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Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study

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ABSTRACT

White matter microstructural integrity has been related to cognition. Yet, the potential role of specific white matter tracts on top of a global white matter effect remains unclear, especially when considering specific cognitive domains. Therefore, we determined the tract-specific effect of white matter microstructure on global cognition and specific cognitive domains. In 4400 nondemented and stroke-free participants (mean age 63.7 years, 55.5% women), we obtained diffusion magnetic resonance imaging parameters (fractional anisotropy and mean diffusivity) in 14 white matter tracts using probabilistic tractography and assessed cognitive performance with a cognitive test battery. Tract-specific white matter microstructure in all supratentorial tracts was associated with poorer global cognition. Lower fractional anisotropy in association tracts, primarily the inferior fronto-occipital fasciculus, and higher mean diffusivity in projection tracts, in particular the posterior thalamic radiation, most strongly related to poorer cognition. Altered white matter microstructure related to poorer information processing speed, executive functioning, and motor speed, but not to memory. Tract-specific microstructural changes may aid in better understanding the mechanism of cognitive impairment and neurodegenerative diseases.

1. Introduction

Brain white matter damage is increasingly recognized as an important factor in the pathophysiology of cognitive impairment and dementia (Brun and Englund, 1986; Pievani et al., 2010; Sexton et al., 2011; Wang et al., 2012). Evidence shows that macrostructural white matter changes, such as white matter lesions, white matter atrophy, and lacunes, relate to poorer cognitive performance. Studies have already suggested a regional pattern of association between these macrostructural white matter changes and specific cognitive domains (Benjamin et al., 2014; Smith et al., 2014; Vernooij et al., 2009). At the same time, it is thought that such conventional markers only represent the tip of the iceberg of white matter changes. Focusing on microstructural changes by means of the microstructural integrity of the white matter may provide a more in-depth insight of alterations in the white matter. Perhaps more importantly, the white matter is not a bulk substance but consists of different white matter tracts, which are important for the connection of different cortical regions (Doricchi et al., 2008). Changes in white matter microstructural integrity are accompanied by changes in diffusion magnetic resonance imaging (MRI) parameters. Fractional anisotropy (FA) is generally lower and mean diffusivity (MD) is generally higher (with exceptions) in older or diseased brains, which is thought to reflect reduced white matter microstructure (Beaulieu, 2002; Maclullich et al., 2009).

Altered microstructure of white matter tracts, for example, as a result of aging or pathologic processes, is presumed to lead to loss of communication between cortical regions, resulting in poorer cognitive performance, the so-called “disconnection hypothesis” (Nazeri et al., 2015; O’Sullivan et al., 2001; Salat et al., 2005; Teipel et al., 2014; Vernooij et al., 2009). Information processing speed and executive function are the most consistently impaired cognitive functions that have been related to white matter damage (Santiago et al., 2015; Tuladhar et al., 2015; Zhang et al., 2015). However, the potential role of specific white matter tracts on top of a global white matter effect in cognitive performance remains unclear, especially when considering specific cognitive domains. It is necessary to investigate these potential roles for specific white matter tracts to

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elucidate probable mechanism of cognitive impairment and neurodegenerative diseases. Therefore, the purpose of this study was to determine the tract-specific effect of white matter microstructure on global cognition and specific cognitive domains in a large, middle aged, and elderly population of 4400 persons from the population-based Rotterdam Study (Hofman et al., 2015), using diffusion MRI.

2. Materials and methods

2.1. Study population

This study is based on participants from the Rotterdam Study, an ongoing, prospective, population-based cohort study including participants of 45 years and older living in Ommoord, a suburb of Rotterdam (Hofman et al., 2015). From 2005 onward, MRI scanning was included in the study protocol (Ikram et al., 2011). Between 2006 and 2011, 5430 nondemented participants without contraindications for MRI (including claustrophobia) were eligible for scanning. Among these persons, 4841 underwent a multisequence MRI acquisition of the brain, including diffusion-weighted MRI scanning. We excluded scans with incomplete acquisitions ($n = 53$), scans with artifacts hampering automated processing ($n = 112$), and scans with MRI-defined cortical infarcts ($n = 160$). We additionally excluded 116 participants with history of clinical stroke. This resulted in 4400 individuals with analyzable MRI data. Of these, 3876 participants had fully available cognition data. MRI scanning and cognitive assessment took place at the same visit, apart from 677 participants who underwent MRI scanning on average 1.9 years (standard deviation [SD] 0.6) before cognitive assessment.

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants gave written informed consent.

2.2. MRI acquisition and processing

We performed multisequence MRI on a 1.5-T MRI scanner (GE Signa Excite), undergoing a quality assurance protocol keeping the system unchanged (no major updates or upgrades) for the period of inclusion. The imaging protocol was described extensively elsewhere (Ikram et al., 2011). Because of a technical problem between February 2007 and May 2008, 1312 subjects were scanned with the phase and frequency encoding directions swapped for the diffusion acquisition, which led to a mild ghosting artifact in the phase encoding direction (de Groot et al., 2015). This was treated as a potential confounder in the analysis (see Section 2.7).

An automated tissue segmentation approach was used to classify scans into gray matter, white matter, cerebrospinal fluid (CSF), and background tissue. Intracranial volume (ICV) (excluding the cerebellum and surrounding CSF) was estimated by summing total gray and white matter and CSF volumes and used to correct for head size (Vrooman et al., 2007).

White matter lesions (WMLs) were identified using an automated postprocessing step based on the fluid-attenuated inversion recovery image and the tissue segmentation (de Boer et al., 2009). We visually assessed the presence of infarcts on structural MRI sequences, and in case of involvement of cortical gray matter, we classified them as cortical infarcts.

2.3. Diffusion-MRI processing and tractography

For diffusion MRI, we performed a single shot, diffusion-weighted spin echo echo-planar imaging sequence. Maximum b value was 1000 seconds/mm^2 in 25 noncollinear directions; 3 volumes were acquired without diffusion weighting (b value = 0 second/mm^2). All diffusion data were preprocessed using a standardized pipeline (Koppelmans et al., 2014). In short, eddy current and head-motion correction were performed on the diffusion data. The resampled data were used to fit diffusion tensors, allowing (in combination with the tissue segmentation) computation of global mean FA and MD in the normal-appearing white matter.

The diffusion data were also used to segment white matter tracts using a diffusion tractography approach described previously (de Groot et al., 2015). For 14 different white matter tracts (11 of which segmented bilaterally), tract-specific white matter microstructural diffusion-MRI parameters (median FA and MD) were obtained with subsequent combination of left and right measures (Fig. 1) (de Groot et al., 2015). The average reproducibility of our tract-specific measurements was 87%, which is good (de Groot et al., 2015). We standardized tract-specific diffusion-MRI parameters (0 mean and unit SD) to facilitate comparison of associations. Tracts were categorized, based on anatomy, into brainstem tracts, projection tracts, association tracts, limbic system tracts, and callosal tracts (de Groot et al., 2015).

Tract segmentations were also used to acquire tract-specific white matter volumes and by combining the tissue and tract segmentation tract-specific WML volumes. Tract-specific WML volumes were natural-log transformed, to account for their skewed distribution.

The cerebellum could not be fully incorporated in the field of view of the diffusion-MRI scan, resulting in partial coverage of the medial lemniscus at the lower border of the scan. To overcome this problem, alternative seed masks for tractography were selected until reasonable coverage was achieved (de Groot et al., 2015). This correction was treated as a potential confounder in all models that included the medial lemniscus (see Section 2.7).

2.4. Assessment of cognitive function

Cognitive function was assessed in all the participants with the following cognitive test battery: 15-Word Learning Test (15-WLT),

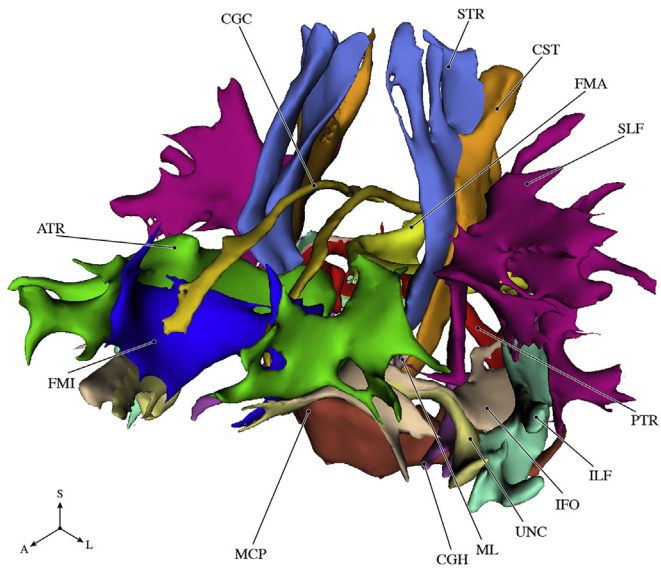

Fig. 1. Overview of white matter tracts. Abbreviations: A, anterior; ATR, anterior thalamic radiation; CGC, cingulate gyrus part of cingulum; CGH, parahippocampal part of cingulum; CST, corticospinal tract; FMA, forceps major; FMI, forceps minor; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L, lateral; MCP, middle cerebellar peduncle; ML, medial lemniscus; PTR, posterior thalamic radiation; S, superior; SLF, superior longitudinal fasciculus; STR, superior thalamic radiation; and UNC, uncinated fasciculus.

which tests immediate and delayed recall to investigate memory (Bleecker et al., 1988); Stroop Tests (reading, color-naming, and interference), which tap into information processing speed and executive function (Goethals et al., 2004; Golden, 1976); Letter-Digit Substitution Task (Lezak, 1984) and Word Fluency Test (WFT) (Welsh et al., 1994), both of which test executive function; and the Purdue Pegboard Test to measure fine motor speed (Desrosiers et al., 1995).

To aid comparison across cognitive tests, we generated *z* scores for each cognitive test. The *z* scores for the Stroop Tests were inverted: higher scores on the Stroop test indicate a poorer performance, whereas higher scores on the other cognitive tests indicate better cognitive performance. In addition, we also investigated global cognition by constructing a g-factor using a principal component analysis on the delayed recall score of the 15-WLT, Stroop Interference Test, Letter-Digit Substitution Task, Word Fluency Test, and Purdue Pegboard Test (Hoogendam et al., 2014).

2.5. Ascertainment of dementia and clinical stroke

Prevalent dementia and clinical stroke were ascertained as previously described (Akoudad et al., 2015; Roth et al., 1986; Schrijvers et al., 2012), and these patients were excluded.

2.6. Other measurements

The following cardiovascular risk factors, based on information derived from home interviews and physical examinations during the center visit, were assessed. Blood pressure was measured twice in sitting position using a random-zero sphygmomanometer, and the average of 2 measurements was used in the analyses. Information on the use of antihypertensive medication was collected by using questionnaires and by checking the medication cabinets of the participants. Total serum cholesterol and high-density lipoprotein cholesterol were determined in blood serum, taking lipid-lowering medication into account. Smoking was assessed by interview and coded as never, former, and current. Diabetes mellitus status was determined based on fasting serum glucose level ($\geq$7.0 mmol/L), if unavailable, nonfasting serum glucose level ($\geq$11.1 mmol/L), or the use of antidiabetic medication (Hofman et al., 2015). The participants' attained level of education was collected and was categorized into 7 categories, ranging from primary education only to university level.

Missing values on cardiovascular risk factors and education (<3% for all variables) were imputed by multiple imputation ($n = 5$), based on age, sex, education, serum cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, diastolic blood pressure, antihypertensive medication, lipid-lowering medication, smoking, and diabetes.

Apolipoprotein E (APOE)-ε4 allele carriership was assessed on coded genomic DNA samples (Wenham et al., 1991). APOE genotype was in Hardy-Weinberg equilibrium.

2.7. Statistical analysis

First, we created scatterplots correlating tract-specific diffusion parameters with global cognition (g-factor), adjusted for age and sex, to explore linearity of the associations. Next, associations of tract-specific diffusion measurements with cognitive performance were evaluated using multivariable linear regression models. Standardized betas and 95% confidence intervals (CIs) were estimated on standardized FA or MD within each tract. We performed analyses in 3 models. In model I, analyses were adjusted for age, sex, education, ICV, tract-specific white matter volume, and tract-specific WML volume. In model II, we additionally adjusted for cardiovascular risk factors and *APOE-ε4* allele carriership, to study whether there were pathways relating white matter microstructure to cognition, other than those involving these factors. This is relevant because vascular factors may be considered either confounders or part of the causal chain from vascular factors through white matter microstructure to cognition. We furthermore applied model III, which additionally adjusted for global FA (for analyses with tract-specific FA as determinant) or for global MD (for analyses with tract-specific MD as determinant) on top of model II, to study whether specific tracts provided additional information above global white matter diffusion-MRI parameters. In all analyses, we treated the phase encoding direction of the diffusion scan as a potential confounder. For analyses in which the medial lemniscus was studied, we additionally adjusted for the variable position of seed masks, as explained earlier.

We compared effect sizes across associations of different tracts and cognitive tests using *Z* tests $(\text{beta}_1 - \text{beta}_2)/\sqrt{(\text{standard error}_1^2 + \text{standard error}_2^2)}$ to investigate whether the association with cognition in certain tracts was significantly different across tracts. For all betas and standard errors, see Supplementary Table A1. Moreover, we performed a series of sensitivity analyses, excluding the participants who underwent MRI scanning on average 1.9 years before cognitive assessment, and we also excluded participants with a Mini-Mental State Examination (MMSE) <26. We corrected the *p* value (alpha level of 0.05) for multiple comparisons using Šidák correction, after estimating the number of independent tests, resulting in a threshold for significance of $p < 0.0006$ (Nyholt, 2004, 2005). All analyses were carried out using R, version 2.15.0.

3. Results

Table 1 presents the characteristics of the study population. Mean age of the participants was 63.7 ± 11.1 years, and 55.5% were women. Scatterplots correlating tract-specific diffusion parameters with global cognition (g-factor), adjusted for age and sex, are shown in Supplementary Figs. A1 and A2.

The association of tract-specific diffusion parameters and global cognition is presented in Table 2 and in Fig. 2. Lower FA and higher MD in all tracts (except for brainstem tracts) were associated with lower global cognition. For FA, white matter microstructure in the association tracts followed by the callosal tracts was most strongly related with global cognition. After adjusting for cardiovascular risk factors and *APOE-ε4* allele carriership (model II), the mean difference in g-factor (*z* score) per SD increase of FA in the association tracts ranged from 0.09 (CI: 0.06, 0.12) to 0.12 (CI: 0.09, 0.16), in the callosal tracts from 0.09 (CI: 0.05, 0.12) to 0.11 (CI: 0.08, 0.14). For MD, white matter microstructure in the projection tracts, followed by the association tracts, was most strongly related with global cognition. Mean difference in *z* score for the g-factor per SD increase of MD in the projection tracts, after adjusting for cardiovascular risk factors and *APOE-ε4* allele carriership, ranged from −0.16 (CI: −0.20, −0.13) to −0.18 (CI: −0.22, −0.14), in the association tracts from −0.11 (CI: −0.14, −0.08) to −0.16 (CI: −0.20, −0.12). After controlling for global FA or global MD (model III), the associations attenuated, but most of the associations remained significant. Table 3 presents the associations of white matter microstructure with cognitive performance on separate cognitive tests after adjustment for age, sex, education, ICV, tract-specific white matter volume, tract-specific WML volume, cardiovascular risk factors, and *APOE-ε4* allele carriership (model II). Higher values of FA in all tracts (except the brain stem tracts), but mainly in the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus (association tracts), forceps minor (callosal tract),

Table 1
Population characteristics

Characteristics	Total ($N = 4400$)
Age, y	63.7 (11.1)
Sex, F	2444 (55.5)
Cognitive tests results[a]	
WLT, immediate recall (sum of 3 trials)	23.3 (6.5)
WLT, delayed recall	7.7 (2.9)
Stroop Test	
Reading subtask of Stroop Test, s	17.0 (3.4)
Color naming subtask of Stroop Test, s	23.2 (4.6)
Interference subtask of Stroop Test, s	47.7 (17.2)
Letter-Digit Substitution Task, number of correct digits	30.4 (7.1)
Word Fluency Test, number of animals	23.0 (6.0)
Purdue Pegboard Test, number of pins placed	10.5 (1.9)
Education[b]	3 (1–4)
Systolic blood pressure, mmHg	139.3 (21.5)
Diastolic blood pressure, mmHg	83.1 (10.8)
Blood pressure–lowering medication	1555 (35.3)
Serum cholesterol, mmol/L	5.5 (1.1)
HDL cholesterol, mmol/L	1.5 (0.4)
Lipid-lowering medication	1231 (28.0)
Smoking	
Never	1363 (31.0)
Former	2130 (48.4)
Current	907 (20.6)
Diabetes mellitus	413 (9.4)
APOE-ε4 allele carriership	1184 (28.8)
Normal appearing white matter volume, mL	404.1 (61.6)
ICV, mL	1340.0 (133.1)
White matter lesion volume[b], mL	2.9 (1.6–6.0)
Mean FA	0.3 (0.02)
Mean MD, 10^{-3} mm^2/second	0.7 (0.03)

Continuous variables are presented as means (standard deviations) and categorical variables as *n* (%). Data on *APOE-ε4* allele carriership were missing in 287 persons. Global FA and global MD were missing in 173 participants because of failed segmentation.

Key: APOE-ε4, apolipoprotein E-ε4; F, female; FA, fractional anisotropy; ICV, intracranial volume; HDL, high-density lipoprotein; MD, mean diffusivity × 10^{-3} mm^2/seconds; *N*, number of participants; WLT, Word Learning Test.

[a] Cognitive tests were available for WLT, immediate recall, in $n = 4186$, WLT, delayed recall, in $n = 4134$, reading subtask of Stroop Test in $n = 4207$, color naming subtask of Stroop Test in $n = 4207$, interference subtask of Stroop Test in $n = 4200$, Letter-Digit Substitution Task in $n = 4234$, Word Fluency Test in $n = 4272$, and Purdue Pegboard Test in $n = 4087$.

[b] Education and white matter lesion volume are presented as median (interquartile range).

and the posterior thalamic radiation (projection tract), were generally associated with a better performance on the Stroop Tests, Letter-Digit Substitution Task, the Purdue Pegboard Test, and, to a lesser degree, on the Word Fluency Test. Higher values of MD in all tracts, but mainly in the projection tracts (especially in the posterior thalamic radiation) and in the association tracts, in particular in the inferior fronto-occipital fasciculus, were associated with poorer performance on the Stroop Tests, Letter-Digit Substitution Task, the Purdue Pegboard Test, and, also to a lesser degree, on the Word Fluency Test. Additionally, adjusting for global FA or global MD (Table 4) attenuated most of the associations, but most of the projection and association tracts remained significant, with again the strongest associations for the inferior fronto-occipital fasciculus and the posterior thalamic radiation. We did not find any association between tract-specific microstructure and memory (15-WLTs). Overall, the effect sizes of the projection, association, and callosal tracts with the different cognitive tests were significantly larger than the effect sizes of the brain stem and the limbic system (data not shown). This was particularly true for the posterior thalamic radiation and the inferior fronto-occipital fasciculus, which showed strongest effects among all tracts.

Excluding 677 participants who underwent MRI scanning on average 1.9 years before cognitive assessment yielded similar findings (data not shown). Also, excluding participants with a MMSE <26 yielded similar results (data not shown). There was no significant interaction between the microstructure of any of the tracts and *APOE-ε4* allele carriership after correction for multiple testing.

4. Discussion

In this study among middle-aged and elderly persons, altered tract-specific white matter microstructure in all supratentorial tracts was associated with poorer cognitive performance, independent from age and macrostructural white matter pathology. Specifically, we found that these associations were driven by lower FA and higher MD, which have been suggested to reflect reduced white matter microstructural integrity (Beaulieu, 2002). Altered supratentorial tract-specific white matter microstructure was related to poorer information processing speed, executive function, and motor speed, but not to memory. We found tract-specific differences for associations with cognitive function: among the 14 white matter tracts, the microstructural integrity in the posterior thalamic radiation (projection tract) and the inferior fronto-occipital fasciculus (association tract) were most strongly associated with cognitive performance.

Strengths of this study include the large sample size and the population-based setting. Furthermore, we performed a tract-specific analysis in 14 main white matter tracts, and the tract-specific measurements were performed with fully automated, publicly available methods (de Groot et al., 2013).

Some limitations need to be considered. Because of the cross-sectional design, no conclusions can be drawn on the directionality of causality of the associations. Furthermore, the evaluation of cognitive performance in this study is less extensive compared with some other studies. However, we constructed a g-factor as a marker of global cognition using 5 different cognitive test variables, under the assumption that these tests are representative of various cognitive domains. This facilitates comparison with other studies, even when the incorporated cognitive tests are slightly different because g-factors constructed of different cognitive tests across different test batteries are highly correlated and can be interpreted as stable factors in a variety of cognitive domains (Johnson, 2008).

We performed a complete-case analysis to construct a g-factor and this might have caused some selection bias, as persons who did not have values for all cognitive tests were not included. Another aspect to note is that we used median FA and MD in each white matter tract. Although the median is more robust to variation in the tails of the measurement distributions compared to the mean, capturing an entire tract in a single measurement discards spatial information that is retained in voxel-based techniques. Finally, the cerebellum could not be fully incorporated in the field of view, making analyses on brain stem tracts less reliable.

Several papers have studied the association of white matter microstructure and cognition (Burzynska et al., 2015; Kuznetsova et al., 2015; Metzler-Baddeley et al., 2012; Penke et al., 2010; Vernooij et al., 2009). A global white matter effect has already been associated with cognition. The main novelty of our article is that we show that tract-specific diffusion MRI measures (when adjusted for global diffusion-MRI measures) provide more information above global diffusion-MRI measures. Furthermore, by using a cognitive test battery rather than a single test, our study is not limited to a specific cognitive domain.

In a previous study investigating the association of age and white matter microstructure, in the same community-dwelling population, a widespread altered (except for the sensorimotor tracts, including brainstem tracts) white matter microstructural

Table 2
Associations of FA and MD with global cognition (g-factor)

White matter tracts	FA			MD		
	Model I	Model II	Model III	Model I	Model II	Model III
Brainstem tracts						
Middle cerebellar peduncle	−0.01 (−0.05, 0.03)	−0.01 (−0.05, 0.03)	−0.01 (−0.05, 0.03)	−0.01 (−0.04, 0.02)	0.00 (−0.03, 0.03)	0.02 (−0.01, 0.05)
Medial lemniscus[a]	0.03 (0.00, 0.06)	0.03 (0.00, 0.06)	0.01 (−0.02, 0.05)	**−0.05 (−0.08, −0.02)**	−0.04 (−0.07, −0.01)	0.00 (−0.03, 0.03)
Projection tracts						
Corticospinal tract	0.01 (−0.02, 0.03)	0.01 (−0.02, 0.04)	−0.02 (−0.05, 0.01)	**−0.17 (−0.20, −0.13)**	**−0.16 (−0.19, −0.12)**	**−0.11 (−0.17, −0.06)**
Anterior thalamic radiation	**0.07 (0.04, 0.10)**	**0.07 (0.04, 0.10)**	0.04 (0.00, 0.08)	**−0.17 (−0.21, −0.13)**	**−0.16 (−0.20, −0.12)**	**−0.13 (−0.19, −0.07)**
Superior thalamic radiation	0.01 (−0.02, 0.04)	0.01 (−0.01, 0.04)	−0.02 (−0.05, 0.01)	**−0.17 (−0.21, −0.13)**	**−0.16 (−0.20, −0.13)**	**−0.13 (−0.19, −0.07)**
Posterior thalamic radiation	**0.11 (0.08, 0.14)**	**0.10 (0.07, 0.14)**	**0.09 (0.05, 0.13)**	**−0.19 (−0.23, −0.15)**	**−0.18 (−0.22, −0.14)**	**−0.14 (−0.19, −0.09)**
Association tracts						
Superior longitudinal fasciculus	**0.09 (0.06, 0.12)**	**0.09 (0.06, 0.12)**	0.06 (0.01, 0.11)	**−0.13 (−0.16, −0.09)**	**−0.13 (−0.16, −0.09)**	−0.06 (−0.13, 0.00)
Inferior longitudinal fasciculus	**0.11 (0.08, 0.14)**	**0.10 (0.07, 0.13)**	**0.09 (0.05, 0.13)**	**−0.14 (−0.18, −0.10)**	**−0.13 (−0.17, −0.10)**	−0.10 (−0.16, −0.04)
Inferior fronto–occipital fasciculus	**0.13 (0.10, 0.16)**	**0.12 (0.09, 0.16)**	**0.11 (0.07, 0.15)**	**−0.17 (−0.20, −0.13)**	**−0.16 (−0.20, −0.12)**	**−0.13 (−0.20, −0.07)**
Uncinate fasciculus	**0.06 (0.03, 0.09)**	0.06 (0.02, 0.09)	−0.01 (−0.05, 0.04)	**−0.11 (−0.14, −0.08)**	**−0.11 (−0.14, −0.08)**	−0.02 (−0.08, 0.04)
Limbic system tracts						
Cingulate gyrus part of cingulum	**0.07 (0.05, 0.10)**	**0.07 (0.04, 0.10)**	0.04 (0.01, 0.07)	**−0.09 (−0.11, −0.06)**	**−0.08 (−0.11, −0.05)**	0.00 (−0.04, 0.04)
Parahippocampal part of cingulum	**0.05 (0.02, 0.08)**	**0.05 (0.02, 0.08)**	0.03 (0.00, 0.06)	**−0.07 (−0.10, −0.04)**	**−0.07 (−0.10, −0.04)**	−0.03 (−0.06, 0.00)
Callosal tracts						
Forceps major	**0.09 (0.06, 0.12)**	**0.09 (0.05, 0.12)**	0.06 (0.02, 0.10)	**−0.12 (−0.16, −0.09)**	**−0.12 (−0.16, −0.08)**	−0.07 (−0.12, −0.02)
Forceps minor	**0.12 (0.09, 0.15)**	**0.11 (0.08, 0.14)**	0.07 (0.03, 0.11)	**−0.15 (−0.18, −0.12)**	**−0.14 (−0.18, −0.11)**	−0.07 (−0.13, −0.02)

Values represent the mean differences in *z* score (95% confidence interval) of the g-factor per standard deviation increase of FA or MD. Results in bold were significant after correction for multiple testing ($p < 6.0 \times 10^{-4}$). Model I: adjusted for age, sex, education, intracranial volume, WM, and log-transformed white matter lesion volumes of the investigated tract. Model II: model I and additionally adjusted for cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, antihypertensive medication, serum cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, smoking, and diabetes) and *apolipoprotein E-ε4* (*APOE-ε4*) allele carriership. Model III: model II and additionally adjusted for mean global FA or mean global MD.
Key: FA, fractional anisotropy; g-factor, general cognitive factor (incorporating Word Learning Test, delayed recall, interference subtask of Stroop Test, Letter-Digit Substitution Test, Word Fluency Test, and Purdue Pegboard Test); MD, mean diffusivity $\times 10^{-3}$ mm^2/second, g-factor available in $N = 3876$; WM, white matter.
[a] Additionally adjusted for the variable position of the seed mask.

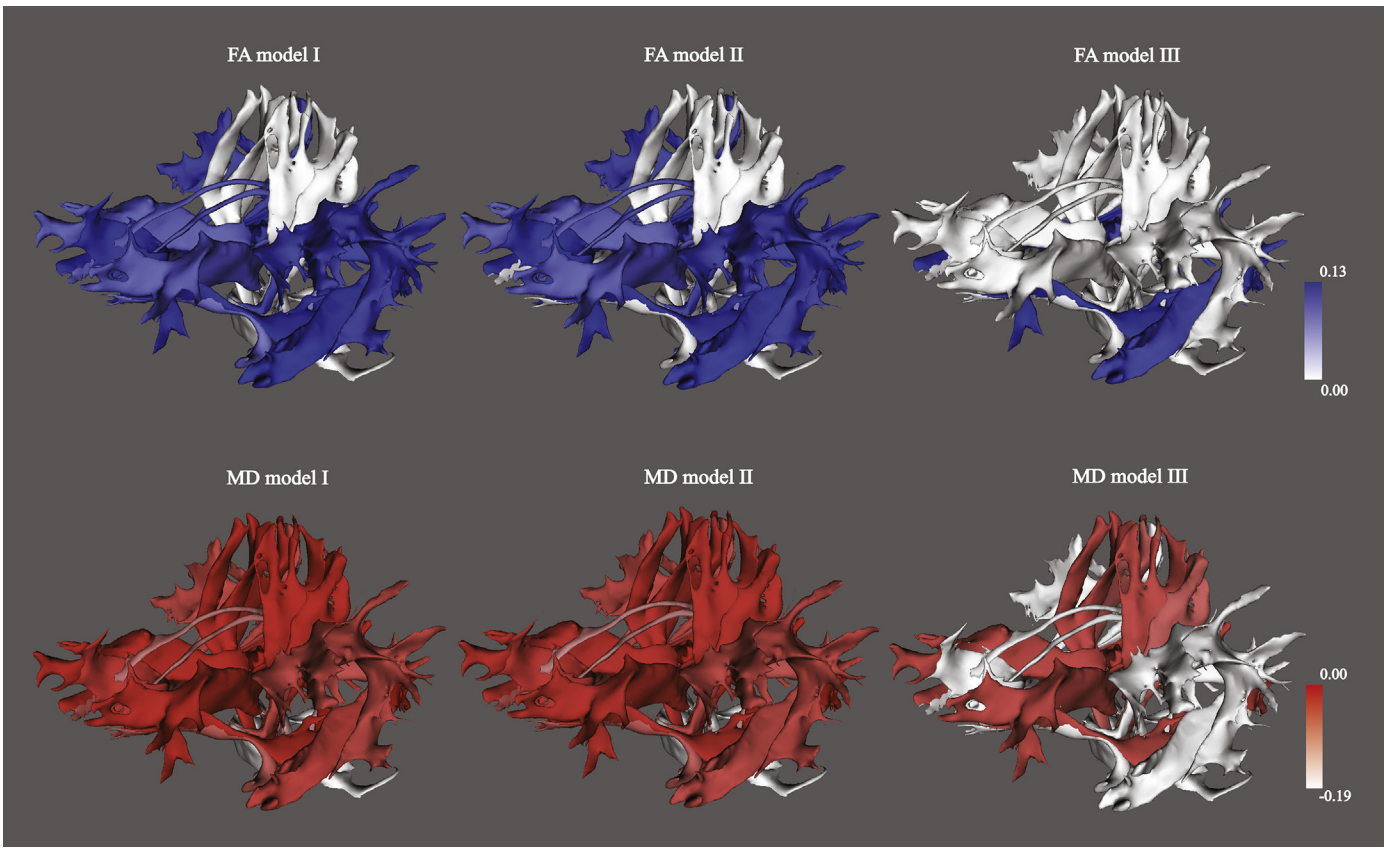

Fig. 2. Diffusion-magnetic resonance imaging measures and global cognition. Mean differences in *z* score of global cognition for all 14 white matter tracts in the population, presented in a single-subject anatomy for visualization. Colors reflect the mean differences in *z* score per standard deviation increase of FA (row 1) or MD (row 2), adjusted for age, sex, education, ICV, tract-specific WM volume, and tract-specific WML volume (model I). Model II is model I and additionally adjusted for cardiovascular risk factors and *APOE-ε4* allele carriership. Model III adjusts for global FA or global MD on top of model II. Higher strength of association is depicted in darker blue for positive associations and darker red for negative associations, with nonsignificant associations displayed in white. Abbreviations: APOE-ε4, apolipoprotein E-ε4; FA, fractional anisotropy; ICV, intracranial volume; MD, mean diffusivity; and WML, white matter lesion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Associations of tract-specific FA and MD with separate cognitive tests

White matter tracts	Immediate memory	Delayed memory	Stroop 1	Stroop 2	Stroop 3	LDST	Word Fluency	Pudue Pegboard
FA								
Brainstem tracts								
Middle cerebellar peduncle	0.01	0.01	-0.03	-0.01	0.03	0.01	-0.02	0.02
Medial lemniscus [a]	0.01	0.01	0.04	0.03	0.01	0.05	0.04	-0.01
Projection tracts								
Corticospinal tract	-0.02	-0.01	0.00	0.02	0.01	0.03	-0.01	0.01
Anterior thalamic radiation	0.03	0.02	0.05	0.08	0.07	0.07	0.02	0.05
Superior thalamic radiation	0.00	0.01	0.01	0.02	0.03	0.02	0.00	0.01
Posterior thalamic radiation	0.01	-0.01	0.06	0.09	0.10	0.12	0.05	0.12
Association tracts								
Superior longitudinal fasciculus	0.01	0.00	0.09	0.10	0.10	0.09	0.04	0.09
Inferior longitudinal fasciculus	0.01	-0.01	0.07	0.10	0.11	0.10	0.05	0.09
Inferior fronto-occipital fasciculus	0.01	-0.01	0.10	0.12	0.12	0.13	0.09	0.11
Uncinate fasciculus	-0.01	-0.01	0.03	0.05	0.05	0.06	0.03	0.05
Limbic system tracts								
Cingulate gyrus part of cingulum	0.00	-0.03	0.06	0.09	0.09	0.07	0.04	0.05
Parahippocampal part of cingulum	-0.01	0.00	0.04	0.05	0.06	0.03	0.08	0.04
Callosal tracts								
Forceps major	0.03	0.01	0.08	0.08	0.09	0.08	0.05	0.09
Forceps minor	0.01	0.00	0.10	0.13	0.11	0.11	0.05	0.11
MD								
Brainstem tracts								
Middle cerebellar peduncle	0.00	0.00	-0.01	-0.01	-0.04	-0.01	0.00	0.01
Medial lemniscus [a]	0.01	0.01	0.00	-0.02	-0.06	0.05	-0.02	-0.01
Projection tracts								
Corticospinal tract	-0.04	-0.03	-0.09	-0.13	-0.13	-0.15	-0.10	-0.13
Anterior thalamic radiation	-0.05	-0.05	-0.10	-0.13	-0.16	-0.14	-0.10	-0.10
Superior thalamic radiation	-0.03	-0.03	-0.10	-0.13	-0.15	-0.15	-0.10	-0.12
Posterior thalamic radiation	-0.05	-0.04	-0.11	-0.16	-0.18	-0.16	-0.11	-0.13
Association tracts								
Superior longitudinal fasciculus	-0.01	-0.02	-0.09	-0.11	-0.12	-0.13	-0.07	-0.09
Inferior longitudinal fasciculus	-0.03	-0.02	-0.09	-0.12	-0.15	-0.12	-0.08	-0.10
Inferior fronto-occipital fasciculus	-0.04	-0.03	-0.11	-0.14	-0.17	-0.14	-0.10	-0.14
Uncinate fasciculus	0.01	-0.01	-0.04	-0.07	-0.10	-0.11	-0.07	-0.08
Limbic system tracts								
Cingulate gyrus part of cingulum	0.01	0.01	-0.02	-0.04	-0.07	-0.07	-0.05	-0.06
Parahippocampal part of cingulum	-0.02	-0.04	-0.01	-0.02	-0.07	-0.04	-0.06	-0.02
Callosal tracts								
Forceps major	-0.01	-0.02	-0.09	-0.08	-0.11	-0.10	-0.07	-0.09
Forceps minor	-0.03	-0.03	-0.09	-0.13	-0.13	-0.14	-0.09	-0.13

Values represent the mean differences in *z* score of each cognitive test per standard deviation increase of FA or MD. The colored cells represent significant associations surviving multiple testing ($p < 6.0 \times 10^{-4}$) and the intensity in red and blue reflects the magnitude of the associations whereby darker colors reflect stronger associations. Results are adjusted for age, sex, education, intracranial volume, WM, and log-transformed white matter volumes of the investigated tract, cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, antihypertensive medication, serum cholesterol, HD cholesterol, lipid-lowering medication, smoking, and diabetes), and *apolipoprotein E-ε4* (*APOE-ε4*) allele carriership.
Key: FA, fractional anisotropy; LDST, Letter-Digit Substitution Task; MD, mean diffusivity $\times 10^{-3}$ mm^2/second; WM, white matter.
[a] Additionally adjusted for the variable position of the seed mask.

integrity with age was found (de Groot et al., 2015). In extension to this study, we now demonstrate that altered microstructural integrity of the same supratentorial tracts is associated with poorer cognitive performance, independent from age and cardiovascular risk factors. Also, after excluding participants with possible mild cognitive impairment (MMSE <26), the associations remained significant.

The association between tract-specific white matter microstructure and global cognition was particularly driven by information processing speed, executive function, and motor speed, but not

Table 4
Associations of tract-specific FA and MD with separate cognitive tests adjusted for global DTI

White matter tracts	Immediate memory	Delayed memory	Stroop 1	Stroop 2	Stroop 3	LDST	Word Fluency	Purdue Pegboard
FA								
Brainstem tracts								
Middle cerebellar peduncle	0.02	0.02	-0.03	-0.01	0.03	0.01	-0.02	-0.03
Medial lemniscus [a]	0.01	0.01	0.03	0.01	-0.01	0.03	0.03	-0.03
Projection tracts								
Corticospinal tract	-0.02	-0.01	-0.03	-0.02	-0.02	0.00	-0.01	-0.02
Anterior thalamic radiation	0.04	0.04	0.03	0.05	0.04	0.04	0.01	0.00
Superior thalamic radiation	0.00	0.01	-0.01	-0.01	0.01	0.00	-0.01	-0.03
Posterior thalamic radiation	0.02	0.00	0.04	0.06	0.08	0.10	0.05	0.08
Association tracts								
Superior longitudinal fasciculus	-0.01	0.01	0.07	0.08	0.06	0.08	0.05	0.05
Inferior longitudinal fasciculus	0.02	0.00	0.04	0.07	0.11	0.10	0.05	0.06
Inferior fronto-occipital fasciculus	0.01	-0.01	0.09	0.10	0.10	0.12	0.11	0.08
Uncinate fasciculus	-0.04	-0.02	-0.02	-0.02	-0.01	0.00	0.02	-0.01
Limbic system tracts								
Cingulate gyrus part of cingulum	-0.01	-0.03	0.03	0.06	0.06	0.05	0.03	0.01
Parahippocampal part of cingulum	-0.02	-0.01	0.03	0.03	0.04	0.01	0.07	0.02
Callosal tracts								
Forceps major	0.02	0.02	0.06	0.05	0.07	0.05	0.06	0.05
Forceps minor	-0.01	-0.01	0.07	0.08	0.07	0.08	0.03	0.07
MD								
Brainstem tracts								
Middle cerebellar peduncle	0.01	0.00	0.00	0.00	-0.02	0.01	0.01	0.02
Medial lemniscus [a]	0.01	0.01	0.02	0.02	-0.03	0.00	-0.01	0.03
Projection tracts								
Corticospinal tract	-0.05	-0.04	-0.11	-0.09	-0.11	-0.10	-0.08	-0.11
Anterior thalamic radiation	-0.09	-0.08	-0.10	-0.10	-0.18	-0.09	-0.08	-0.08
Superior thalamic radiation	-0.06	-0.06	-0.12	-0.11	-0.17	-0.10	-0.09	-0.10
Posterior thalamic radiation	-0.06	-0.06	-0.11	-0.14	-0.18	-0.10	-0.10	-0.09
Association tracts								
Superior longitudinal fasciculus	-0.01	-0.05	-0.08	-0.06	-0.09	-0.06	-0.06	-0.05
Inferior longitudinal fasciculus	-0.04	-0.06	-0.10	-0.08	-0.19	-0.05	-0.04	-0.07
Inferior fronto-occipital fasciculus	-0.08	-0.09	-0.13	-0.11	-0.20	-0.06	-0.10	-0.13
Uncinate fasciculus	0.04	0.01	0.01	0.03	-0.03	-0.02	-0.03	-0.01
Limbic system tracts								
Cingulate gyrus part of cingulum	0.05	0.03	0.05	0.06	0.00	0.02	-0.02	0.01
Parahippocampal part of cingulum	-0.02	-0.06	0.01	0.02	-0.04	0.02	-0.04	0.00
Callosal tracts								
Forceps major	-0.02	-0.02	-0.09	-0.04	-0.09	-0.04	-0.06	-0.04
Forceps minor	-0.03	-0.05	-0.07	-0.07	-0.06	-0.06	-0.03	-0.11

Values represent the mean differences in *z* score of each cognitive test per standard deviation increase of FA or MD. The colored cells represent significant associations surviving multiple testing ($p < 6.0 \times 10^{-4}$), and the intensity in red and blue reflects the magnitude of the associations whereby darker colors reflect stronger associations. Results are adjusted for age, sex, education, intracranial volume, WM, and log-transformed white matter volumes of the investigated tract, cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, antihypertensive medication, serum cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, smoking, and diabetes), *apolipoprotein E-ε4* (*APOE-ε4*) allele carriership, and additionally for global DTI parameters (global FA or global MD).
Key: FA, fractional anisotropy; LDST, Letter-Digit Substitution Task; MD, mean diffusivity $\times 10^{-3}$ mm^2/second; WM, white matter.
[a] Additionally adjusted for the variable position of the seed mask.

by memory. Only few tract-specific studies investigated the association of microstructural integrity of brain white matter with cognition in asymptomatic participants (Charlton et al., 2006; Kuznetsova et al., 2015; Laukka et al., 2013; Lopez-Oloriz et al., 2014; Salami et al., 2012; Voineskos et al., 2012; Ystad et al., 2011). Some studies concluded that white matter throughout the brain was associated with cognitive performance and reported no specific role for any white matter tract (Kuznetsova et al., 2015). Other

studies found a tract-specific effect in which altered microstructural integrity in association and callosal tracts associated with poorer information processing speed and executive function (Laukka et al., 2013; Lopez-Oloriz et al., 2014; Salami et al., 2012; Voineskos et al., 2012; Ystad et al., 2011) and with poorer motor speed (Voineskos et al., 2012), which is in line with our findings. However, some previous studies associated altered tract-specific white matter microstructure with memory, in contrast to our results (Charlton et al., 2006; Metzler-Baddeley et al., 2011; Voineskos et al., 2012). Our study differs from these studies in that we investigated a larger sample, and we took white matter atrophy and white matter lesion volume into account and thus adjusted for macrostructural white matter changes, which may have driven the association with memory function in the previous research. Furthermore, other studies incorporated different memory tests and cognitive domains (e.g., impaired error monitoring) and different white matter tracts (e.g., fornix) (Metzler-Baddeley et al., 2011).

We did not find similar associations with cognitive function across all tracts. We found the strongest associations between white matter microstructure and cognition in the posterior thalamic radiation and the inferior-occipital fasciculus. This is largely in line with previous studies performed in specific patient-populations such as in secondary-progressive multiple sclerosis, subcortical ischemic vascular disease (Lin et al., 2015; Yu et al., 2012), and coronary artery disease (Santiago et al., 2015). We can hypothesize on the basis of this finding using the previously described "disconnection hypothesis" (Hogan et al., 2006). The posterior thalamic radiation connects the thalamus with the posterior parietal and occipital lobes (Aralasmak et al., 2006) and plays a key role connecting visual and motor processes. The inferior fronto-occipital fasciculus connects frontal cortical regions with posterolateral temporal and occipital regions and is involved in language function and in visual spatial function that influences coordinative abilities (Schmahmann et al., 2008; Voineskos et al., 2012). Information processing speed and executive function are partly dependent on language function and on visual capabilities; motor speed depends on coordinative abilities. Damage to the tracts integrating these processes may, therefore, lead to poorer cognitive performance in these domains.

The role of *APOE-ε4* allele carriership in white matter microstructural integrity and cognition is still under debate. We found no significant interaction between *APOE-ε4* allele carriership and white matter microstructural integrity in the association with cognition, in line with the previous studies (Nyberg and Salami 2014; Wang et al., 2015). This may indicate that although *APOE-ε4* allele carriership is a major genetic risk factor for cognitive impairment and Alzheimer's disease, this may not be mediated by altered white matter microstructural integrity.

Lower values of FA in the association tracts were most strongly associated with poorer cognitive performance. In contrast, higher values of MD in the projections tracts were most strongly associated with impaired cognition. The disparity in associations among FA, MD, and cognitive performance might indicate that FA and MD reflect different pathophysiology. The lack of specificity in the interpretation of diffusion-MRI parameters prevents clear-cut conclusions on the exact mechanisms underlying the changes in diffusion-MRI parameters. It can be hypothesized that FA is dominated by tract coherence and axonal loss and MD by (volume of) extracellular fluid (Maclullich et al., 2009; Vernooij et al., 2009). Apart from a biological difference, MD seems to be more sensitive to changes in regions with crossing tracts (Jeurissen et al., 2013) and because voxels of projection tracts (corticospinal tract and superior thalamic radiation) contain large volumes of crossing-tract anatomy, this might explain part of the disparity observed (de Groot et al., 2015). Our observation that after adjustments for global diffusion parameters, the various associations remained significant, at least indicates that there is variation in tracts beyond global diffusion-MRI parameters and suggests local or functional differences in patterns of white matter neurodegeneration.

5. Conclusions

Tract-specific diffusion-MRI parameters provide insight into the association between white matter tracts and cognitive performance beyond global diffusion-MRI parameters. This study provides novel etiological insight into the relation of the location of brain damage and cognitive performance; in other words, it provides insight in which tract influences which specific cognitive domain. Second, our findings may also have clinical implications. For instance, knowledge on tract-specific effects on cognition may inform clinicians to predict which cognitive domains may be most affected depending on the location of a stroke. Finally, given the importance of recognizing pathways leading to cognitive impairment and dementia, our results may aid in developing new biomarkers for cognitive impairment and neurodegenerative diseases and may lead to better recognition of persons at risk.

Disclosure statement

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AH, GPK, WJN, AvdL, MWV, and MAI designed the study and provided funding and supervision; LGMC and MdG collected and analyzed the data; and LGMC, MdG, MWV, and MAI interpreted the results and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. LGMC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All listed authors meet all 4 criteria for authorship according to the guidelines of the International Committee of Medical Journal Editors, as revised in 2013. Funding was obtained from the Internationale Stichting Alzheimer Onderzoek #12533, European Union Seventh Framework Programma (FP7/2007–2013) under grant agreement no. 601055, VPH-Dare@IT (FP7-ICT-2011-9–601055), and the STW perspectief programme Population Imaging Genetics (ImaGene) projects 12722 and 12723, supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organisation for scientific research (NWO) and partly funded by the Dutch Ministry of Economic Affairs. None of the funding sources influenced design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.11.021.

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