

White Matter Microstructural Damage in Small Vessel Disease Is Associated With Montreal Cognitive Assessment But Not With Mini Mental State Examination Performances

Vascular Mild Cognitive Impairment Tuscany Study

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Background and Purpose—Montreal Cognitive Assessment (MoCA) has been proposed as a screening tool in vascular cognitive impairment. Diffusion tensor imaging is sensitive to white matter microstructural damage. We investigated if diffusion tensor imaging-derived indices are more strongly associated with performances on MoCA or on the widely used mini mental state examination in patients with mild cognitive impairment and small vessel disease.

Methods—Mild cognitive impairment patients with moderate/severe degrees of white matter hyperintensities on MRI were enrolled. Lacunar infarcts, cortical atrophy, medial temporal lobe atrophy and median values of mean diffusivity and fractional anisotropy of the cerebral white matter were studied and correlated with cognitive tests performances.

Results—Seventy-six patients (mean age 75.1 ± 6.8 years, mean years of education 8.0 ± 4.3) were assessed. In univariate analyses, a significant association of both MoCA and mini mental state examination scores with age, education, cortical atrophy, and medial temporal lobe atrophy was found, whereas mean diffusivity and fractional anisotropy were associated with MoCA. In partial correlation analyses, adjusting for all demographic and neuroimaging variables, both mean diffusivity and fractional anisotropy were associated only with MoCA (mean diffusivity: $r = -0.275$, $P = 0.023$; fractional anisotropy: $r = 0.246$, $P = 0.043$).

Conclusions—In patients with mild cognitive impairment and small vessel disease, diffusion tensor imaging-measured white matter microstructural damage is more related to MoCA than mini mental state examination performances. MoCA is suited for the cognitive screening of patients with small vessel disease. (*Stroke*. 2015;46:262-264. DOI: 10.1161/STROKEAHA.114.007553.)

Key Words: cerebral small vessel disease ■ diffusion tensor imaging

The term vascular cognitive impairment refers to cognitive impairment, of any degree, associated with cerebrovascular diseases, among which small vessel disease (SVD) is the most frequent cause.^{1,2}

Montreal Cognitive Assessment (MoCA) has been proposed as a screening tool in vascular cognitive impairment because, differently from the widely used mini mental state examination (MMSE), it includes attentional, psychomotor speed, and executive tasks.³⁻⁶

Diffusion tensor imaging (DTI) is an MRI technique able to detect changes in white matter microstructure that are not evidenced on conventional MRI, but may have a clinical effect.⁷

We assessed whether white matter microstructural damage as measured with DTI in patients with mild cognitive impairment (MCI) and SVD is more strongly reflected by MoCA than MMSE performances. If this holds true, it would support the hypothesis that MoCA is more suited than MMSE as a cognitive screening tool to assess patients with MCI related to SVD.

Methods

The Vascular Mild Cognitive Impairment Tuscany (VMCI-Tuscany) study is a multicenter, prospective, observational study designed to estimate the effect of a large set of clinical, neuroimaging, and biological markers of SVD in predicting the transition from MCI to dementia.⁸ To be included, patients had (1) MCI (Winblad criteria)⁹

Received September 24, 2014; final revision received October 20, 2014; accepted October 21, 2014.

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The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.007553/-/DC1>.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.114.007553

and (2) moderate to severe degrees of white matter hyperintensities (WMH) on MRI, (modified Fazekas scale).¹⁰ The local ethics committee approved the study and informed consent was obtained from all participants.

At baseline, demographic variables (age, education, and sex) were collected, and both MoCA and MMSE were administered. For cut-off values and correction of age and education effect, we used norms validated in the Italian population.^{5,6} Conventional MRI features included lacunar infarcts, WMH, global cortical atrophy, and medial temporal lobe atrophy. Median values of mean diffusivity (MD) and fractional anisotropy of the cerebral white matter were used as DTI-derived indices (Figure). Other details of study methodology, clinical and MRI protocol are presented in the online-only Data Supplement.

Statistical analysis included adjusted partial correlation analysis between MoCA, MMSE, and DTI-derived indices (see online-only Data Supplement).

Results

At baseline, 76 patients had both clinical and DTI assessment (Table 1; see online-only Data Supplement).

Univariate analyses showed a significant association of both MoCA and MMSE with age, education, cortical global atrophy, and medial temporal lobe atrophy, whereas no association emerged with WMH and lacunar infarcts. MD and fractional anisotropy only correlated with MoCA score (Table 2).

In partial correlation analysis between MoCA, MMSE, and DTI-derived indices, adjusted for demographics and conventional MRI variables, only MoCA proved significantly associated with MD ($r=-0.275$, $P=0.023$) and fractional anisotropy ($r=0.246$, $P=0.043$). No significant correlation was observed between MMSE- and DTI-derived indices (MD: $r=-0.107$, $P=0.385$; fractional anisotropy: $r=0.219$, $P=0.073$).

Concerning MoCA subtests, correlation analysis showed a significant association between MD and visuoexecutive ($\rho=-0.372$, $P=0.001$) and attentional ($r_{bp}=-0.259$, $P=0.026$) tasks (Table in the online-only Data Supplement).

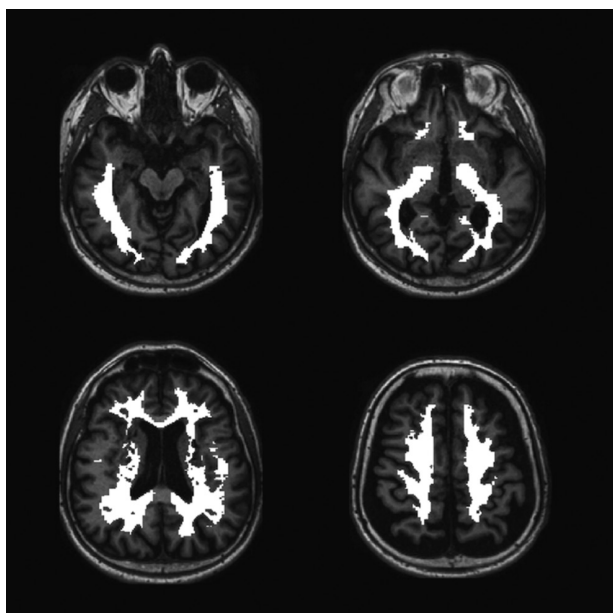


Figure. Automatic white matter segmentation mask in 1 patient with Fazekas grade 2 white matter hyperintensities on fluid-attenuated inversion recovery.

Table 1. Demographic, Clinical, and MRI Characteristics

n=76	Mean±SD or Percentage (%)
Age (y)	75.1±6.8
Education (y)	8.0±4.3
Sex	
Female	44.7
Male	55.3
MMSE score	26.1±3.3
MMSE performance (impaired)	14.6
MoCA score	18.9±5.7
MoCA performance (impaired)	26.7
Lacunar infarcts	
n=0	28.9
n=1–3	32.9
n>3	38.2
Fazekas	
Grade 2	48.7
Grade 3	51.3
Global atrophy	
Grade 1	18.4
Grade 2	67.1
Grade 3	14.5
MTA	3.1±0.9
Median MD cerebral WM	$0.82 \times 10^{-3} \pm 0.37 \times 10^{-4}$
Median FA cerebral WM	0.4±0.2

FA indicates fractional anisotropy; MD, mean diffusivity; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment; MTA, medial temporal lobe atrophy; and WM, white matter.

Discussion

In our sample of patients with MCI and SVD, white matter microstructural damage, as evaluated by DTI-derived indices, was related to MoCA but not to MMSE performances, supporting the hypothesis that MoCA is more sensitive to the presence of subtle SVD.

One limitation of the study is that our cohort might not be purely vascular as imaging markers of neurodegeneration, are present. This reflects the frequent coexistence of vascular and degenerative mechanisms in the aging brain.

We found no statistically significant difference between patients with moderate and severe WMH in terms of MMSE or MoCA scores. This maybe due to a loss of accuracy in discriminating among patients subgroup using cognitive screening tests once a certain degree of SVD is reached. However, patients with severe WMH had on average a 2-point lower score on MoCA in comparison with those with moderate WMH.

Consistent with our hypothesis and results, other studies showed that DTI-derived indices correlated with executive dysfunction in patients with SVD,⁷ whereas conflicting results derive from previous studies comparing MoCA and MMSE in patients with SVD.¹¹

Our data confirm the hypothesis that microstructural damage related to SVD is more expressed by MoCA than

Table 2. Univariate Analysis: Association Between Demographic, Neuroimaging Variables, and MMSE and MoCA Score

	MMSE	PValues	MoCA	PValues
Age	-0.246*	0.032	-0.435*	<0.001
Education (y)	0.428*	<0.001	0.522*	<0.001
Sex				
Female	25.3±3.5	0.041†	17.6±6.0	NS†
Male	26.8±2.9		19.9±5.4	
Lacunar infarcts				
n=0	25.2±4.0	NS§	19.5±5.6	NS§
n=1–3	26.6±3.3		18.0±6.0	
n>3	26.4±2.5		19.2±5.7	
Fazekas				
Grade 2	26.5±3.1	NS†	20.1±5.6	NS†
Grade 3	25.8±3.4		17.8±5.7	
Global atrophy				
Grade 1	28.3±1.2	0.004§	23.5±2.8	0.006§
Grade 2	26.0±3.1		18.0±5.7	
Grade 3	24.1±4.5		17.6±6.4	
MTA	-0.284*	0.013	-0.293*	0.011
Median MD cerebral WM	-0.210*	NS	-0.415*	<0.001
Median FA cerebral WM	0.176*	NS	0.251*	0.030

FA indicates fractional anisotropy; MD, median diffusivity; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment; MTA, medial temporal lobe atrophy; NS, not significant; and WM, white matter.

*Pearson *r*.

†Student *t* test.

§ANOVA.

MMSE performances and that MoCA is a suited screening tool for patients with SVD. This is probably because of the psychometrical structure of MoCA, in particular the presence of items reflecting executive functions and psychomotor speed.

Acknowledgments

Vascular Mild Cognitive Impairment Tuscany (VMCI-Tuscany) study participants are reported in supplemental material.

Sources of Funding

Vascular Mild Cognitive Impairment Tuscany (VMCI-Tuscany) study is funded by Tuscany region. Dr Salvadori is currently supported by a project funded by Tuscany region and Health Ministry (Grant number: RF-2010-2321706, Principal Investigator: Dr Pantoni).

Disclosures

None.

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Stroke. 2015;46:262-264; originally published online November 13, 2014;
doi: 10.1161/STROKEAHA.114.007553

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/46/1/262>

Data Supplement (unedited) at:

<http://stroke.ahajournals.org/content/suppl/2014/11/13/STROKEAHA.114.007553.DC1.html>
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Supplemental material

White matter microstructural damage in SVD is associated with MoCA but not with MMSE performances: VMCI-Tuscany Study

Methodology and study protocol of the VMCI-Tuscany Study

The Vascular Mild Cognitive Impairment (VMCI) Tuscany Study is a multicenter, prospective, observational study, carried out in the Tuscany region of Italy, and aimed at estimating the role of a large set of clinical, cognitive, neuroimaging, and biological markers of SVD as independent predictors of the transition from MCI to dementia. According to the study protocol, at baseline, each enrolled patient undergoes an extensive clinical, functional and neuropsychological assessment, an MRI examination, and the collection of blood samples.

MRI assessment

MRI protocol

Patients were examined on a 1.5 T system (Intera, Philips Medical System, Best, The Netherlands) with 33 mT/m gradients capability and a head coil with SENSE technology. The examination protocol was previously described and included a sagittal T1 sequence, an axial FLAIR sequence, and an axial single-shot echo planar imaging sequence for DTI (diffusion sensitizing gradients applied along 15 non-collinear directions using b value of 0 (b0 image) and 1000 s/mm²) [1].

Conventional MRI features

For the purpose of the present investigation the following features were evaluated: a) lacunar infarcts visible on MRI were defined as hypointense lesions on T1 imaging with corresponding hyperintense lesion on FLAIR images with a diameter <20 mm; lacunar infarcts were classified as absent, 1-3, and >3; b) deep WMH on FLAIR graded according to the modified Fazekas scale [2]. A score of 2 (moderate) was attributed to beginning confluent lesions and a score of 3 (severe) to large confluent lesions [2]; d) global cortical atrophy using the scale of Pasquier et al. that assesses sulci opening of sulci and narrowing of gyri [3]. Scores 0–3 represent absent, mild, moderate, and severe cortical atrophy, respectively; e) medial temporal lobe atrophy (MTA) assessed by means of the Scheltens' scale [4]. This scale assesses coronal T1-weighted images acquired parallel to the brainstem. Scores 0–4 indicate progressive medial temporal volume loss. The above MRI features were visually evaluated in all patients by one experienced neurologist (AP).

Patients with incidental non-lacunar infarcts in the cerebral cortex, cerebellum, or brainstem were excluded to avoid a possible confounding effect on DTI analysis and also to have a more homogenous patients sample.

DTI and analysis of microstructural damage of cerebral WM

Diffusion-weighted images were corrected for head motion and eddy current distortions using FDT (FMRIB's Diffusion Toolbox 2.0), part of FSL 5.0.2 [5] after which brain tissue was segmented using BET, also part of FSL [6]. The b-matrix was reoriented by applying the rotational part of the affine transformation employed in the eddy-correction step [7]. A tensor model was fitted to the raw data using a constrained nonlinear least squares procedure implemented in the software package CAMINO, and residual non-positive definite tensors (in isolated regions where the nonlinear algorithm failed to converge, mainly located at the edge of the brain) were removed by tensor interpolation in the log-euclidean domain [8]. Mean diffusivity (MD) and fractional anisotropy (FA) maps were then computed from the estimated tensor field.

The segmentation method employed to obtain cerebral WM masks was previously detailed [9]. Briefly, WM segmentation on T1-weighted images was carried out using FAST 4, part of FSL [10]. To reduce partial volume effects, a preliminary WM mask was obtained by retaining only those

voxels which had a tissue class probability equal to or above 0.75. In order to select identical cerebral regions across subjects, a standard space (MNI152 average normal brain) WM mask was mapped onto each subject's native space and multiplied by each subject's WM mask (Figure 1). Resulting WM masks were successively mapped onto native diffusion space by applying intra-subject affine transformations (12 degrees of freedom) between the T1 and b0 images [11] in order to compute WM-wide MD and FA statistics for each subject. The inter-subject agreement of our WM segmentation was assessed by using inverse transformations to map single subject WM masks to standard space, averaging and calculating descriptive statistics of the resultant agreement image. The inter-subject agreement was substantial (median 87%, mode: 97%, s.d. 19%). While several metrics can be used to evaluate the MD and FA properties of brain tissue [12], in the present study we employed median values of MD and FA to characterize the microstructural properties of cerebral WM.

Statistical analysis

Descriptive analyses were used to briefly characterize the baseline sample in terms of demographic, clinical and neuroimaging features. Bivariate statistical analyses (independent samples t test, ANOVA, Pearson's r) were used to exclude statistical significant differences between the group composed by the excluded patients for DTI data unavailability and presence of non-lacunar infarcts and the final sample (data not shown). The considered variables were age, education, gender, MoCA, MMSE, lacunar infarcts, WMH, global cortical atrophy, MTA, and median value of MD and FA of the cerebral WM.

Bivariate statistical analyses (independent samples t test, ANOVA, Pearson's r) were used to evaluate the association of demographic and neuroimaging variables, with MoCA and MMSE total score. The considered variables were: demographic characteristics (age, education level, and gender), conventional MRI features (lacunar infarcts, WM hyperintensities, global cortical atrophy, MTA), DTI-derived features (median value of MD and FA of the cerebral WM), and MoCA and MMSE total score.

To evaluate which test was more strongly associated with DTI-derived indices we performed a model of partial correlation analysis adjusting for demographic variables (age, education level, and gender) and conventional MRI features (lacunar infarcts, WMH, global cortical atrophy, MTA). In order to evaluate if psychometrical structure of MoCA influenced the possible association with DTI parameters, correlation analysis (Spearman's Rho and biserial point r_{bp}) were performed for each single subtest (visuoexecutive, naming, digit span, attention, calculation, language, verbal fluency, abstraction, recall, and orientation). All data analyses were performed using SPSS 20.

Definition of the final sample included in this study

From December 2011 to March 2013, 104 patients were enrolled in the VMCI-Tuscany Study in the Florence center, where the MRI protocol included also DTI evaluation. For the purposes of the present study, 7 patients were excluded because DTI imaging was not available for technical reasons, 21 patients were excluded for the presence of non-lacunar infarcts in the cerebral cortex, cerebellum or brainstem. No statistically significant differences between excluded and final sample patients were found in terms of age, education, gender, MoCA, MMSE, and MRI features.

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Supplemental table I. Association between each MoCA subtest and DTI parameters

MoCA subtest	Median MD cerebral WM	Median FA cerebral WM
Visuoexecutive	-0.372 [*] , p=0.001	0.279 [*] , p=0.015
Naming	-0.148 [*] , p=0.206	0.026 [*] , p=0.825
Digit Span	-0.255 [*] , p=0.028	0.185 [*] , p=0.114
Attention	-0.259 [§] , p=0.026	0.147 [§] , p=0.212
Calculation	-0.077 [*] , p=0.514	0.061 [*] , p=0.608
Language	-0.141 [*] , p=0.232	0.156 [*] , p=0.185
Verbal fluency	-0.095 [§] , p=0.421	0.030 [§] , p=0.797
Abstraction	-0.239 [*] , p=0.040	0.139 [*] , p=0.237
Recall	-0.241 [*] , p=0.039	0.057 [*] , p=0.628
Orientation	-0.138 [*] , p=0.238	0.001 [*] , p=0.997

MD: mean diffusivity

FA: fractional anisotropy

^{*} Spearman ρ

[§] biserial point r_{bp}

Appendix. List of participating centers and personnel in the VMCI-Tuscany.

University of Florence: (Coordinating Center): Domenico Inzitari (Study coordinator), Rosanna Abbate, Maria Boddi, Francesca Cesari, Laura Ciolli, Mirella Coppo, Alessandra Del Bene, Stefano Diciotti, Andrea Ginestroni, Betti Giusti, Anna Maria Gori, Sandro Marini, Mario Mascalchi, Serena Nannucci, Leonardo Pantoni, Marco Pasi, Francesca Pescini, Anna Poggesi, Giovanni Pracucci, Emilia Salvadori, Raffaella Valenti.

University of Pisa: Ubaldo Bonuccelli, Paolo Cecchi, Alberto Chiti, Mirco Cosottini, Giovanni Orlandi, Cristina Pagni, Gabriele Siciliano, Gloria Tognoni.

University of Siena: Antonio Federico, Nicola De Stefano, Iaria Di Donato, Maria Teresa Dotti, Patrizia Formichi, Claudia Gambetti, Antonio Giorgio, Francesca Rossi, Laura Stromillo, Enza Zicari.

Tuscany Region: Arezzo (Paolo Zolo, Alessandro Tiezzi); Empoli (Elisabetta Bertini, Stefania Brotini, Leonello Guidi, Maria Lombardi, Stefania Mugnai, Antonella Notarelli); Florence (Laura Bracco, Massimo Cadelo, Renzo Cisbani, Luciano Gabbani, Guido Gori, Lorella Lambertucci, Luca Massacesi, Enrico Mossello, Marco Paganini, Maristella Piccininni, Francesco Pinto, Claudia Pozzi, Sandro Sorbi, Gaetano Zaccara); Grosseto (Tiziano Borgogni, Mario Mancuso, Roberto Marconi); Lucca (Monica Mazzoni, Marco Vista); Livorno (Giuseppe Meucci, Giovanna Bellini); Massa Carrara (Luciano Gabrielli); Pisa (Cristina Frittelli, Renato Galli, Gianna Gambaccini); Pistoia (Stefano Bartolini, Carlo Biagini, Veronica Caleri, Paola Vanni); Prato (Donatella Calvani, Carla Giorgi, Stefano Magnolfi, Pasquale Palumbo, Carlo Valente); Siena (Alessandro Rossi, Rossana Tassi, Stefania Boschi); Viareggio (Filippo Baldacci).

Abstract

脳小血管病における白質の微細構造の障害はモントリオール認知評価検査と関連するが、ミニメンタルステート検査の成績とは関連しない

Vascular Mild Cognitive Impairment Tuscany 研究

White Matter Microstructural Damage in Small Vessel Disease Is Associated With Montreal Cognitive Assessment But Not With Mini Mental State Examination Performances

Vascular Mild Cognitive Impairment Tuscany Study

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背景および目的：血管性認知障害のスクリーニング手段としてモントリオール認知評価検査 (MoCA) が推奨されている。拡散テンソル画像は白質の微細構造の障害に対する感度が高い。本研究では、軽度認知障害と脳小血管病を有する患者において、拡散テンソル画像による指標が MoCA のスコアとより強く関連するか、あるいは汎用されているミニメンタルステート検査のスコアと強く関連するかについて検討した。

方法：中等度から重度の白質高信号病変が MRI 上で認められた軽度認知障害患者を本研究に登録した。ラクナ梗塞、皮質萎縮、側頭葉内側部萎縮、および大脳白質の平均拡散係数および異方性比率の中央値を調べて認知機能検査のスコアと関連付けた。

結果：患者 76 例 (平均年齢: 75.1 ± 6.8 歳, 平均教育年数: 8.0

± 4.3 年) を評価した。単変量解析では、年齢、教育、皮質萎縮、および側頭葉内側部萎縮が MoCA とミニメンタルステート検査の両方のスコアと有意に関連することが明らかになったが、平均拡散係数と異方性比率は MoCA とのみ関連していた。偏相関分析でも、全ての人口統計学的変数と神経画像検査の変数で調整したところ、平均拡散係数および異方性比率はいずれも MoCA とのみ関連していた (平均拡散係数: $r = -0.275$, $p = 0.023$; 異方性比率: $r = 0.246$, $p = 0.043$)。

結論：軽度認知障害と脳小血管病を有する患者では、拡散テンソル画像で測定した白質の微細構造の障害はミニメンタルステート検査よりも MoCA のスコアとの関連が強い。MoCA は小血管病を有する患者の認知機能のスクリーニングに適している。

Stroke 2015; 46:262-264. DOI: 10.1161/STROKEAHA.114.007553.

表 2 単変量解析：人口統計学的変数および神経画像検査の変数と MMSE および MoCA スコアとの関連

	MMSE	p 値	MoCA	p 値
年齢	-0.246*	0.032	-0.435*	< 0.001
教育 (年)	0.428*	< 0.001	0.522*	< 0.001
性別				
女性	25.3 ± 3.5	0.041 †	17.6 ± 6.0	NS †
男性	26.8 ± 2.9		19.9 ± 5.4	
ラクナ梗塞				
n = 0	25.2 ± 4.0	NS §	19.5 ± 5.6	NS §
n = 1 ~ 3	26.6 ± 3.3		18.0 ± 6.0	
n > 3	26.4 ± 2.5		19.2 ± 5.7	
Fazekas 分類				
グレード 2	26.5 ± 3.1	NS †	20.1 ± 5.6	NS †
グレード 3	25.8 ± 3.4		17.8 ± 5.7	
全体的な萎縮				
グレード 1	28.3 ± 1.2	0.004 §	23.5 ± 2.8	0.006 §
グレード 2	26.0 ± 3.1		18.0 ± 5.7	
グレード 3	24.1 ± 4.5		17.6 ± 6.4	
MTA	-0.284*	0.013	-0.293*	0.011
大脳白質の MD 中央値	-0.210*	NS	-0.415*	< 0.001
大脳白質の FA 中央値	0.176*	NS	0.251*	0.030

FA: 異方性比率, MD: 平均拡散係数, MMSE: ミニメンタルステート検査, MoCA: モントリオール認知評価検査, MTA: 側頭葉内側部萎縮, NS: 有意ではない, WM: 白質。

* ピアソン r 。

† スチューデント t 検定。

§ ANOVA。