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ORIGINAL ARTICLE

Microstructural Gray Matter Integrity Deteriorates After an Ischemic Stroke and Is Associated with Processing Speed

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Abstract

Microstructural changes after an ischemic stroke (IS) have mainly been described in white matter. Data evaluating microstructural changes in gray matter (GM) remain scarce. The aim of the present study was to evaluate the integrity of GM on longitudinal data using mean diffusivity (MD), and its influence on post-IS cognitive performances. A prospective study was conducted, including supra-tentorial IS patients without pre-stroke disability. A cognitive assessment was performed at baseline and 1 year, including a Montreal Cognitive Assessment, an Isaacs set test, and a Zazzo cancelation task (ZCT): completion time and number of errors. A 3-T brain MRI was performed at the same two time-points, including diffusion tensor imaging for the assessment of GM MD. GM volume was also computed, and changes in GM volume and GM MD were evaluated, followed by the assessment of the relationship between these structural changes and changes in cognitive performances. One hundred and four patients were included (age 68.5 ± 21.5, 38.5% female). While no GM volume loss was observed, GM MD increased between baseline and 1 year. The increase of GM MD in left fronto-temporal regions (dorsolateral prefrontal cortex, superior and medial temporal gyrus, $p < 0.05$, Threshold-Free Cluster Enhancement, 5000 permutations) was associated with an increase time to complete ZCT, regardless of demographic confounders, IS volume and location, GM, and white matter hyperintensity volume. GM integrity deterioration was thus associated with processing speed slowdown, and appears to be a biomarker of cognitive frailty. This broadens the knowledge of post-IS cognitive impairment mechanisms.

Keywords Diffusion tensor imaging · Gray matter · Processing speed · Stroke · Longitudinal

Abbreviations

DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
ET	Echo time
FLAIR	Fluid-attenuated inversion recovery
FOV	Field of view
FSL	FMRIB software library
FEW	Family-wise error
GM	Gray matter
IQCODE	Informant Questionnaire in Cognitive Decline in the Elderly
IS	Ischemic stroke
IST	Isaacs set test
MD	Mean diffusivity
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
NIHSS	National Institute of Health Stroke Score
RT	Repetition time

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SPM	Statistical parametric mapping
TFCE	Threshold-free cluster enhancement
TIV	Total intracranial volume
WMH	White matter hyperintensities
ZCT	Zazzo's cancelation task

Introduction

Ischemic stroke (IS) is a major cause of cognitive dysfunctioning and disability [1]. The identification of early prognostic factors and the understanding of post-IS cognitive evolution mechanisms through brain MRI are in constant development. Macrostructural biomarkers such as white matter hyperintensities (WMH) and brain atrophy have been first recognized to be associated with cognitive changes [2]. More recently, microstructural abnormalities in normal-appearing white matter, preceding macrostructural lesions, have been identified to influence the cognitive prognosis [3, 4]. Diffusion MRI was firstly used to describe white matter structural state. The computation of fraction of anisotropy based on a diffusion tensor model gives access to directionality information inside a voxel, which is an important parameter when considering fiber tracts. Besides white matter, the microstructural analysis of gray matter (GM) based on diffusion sequences has been reported to be informative in aging and in neurodegenerative diseases. While in healthy older adults [5], significant higher mean diffusivity (MD) has been reported with aging in the GM of temporal and parietal lobes and associated with cognitive variability, in Alzheimer's disease [6], increased MD in hippocampus, amygdala, temporoparietal cortices, posterior cingulate cortex, and precuneus has been associated with the risk of cognitive decline and of conversion from mild cognitive impairment to Alzheimer's disease. Data investigating GM integrity in the area of stroke remain scarce, but microstructural alterations have been reported in the thalamus, putamen, and globus pallidus of genetic cerebral arteriopathy subjects, and associated with global cognitive functions or executive functions [7, 8], suggesting neurodegenerative phenomenon. We hypothesized that GM microstructural integrity alteration is a biomarker of cognitive frailty associated with the risk of post-IS cognitive impairment. The aim of the present study was to evaluate the influence of GM integrity on cognitive outcome, using diffusion tensor imaging (DTI) on longitudinal data covering a period of 1 year after an IS. Due to its higher cellular composition than white matter, GM integrity was evaluated through the computation of MD. Indeed, fractional anisotropy allows the quantification of water diffusion in a privileged direction along myelinated fibers that are more present in white matter, whereas MD allows the assessment of the average diffusion in all directions, which is more appropriate to evaluate GM microstructure. The detection of such prognosis biomarkers could refine the pathophysiology of post-IS cognitive outcome, and could help to initiate early rehabilitation strategies to the more vulnerable patients, in order to delay the emergence of cognitive decline.

Materials and Methods

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

Subjects

We used data from the "Brain Before Stroke" study, a consecutive prospective and monocentric study conducted at the University Bordeaux Hospital, with a period of recruitment between June 2012 and February 2015. Four hundred and twenty-eight patients presenting with clinical signs of IS were initially approached during the recruitment period, and they were subsequently excluded according to the following inclusion and exclusion criteria. The inclusion criteria were men and women > 18 years old with a clinical diagnosis of supra-tentorial IS defined by the National Institute of Health Stroke Score (NIHSS) between 1 and 25, and confirmed on a brain MRI performed between 24 and 72 h after symptom onset. The exclusion criteria were a severe neurological deficit, including aphasia, hindering the clinical and radiological assessments, a previous neurological disability or dementia leading to a modified Rankin scale > 1, 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.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was accepted by the regional French Human Protection Committee (CPP 2012/19 2012-A00190-43). All participants or their legal representative gave informed written consent.

Longitudinal Follow-up and Cognitive Outcome Variables

A clinical assessment and a 3 T brain MRI (General Electrics Medical Systems Discovery MR750W) were performed at baseline (i.e., between 24 and 72 h after symptoms onset) and at 1 year. The clinical assessment was performed by a stroke neurologist blinded to radiological data, and included a NIHSS, a Montreal Cognitive Assessment (MoCA; 9) for the evaluation of global cognitive functions outcome, an

Isaacs set test (IST; 10), evaluating categorical verbal fluencies, and a Zazzo's cancelation task (ZCT; 11), evaluating processing speed and attentional functions, with the completion time of the task, and the number of errors. The choice of this set of cognitive tests was based on a neuropsychological work up used in a previous study [9], which included an IST, a ZCT, and a test evaluating global cognitive functions (MoCA in the present study). An Informant Questionnaire in Cognitive Decline in the Elderly (IQCODE; 13) was also performed at baseline to detect pre-stroke cognitive decline.

Imaging Protocol

The imaging protocol conducted at the two time-points was identical and performed on the same scanner. The following sequences were performed: diffusion weighted imaging (DWI, echo time [ET] / repetition time [RT] 82/9000, field of view [FOV] 24×24 cm^2, matrix 128×128, slice thickness 4 mm, gap between slices 0.5 mm), DTI (ET/RT 105/15000 ms, FOV 24×21.6 cm^2, matrix 160×160, 16 diffusion directions, $b = 1000$ s/mm^2), 3D T1-wi (196 slices, ET/RT/inversion time 3.3/8.6/450, 12° flip angle, FOV 24×24 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 24×24 cm^2, matrix 288×224, slice thickness 1.8 mm).

Imaging Post-Processing

The location of IS was recorded according to the cerebral arterial territory involved for cortical IS (middle, anterior, posterior cerebral arteries, or ≥ 2 arterial territories), and in lacunar IS for small deep infarcts defined by the Standards for Reporting Vascular changes on neuroimaging [10]. The volumes of IS at baseline and WMH at baseline and 1 year were generated from masks segmented using the 3D slicer 4.3.1 software (www.slicer.org; a pre-detection tool of the lesions edges was used, with manual correction) on DWI and FLAIR sequences, respectively. Masks of GM at the two time-points were obtained using Statistical Parametric Mapping (SPM) 12 [11] on the basis of 3D T1-wi and FLAIR after magnetic field inhomogeneities correction with the Advanced Normalization Tools software [12], and coregistration of FLAIR on T1-wi with rigid and affine transformations. The deformation field obtained from the SPM segmentation was applied on the IS and WMH masks, allowing the production of a new tissue probability map and the segmentation of IS and WMH in an additional tissue class. The segmentation resulted also in masks of white matter and cerebrospinal fluid. The addition of all the volumes formed the total intracranial volume (TIV). IS, WMH, and GM were expressed as ratio of TIV in all analyses. The normalized modulated warped GM partitions were smoothed with an 8-mm full width half height Gaussian kernel, and 1-year images were resliced to match the space of baseline images before the conduction of statistical analyses.

Subsequently, the post-processing of DTI sequences was performed using FMRIB Software Library (FSL 5.0.2, http://www.fmrib.ox.ac.uk/fsl) — Brain Extraction Tool. The images were corrected for eddy current distortions, and non-brain voxels were removed. Individual maps of MD were generated using the FMRIB's Diffusion Toolbox from FSL. The maps were normalized in the Montreal Neurological Institute (MNI) space, and smoothed with an 8-mm full width half height Gaussian kernel to perform the statistical analyses on SPM 12 using the Threshold-Free Cluster Enhancement (TFCE, http://www.neuro.uni-jena.de/tfce/), a toolbox allowing non-parametric statistics applied to statistical parametric SPM design. A mean mask of GM of the sample constructed from the mean of normalized GM masks of each subject was applied to evaluate microstructural integrity only in GM.

Statistical Analyses

Clinical scores and radiological data of complete cases at the two time-points were compared using the Friedman's rank-sum test for repeated measures. Analyses were performed with the R software 4.0.2. Statistical significance was set at $p < 0.05$.

Subsequently, the volumes of GM were compared between baseline and 1 year using SPM 12. Age, female gender, educational level, IS volume and location, WMH volume, and TIV were added as covariates. Family-wise error rate (FWE)-corrected p-value < 0.05 for 100 contiguous voxels was considered statistically significant.

Then, to compare GM MD variability between baseline and 1 year, we performed SPM 12 analyses using the TFCE toolbox, which allows non-parametric statistics applied to statistical parametric SPM design. The Smith-permutation method was used to deal with nuisance variables, 5000 permutations. We first compared MD maps between the two time-points using paired two-samples t-test. Secondly, we evaluated the relationship between changes in MD maps and changes in cognitive scores using two-samples t-test, and applying the contrast (positive and negative) on the cognitive score. Age, female gender, educational level, IS, WMH, GM volumes (as ratio of TIV), and IS location were added as covariates. Lastly, to overcome the issue of IS contribution in the results, we performed the same analyses in right and left-sided IS, splitting the sample according to their IS hemispheric side. Statistical significance was set at FWE-corrected $p < 0.05$ for 100 contiguous voxels. The significant regions were labeled using their MNI coordinates and

the MNI2TAL web application (https://bioimagesuiteweb.github.io).

Results

Characteristics of the Patients

One hundred and four patients (median age 68.5, IQR 21.5, 38.5% female) were included in the analyses (see Flow chart in Supplemental Fig. I). Characteristics of the population are described in Table 1. Right ($n=60$, 58%) and left-sided ($n=41$, 39%) IS patients were similar regarding demographic, cardiovascular risk factors (except for smoking, more frequent in left-sided IS patients 39% versus 15%, $p=0.01$), IS volume at baseline, WMH, and GM volume at baseline and 1 year (Supplemental Table II). We observed a significant improvement of NIHSS and MoCA ($p<0.001$) between baseline and 1 year, but a tendency to increase ZCT completion time ($p=0.07$, Fig. 1).

Table 1 Characteristics of the population

	$N=104$
Age, median (IQR)	68.5 (21.5)
Female gender, *n* (%)	40 (38.5)
Educational level ($N=91$), *n* (%)	
None	2 (2.2)
Primary	22 (24.2)
Junior high school	25 (27.4)
Secondary high school/baccalaureate	16 (17.6)
Superior	26 (28.6)
IQCODE, median (IQR)	3 (0.1)
Hypertension, *n* (%)	58 (55.8)
Diabetes mellitus, *n* (%)	19 (18.3)
Dyslipidemia, *n* (%)	43 (41.4)
Smoking, *n* (%)	25 (24)
IS hemispheric side, *n* (%)	
Right	60 (58)
Left	41 (39)
Bilateral	3 (3)
IS location, *n* (%)	
Middle cerebral artery territory	57 (54.8)
Anterior cerebral artery territory	6 (5.7)
Posterior cerebral artery territory	10 (9.6)
≥ 2 cerebral artery territories	9 (8.7)
Small deep infarcts	22 (21.2)
IS volume at baseline, median.10^{-2} (IQR)	0.78 (2)
WMH volume, median.10^{-2} (IQR)	
Baseline	0.34 (0.78)
1 year	0.4 (0.85)
GM volume, median.10^{-2} (IQR)	
Baseline	46.6 (3.74)
1 year	47.9 (3.62)

IS volume is expressed as ratio of TIV

GM Volume Analyses Using Voxel-Based Morphometry

The SPM analyses comparing GM volumes between baseline and 1 year did not show GM regions with significant GM volume loss between the two time-points.

DTI Analyses

The statistical models performed to estimate GM MD changes between the two time-points revealed a significant increase of MD in extended bilateral GM regions including fronto-temporo-parietal regions (Fig. 2A). As expected, when splitting the sample into right and left-sided IS, GM MD increased in the lesional hemisphere (Fig. 2C and E). The longitudinal analyses contrasting the cognitive scores showed a positive association between changes in MD and changes in ZCT completion time in the left dorsolateral prefrontal cortex ($p=0.007$, TFCE, 5000 permutations), left superior temporal gyrus ($p=0.008$), and left medial temporal gyrus ($p=0.009$, Fig. 2B and Supplemental Table III). In other words, an increased MD over the year of follow-up was associated with longer ZCT completion time. The same results were observed only in right-sided IS (i.e., in the non-lesional hemisphere of right-sided IS, Fig. 2B). No significant association was found with the other cognitive scores in all samples or in right and left-sided IS.

Discussion

The main results of the present study are that the microstructural integrity of GM deteriorates after an IS, even in the absence of significant GM volume loss. This deterioration, demonstrated by an increase of MD, is associated with a processing speed slowdown, mainly in left fronto-temporal regions. Although microstructural abnormalities are usually evaluated in white matter, few studies have considered the application of DTI in GM, as the identification of early abnormalities before the apparition of visible macrostructural changes [5, 6, 13]. In accordance with this hypothesis, we found microstructural GM alterations while no GM volume loss was observed, which may be a marker of GM embrittlement, predictive of forthcoming cognitive dysfunctioning.

Age is a known factor associated with GM microstructral alterations, higher GM MD being reported in healthy older adults aged ≥ 70 years old, compared with younger subjects [5]. An age-related GM MD increase is possible in the

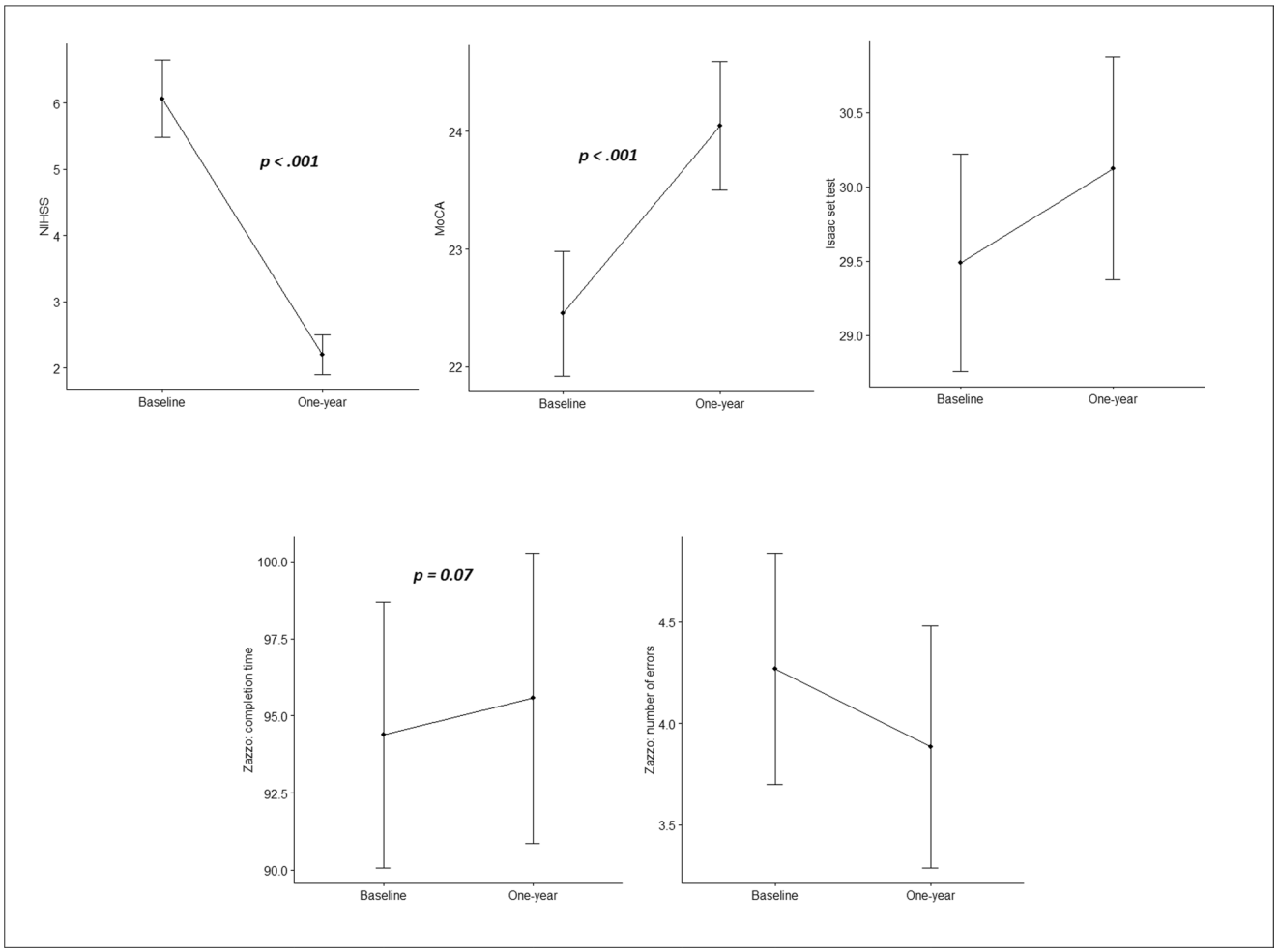

Fig. 1 Evolution of clinical scores between baseline and 1 year after IS (means and standard error of the means)

present study, but the results remained even after age correction, making less likely the age-related effect. Although, comparisons with a control group of similar age and without IS would be needed to ascertain this assumption. The deterioration of GM microstructure related to the new IS lesion might be a more accurate explanation, in the same way that associations were described between normal-appearing white matter, cognitive and functional outcome after an IS into the ipsilesional and contralesional hemispheres [3, 4, 14]. Such associations might be the downstream consequences of Wallerian degeneration and diaschisis phenomenon, but they also might be related to earlier microstructural abnormalities in GM in the first hours after IS [15], or fostered by pre-stroke microstructural abnormalities, as suggested in neurodegenerative diseases [6]. Although our patients were free from pre-stroke cognitive impairment, we cannot prejudge the existence of a primary asymptomatic neurodegenerative cortical disease, and we cannot exclude the existence of undetected subtle cognitive changes supported by GM microstructural alterations.

Interestingly, GM MD changes were most likely associated with processing speed. Processing speed is one of the cognitive domains more impaired after IS, until 60 to 70% [16, 17], and requires undamaged white matter fiber tracts to support information transfer [18, 19]. The progressive secondary neurodegeneration enhanced by the IS over the year of follow-up through Wallerian degeneration might explain the greater impact on processing speed. Moreover, we observed an impact of GM MD deterioration on processing speed only in right-sided IS. The relevant regions remained in left fronto-temporal areas, which were regions of normal-appearing GM, thus excluding a direct effect of IS location. In left-sided IS, we did not observe associations between ZCT completion time and GM MD. We can hypothesize that the value of IS location in left-sided IS was more important, overwhelming the value of GM MD deterioration. Indeed, IS in the left-side hemisphere have been associated with poorer cognitive and functional outcome [20, 21].

Secondary neurodegeneration has mainly been described in subcortical GM as thalamus [22, 23], given its complex

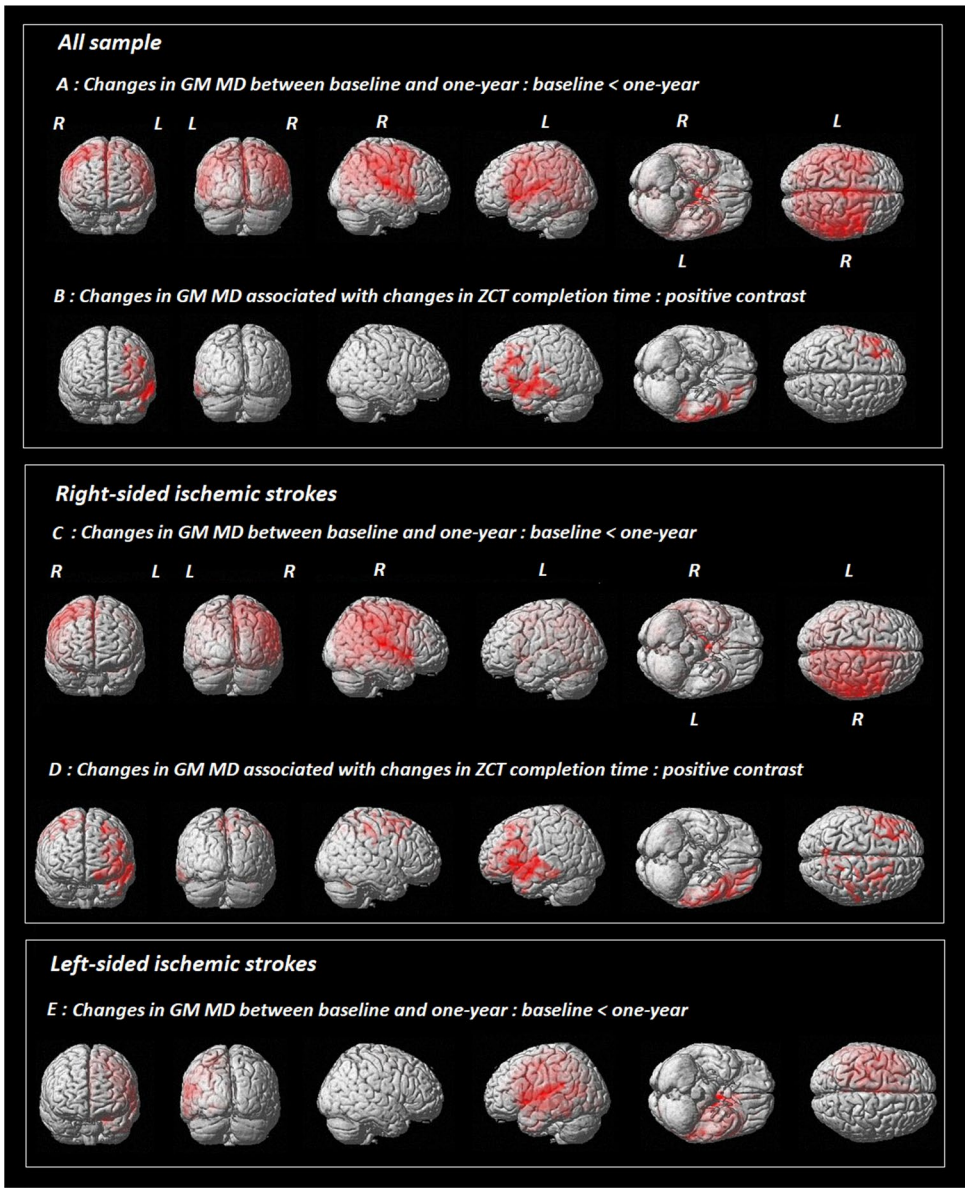

Fig. 2 Changes in GM MD and associations with cognitive performances in all the sample, right-sided and left-sided ischemic strokes. Age, gender, educational level, IS, GM, WMH volumes (as ratio of TIV), and IS location were added as covariates in all the analyses. Areas in red color represent the regions where significant associations were found (FWE-corrected $p < 0.05$, cluster extend = 100)

input and output connections. The SPM approach has the advantage to explore GM in whole brain, without the requirement to focus on limited regions of interest. Herein, we mainly observed the relevance of cortical regions, but longer follow-up might be needed to explore the reach of subcortical GM by secondary neurodegeneration through cortico-subcortical loops involvement.

We chose to consider GM integrity by the assessment of MD given the more cellular content of GM with less myelinated fibers compared with white matter. Additional SPM analyses were still performed with fractional anisotropy maps, but we did not find significant results (data not shown). That is in accordance with the choice to focus on MD for the exploration of microstructural abnormalities in GM. However, in other neurological conditions as multiple sclerosis, a decrease of normal-appearing GM fractional anisotropy related to axonal degeneration has been steadily reported [13, 24].

The results of the present study must be interpreted with the awareness of some limitations. First, although we used validated techniques to segment GM to cerebrospinal fluid, we cannot exclude some inaccuracies in the computation of DTI parameters in GM due to partial volume effects. The use of higher diffusion *b*-values and novel techniques of neurite orientation dispersion and density imaging (NODDI) should be considered in the future for the characterization of GM microstructural changes [25]. Secondly, the association between GM MD changes and ZCT completion time survived multiple comparisons, but the evaluation of processing speed was based solely on this test. Further studies with extended

neuropsychological assessment should be conducted to support this result. Third, only patients with mild to moderate IS severity were able to perform all the clinical and radiological assessment, limiting the generalizability of the results to more severe patients. Fourth, although the longitudinal design of the study permitted, in a way, to consider each patient as his own control, the inclusion of a control group without stroke should be considered in further studies. Finally, even though the results were controlled for the main demographic and radiological factors known to be associated with post-stroke cognitive impairment, we did not record the medications of the patients as psychotropic medications, not allowing us to evaluate their potential impact on cognitive functions and on the values of GM MD. Nevertheless, the modification of DTI metrics by psychotropic medications remains a matter of debate, and most DTI studies in affective disorders showed no association between DTI metrics in white matter and current medication [26].

Conclusion

Microstructural GM change occur after an IS, before the apparition of GM volume loss, and is a marker of cognitive frailty associated with the risk of subsequent cognitive dysfunction. Increased GM MD mainly in left fronto-temporal regions was associated with slower processing speed, suggestive of a secondary neurodegeneration. The upstream identification of microstructural abnormalities, before the apparition of macrostructural changes, should help to detect patients with a higher risk of cognitive dysfunction. Further longitudinal studies are needed to evaluate the worsening or reversibility of these abnormalities, and the effect of interventional rehabilitation measures.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12975-022-01020-9.

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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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