

# **White matter imaging correlates of early cognitive impairment detected by the MoCA after TIA and minor stroke**

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Among screening tools for cognitive impairment in large cohorts, the Montreal Cognitive assessment (MoCA) appears to be more sensitive to early cognitive impairment than the Mini-Mental State Examination (MMSE), particularly after transient ischemic attack (TIA) or minor stroke. We reasoned that if MoCA-detected early cognitive impairment is pathologically significant, then it should be specifically associated with the presence of white matter hyperintensities (WMH) and reduced fractional anisotropy (FA) on MRI.

**METHODS:** Consecutive eligible patients with TIA or minor stroke (Oxford Vascular Study) underwent MRI and cognitive assessment. We correlated MoCA and MMSE scores with WMH and FA, then specifically studied patients with low MoCA and normal MMSE.

**RESULTS:** Among 400 patients, MoCA and MMSE scores were significantly correlated (all  $p < 0.001$ ) with WMH volumes ( $r_{\text{MoCA}} = -0.336$ ,  $r_{\text{MMSE}} = -0.297$ ) and FA ( $r_{\text{MoCA}} = 0.409$ ,  $r_{\text{MMSE}} = 0.369$ ), and -on voxel-wise analyses- with WMH in frontal white matter and reduced FA in almost all white matter tracts. However, only the MoCA was independently correlated with WMH volumes ( $r = -0.183$ ,  $p < 0.001$ ), average FA values ( $r = 0.218$ ,  $p < 0.001$ ), and voxel-wise reduced FA in anterior tracts after controlling for the MMSE. In addition, patients with low MoCA but normal MMSE ( $N = 57$ ) had higher WMH volumes ( $t = 3.1$ ,  $p = 0.002$ ), lower average FA ( $t = -4.0$ ,  $p < 0.001$ ), and lower voxel-wise FA in almost all white matter tracts than those with normal MoCA and MMSE ( $N = 238$ ).

**CONCLUSIONS:** In patients with TIA or minor stroke, early cognitive impairment detected with the MoCA but not with the MMSE was independently associated with white matter damage on MRI, particularly reduced FA.

## INTRODUCTION

Although TIA and minor stroke often cause no long-term physical disability, they are associated with increased longer-term risk of dementia, particularly Vascular Cognitive Impairment (VCI)<sup>1, 2</sup>. There is therefore a need for well-validated screening tools to efficiently detect cognitive impairment in patients who had minor cerebrovascular events and are therefore at risk of developing VCI, both in clinical practice and in large-scale clinical research studies. Among the scales currently used, the Montreal Cognitive assessment scale (MoCA) captures substantially more cognitive impairment than the Mini-Mental State Examination (MMSE),<sup>3</sup> predominantly visuoexecutive dysfunction,<sup>4</sup> although it may simply be a more difficult test than the MMSE (which has a ceiling effect). Studies have shown that the most prevalent pathological lesions associated with VCI involve the white matter<sup>5-7</sup> and that MRI-based measures of white matter damage best correlate with cognitive deficits in patients with VCI<sup>8, 9</sup>. It is therefore expected that if MoCA-detected impairment is indeed pathologically significant, then it should be closely associated with white matter damage on MRI.

We showed previously that patients with abnormal MoCA but normal MMSE scores are more functionally impaired than those with normal MMSE and MoCA scores,<sup>10</sup> and have more hypertension and greater arterial stiffness.<sup>11</sup> However, MoCA-detected cognitive impairment should ideally be validated against direct measures of cerebral pathology, particularly MRI-detected white matter macroscopic damage visible as white matter hyperintensity (WMH) and microstructural damage measured with Diffusion Tensor Imaging (DTI). WMH has been associated with increased risk of functional impairment, dementia, stroke and death.<sup>12, 13</sup> DTI provides more fine-grained measures of white matter integrity, namely as fractional anisotropy (FA, indicating the deviation from pure isotropic diffusion of

water mobility) and mean diffusivity (MD, indicating the magnitude of diffusion of the water molecules). These have been shown to more closely correlate with cognitive deficits in patients with VCI.<sup>8</sup> We hypothesised that in patients with TIA and minor stroke, early cognitive impairment shown by low MoCA score but normal MMSE would be associated with lower FA and that the overall correlation with measures of white matter damage would be higher for scores on MoCA than on MMSE.

## **METHODS**

### **Study population**

Patients with TIA/minor stroke ( $\text{NIHSS} \leq 3$ ) who were enrolled in the Oxford Vascular Study (OXVASC)<sup>14</sup> between March 2012 and December 2014 were eligible for inclusion.

OXVASC is an ongoing population-based study of the incidence and outcome of all acute vascular events in a population of 92728 individuals registered with 100 primary care physicians in nine practices in Oxfordshire, UK. Multiple methods of ascertainment are used for patients with TIA or stroke, including a daily, rapid-access TIA/stroke clinic, to which participating physicians and the local emergency department refer all individuals with suspected TIA or minor stroke.<sup>14</sup> Written informed consent or assent from relatives was obtained in all participants. OXVASC was approved by the local research ethics committee (OREC A: 05/Q1604/70). Patients were assessed in the acute phase by a neurologist or stroke physician and all presentations and investigations were reviewed by the senior study neurologist (PMR). MRI brain imaging was performed routinely at baseline in all patients without a contraindication. In addition to routine clinical sequences, the sequences described below were performed in all cases. Patients were followed-up face-to-face by a study neurologist at one month and cognitive screening was done with both MMSE and MoCA. For the purposes of the present study additional exclusion criteria were: (i) presence of intracranial haemorrhage, (ii) intracranial space occupying lesion, (iii) brain defect due to previous neurosurgery or developmental anomalies, (iv) evidence of chronic or acute infarcts larger than 2 cm on T1-, T2-weighted or diffusion weighted MRI (DWI) sequences; (v) significant movement artefacts on MRI that would impair registration.

## **Imaging protocol**

All images were acquired on a 3-T Verio MRI scanner. The protocol included FLAIR (TR/TE/TI=9000/94.0/2500 ms, flip angle 150°, FOV 200 mm, voxel size 0.8x0.8x5 mm with 1.5 mm inter-slice gap), post-Gadolinium T1-weighted (TR/TE/TI= 1250/4.63/900 ms, flip angle 16°, FOV 220 mm, voxel-size 1.1x1.1x3 mm with 1.5 mm inter-slice gap), diffusion-weighted (TR/TE= 1250/4.63/900 ms, flip angle 16°, FOV 220 mm, voxel-size 1.8x1.8x4 mm with 1.2 mm inter-slice gap, 12 directions, b-value 1000 s/mm<sup>2</sup>), and gradient-echo (TR/TE= 504/15 ms, flip angle 20°, FOV 240 mm, voxel-size 0.9x0.8x5 mm with 1 mm inter-slice gap).

## **Measurements of macroscopic white matter damage: WMH**

WMHs were automatically segmented on FLAIR images with a newly developed tool, BIANCA (Brain Intensity AbNormality Classification Algorithm), a fully-automated, supervised method for WMH detection, based on the k-nearest neighbour (k-NN) algorithm, which gives the probability per voxel of being WMH.<sup>15</sup>

The total WMH volume was calculated from the voxels exceeding a probability of 0.9 of being WMH and located within a white matter mask. Obtained values were adjusted for the total intracranial volume and log transformed due to their skewed distribution,<sup>16</sup> then analysed with SPSS (version 22.0).

For voxel-wise analyses, the thresholded and masked WMH maps were binarised and transformed into MNI standard space, using FNIRT.<sup>17</sup> We further thresholded the transformed maps at 0.5 and applied spatial smoothing of FWHM=6mm to compensate for registration errors. The obtained images entered in the statistical analysis performed with non-parametric permutation tests using randomise tool in FSL,<sup>18</sup> with age as nuisance covariate, and restricted to a white matter mask. Results were considered significant at

$p_{\text{corr}} < 0.05$  fully corrected for multiple comparisons using family-wise error correction at the voxel-level.<sup>18</sup>

### **Measurements of microstructural white matter damage: DTI**

Diffusion-weighted images were corrected for head motion and eddy currents, then FA and MD images were created by fitting a tensor model to the diffusion data using FDT,<sup>19</sup> and brain-extracted using BET. All subjects' data were then aligned into a common space using FNIRT. Average FA and MD values from the atlas were extracted from a mask including all the main white matter tracts in the ICBM DTI atlas<sup>20</sup> and analysed with SPSS (version 22.0). For simplicity, we report results from FA analyses (see Supplemental Material for MD results).

Voxel-wise analyses of the FA data were carried out using TBSS (Tract-Based Spatial Statistics).<sup>21</sup> The mean FA image was created from the previously aligned FA images and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics performed with non-parametric permutation tests using randomise tool in FSL,<sup>18</sup> with age as nuisance covariate. Results within the average skeleton were considered significant at  $p_{\text{corr}} < 0.05$  fully corrected for multiple comparisons using TFCE correction.

### **Statistical analyses**

Firstly, we investigated correlations of WMH volume and average FA and MD values from the atlas with the MoCA and MMSE across the whole sample by bivariate correlations and partial correlations that included the other cognitive score, demographical variables (age, education, sex) and imaging variables (hippocampal volume, brain volume, and lacunar



infarcts) using SPSS version 22.0. For this purpose, measurements of hippocampal volumes were obtained by manual segmentation on FLAIR images. Brain volume was calculated as volume of the brain-extracted images from FLAIR images using FSL BET.<sup>22</sup> Lacunar infarcts were defined as hypointense lesions on T1 imaging with corresponding hyperintense lesion on FLAIR images with a diameter <15 mm and classified as absent, 1 to 3, or >3<sup>23</sup>.

We also performed correlational analyses at voxel-wise level between MoCA and MMSE scores and the WMH maps and skeletonised FA maps to localise, respectively, white matter regions and tracts specifically correlated with the scores. Voxel-wise analyses were performed with age as a covariate and also repeated adding the other cognitive score as additional covariate (see details above).

Secondly, we compared groups of patients obtained by dividing the sample according the accepted cutoffs of MMSE<27 and MoCA<26 to indicate cognitive impairment<sup>10</sup>: (g1) normal MMSE and MoCA, (g2) normal MMSE, abnormal MoCA, (g3) Normal MoCA, abnormal MMSE, (g4) abnormal MMSE and MoCA (Figure 1). The groups were compared using  $\chi^2$  test or ANOVA as appropriate (SPSS version 22.0). We were especially interested in the planned comparisons between g2 versus g1, which indicates the added apparent value of the MoCA over the MMSE in picking up early cognitive impairment. Since there were significant differences in age and education between the groups in that g1 was younger than g2 ( $p=0.005$ ) and g4 ( $p<0.001$ ) and had higher education than g2 ( $p=0.05$ ), g3 and g4 ( $p<0.001$ ), we adjusted for age and education all the comparisons.

We performed the same group comparisons also at the voxel-wise level on WMH maps and skeletonised FA maps to study the anatomical localisation of between-groups age- and education-adjusted differences in WMH and FA (details above).



## RESULTS

Among 400 consecutive eligible patients, three were excluded due to subsequently diagnosed WMH mimics (multiple sclerosis and CADASIL). The majority of patients (72%) has had a TIA (N=286, mean age 66.9, female sex 49.7%), whereas 28% has had a minor stroke (N=111, mean age 67.9, female sex 45.9%). There were no significant differences in demographical variables between TIA and minor-stroke patients (age  $p=0.543$ , sex  $p=0.507$ ). Table 1 reports the characteristics of the 397 patients included in the analyses of WMH. FLAIR images, used for detection of WMH, were available for all the 397 subjects, whereas 12-directions DWI images, used for measuring FA (and MD), were acquired from a subsample of consecutive 333 subjects, as this sequence was not initially included in the protocol. Analyses on WMH were repeated in the subsample of 333 subjects who had both imaging modalities and gave similar results (see Supplemental Figure I). Among the included patients, 26 (15 female sex; mean age 77.4 years) fulfilled criteria for clinical diagnosis of vascular dementia or major vascular cognitive disorder.<sup>2</sup> There were no patients with a clinical diagnosis of purely neurodegenerative dementia.

## Correlations

In univariate analyses, MoCA and MMSE scores were significantly negatively correlated with WMH volumes (MoCA  $r_{397}=-0.336$ , MMSE  $r_{397}=-0.297$ ,  $p_s<0.001$ ) and positively correlated with average FA values from the atlas (MoCA  $r_{333}=0.409$ , MMSE  $r_{333}=0.369$ ,  $p_s<0.001$ ). However, in partial correlation analyses, the MoCA was still significantly correlated with WMH volumes ( $r_{394}=-0.183$ ,  $p<0.001$ ) and average FA values ( $r_{330}=0.218$ ,  $p<0.001$ ) when controlling for the effect of MMSE. In contrast, the MMSE did not correlate with WMH volumes ( $r_{394}=-0.081$ ,  $p=0.108$ ) and average FA values ( $r_{330}=0.101$ ,  $p=0.067$ ) when controlling for the effect of the MoCA. Reciprocal relationships did not change when including age, education, sex, hippocampal volume, brain volume, and number of lacunar infarcts as additional covariates (Table 2), nor were significantly different between patients with TIA and patients with minor stroke (Supplementary Table I).

Voxel-wise WMH correlational analyses showed that lower MoCA and MMSE scores were each associated with higher likelihood (voxel-corrected  $p<0.05$ ) of having WMH in the frontal periventricular white matter bilaterally, including anterior and superior corona radiata, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus (Figure 2). Voxel-wise correlations between each cognitive score and WMH were not significant when controlling for the other cognitive score.

Voxel-wise TBSS correlational analyses showed that lower MoCA and MMSE scores were associated with lower FA values in almost all the tracts of the white matter skeleton (Figure 3, A and B). Notably, the voxel-wise correlations between MoCA and FA remained significant in the anterior thalamic radiation and forceps major after controlling for the effect of MMSE (Figure 3, C), whereas the voxel-wise correlation between MMSE and FA was not significant after controlling for the effect of MoCA.

## Groups comparison

Patients with low MoCA and normal MMSE (g2, MoCA<26, MMSE $\geq$ 27, N<sub>WMH</sub>=57 N<sub>FA</sub>=46) had significantly higher WMH volumes ( $t=3.1$ ,  $p=0.002$ ) than patients with normal MoCA and MMSE (g1, MoCA $\geq$ 26, MMSE $\geq$ 27, N<sub>WMH</sub>=238 N<sub>FA</sub>=200), but these differences were no longer significant when controlling for the effect of age, education, or both ( $t=1.6$ ,  $p=0.100$ ). However, these patients with low MoCA and normal MMSE (g2) had lower average FA values from the atlas ( $t=-4.0$ ,  $p<0.001$ ) than patients with normal MoCA and MMSE (g1), which remained significant after controlling for the effect of age ( $t=2.6$ ,  $p=0.009$ ), education ( $t=3.4$ ,  $p=0.001$ ), or both ( $t=2.1$ ,  $p=0.032$ ). In contrast, patients with normal MoCA and low MMSE (g3, MoCA $\geq$ 26, MMSE<27, N<sub>WMH</sub>=29 N<sub>FA</sub>=23) had no significant differences in WMH volumes ( $t=1.2$ ,  $p=0.221$ ) or average FA values from the atlas ( $t=0.8$ ,  $p=0.414$ ) relative to patients with normal MoCA and MMSE (g1). Further comparisons are reported in Supplemental Material and Supplemental Figure II.

Voxel-wise, age-corrected group comparisons showed no significant differences in WMH localisation and load between patients with low MoCA but normal MMSE (g2) and patients with normal MoCA and MMSE (g1). However, patients with low MoCA and normal MMSE (g2) had lower FA in almost all white matter tracts relative to those who had normal MMSE and normal MoCA (g1) (Figure 4, B). No voxel-wise significant differences in WMH or FA were found between g1 and g3 (subjects with normal MoCA and MMSE with respect to those with abnormal MMSE and normal MoCA). As expected, there were significant WMH voxel-wise differences between patients with normal MMSE and MoCA (g1) and those with low MMSE and low MoCA (g4), mainly localised in the bilateral frontal white matter. Similarly, TBSS comparisons showed significantly higher FA in g1 with respect to g4 (Figure 4, A).

## DISCUSSION

We aimed to study the white matter correlates of MoCA and MMSE to specifically test if the MoCA is more independently correlated white matter damage in patients who had minor cerebrovascular events relative to the MMSE. We showed that, although both MoCA and MMSE scores correlated with measures of white matter damage and, at the voxel-level, with the presence of WMH in frontal anterior regions and lower FA in all white matter tracts, these associations were stronger for the MoCA and remained significant even when controlling for the effect of the MMSE. In addition, early cognitive impairment shown by a low MoCA score but normal MMSE was specifically associated with widespread reduced measures of microstructural white matter integrity (FA).

Because patients who had a cerebrovascular event are at higher risk of developing vascular cognitive impairment (VCI), the OxVASC study represents a unique enriched cohort for the study of mechanisms leading to VCI. In the present study we excluded patients with disabling stroke or large lesions on imaging and only used non-hyperacute cognitive scores so that we could assume that the resulting associations between MoCA/MMSE and white matter damage were not a direct consequence of the acute cerebrovascular damage itself, but rather expression of a shared predisposition to both cerebrovascular disease and VCI.

Multivariate correlational analyses showed a greater association of the MoCA with measures of white matter damage in that only the MoCA was independently correlated with WMH volumes and average FA (and MD) after controlling for age and MMSE. Previous studies have shown significant correlations between cognitive scores and measures of volumes of WMH in non-demented elderly individuals,<sup>24-27</sup> patients with manifest arterial disease,<sup>28</sup> and patients with vascular dementia.<sup>29</sup> Others have shown significant correlations between

cognitive scores and FA values in non-demented elderly individuals<sup>30</sup> including those with small vessel disease.<sup>8, 31</sup> Because the aim of these previous studies was to identify the cognitive correlates of white matter lesions, cognition needed to be assessed with extended neuropsychological batteries, which cannot however be routinely used as screening tools in clinical practice or large-scale clinical research studies. Only few studies have specifically explored the imaging correlates of screening tools such as MMSE and/or MoCA.<sup>23, 29, 32</sup> Of these, a recent study on patients with vascular Mild Cognitive Impairment reported a significant association of the MoCA with FA but not with WMH volumes.<sup>23</sup> A large study on young and healthy participants showed no significant association between MoCA and WMH volumes.<sup>32</sup> However, since there were no studies in patients with TIA or minor-stroke, in the present manuscript we showed for the first time a greater association of the MoCA with measures of macroscopic (WMH) and microstructural (FA) white matter damage in a prospective population-based cohort of patients seen in a TIA clinic.

The availability of voxel-wise measurement of WMH and FA allowed us to study the anatomical localisation of the white matter damage specifically associated with cognitive impairment. Voxel-wise analyses have only been done previously in small samples of patients with subcortical vascular cognitive impairment,<sup>33</sup> or in large samples of non-demented community dwelling elderly.<sup>31, 34, 35</sup> We showed in a large cohort of patients with TIA or minor stroke that both lower MoCA and MMSE scores were associated with higher likelihood of having WMH in bilateral frontal periventricular WM and lower FA in almost all white matter tracts of the brain. The widespread involvement of WM tracts resulting from voxel-wise correlational FA analyses for both MMSE and MoCA suggests that white matter microstructural integrity measured with FA is diffusely associated with cognitive performance in patients with TIA or minor stroke. It also suggests that the effect of vascular

damage potentially responsible for vascular cognitive impairment is widespread by the time it can be detected by changes in MMSE and MoCA, although this needs to be specifically assessed in further longitudinal studies.

Importantly, voxel-wise correlational analyses showed that the MoCA was still independently associated with lower FA in anterior tracts including the anterior thalamic radiation and forceps major after adjusting for the effect of the MMSE, supporting the notion that the MoCA targets more frontal/executive functions frequently impaired in vascular cognitive impairment.<sup>3, 4</sup> The equivalent MMSE correlational TBSS analysis adjusted for MoCA did not give significant results instead, suggesting that the MMSE does not pick up further white matter pathology relative to the MoCA.

Population-based studies had previously shown that, following a TIA or minor stroke, patients frequently have low MoCA but normal MMSE scores. These patients seem to be more functionally impaired than those who have both normal MoCA and MMSE scores, and are more likely to have hypertensive arteriopathy. We therefore specifically focused on this patients group and showed that, in a subsequent prospective similar cohort, patients with low MoCA and normal MMSE had lower average FA values and higher average MD values than patients with normal MoCA and MMSE, which remained significant after controlling for age and education. They also had greater WMH volumes but not significantly so after controlling for age and education. This was clearly reflected in the age-corrected voxel-level analyses that showed no significant differences in WMH but widespread reduced FA in patients with low MoCA and normal MMSE, which involved almost all the white matter tracts of the brain. These findings suggest that low MoCA identifies patients with abnormal FA among those with normal MMSE, whereas low MMSE does not pick up any further white matter



differences among patients with normal MoCA. Thus, MoCA-detected early cognitive impairment is pathologically significant and reflects widespread damage to the microstructural integrity of the white matter measured with FA, but –interestingly- not greater macroscopic damage visible on MRI as WMH. This confirms our hypothesis that early cognitive impairment shown by low MoCA score but normal MMSE would be associated with subtle, fine-grained microstructural damage, likely to represent an early phase of the process leading to macroscopic damage visible on conventional MRI and advanced dementia.

One limitation of this study is that it was cross-sectional. Longitudinal assessment would have been required to determine whether early changes in the MoCA are predictive of cognitive decline. Another limitation is that differences between MoCA and MMSE were not corroborated by formal neuropsychological testing in all our patients. However, we have previously validated the MoCA and MMSE against neuropsychological standards in our cohort,<sup>36</sup> and our aim was to study the imaging correlates of these screening tools rather than to identify the detailed cognitive correlates of white matter lesions, which have been already done extensively in previous studies.<sup>8, 24-28, 30</sup> But it is important to emphasise that, although we showed that the MoCA has greater value than the MMSE in detecting pathologically relevant early cognitive impairment, it remains a screening tool to identify patients whose cognitive picture should then be further characterised with extended neuropsychological assessments if clinically indicated. Lastly, a further limitation of this study is that the reported analyses were not adjusted for the presence of subclinical depression or other neuropsychiatric disorders, which may have influenced the correlations with cognitive screening tools. However, we would expect any confounding to be similar for the MoCA and MMSE.

In conclusion, early cognitive impairment detected by the MoCA and not by the MMSE has well-defined white matter correlates and is therefore pathologically significant. More precisely, the MoCA is independently associated with measures of microstructural white matter damage, which have been suggested to be more sensitive surrogate markers of vascular cognitive impairment relative to other imaging measures of white matter damage including WMH. It is therefore a valid cognitive scale in screening for early vascular cognitive impairment.

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## **Disclosures**

None

## References

1. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2011;42:2672-2713
2. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: A vascog statement. *Alzheimer disease and associated disorders*. 2014;28:206-218
3. Pendlebury ST, Markwick A, de Jager CA, Zamboni G, Wilcock GK, Rothwell PM. Differences in cognitive profile between tia, stroke and elderly memory research subjects: A comparison of the mmse and moca. *Cerebrovasc Dis*. 2012;34:48-54
4. Mai LM, Sposato LA, Rothwell PM, Hachinski V, Pendlebury ST. A comparison between the moca and the mmse visuoexecutive sub-tests in detecting abnormalities in tia/stroke patients. *International journal of stroke : official journal of the International Stroke Society*. 2016;11:420-424
5. Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment-a critical update. *Front Aging Neurosci*. 2013;5:17
6. Love S, Miners JS. White matter hypoperfusion and damage in dementia: Post-mortem assessment. *Brain pathology*. 2015;25:99-107
7. Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, et al. Neuropathological basis of magnetic resonance images in aging and dementia. *Annals of neurology*. 2008;63:72-80
8. Nitkunan A, Barrick TR, Charlton RA, Clark CA, Markus HS. Multimodal mri in cerebral small vessel disease: Its relationship with cognition and sensitivity to change over time. *Stroke; a journal of cerebral circulation*. 2008;39:1999-2005
9. Benjamin P, Zeestraten E, Lambert C, Ster IC, Williams OA, Lawrence AJ, et al. Progression of mri markers in cerebral small vessel disease: Sample size considerations for clinical trials. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016;36:228-240
10. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by mini-mental state examination versus the montreal cognitive assessment in patients with transient ischemic attack and stroke: A population-based study. *Stroke; a journal of cerebral circulation*. 2010;41:1290-1293

11. Webb AJ, Pendlebury ST, Li L, Simoni M, Lovett N, Mehta Z, et al. Validation of the montreal cognitive assessment versus mini-mental state examination against hypertension and hypertensive arteriopathy after transient ischemic attack or minor stroke. *Stroke; a journal of cerebral circulation*. 2014;45:3337-3342
12. Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: Three year follow-up of ladis (leukoaraiosis and disability) study cohort. *Bmj*. 2009;339:b2477
13. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *Bmj*. 2010;341:c3666
14. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in oxfordshire, uk from 1981 to 2004 (oxford vascular study). *Lancet*. 2004;363:1925-1933
15. Griffanti L, Zamboni G, Khan A, Li L, Bonifacio G, Sundaresan V, et al. Bianca (brain intensity abnormality classification algorithm): A new tool for automated segmentation of white matter hyperintensities. *NeuroImage*. 2016;141:191-205
16. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, et al. Stroke risk profile predicts white matter hyperintensity volume: The framingham study. *Stroke; a journal of cerebral circulation*. 2004;35:1857-1861
17. Andersson JLR, Jenkinson M, Smith S. Non-linear optimisation. *FMRIB Analysis Group Technical Reports*. <http://www.fmrib.ox.ac.uk/analysis/techrep> Publication date June 28, 2007. Accessed January 20, 2017
18. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *NeuroImage*. 2014;92:381-397
19. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted mr imaging. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2003;50:1077-1088
20. Mori S. *Mri atlas of human white matter*. Amsterdam ; Oxford: Elsevier; 2005.
21. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006;31:1487-1505

22. Smith SM. Fast robust automated brain extraction. *Human brain mapping*. 2002;17:143-155
23. Pasi M, Salvadori E, Poggesi A, Ciolli L, Del Bene A, Marini S, et al. 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. *Stroke; a journal of cerebral circulation*. 2015;46:262-264
24. de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, et al. Cerebral white matter lesions and cognitive function: The rotterdam scan study. *Annals of neurology*. 2000;47:145-151
25. Dong C, Nabizadeh N, Caunca M, Cheung YK, Rundek T, Elkind MS, et al. Cognitive correlates of white matter lesion load and brain atrophy: The northern manhattan study. *Neurology*. 2015;85:441-449
26. Arvanitakis Z, Fleischman DA, Arfanakis K, Leurgans SE, Barnes LL, Bennett DA. Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment. *Brain structure & function*. 2016;221:2135-2146
27. Knopman DS, Griswold ME, Lirio ST, Gottesman RF, Kantarci K, Sharrett AR, et al. Vascular imaging abnormalities and cognition: Mediation by cortical volume in nondemented individuals: Atherosclerosis risk in communities-neurocognitive study. *Stroke; a journal of cerebral circulation*. 2015;46:433-440
28. Biesbroek JM, Kuijf HJ, van der Graaf Y, Vincken KL, Postma A, Mali WP, et al. Association between subcortical vascular lesion location and cognition: A voxel-based and tract-based lesion-symptom mapping study. The smart-mr study. *PloS one*. 2013;8:e60541
29. Gootjes L, Teipel SJ, Zebuhr Y, Schwarz R, Leinsinger G, Scheltens P, et al. Regional distribution of white matter hyperintensities in vascular dementia, alzheimer's disease and healthy aging. *Dementia and geriatric cognitive disorders*. 2004;18:180-188
30. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, et al. White matter microstructural integrity and cognitive function in a general elderly population. *Archives of general psychiatry*. 2009;66:545-553
31. Tuladhar AM, Reid AT, Shumskaya E, de Laat KF, van Norden AG, van Dijk EJ, et al. Relationship between white matter hyperintensities, cortical thickness, and cognition. *Stroke; a journal of cerebral circulation*. 2015;46:425-432

32. Gupta M, King KS, Srinivasa R, Weiner MF, Hulseley K, Ayers CR, et al. Association of 3.0-t brain magnetic resonance imaging biomarkers with cognitive function in the dallas heart study. *JAMA neurology*. 2015;72:170-175
33. Kim SH, Park JS, Ahn HJ, Seo SW, Lee JM, Kim ST, et al. Voxel-based analysis of diffusion tensor imaging in patients with subcortical vascular cognitive impairment: Correlates with cognitive and motor deficits. *Journal of neuroimaging : official journal of the American Society of Neuroimaging*. 2011;21:317-324
34. Duering M, Gesierich B, Seiler S, Pirpamer L, Gonik M, Hofer E, et al. Strategic white matter tracts for processing speed deficits in age-related small vessel disease. *Neurology*. 2014;82:1946-1950
35. Jacobs HI, Leritz EC, Williams VJ, Van Boxtel MP, van der Elst W, Jolles J, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. *Human brain mapping*. 2013;34:77-95
36. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. Moca, ace-r, and mmse versus the national institute of neurological disorders and stroke-canadian stroke network vascular cognitive impairment harmonization standards neuropsychological battery after tia and stroke. *Stroke; a journal of cerebral circulation*. 2012;43:464-469

## Figures Legends

### Figure 1 Patients' subgroups

Patients were divided in four groups according to MMSE and MoCA scores. Accepted cutoffs of MMSE<27 and MoCA<26 were used to indicate cognitive impairment. Dark grey bubbles (g2) indicate those patients who scored  $\geq 27$  on the MMSE but <26 on the MoCA.

The area of the bubbles is proportional to the number of subjects.

### Figure 2. Voxel-wise WMH correlational analyses.

A: In blue-light blue, white matter regions of significant negative correlation between WMH and MoCA.

B: In red-yellow, white matter regions of significant negative correlation between WMH and MMSE.

All analyses are adjusted for age.

### Figure 3. Voxel-wise FA correlational analyses.

A: In blue, white matter tracts of significant positive correlation between FA and MoCA.

B: In red, white matter tracts of significant positive correlation between FA and MMSE.

**C: In blue**, white matter tracts of significant positive correlation between FA and MoCA after controlling for the effect of MMSE.

All analyses are adjusted for age.

### Figure 4. Voxel-wise groups comparison (WMH and FA).



A: white matter tracts (in blue) in which patients with low MoCA but normal MMSE (g2) had lower FA relative to those who had normal MoCA and MMSE (g1). Differences in WMH were not significant when controlling for age.

B: White matter tracts of significant lower FA (in blue) and regions of significantly higher WMH (in red) between patients with normal MMSE and MoCA (g1) with respect to those with abnormal MMSE and MoCA (g4).

All comparisons are adjusted for age.

**Table 1. Clinical, imaging and cognitive features.**

		<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>
	TOTAL	(normal MoCA, normal MMSE)	(low MoCA, normal MMSE)	(normal MoCA, low MMSE)	(low MoCA, low MMSE)
<b>Clinical data</b>					
N <sub>WMH</sub> (N <sub>FA</sub> )	397 (333)	238 (200)	57 (46)	29 (23)	73 (64)
Age	67.18±14.14	64.17±13.31	69.81±14.39	66.80±15.84	75.05±12.60
Female Sex (%)	193 (48.6%)	111 (46.6%)	27 (47.4%)	15 (52.7%)	40 (54.3%)
Education (years)	12.99±4.08	13.94±4.58	12.41±3.19	11.35±1.85	10.97±2.14
Event type (% of TIA, others minor stroke)	286 (72.0%)	173 (72.2%)	40 (70.2%)	22 (75.9%)	51 (69.9%)
Smoker (%)	144 (36.8%)	99 (41.9%)	15 (26.3%)	10 (35.7%)	20 (28.6%)
Hypertension (%)	200 (50.8%)	131 (55.5%)	24 (42.1%)	17 (58.6%)	28 (38.9%)
Diabetes (%)	41 (10.4%)	18 (7.6%)	7 (12.3%)	4 (13.8%)	12 (16.7%)
Atrial fibrillation (%)	53 (13.5%)	25 (10.6%)	12 (21.1%)	2 (6.9%)	14 (19.4%)
Hyperlipidaemia (%)	122 (31.0%)	72 (30.5%)	18 (31.6%)	7 (24.1%)	25 (34.7%)
<b>MRI measures</b>					
Average FA (atlas)	0.48±0.04	0.49±0.03	0.47±0.03	0.49±0.04	0.46±0.04
WMH volume (adjusted,%)	0.74±0.77	0.58±0.58	0.83±0.71	0.78±0.68	1.20±1.16
Brain volume (mm <sup>3</sup> )	1019795.67	1041310.54	1003766.16	1023712.19	957877.56
Hippocampal vol (adjusted,%)	0.30±0.07	0.31±0.07	0.30±0.08	0.30±0.07	0.27±0.06
<b>Cognitive scores</b>					
MOCA total/30	26.23±3.47	28.30±1.29	23.42±1.95	27.10±1.32	21.23±3.44
MMSE total/30	27.53±2.75	28.85±1.01	28.12±1.08	25.72±0.53	23.30±3.61

**Table 2 Correlations of MoCA and MMSE scores with imaging variables**

	WMH					FA				
	N	MoCA		MMSE		N	MoCA		MMSE	
		Pearson <i>r</i>	P value	Pearson <i>r</i>	P value		Pearson <i>r</i>	P value	Pearson <i>r</i>	P value
Univariate	397	-0.336	<0.001	-0.297	<0.001	333	0.409	<0.001	0.369	<0.001
Adjusted for MMSE	<b>394</b>	<b>-0.183</b>	<b>&lt;0.001</b>	----	----	<b>330</b>	<b>0.218</b>	<b>&lt;0.001</b>	----	----
Adjusted for MoCA	394	----	----	-0.081	0.108	330	----	----	0.101	0.067
Adjusted for age	394	-0.193	<0.001	-0.154	0.002	330	0.292	<0.001	0.257	<0.001
Adjusted for MMSE, age	<b>393</b>	<b>-0.120</b>	<b>0.017</b>	----	----	<b>329</b>	<b>0.157</b>	<b>0.004</b>	----	----
Adjusted for MoCA, age	393	----	----	-0.027	0.591	329	----	----	0.076	0.165
Adjusted for age, education, sex, hippocampal & brain volumes, lacunes	385	-0.201	<0.001	-0.147	0.006	321	0.262	<0.001	0.218	<0.001
Adjusted for MMSE, age, sex, hippocampal & brain volumes, lacunes	<b>384</b>	<b>-0.139</b>	<b>0.010</b>	----	----	<b>320</b>	<b>0.156</b>	<b>0.008</b>	----	----
Adjusted for MoCA, age, sex, hippocampal & brain volumes, lacunes	384	----	----	-0.007	0.903	320	----	----	0.045	0.451

In bold, multivariate correlations remaining significant for the MoCA when controlling for the MMSE, but not for the MMSE when controlling for the MoCA.

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