Baseline white matter microstructural integrity is not related to cognitive decline after 5 years: The RUN DMC study

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A R T I C L E   I N F O

A B S T R A C T

Objectives: Traditional markers of cerebral small vessel disease (SVD) are related to cognition and cognitive decline, but this relation is weak. Therefore other factors may determine the transition from intact cognitive performance to cognitive decline, such as the damage of the cerebral white matter at the microstructural level. Little is known about the association between microstructural integrity of the white matter and changes in cognition. In this study we investigated the relation between baseline microstructural integrity and change in cognitive function.

Methods: 503 participants of the RUN DMC study with SVD without dementia, 398 of whom (79.1%) underwent repeated cognitive testing at follow-up, with a mean follow-up time of 5.4 years ($\pm$ SD 0.2), and among others FLAIR MRI and diffusion tensor imaging (DTI). At baseline Mean Diffusivity (MD) and mean Fractional Anisotropy (FA) were measured in both white matter hyperintensities (WMH) and normal appearing white matter (NAWM). A linear regression analysis was performed assessing the association between baseline diffusion parameters and decline in cognitive domains.

Results: An inverse association was found between baseline MD in the NAWM and decline in Cognitive Index ($\beta =$ 0.17; p = 0.035), adjusted for age, sex, education, presence of depressive symptoms at baseline, normalized TBV, lacunes and WMH volume. However, no significant associations were found between diffusion parameters and decline in any cognitive domain after Bonferroni correction.

Conclusions: In contrast to cross-sectional studies, in older adults with SVD microstructural integrity of the white matter as assessed with DTI is not related to decline in global cognitive function or any other subdomain.

1. Introduction

Cerebral small vessel disease (SVD) is very common in older adults [1] and is related to cognitive decline and dementia [2]. However, not everyone with SVD visible on conventional structural MRI eventually develops cognitive decline or dementia. Therefore other factors may determine the transition from intact cognitive performance to cognitive decline, such as the damage of the cerebral white matter at the microstructural level. The interconnected neural networks, crucial for cognitive performance, are hypothesized to be disconnected by this damage

in the white matter microstructure, also known as the "disconnection syndrome" [3].

As identical appearing white matter hyperintensities (WMH) on FLAIR MRI scanning are histopathologically heterogeneous [4], possibly only WMH with the highest loss of structural integrity are related to cognitive decline. Furthermore the degree of structural integrity of the surrounding normal appearing white matter (NAWM) might be important in cognitive decline. As conventional MRI is not sensitive to detect subtle damage of the white matter (WM), diffusion tensor imaging (DTI), using the diffusion properties of water molecules might be of use to provide an early marker for this cognitive decline [5,6]. A low Fractional Anisotropy (FA) and high Mean Diffusivity (MD) are believed to represent low microstructural integrity [7].

A low microstructural integrity of the WM has been associated with lower cognitive performance in both population based studies

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[8–10] and older adults with SVD, albeit at the cross-sectional level [11–14]. Some of these studies even found that DTI parameters correlated better with cognitive performance than traditional markers of SVD in patients with cognitive impairment [13], suggesting an important role of low WM microstructural integrity in cognitive impairment. At a cross-sectional level we showed that cognitive performance was associated with white matter microstructural integrity independent of traditional markers of SVD, both in the WMH and NAWM [12] and in specific WM tracts [14]. However, we additionally showed that DTI of the NAWM and WMH had only limited additional value to the traditional SVD parameters in explaining the variance in cognitive function [15]. Two smaller prospective DTI studies did not find an association between microstructural integrity and cognitive functioning at follow-up [16,17]. A larger longitudinal study using diffusion weighted imaging (DWI) in individuals with SVD showed that DWI parameters within the NAWM were related to cognitive decline after 3 years follow-up [18]. We, however, recently showed no relation between microstructural integrity of the WM and incident dementia after five years [19].Therefore, taken together, the results found in prospective studies were weak and conflicting.

We therefore investigated whether baseline microstructural integrity as assessed by DTI, both within the WMH and the NAWM, independently of classic SVD characteristics predicts decline in several cognitive domains after 5 years. Furthermore we investigated if this relation was different in those with low, moderate and high WMH severity at baseline.

2. Material and methods

2.1. Study population

The Radboud University Nijmegen Diffusion Tensor and Magnetic resonance Cohort (RUN DMC) study prospectively investigates risk factors and clinical consequences of brain changes as assessed by MRI among 503 50–85 year old non-demented older adults with cerebral SVD. The selection procedure of the participants and the study rationale and protocol were described in detail previously [20]. In short, on the basis of established research criteria, SVD was a radiological diagnosis, defined as the presence of lacunes and/or WMH on neuro-imaging [21]. Symptoms of SVD include acute symptoms, such as TIAs or lacunar syndromes, or subacute manifestations such as cognitive, motor disturbances and/or depressive symptoms [21]. The baseline data collection was performed in 2006. The main exclusion criteria were dementia, (psychiatric) disease interfering with cognitive testing or follow-up, WMH or SVD mimics and MRI contra-indications or known claustrophobia [20].

Follow-up was completed in 2012 (mean follow-up time 5.2 years (SD 0.7). Of the 503 baseline participants, 2 were lost to follow-up (but not deceased according to the Dutch Municipal Personal Records database) and 49 had died. From all remaining 442 participants follow-up was available (face-to-face follow-up was performed in 398 participants, 54 consented to the collection of clinical endpoints via their general practitioner (Fig. 1)).

2.2. Cognitive function

Participants underwent the same neuropsychological test battery both at baseline and during follow-up examination, covering the main cognitive domains. These tests have been previously applied in large-scale epidemiological studies [22,23]. The test battery included the Mini-Mental State Examination (MMSE) [24], verbal fluency (animals and profession naming) [25], Rey Auditory Verbal Learning Test (RALVT; 3-trial version) [26,27], Symbol Digit Substitution Task (SDST) [28], Stroop Color Word Test (short form) [29], Paper–Pencil Memory Scanning Task [30], Rey Complex Figure Task

(RCFT) [31] and Verbal Series Attention Test (VSAT) [32]. The same versions of the tests were used for baseline and follow-up assessment.

Speed–Accuracy Trade-Off (SAT) scores were calculated where appropriate [accuracy(%)/reaction time], to adjust for a number of faults. Performance across tests was made comparable by transforming the raw test scores into z-scores (individual test score minus mean test score, divided by the standard deviation). z-Scores for both baseline and follow-up were calculated using the mean and SD of the baseline tests [33]. Higher z-scores always indicate a better performance.

Change in cognitive functioning for separate cognitive domains was calculated within-subject, by subtracting the baseline domain compound score from the follow-up domain compound score.

Subsequently, compound scores for global cognitive function (Cognitive Index), memory (verbal and visuospatial memory) and executive function (psychomotorspeed, fluency, inhibition and attention) were calculated. The Cognitive Index was constructed to obtain a more robust outcome measure for global cognition. This was calculated as the mean of the z-scores of the SAT score of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the mean of the SAT score of the reading task of the Stroop test, the mean of the SDST, and the mean of the added score on the three learning trials of the RAVLT and the mean of the delayed recall of this test [22].

Verbal memory is a compound score of the mean of z-scores of the total correct words on the three learning trials of the RALVT and the delayed recall of this test. Visuospatial memory is calculated from the mean of the z-scores of the immediate recall and delayed recall trial of the RCFT. Psychomotorspeed was calculated as the mean of the z-scores of the SAT score of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the mean of the SAT score of the reading task of the Stroop test and the mean of the SDST. Verbal fluency was calculated from the mean of the z-scores of both fluency conditions. Inhibition was measured using the following formula: dividing the Stroop part III SAT score by the mean of the SAT scores of parts I and II. Afterwards a z-score for inhibition was calculated. Attention was computed as the z-score of the SAT score of the total time of the VSAT. If one test of a particular domain was missing, the domain score was computed using the remaining tests of that domain (this occurred in less than 6.3% in the subdomains). For 98% of all participants a score for Cognitive Index was available, of whom 90% completed all five subtests without recording of any test problems. Tests included in the calculation of the change in domain scores and the reasons for exclusion are shown in the Supplementary table.

2.3. MRI resonance imaging protocol

MRI scans of all participants were acquired on a single 1.5-Tesla MRI scanner (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). The protocol included the following whole brain scans: a T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) imaging (TR/TE/TI 2250/3.68/850 ms; flip angle 15°; voxel size $1.0 \times 1.0 \times 1.0$ mm); fluid-attenuated inversion recovery (FLAIR) pulse sequences (TR/TE/TI 9000/84/2200 ms; voxel size $1.0 \times 1.2 \times 5.0$ mm, with an interslice gap of 1 mm); a transversal T2*weighted gradient echo sequence (TR/TE 800/26 ms; voxel size $1.3 \times 1.0 \times 6.0$ mm, with an interslice gap of 1 mm) and a Diffusion Tensor Imaging (DTI) sequence (TR/TE 10100/93 ms; voxel size $2.5 \times 2.5 \times 2.5$ mm; 4 unweighted scans, 30 diffusion weighted scans with b-value $= 900$ s mm^{-2}) [20].

2.4. MRI analysis

WMH were manually segmented on FLAIR images and the total WMH volume was calculated by summing the segmented areas multiplied by slice thickness. The ratings of lacunes and microbleeds were revised according to the recently published STRIVE-criteria, by trained raters blinded to all clinical data [34]. Excellent intra- and inter-rater
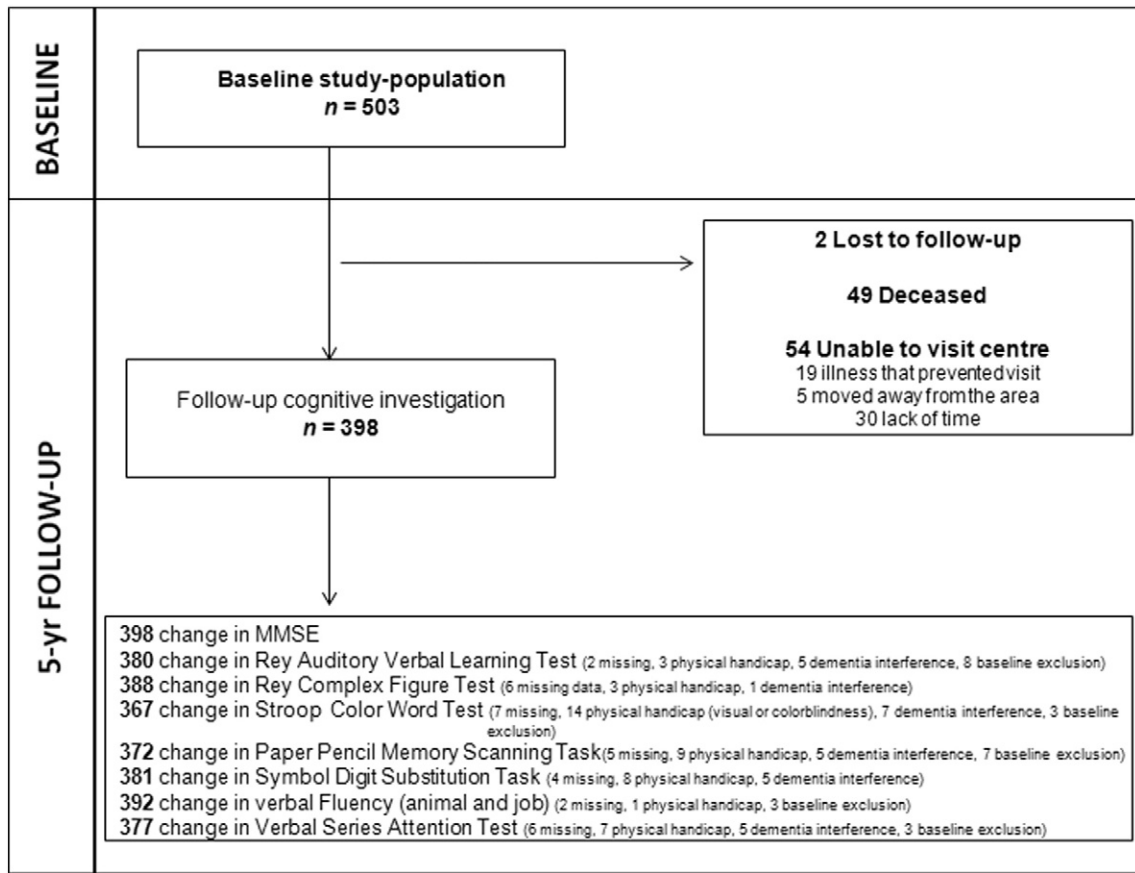
Fig. 1. Flowchart study design baseline and follow-up. Baseline and follow-up study population are indicated by double-lined boxes. MRI: magnetic resonance imaging.

reliabilities were found with weighted kappa of 0.87 and 0.95 respectively for the presence of lacunes and 0.85 and 0.86 for the presence of microbleeds, calculated in 10% of the scans. Inter-rater reliability (assessed using the intra-class correlation coefficient) for total WMH volume was 0.99.

To obtain the gray matter (GM), WM and cerebro spinal fluid (CSF) volume, segmentation of the T1 MPRAGE images was revised using a recent version of Statistical Parametric Mapping 12 unified segmentation routines (SPM12; Wellcome Department of Cognitive Neurology, University College London, UK (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/).All images were visually checked for co-registration errors and for motion and/or segmentation artifacts. The intracranial volume (ICV) was calculated by summing the volumes of GM, WM and CSF, by multiplying the probabilistic tissue segmentations by the voxel volume. Total brain volume (TBV) was taken as the sum of total GM and WM. All volumes were normalized to total ICV.

2.5. DTI-analysis

Diffusion data were preprocessed and analyzed according to an extensively earlier described procedure [20]. The diffusion weighted images of each participant were realigned on the unweighted image using mutual information based co-registration routines from SPM5. The diffusion tensor and its eigenvalues were computed using linear regression, using an SPM5 add-on (http://sourdeforge.net/projects/spmtools). The spurious negative values were set to zero, after which the tensor derivates MD and FA were calculated [35]. The mean unweighted image was used to compute the co-registration parameters to the anatomical T1 image (SPM5 mutual information co-registration), which were then applied to all diffusion weighed images and derivates. All images were visually checked for motion

artifacts and co-registration errors. The mean MD and FA were then calculated in the WMH, NAWM and total WM.

2.6. Other parameters

Education was classified using 7 categories (1 being less than primary school, 7 reflecting academic degree) and then dichotomized in a group having only or less than primary school and a group having more than primary education [36]. Depressive symptoms were assessed with the 20-item Centre of Epidemiologic Studies Depression Scale (CES-D); they were considered present in participants with CES-D ≥ 16 and/or participants who currently used anti-depressive medication, taken for depression [20,37].

2.7. Statistical analysis

Baseline characteristics are presented as mean and standard deviation (SD) for the participants who had a face-to-face follow-up and those without. For the WMH median and interquartile range (IQR) is shown. Group-differences between participants and non-participants are calculated with age and sex-adjusted ANOVA or logistic regression for categorical variables. The associations between baseline microstructural integrity of the NAWM and WMH and the decline in different cognitive domains were assessed by means of linear regression analysis. The variance inflation factor (VIF) was calculated for all regression models to investigate if multicollinearity was present. The VIF scores were low for all multiple regression models (scores below 3, where scores above 5 is considered high multicollinearity). Data were presented as standardized betas. To correct for multiple testing, Bonferroni correction was used, therefore α was set to 0.007. The analyses were adjusted for the possible confounders age, sex, education level, presence of depressive symptoms, TBV, lacunes and for WMH volume where

appropriate. A secondary analysis using stepwise backward selection was performed to confirm these results. First, age, sex and education were forced into the model and a backward stepwise selection procedure was used on the full regression model to remove the variables from the model one at a time, until these had p values smaller than 0.10. To investigate if the microstructural integrity of the WM played a different role in the decline in cognition in those who have limited SVD on FLAIR MRI vs. those who have a higher degree of SVD, we repeated this analysis in strata (tertiles) of WMH volume. A post-hoc analysis was performed, using age and sex-adjusted ANOVA, to investigate whether the microstructural integrity within the WMH and NAWM of the 10% least decliners and the 10% worst decliners in Cognitive Index differed.

3. Results

Baseline demographics and neuro-imaging characteristics of the 398 participants in the in-person follow-up examination and the 105 subjects who did not participate are shown in Table 1. Average mean follow-up duration was 5.4 years (SD 0.2; range 4.5–6.2). Participants who did not return for in person-follow-up were significantly older at baseline, had a higher WMH volume, more lacunes, lower GM volume and a lower microstructural integrity of the WM compared with those with follow-up examination, adjusted for age and sex.

Fig. 2 shows the compound z-scores of the cognitive domains at baseline and follow-up. Decline in cognitive performance is observed in all domains except visuospatial memory and concept shifting.

A correlation matrix with the predictors in the dataset is presented as Supplementary Table C. Low microstructural integrity (measured by MD) in the NAWM was related to decline in Cognitive Index ($\beta = 0.17$; $p = 0.035$), adjusted for age, sex, education, presence of depressive symptoms at baseline, normalized TBV, lacunes and WMH volume,

however this was no longer significant after Bonferroni correction. No significant relation was found between white matter microstructural integrity and decline in any of the other cognitive sub-domains, adjusted for the abovementioned confounders after Bonferroni correction (Table 2). There was no significant relation found between diffusion parameters in the total white matter and any of the cognitive domains. Backward stepwise selection of all models confirmed these results (data not shown).

After stratification in tertiles of baseline WMH severity, we did not find a relation between white matter microstructural integrity and cognitive decline, in those with mild, moderate and WMH load, adjusted for the abovementioned confounders (data not shown).

A post-hoc analysis investigating the microstructural integrity within the WMH and NAWM in the 10% with the least decline in Cognitive Index and the 10% highest decliners, showed no significant difference in the mean MD or FA in both the WMH and NAWM, adjusted for age and sex.

4. Discussion

In older adults with SVD, microstructural integrity in the white matter was not related with decline in global cognitive performance in all separate cognitive domains after adjustment for possible confounders, after 5 years of follow-up. This finding was independent of WMH severity. This finding is in line with our previous findings, in which we found only limited additional value to conventional SVD parameters in explaining the variance in cognitive function [15], and the lack of relation between diffusion parameters and incident dementia after 5 years [19]. Probably other factors, apart from WM microstructural integrity play a role in cognitive decline over time.

Several methodological issues must be addressed. First and foremost, 79.1% of the baseline study population was available at follow-

Table 1
Baseline characteristics of the study population study-population

Data shown represent the numbers of subjects (%), mean (SD) or median †(interquartile range), ^age and sex adjusted where appropriate (ANOVA or logistic regression'). MMSE: Mini-Mental State Examination, ml: milliliters, SD: standard deviation, WMH: White Matter Hyperintensities, NAWM: normal appearing white matter, FA: Fractional Anisotropy, MD: Mean Diffusivity (10^{-3} mm^2/s). Brain volumes represent the normalized brain volumes to the total ICV. *One was excluded because of missing cognitive data, **five were excluded because of missing values of depressive symptoms, ***three were excluded because of missing values of microbleeds, ****three were excluded because of missing values of hippocampal volume. ᵉ3 were additionally excluded for the DTI analysis because of baseline DTI-scan artifacts.

	Follow-up-complete	No follow-up examination	p-Value for difference^
Demographics	(n = 398)	(n = 105)	
Age at baseline (SD)	64.5 (8.5)	70.0 (8.4)	**p < 0.001**
Sex, male (n, %)	227 (57.0)	57 (54.3)	p = 0.554ˡ
Education, only primary (n, %)	33 (8.3)	16 (15.2)	p = 0.396ˡ
MMSE (SD)	28.3 (1.6)	27.6 (1.8)	**p = 0.042**
Cognitive Index (SD)*	0.10 (0.76)	−0.44 (0.70)	**p < 0.001**
Depressive symptoms (n, %)**	266 (67.5)	65 (62.5)	p = 0.378ˡ
MRI characteristics	(n = 397)	(n = 105)	
Intracranial volume, ml (SD)	1459.0 (134.7)	1445.9 (147.3)	p = 0.707
White matter volume, ml (SD)	468.0 (39.6)	450.9 (57.1)	p = 0.285
WMH volume, ml (IQR)†	6.0 (3.2–15.1)	14.4 (6.0–27.2)	**p = 0.004**
NAWM volume, ml (SD)	455.6 (43.4)	430.5 (62.6)	p = 0.055
Lacunes, presence (n, %)	90 (22.7)	44 (41.9)	**p = 0.008ˡ**
Microbleeds, presence (n, %)***	58 (14.6)	23 (21.9)	p = 0.502ˡ
Territorial infarcts, presence (n, %)	40 (10.1)	16 (15.2)	p = 0.422ˡ
Gray matter volume, ml (SD)	621.5 (49.9)	595.3 (48.7)	**p = 0.022**
Total brain volume, ml (SD)	1089.4 (70.3)	1046.2 (77.3)	**p = 0.012**
Hippocampal volume, ml (SD)****	6.83 (0.94)	6.68 (0.97)	p = 0.879
Global DTI characteristicsᵉ	(n = 395)	(n = 104)	
White matter, mean FA, (SD)	0.33 (0.02)	0.32 (0.02)	**p = 0.029**
WMH, mean FA, (SD)	0.34 (0.03)	0.33 (0.03)	p = 0.424
NAWM, mean FA, (SD)	0.33 (0.02)	0.32 (0.02)	**p = 0.026**
White matter, mean MD,(SD)	0.88 (0.04)	0.91 (0.04)	**p = 0.012**
WMH, mean MD, (SD)	0.99 (0.06)	1.02 (0.07)	p = 0.172
NAWM, mean MD, (SD)	0.88 (0.04)	0.91 (0.04)	**p = 0.016**

Bold values indicate significance at p < 0.05.
They performed worse on the raw test scores of almost all cognitive domains at baseline compared with participants who participated (Supplementary Tables A and B).
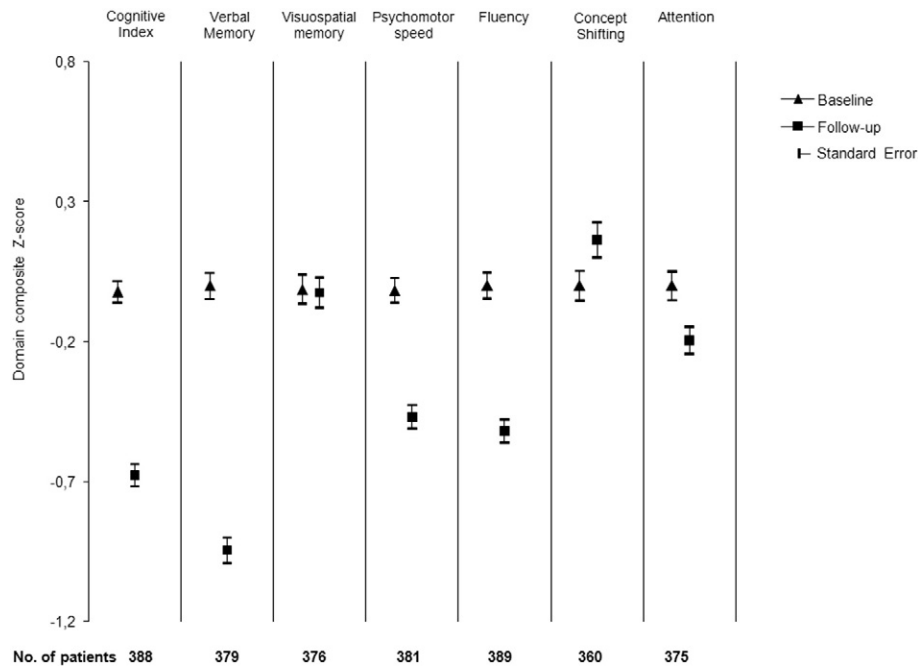
Fig. 2. Composite z-scores at baseline and follow-up. Bar represents the standard error. Apart from the domains visuospatial memory and concept shifting, participants score on average worse on follow-up test than at baseline. z-Scores of the follow-up are calculated with the mean and standard deviation from the baseline.

up for cognitive testing. The dropout might lead to attrition bias, although the response rate is considered high after 5 years. Drop-outs at follow-up were significantly older at baseline, performed less on cognitive testing at baseline and had a higher WMH volume, more lacunes and a lower microstructural integrity at baseline. Since these variables were independently associated with cognitive performance in other studies [14,22,38], exclusion of drop-outs might result in an underestimation of the effect of WM integrity on several cognitive domains. The abovementioned issue is a well known paradox of follow-up studies: To prove a causal relation over time, long follow-up is required, however, the longer the follow-up period, the higher the risk of selective dropout, which itself reduces the magnitude of the effect.

Second, the same cognitive tests have been administered at baseline and follow-up examination. Therefore it is possible that *learning effects* may have occurred. Especially cognitive tests with a memory-component are prone for this learning effect [39]. We think this would have had little effect in our study, because of the relatively long interval between the two moments of testing, and because in almost all cognitive domains, participants declined (Fig. 2), which

would be the opposite when learning effects would have great impact. A strength of our study design is that we collected our data in a single center, which allowed us to administer baseline and follow-up assessments according to identical procedures, using the same test-instructions and even interview-rooms, reducing measurement errors (non-systematic errors of the test score because of coincident fluctuations in concentration, motivation or mood, or differences in the test-procedure), as much as possible [39]. Finally, we were not informed on the genetic APOE status, CSF biomarkers or PET scan at baseline of our participants, which prevented us from further excluding possible neurodegenerative processes.

Three prospective studies described the relation between diffusion parameters and cognitive decline preciously. First, a large prospective study in older adults with SVD [18] reported a relation between baseline diffusion parameters and decline in executive function, memory and speed after a follow-up period of 3 years, after adjustment for age, sex, education, TBV, WMH and lacunes. However, they did not take depressive symptoms into account as a possible confounding factor. This is especially relevant since the same authors reported that depressive

Table 2
The relation between DTI parameters in both the white matter hyperintensities and the normal appearing white matter and decline in global cognitive performance
Numbers represent the standardized β's and are adjusted for age, sex, education, depressive symptoms, normalized total brain volume, lacunes and in the NAWM also for log normalized white matter hyperintensities. Composite z-score of follow-up is standardized to the baseline; (FU-test − mean baseline) / (SD baseline). Significance after Bonferroni correction p < 0.007.

	White Matter Hyperintensities		Normal appearing white matter	
	Mean Diffusivity	Fractional Anisotropy	Mean Diffusivity	Fractional Anisotropy
Global cognitive function				
MMSE	0.04; p = 0.556	− 0.07; p = 0.180	0.14; p = 0.083	− 0.06; p = 0.318
Cognitive Index	0.10; p = 0.122	0.01; p = 0.838	0.17; p = 0.035	− 0.07; p = 0.230
Memory				
Verbal memory	0.07; p = 0.305	0.01; p = 0.903	0.21; p = 0.008	− 0.08; p = 0.190
Visuospatial memory	0.00; p = 0.984	− 0.03; p = 0.555	0.03; p = 0.729	− 0.11; p = 0.068
Executive function and attention				
Psychomotor speed	0.04; p = 0.532	0.02; p = 0.717	0.01; p = 0.889	− 0.02; p = 0.717
Fluency	0.14; p = 0.027	− 0.07; p = 0.188	0.19; p = 0.015	− 0.15; p = 0.016
Inhibition (concept shifting)	0.01; p = 0.916	0.02; p = 0.787	− 0.03; p = 0.718	− 0.12; p = 0.054
Attention	0.09; p = 0.163	− 0.18; p = 0.001	0.03; p = 0.708	− 0.06; p = 0.317

Numbers represent the standardized β's and are adjusted for age, sex, education, depressive symptoms, normalized total brain volume, lacunes and in the NAWM also for log normalized white matter hyperintensities. Composite z-score of follow-up is standardized to the baseline; (FU-test − mean baseline) / (SD baseline). Significance after Bonferroni correction p < 0.007.

symptoms predicted cognitive decline and dementia in their cohort [40]. In our study, the adjustment for depressive symptoms did not weaken the associations between baseline microstructural integrity and cognitive decline. Additional analyses confirmed no mediation effect of depressive symptoms in this relation. This was not expected because the associations between depressive symptoms and worse cognitive performance in older participants have previously extensively been described [41]. Second, a small prospective study (n = 35) with a one-year follow-up in participants with SVD found a relation between diffusion parameters and executive function at a cross-sectional level, however they could not relate diffusion parameters to cognitive decline [17], possibly by the relatively short follow-up period and small numbers. The third study (n = 84) in middle-aged community dwelling individuals found no correlations between baseline DTI parameters and changes in working memory, but showed that decline in working memory was correlated to decline in DTI parameters after 2 years [16]. This study however did not adjust for possible confounders. Taking the previous findings into account, in the future it could be interesting to investigate if the *change* in microstructural integrity over time instead of the baseline microstructural status, causes cognitive decline.

Finally we have to consider we missed the (very weak) association between baseline DTI parameters and cognitive decline, because of a type A error possibly due to limited power and selective drop-out at follow-up, which was in our study, despite the high response, 20.9%. As a result, our sample may consist of participants with a relatively good health and cognitive performance at baseline who may have less chance to deteriorate in cognitive functioning over time. However in our study this seems to be not the case, for post-hoc analyses comparing the microstructural integrity in the 10% least decliners versus the 10% who declined most at follow-up showed no difference in any of the diffusion parameters, both within the WMH or NAWM. Moreover, participants at follow-up with low test-scores because of cognitive problems or dementia have had difficulties performing complex neuropsychological tests which may have resulted in missing data (such as task 3 of the Stroop or the Rey Complex Figure). This may have resulted in an underestimation of the decline in the domains assessed by these tests, which might have weakened the strengths of the associations. Finally, the cognitive change profile in our study shows predominantly a change in verbal memory, which does not reflect the core profile of SVD where deficits in executive function, such as speed and fluency, are most prominent. Probably other factors than white matter microstructural integrity play a role in cognitive decline. Such a factor could be the microstructural integrity of other areas in the brain known to be related to cognitive performance, such as the hippocampus, as we previously showed [42].

5. Conclusions

In summary, in older adults with SVD, microstructural integrity of the WM was not associated with decline in cognitive performance after a 5-year follow-up. These results are not in line with cross-sectional reports, and therefore unexpected. The lack of association might be due to a type A error, due to selective drop-out at follow-up, however this was not supported by a post-hoc analysis. Other factors than microstructural integrity of the white matter might underlie cognitive decline in older adults with SVD.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgments

No conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.bbacli.2015.10.001.

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