the course of the study; agitation; coma; pregnancy or breast-feeding women; and patients under protection of justice.

A written informed consent was obtained from all included patients or their legal representative.

Demographic data were recorded, along with the following cardiovascular risk factors: history of high blood pressure, dyslipidemia, diabetes mellitus, atrial fibrillation, and current smoking.

Clinical Assessment

The clinical assessment was made by a stroke neurologist blinded to radiological data. The severity of IS was assessed by a NIHSS at baseline (i.e., between 24 and 72 h following symptoms onset), 3 months and 1 year. The functional outcome was measured by the mRS at 3 months and 1 year. The Informant Questionnaire in Cognitive Decline in the Elderly (IQCODE) was performed to estimate the presence of pre-stroke cognitive decline [13]. The cognitive evaluation included at the three time-points, a Montreal Cognitive Assessment (MoCA) for the evaluation of global cognition [14], an Isaacs set test (IST) of verbal fluency [15], and a Zazzo's cancellation task (ZCT) for the evaluation of attentional functions and processing speed by the number of errors and the completion time [16]. While higher MoCA and IST scores meant better performances, higher ZCT scores meant worse performances. The baseline mood status was tested using the Hospital Anxiety and Depression (HAD) scale.

Imaging Protocol

Patients were scanned twice at baseline and 1 year later on the same 3 Tesla brain MRI (General Electrics Medical Systems Discovery MR750W) using the following protocol: diffusion weighted imaging (DWI, echo time [ET]/repetition time [RT] 82/9000, field of view [FOV] $24 \times 24 \text{ cm}^2$, matrix 128×128 , slice thickness 4 mm, gap between slices 0.5 mm), DTI (ET/RT 105/15000 ms, FOV $24 \times 21.6 \text{ cm}^2$, matrix 160×160 , 16 diffusion directions, $b = 1000 \text{ s/mm}^2$), 3D T1-wi (196 slices, ET/RT/inversion time 3.3/8.6/450, 12° flip angle, FOV $24 \times 24 \text{ cm}^2$, matrix 256×256 , slice thickness 1 mm, voxel reconstruction with zero padding), and 3D Fluid Attenuated Inversion Recovery (FLAIR, 224 slices, ET/RT/inversion time 142.8/9000/2358, FOV $24 \times 24 \text{ cm}^2$, matrix 288×224 , slice thickness 1.8 mm).

IS, WMH, and Grey Matter (GM) Masks

Imaging processing was achieved by a trained stroke neurologist blinded to clinical data. A mask of IS at baseline and WMH at baseline and 1 year was constructed based on a semi-automatic segmentation (pre-detection tool and manual corrections) on the DWI and FLAIR sequences, respectively, using 3D Slicer 4.3.1 software (www.slicer.org). The volumes of IS and WMH were deducted from this process. A whole brain segmentation was also performed

using a voxel-based morphometry approach with Statistical Parametric Mapping 12 software, MATLAB R2012b [17], based on T1-wi and FLAIR MRI. The resulted volumes of GM, white matter, and cerebrospinal fluid were summed to obtain the total intracranial volume (TIV). The transformation matrices produced by the normalization process during the voxel-based morphometry were applied on the masks of IS to create a new tissue probability map for each patient, allowing a second segmentation with IS in an additional tissue class to obtain GM and white matter maps free of IS lesion. IS and WMH volumes were expressed as ratio of TIV in all analyses.

DTI Processing and NAWM Masks

The DTI images were first corrected for motions and eddy current distortions, and non-brain voxels were removed using the FMRIB Software Library (FSL 5.0.2, <http://www.fmrib.ox.ac.uk/fsl>)—Brain Extraction Tool. Individual maps of Fractional Anisotropy (FA) and Mean Diffusivity (MD) were computed using the FMRIB's Diffusion Toolbox from FSL. Thereafter, the masks of NAWM at baseline and 1 year were constructed. First, white matter mask and WMH mask were coregistered to the *b0* of the DTI sequences, using the Advanced Normalization Tools software. NAWM mask was then obtained by the subtraction of WMH mask from the white matter mask using the FSL « maths » function. The mean values of FA and MD were extracted from the NAWM using the « fslmeants » function, and their evolution between baseline and 1 year was analyzed using mixed models, as described below, along with the calculation of a NAWM FA delta defined by mean FA at 1 year—mean FA at baseline.

Subsequently, nonlinear transformations were applied on DTI images, and each image was registered on the FMRIB58-FA standard template running the Tract-based Spatial Statistics (TBSS) pipeline [18]. Mean FA was thinned (threshold value 0.2) to create mean FA skeleton. The individual maps of FA and MD were projected onto this mean skeleton using the maximum values perpendicular to the skeleton.

Alteration of NAWM integrity was defined by low FA values, and high MD values [19].

Statistical Analyses

The evolution of clinical data was depicted at the three time-points, while radiological data were presented at baseline and 1 year. The associations between demographic, vascular risk factors, radiological data, and DTI measurements were assessed using linear regressions for cross-sectional analyses at baseline and 1 year, and generalized linear mixed models for longitudinal analyses. Subsequently, as there was no significant evolution of mRS over the follow-up, we included

only cognitive scores as dependant variables in the following analyses (i.e., MoCA, IST, ZCT completion time, and number of errors). Longitudinal analyses were conducted in separate models for FA and MD to avoid collinearity. Univariate (supplemental Table 1) and multivariate analyses were performed, including the first and only radiological data (IS volume at baseline, and white matter features at baseline and 1 year: NAWM FA or MD, and WMH volume), followed by models adjusted for demographic (age, gender, educational level), and clinical (NIHSS at the three time-points) variables. Generalized linear mixed models (« lmerTest » package, R software) were used for the analyses. A variance inflation factor > 2.5 was used to detect multicollinearity [20]. The mixed models were validated by visual inspection of residuals and random slopes on histograms which approximated a normal distribution. All analyses were performed with the R software 4.0.2 and statistical significance was set at 0.05. All multivariate analyses were adjusted using Bonferroni correction.

Then, the TBSS procedure [18] was carried on to detect the white matter tracts involved in the preceding results. The General Linear Model setup available on FSL was used to design the longitudinal models (i.e., comparison of baseline and 1 year DTI images based on two-group difference models). The explanatory variables inputted in separated design matrices were MoCA, IST, ZCT completion time, and number of errors at baseline and 1 year. Additional analyses were conducted to evaluate the relevance of baseline cognitive functions. The sample was divided into two groups based on their MoCA scores at baseline: a group with impaired MoCA defined by a MoCA score ≤ 25 [21], and a group without impaired MoCA (≥ 26). Two-way mixed effect ANOVA analyses were conducted to assess the difference of DTI measurement evolution over the year of follow-up between the two groups of patients. The models were corrected for age, gender, educational level, NIHSS, IS volume at baseline, and WMH. Statistical significance was set at 0.05 corrected for multiple comparisons (Threshold Free Cluster enhancement [TFCE] and 5000 permutations). The Johns Hopkins University white matter atlas implemented in FSL was used to labelize the significant white matter tracts.

Results

Subjects

Ninety-five patients had good quality DTI sequences at both time-point baseline and 1 year, and were included in the analyses (median age 69, IQR 20, 38% female). See flow chart in supplemental Fig. 1. The characteristics of the sample are described in Table 1 and 2. Sixty-seven patients (70.5%) had a mRS ≤ 2 at 1 year, and no significant change

Table 1 Characteristics of the population

	<i>N</i> =95
Demographic factors	
Age, median (IQR)	69 (20)
Women, <i>n</i> (%)	36 (38)
Right-handed, <i>n</i> (%)	88 (93)
Educational level, <i>n</i> (%)	<i>N</i> =83
None	2 (2)
Primary	19 (23)
Junior high school	24 (29)
Secondary high school/baccalaureate	13 (16)
Superior	25 (30)
Cardiovascular risk factors, <i>n</i> (%)	
High blood pressure	53 (56)
Dyslipidemia	38 (40)
Current smoking	20 (21)
Diabetes mellitus	15 (16)
Atrial fibrillation	15 (16)
mRS at 1 year, <i>n</i> (%)	
0–1	23 (24.2)–29 (30.5)
2–3	15 (15.8)–20 (21.1)
4–5	7 (7.4)–1 (1.1)
Radiological data	
Stroke hemispheric side, <i>n</i> (%)	
Right-side	54 (57)
Left-side	38 (40)
Right and left-sides	3 (3)
IS volume at baseline (mL), median (IQR)	11.5 (25)

was observed between 3 months and 1 year. Conversely, a significant improvement of NIHSS ($p < 0.001$), MoCA ($p < 0.001$), and IST ($p < 0.001$) was observed over the year of follow-up. The volume of WMH did not significantly change between baseline and 1 year, whereas mean FA in the NAWM decreased, and mean MD in the NAWM increased (Fig. 1 and Table 2).

In univariate analyses, the cardiovascular risk factors high blood pressure and current smoking were associated with mean NAWM DTI measurements at baseline, 1 year, or with the longitudinal evolution of DTI measurements (supplemental Table II). But these associations did not remain after correction for demographic confounders and radiological data, age being the main variable significantly associated with DTI measurements ($\beta = 0.47$, $p = < 0.001$ and $\beta = 0.2$, $p = 0.02$ for the associations between age and NAWM MD at 1 year and NAWM MD increment over the year, respectively). IS volume at baseline was associated with changes in NAWM FA over time ($\beta = 0.24$, $p < 0.001$), meaning that larger IS was associated with more NAWM FA decrement, while WMH volume was associated with NAWM FA at 1 year ($\beta = -0.42$, $p = 0.02$).

Longitudinal Analyses of Changes in DTI Measurements and Changes in Cognitive Functions

In the first models including radiological data, we observed a negative association between the coefficient slopes of NAWM FA and MoCA ($\beta = -0.11$, $p = 0.05$, Table 3). In other words, as we observed a decrease of NAWM FA and an improvement of MoCA (Fig. 1), the results indicated that the more NAWM FA decreased, the less MoCA improved. When separating the population by tertiles of NAWM FA delta between baseline and 1 year (i.e., tertile 1 = highest decrease of FA and tertile 3 = lowest decrease of FA), patients in the first tertile had a higher IS volume at baseline (median IS ratio of TIV 0.012, IQR 0.02 versus 0.006, IQR 0.01 in the first and third tertiles, respectively), but also higher NAWM FA values at baseline than patients in the third tertile (Figs. 2, and 3), while at 1 year, the values got closer between these two groups. These higher NAWM FA values might be explained by their younger age (median age 65.5, IQR 21.3 versus 73, IQR 20.3 in the first and third tertiles, respectively).

Similarly, we observed a positive association between the coefficient slopes of NAWM MD and ZCT completion time

Table 2 Evolution of clinical scores and radiological data over the year of follow-up (median, IQR)

Time	Baseline	3 months	1 year	<i>p</i>
Rankin	-	1 (2)	1 (2)	ns
MoCA	23 (6)	25.5 (6)	25 (5)	<0.001
Isaacs set test	31 (10)	31 (11)	32 (9)	<0.001
ZCT: completion time	89 (64)	77.5 (58.5)	88 (49.5)	ns
ZCT: number of errors	2 (7)	1 (3)	1 (3.5)	ns
NIHSS	4 (6)	1 (3.5)	1 (3)	<0.001
HAD	9 (9)	-	-	
WMH volume, ratio of TIV (0.10^{-2} mL)	0.35 (0.8)	-	0.43 (0.87)	ns
NAWM FA	0.35 (0.04)	-	0.26 (0.04)	<0.001
NAWM MD (0.10^{-3} mm ² /s)	0.92 (0.11)	-	1.12 (0.16)	<0.001

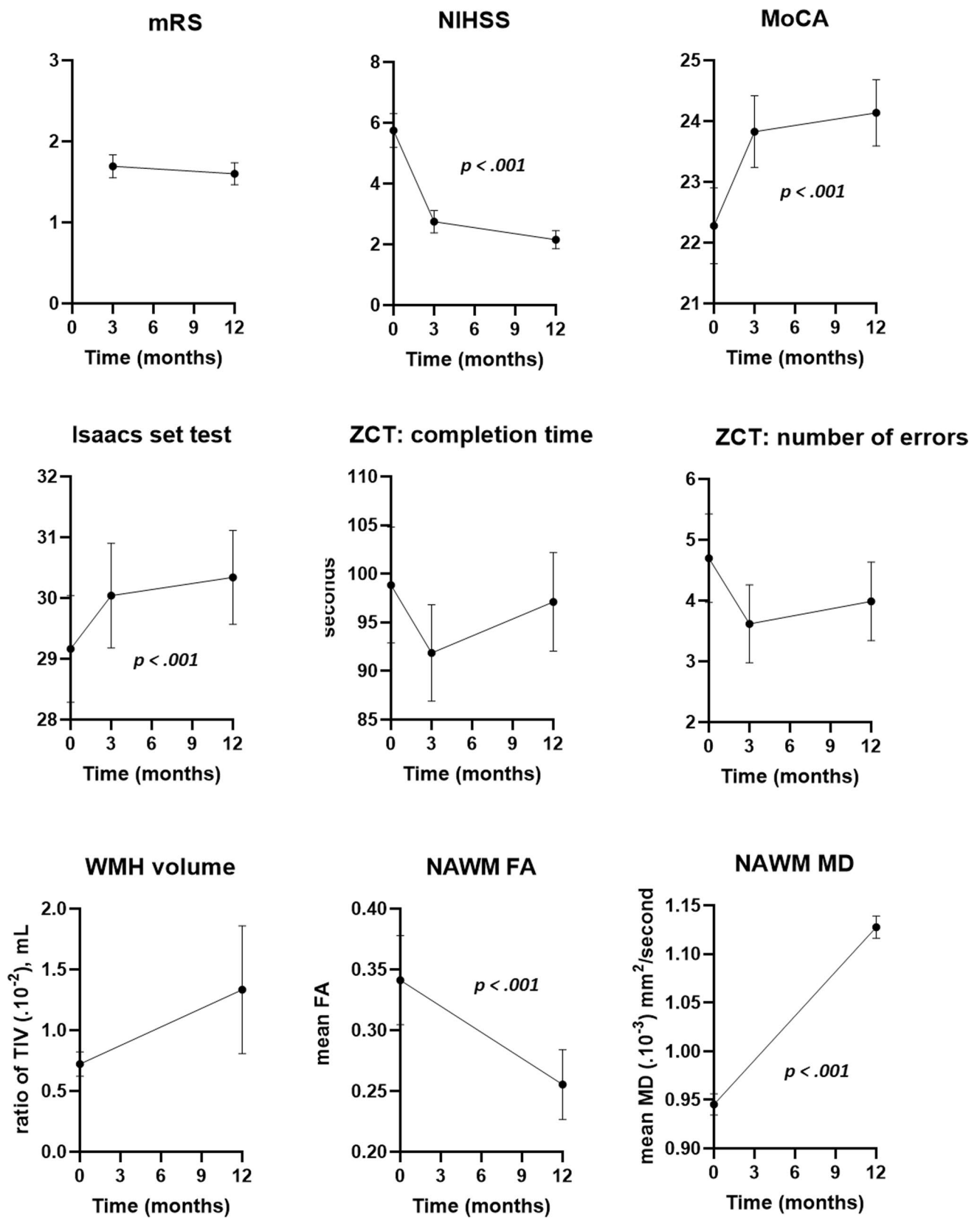


Fig.1 Evolution of functional, clinical scores, and radiological data over the year post-stroke. The scores are presented as means and standard errors of means. The improvement of NIHSS, MoCA,

and Isaacs set test, and the decrease of NAWM FA and increase of NAWM MD over the year after stroke were significant ($p < 0.001$)

Table 3 Analyses of the associations between changes in NAWM FA and changes in cognitive scores

Predictors	MoCA		IST		ZCT: completion time		ZCT: number of errors	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Radiological models								
IS volume at baseline	-0.42 (0.08)	<0.001	-0.35 (0.09)	<0.001	0.19 (0.07)	0.04	0.16 (0.08)	ns
WMH volume	-0.21 (0.07)	0.01	-0.21 (0.08)	0.02	0.17 (0.07)	ns	0.24 (0.08)	0.005
NAWM FA	-0.11 (0.04)	0.05	-0.07 (0.04)	ns	-0.11 (0.06)	ns	-0.02 (0.05)	ns
Clinico-radiological models								
Age	-0.1 (0.08)	ns	-0.19 (0.09)	ns	0.32 (0.08)	0.001	0.13 (0.08)	ns
Female gender	0.07 (0.07)	ns	0.04 (0.08)	ns	-0.03 (0.07)	ns	0.1 (0.07)	ns
Educational level	0.12 (0.07)	ns	0.11 (0.09)	ns	-0.09 (0.07)	ns	-0.24 (0.08)	0.02
NIHSS	-0.38 (0.06)	<0.001	-0.25 (0.06)	<0.001	0.24 (0.07)	0.003	0.31 (0.07)	<0.001
IS volume at baseline	-0.31 (0.07)	<0.001	-0.25 (0.09)	0.04	-0.0007 (0.08)	ns	-0.04 (0.08)	ns
WMH volume	-0.16 (0.07)	ns	-0.17 (0.08)	ns	0.04 (0.07)	ns	0.13 (0.08)	ns
NAWM FA	-0.07 (0.05)	ns	-0.03 (0.04)	ns	-0.15 (0.06)	ns	-0.04 (0.05)	ns

IS and WMH volumes were expressed as ratio of TIV in all analyses. Statistical significance was adjusted using Bonferroni correction

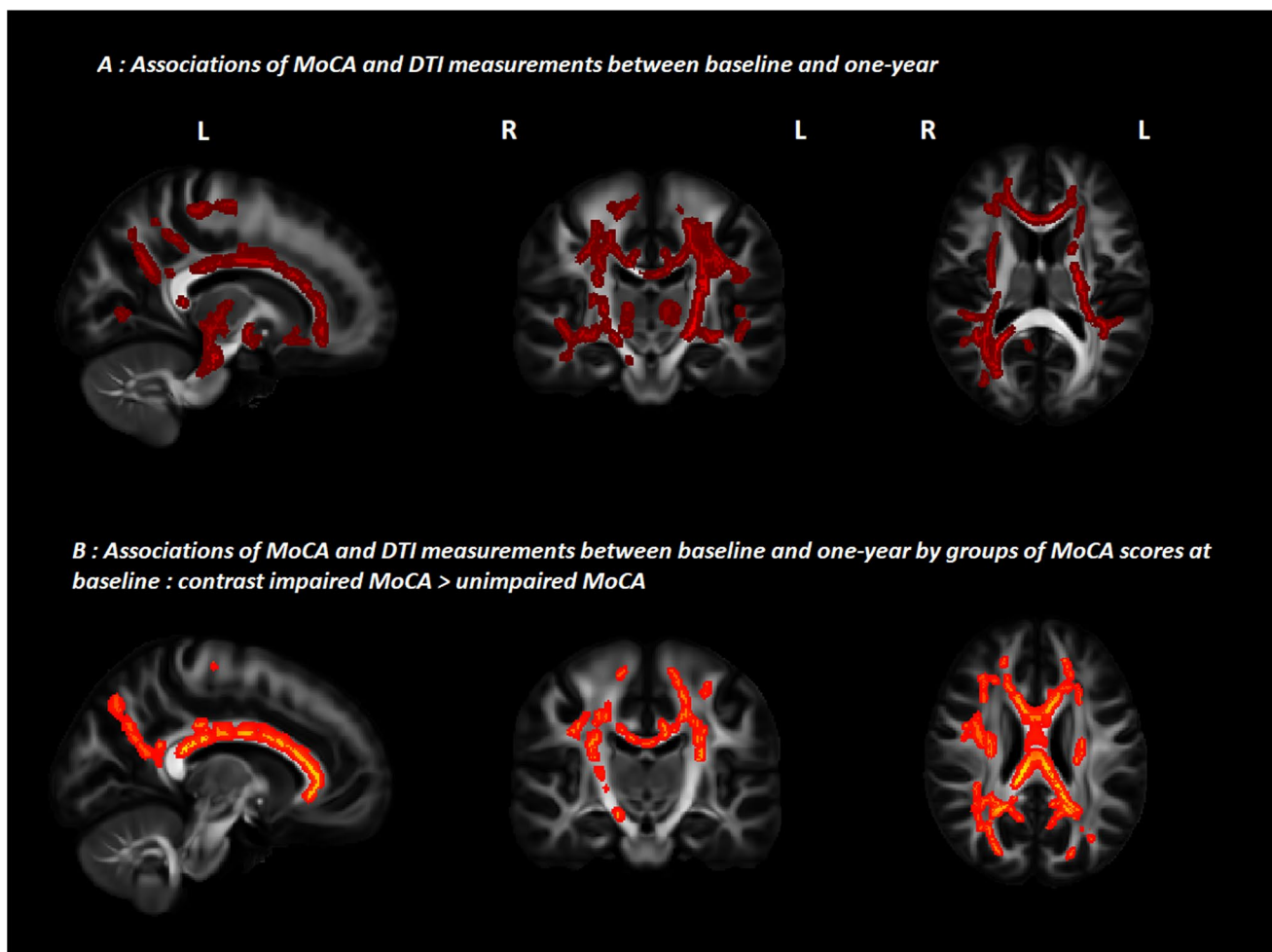


Fig. 2 White matter tracts associated with MoCA scores. *R* right, *L* left. The longitudinal analyses showed for MoCA (**A**) a negative association with FA. When separating the sample by groups of impaired MoCA at baseline and unimpaired MoCA at baseline, a positive association was found with the contrast impaired MoCA > unimpaired

MoCA (**B**), meaning that patients with impaired MoCA had higher FA decrease over the year of follow-up. The results were adjusted for age, female gender, educational level, NIHSS, IS volume at baseline, and WMH volume ($p < 0.05$ corrected from multiple comparisons TFCE and multiple permutations)

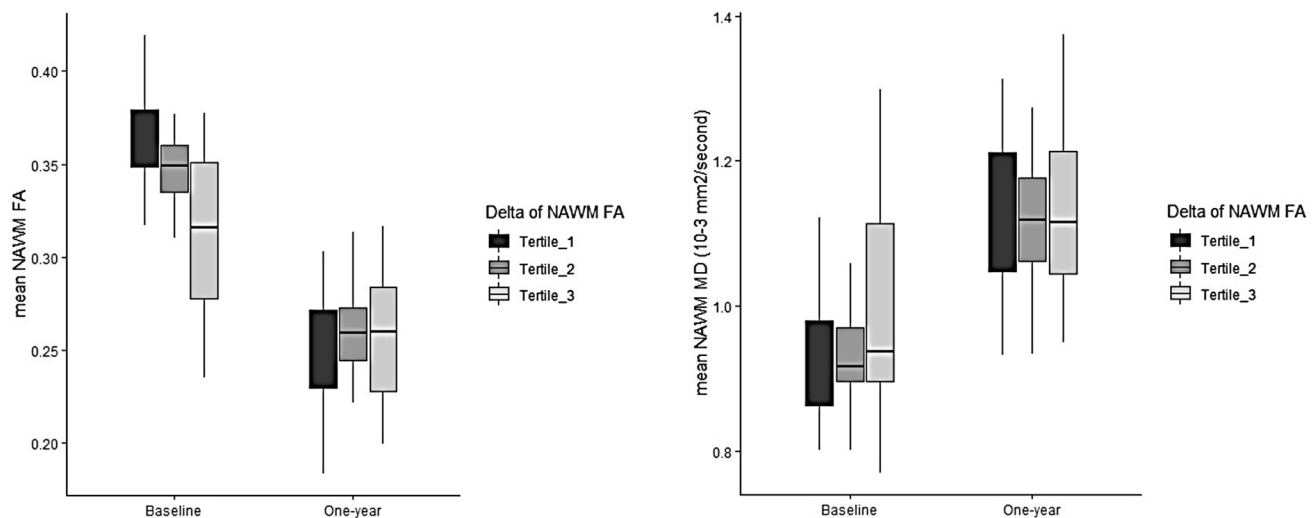


Fig. 3 Evolution of mean NAWM FA and MD by tertiles of NAWM FA delta. The first tertile represents patients with the most important NAWM FA decrease

($\beta = 0.15$, $p = 0.04$, supplemental Table III). These associations did not remain after adjustment for demographic confounders and NIHSS (supplemental Table III).

The TBSS analyses comparing baseline and 1 year DTI images showed that higher decrease of FA was associated with less MoCA improvement between the two time-points, in widespread white matter tracts (Fig. 2A), regardless of demographic confounders, the evolution of NIHSS and WMH. Labeling of the white matter tracts pinpointed is listed in the supplemental Table IV. No significant result was found for the other cognitive scores. The additional analyses performed separating the sample according to their MoCA scores at baseline showed that patients with impaired MoCA ($n = 66$) had higher decrease of FA in widespread white matter fiber tracts, compared with patient without impaired MoCA ($n = 29$, Fig. 2B).

Discussion

The present study shows that in a population of mild to moderate IS, the microstructural integrity of NAWM deteriorates over the year after stroke, and is associated with global cognitive recovery: the patients who deteriorated their NAWM microstructural integrity more had slowed cognitive improvement on MoCA scores. We also observed that those patients had higher FA and lower MD at baseline, probably explained by their younger age as age was an independent factor associated with DTI measurements, among the other demographic and vascular risk factors. Notwithstanding such an advantage at baseline, they had higher IS volume, which might took part in the acceleration of NAWM integrity deterioration through secondary neurodegeneration

[22]. In accordance with this hypothesis, we observed in the multivariate analyses that larger IS was associated with more NAWM FA decrement and less MoCA improvement. Moreover, patients with impaired cognitive functions at baseline had more FA decrease over time, suggesting that this radiological frailty condition was associated with an increase cognitive vulnerability since baseline. Our results highlight the presence of microstructural integrity deterioration in the NAWM even in patients with good functional outcome, and should incite to perform more exhaustive neuropsychological workup to detect potentially disabling cognitive changes. The effect of this brain microstructural alteration on long-term outcome using extended follow-up beyond 1 year should be considered in further studies.

The age-related alteration of NAWM in aging is a well-known process, involving loss of myelin, axonal disruption, ischemia, microglial infiltration, inflammation, amyloid deposition, and leading to macrostructural abnormalities identified as WMH on conventional MRI sequences [23, 24]. In a stroke population, although the integrity of NAWM has been associated with functional and cognitive prognosis 3 months to 1 year post-stroke [5–7, 25], the longitudinal evolution of DTI parameters in the NAWM has not been investigated yet. Referring to the known effect of age on NAWM integrity, we can hypothesize that the deterioration of DTI parameters in the present study could be age-related. However, we observed in the TBSS analyses persistent associations between DTI parameters in various tracts of white matter and clinical scores, regardless of demographic confounders including age. Hence, the effect of age on NAWM might not be the only cause of the alteration, and we cannot exclude an acceleration of NAWM integrity deterioration due to the new IS. Microstructural abnormalities have already been

described in the perilesional area and contralesional hemisphere of stroke patients [26, 27] days to months after stroke compared with healthy subjects, suggestive of direct axonal damage and transneuronal changes through diaschisis. Conversely, we did not observe a significant increase of WMH volume. That might be explained by the delay of the follow-up, i.e., 1 year, as other studies reported a progression of WMH after 3 to 6 years follow-up [28, 29], and mainly in subjects with early confluent WMH, which was not the case of most of the patients of the present study.

Limitations

The reduced number of patients with available radiological and clinical data for the longitudinal analyses is one of the limitations of this study, leading to potential selection bias and ceiling effects. Indeed, the patients who acceded to the 1 year follow-up were finally less severe, preventing the generalization of the results. Nevertheless, despite a population of mild to moderate strokes, we observed significant changes in the integrity of NAWM even in the least severe patients, with significant associations with cognitive outcome. Second, the neuropsychological assessment was based on a neuropsychological battery previously published [30]. Although this battery was short allowing a rapid screening of cognitive impairment, and allowing an in-depth motor assessment, we probably faced with ceiling effects as we did not identify patients with cognitive decline. More exhaustive neuropsychological batteries, control groups, and extended follow-up beyond 1 year should be considered in further studies to evaluate subtle cognitive impairment and evolution. Besides, the use of tests not based on language could be useful to test neuropsychological functions properly.

Conclusion

The microstructural integrity of NAWM worsens over the year following an IS, and is a radiological biomarker associated with cognitive outcome even in functional independent patients. A more important decrease of FA was associated with a cognitive recovery slowdown, suggesting that these patients should be tested with more exhaustive neuropsychological workup on a prolonged follow-up, to detect specific cognitive dysfunction. Further studies are however needed to specify the kinetic of NAWM integrity deteriorations, and its relation to outcome beyond the year after stroke. Beyond the better understanding of physiopathological mechanisms underlying post-stroke recovery, the identification of microstructural abnormalities invisible on conventional sequences might be of particular interest to intensify drug and non-drug intervention, in order to step back from the apparition

of macrostructural abnormalities and to improve long-term daily living ability of these patients.

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Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the regional French Human Protection Committee (CPP 2012/19 2012-A00190-43).

Conflict of Interest The authors declare no competing interests.

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