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The Dimensionality of Between-Person Differences in White Matter Microstructure in Old Age

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Abstract: Between-person differences in white matter microstructure may partly generalize across the brain and partly play out differently for distinct tracts. We used diffusion-tensor imaging and structural equation modeling to investigate this issue in a sample of 260 adults aged 60–87 years. Mean fractional anisotropy and mean diffusivity of seven white matter tracts in each hemisphere were quantified. Results showed good fit of a model positing that individual differences in white matter microstructure are structured according to tracts. A general factor, although accounting for variance in the measures, did not adequately represent the individual differences. This indicates the presence of a substantial amount of tract-specific individual differences in white matter microstructure. In addition, individual differences are to a varying degree shared between tracts, indicating that general factors also affect white matter microstructure. Age-related differences in white matter microstructure were present for all tracts. Correlations among tract factors did not generally increase as a function of age, suggesting that aging is not a process with homogenous effects on white matter microstructure across the brain. These findings highlight the need for future research to examine whether relations between white matter microstructure and diverse outcomes are specific or general. *Hum Brain Mapp 34:1386–1398, 2013.*

Key words: white matter microstructure; individual differences; age differences; structural equation modeling

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INTRODUCTION

Between-person differences in white matter microstructure may generalize across the brain due to genetic and environmental effects that play out in a similar manner for different tracts. However, individual differences may also be localized, for example, at the level of specific tracts. The issue of the dimensionality of between-person differences in white matter integrity is important for the interpretation of findings based on between-person differences. For example, it is common to investigate whether white matter integrity of a particular a priori defined brain region is related to outcomes such as functional brain activity or cognitive performance. If such associations reach significance, then interpretations are often framed in terms of the functional relevance of the investigated white matter region. Appropriate statistical control for the presence of shared variance across white matter regions is sometimes applied. However, when this is not done, such interpretations neglect the possibility that individual differences in the integrity of the region of interest are associated with integrity in other regions of the brain and that it is this shared variance that drives the observed associations [Penke et al., 2010; Salthouse, 2011]. At the other end of the spectrum of analytical methods, various whole brain indices of white matter integrity are constructed. With such approaches, the extent to which global measures adequately represent individual differences in white matter microstructure is unknown. In addition, specific relations between individual tracts or regions and the outcome of interest are often not investigated in a satisfactory manner.

Here, we apply structural equation modeling (SEM) to investigate the dimensionality of white matter microstructure in a sample of 260 adults aged 60–87 years. These individuals were measured with diffusion-tensor imaging (DTI), which we used to assess white matter microstructure by quantifying mean diffusivity (MD) as well as fractional anisotropy (FA) of water diffusion. Mean FA and MD were extracted from seven tracts of interest in each hemisphere, resulting in 14 observed variables for each DTI metric. These variables were used in the SEM analyses.

One advantage of SEM is that latent factors can be formed. The variance of such factors represents the shared individual differences among the indicators of a factor. Measurement error is simultaneously, but separately, estimated. If conclusions are drawn from the estimates at the latent factor level, the influence of error and the biasing influence of differences in measurement error across measures are attenuated. In separate analyses of FA and MD, we used this advantage by specifying a model (Fig. 1A) in which tract factors represent individual differences common across hemispheres for a given tract [cf. Raz et al., 2005]. This theoretical model is based on the long-standing neuroanatomical principle of tract-based organization of connections among gray matter areas [e.g., Catani and Ffytche, 2005; Filley, 2010]. Empirical evidence also supports such a model of the organization of measures of white matter microstructure acquired with DTI [Li et al., in press; Wahl et al., 2010]. For example, Wahl et al. [2010] reported that most of the high correlations among means of FA from a set of 12 tracts were between pairs of homologous tracts in the left and right hemispheres.

Another advantage of SEM is that the accuracy of a model's representation of the data (i.e., the variances and covariances) can be evaluated. We use this feature here to examine whether the postulated tract-based organization of individual differences in white matter microstructure provides an acceptable representation of the data. In addition, alternative representations of the data can be examined, and kept as acceptable alternatives to the original theoretical model, or rejected because they constitute unacceptable representations of the data. The alternative model that we examine here posits that between-person differences generalize across the tracts of interest (Fig. 1B). This is an extreme alternative to the original model postulating that individual differences are primarily organized at the tract level, with individual differences that are shared between pairs of tracts. Recent exploratory factor-analytic work indicates that a general factor explains a substantial amount of variance in white matter microstructure in old age [Penke et al., 2010; see also Wahl et al., 2010]. We expected to replicate this finding, but also to find that a general factor alone provides an inadequate representation of the data. In other words, although general individual differences may be one important principle, individual differences that are specific for tracts and pairs of tracts were predicted to be principles of the organization of white matter microstructure that cannot be disregarded.

Special variants of the issue of the dimensionality of between-person differences concern the extent to which some outcome of interest (e.g., education, disease, and cognition) relates to individual differences in white matter integrity that are specific or general. For example, Penke et al. [2010] examined whether cognitive performance relates to general or regionally specific individual differences in white matter microstructure. They found that the common variance in white matter microstructure across several regions was a significant predictor of performance.

Here, we investigate the dimensionality of age-related differences in white matter integrity. Previous studies have observed pronounced age-related differences in several markers of white matter integrity [Barrick et al., 2010; Burzynska et al., 2010; Madden et al., 2009; O'Sullivan et al., 2001; Raz et al., in press; Schmidt et al., 1993; Sullivan and Pfefferbaum, 2006; Vernooij et al., 2008; Westlye et al., 2010]. Addressing the dimensionality of such age differences is challenging because chronological age is a special outcome variable. That is, mean cross-sectional age trends of a variable is a fallible proxy of individual differences in change that play out over time [Hofer and Sliwinski, 2001; Lindenberger et al., 2011]. We therefore took the route of investigating whether correlations

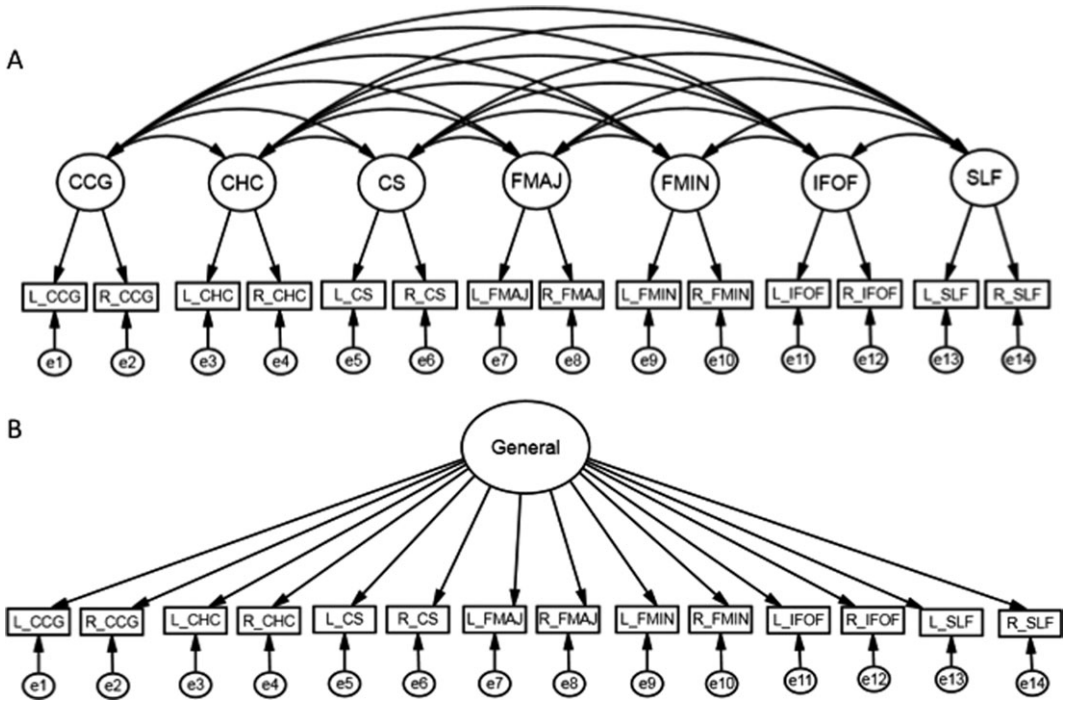

Figure 1.

Graphical representations of estimated structural equation models of between-person differences in white matter microstructure. **A**: A model postulating specific, but related, tract factors. Latent factors are depicted with circles, observed variables with rectangles, regressions with one-headed arrows, and covariances with two-headed arrows. CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; L, left; R, right; e, error. **B**: An alternative model postulating a general factor of white matter microstructure.

among between-person differences in the tract factors increase as a function of age.

The rationale and assumptions behind this approach have been outlined in detail by Hofer et al. [Hofer and Sliwinski, 2001; Hofer et al., 2006; see also Hertzog, 1985; Van Petten, 2004]. Briefly, the reasoning goes as follows: The rank ordering of individuals on a given score (e.g., mean FA of a given tract) at a particular age (e.g., age 70) can be considered to be determined by individual differences at some initial age (e.g., at age 30) plus any individual differences in change up to the particular age (i.e., from age 30 to 70). Under the assumption that between-person differences in the aging of white matter integrity are indeed present, the rank ordering of individuals' white matter integrity should thus be more strongly determined by aging-related changes in samples of older adults than in samples of younger adults. In other words, the older an individiual, the more has aging had time to influence the individual's brain integrity. Therefore, the older a sample, the more do the covariances across variables reflect aging-related influences and the less do they reflect initial individual differences. Accordingly, if individual differences in rates of aging of different tracts are associated, then the correlations among between-person differences in the integrity of different tracts should increase as a function of age.

MATERIALS AND METHODS

Participants

Participants (n = 260; $\text{range}_{\text{age}}$ = 60–87 years; M_{age} = 71.8 years; SD_{age} = 9.0 years) were recruited from a larger population-based epidemiological study, the Swedish National study of Aging and Care in Kungsholmen (SNAC-K). Of those contacted for taking part in this study, 75% participated. This resulted in a sample of 3,363 elderly individuals. The SNAC-K sample was stratified on age (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99+ years) at baseline. Information on past events and present medical, psychological, and social status were assessed through interviews and clinical examinations. The first data collection was completed in June 2004, and follow-up data collection is ongoing. During the first data collection, a subsample of noninstitutionalized and nondisabled participants who were eligible for magnetic resonance imaging

TABLE I. Participant characteristics

		Education		Vocabulary		MMSE	
Age group (years)	*n* (M/W)	*M*	SD	*M*	SD	*M*	SD
60	63 (26/37)	14.1	3.2	25.3	3.2	29.5	0.5
66	48 (16/32)	12.9	3.8	24.7	3.3	29.3	1.0
72	40 (15/25)	11.2	3.4	23.8	3.8	29.1	1.0
78	44 (14/30)	11.7	4.2	22.5	4.9	29.0	1.1
81	31 (11/20)	11.0	4.9	22.4	4.8	28.8	0.9
84	22 (6/16)	11.1	3.2	23.5	4.3	28.9	0.8
87	12 (5/7)	10.2	3.0	20.0	5.2	28.0	1.8
60–72	151 (57/94)	13.0	3.6	24.7	3.4	29.3	0.9
78–87	109 (36/73)	11.2	4.1	22.4	4.8	28.8	1.1
Total	260 (93/167)	12.2	3.9	23.7	4.2	29.1	1.0

Note: Education, years of education; vocabulary, A 30-item, multiple-choice synonym test [Dureman, 1960]; MMSE, mini-mental state examination [Folstein et al., 1975]; M, men; W, women.

(MRI) was randomly selected to undergo MRI. The effective sample used in this study included participants with acceptable quality of the diffusion-tensor images. Participants with dementia diagnoses, schizophrenia diagnosis, bipolar disorder diagnosis, self-reported stroke, stroke observed on the MR images, self-reported Parkinson's disease, or self-reported epilepsy were excluded. Because very few participants were older than 87 years, we excluded these subjects to have more homogenous age groups in the multiple group analyses, which included age groups of 60–72 ($n = 151$; $\text{mean}_{age} = 65.1$; $\text{SD}_{age} = 4.9$) and 78–87 ($n = 109$; $\text{mean}_{age} = 81.1$; $\text{SD}_{age} = 3.1$) years. Table I reports mean age, years of education, vocabulary [Dureman, 1960], and mini-mental state examination [Folstein et al., 1975] as a function of age group. Potential selectivity of the effective sample for DTI analyses in relation to the total population-based nondemented sample in SNAC-K was computed on these background variables. Selectivity was expressed in an effect-size metric $[(M_{effective} - M_{total})/\text{SD}_{Total}]$ separately for the age groups of 60–72 and 78–87 years. Selectivity, due to all sources of nonparticipation in the DTI sample, was negligible (−0.11 to 0.21 SD; median = 0.11 SD).

MRI Acquisition

All MRI measurements were conducted using a 1.5 T scanner (Philips Intera, The Netherlands). DTI data were acquired using a single-shot diffusion-weighted echoplanar imaging sequence with the following parameters: FOV = 230 × 138 mm^2; 128 × 77 matrix; TE = 104 ms; TR = 6,838 ms; slice thickness = 5 mm with 1 mm gap; *b*-value 600 s/mm^2. For all participants, a DTI scheme with six noncollinear diffusion-weighting gradient directions was used to determine the diffusion tensor set.

Preprocessing and Preliminary Analyses

The DTI data from each subject were analyzed using an iterative optimization algorithm that takes into consideration the following three models: (1) eddy current artifacts correction by estimating the whole brain based on shearing, scaling, and translation effects; (2) motion artifact correction based on 3D rigid-body motions; and (3) second-order self-diffusion tensor elements calculation based on the Stejskal-Tanner equation. After the diffusion tensor calculation, MD and FA were derived on voxel-by-voxel basis using the following steps: (1) estimation of eigenvalues and eigenvectors of the diffusion tensor using the single-value decomposition algorithm; (2) calculation of MD as the mean of the diagonal elements; and (3) calculation of FA according to its definition [Basser and Pierpaoli, 1996].

The FA data was further processed using tract-based spatial statistics [TBSS; Smith et al., 2006], which is part of FSL [Smith et al., 2004]. Briefly, the images were aligned into a common space, using nonlinear registration [Andersson et al., 2007a,b] to the FMRIB58_FA standard-space image. The mean FA image was then thinned to create a mean FA skeleton, which represents the centerlines of all tracts common to the sample. We thresholded and binarized the mean skeleton at FA > 0.2 to reduce the likelihood of partial voluming. This resulted in a final skeleton mask that included 103,847 voxels. Each participant's aligned FA data were then projected onto this skeleton, which results in individual skeleton images. The MD images were processed based on the results of the processing of the FA images, yielding individual MD skeletons sampled from voxels with FA > 0.2.

Voxel-wise DTI analyses of these skeleton images were performed using permutation-based inference [Nichols and Holmes, 2002] as implemented in the FSL-tool "randomize." We tested for linear and quadratic relations to age for FA and MD. Five thousand permutations were

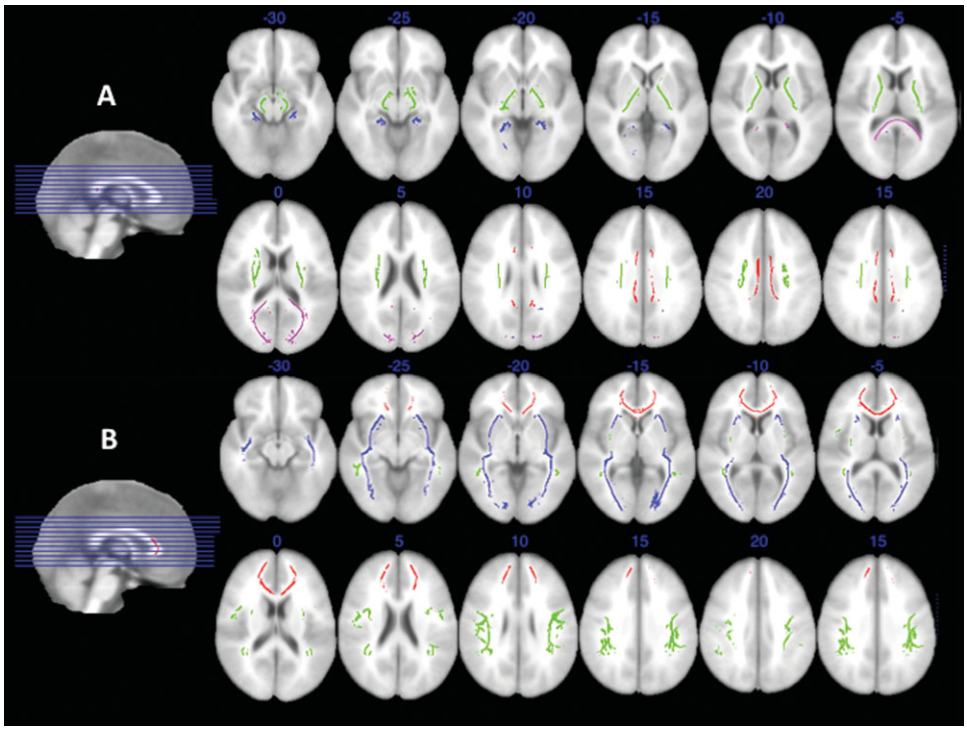

Figure 2.

Regions of interests in the TBSS skeleton from which mean fractional anisotropy and mean diffusivity were extracted for each individual. The regions of interest were based on modified (see "Methods" section, for details) probabilistic template masks emanating from the Catani tractography atlas [Catani and Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2011] and the JHU white-matter tractography atlas [Hua et al., 2008; Wakana et al., 2004]. **A**: Red, cingulum cingulate gyrus; blue, cingulum hippocampus; green, corticospinal tract; violet, forceps major. **B**: Red, forceps minor; blue, inferior fronto-occipital fasciculus; green, superior longitudinal fasciculus. The backdrop image is the MNI ICBM template.

performed for each contrast. The threshold for statistical significance was $P < 0.001$, corrected for multiple comparisons across space and using threshold-free cluster enhancement [Smith and Nichols, 2009].

To prepare the data for SEM, we produced masks of seven tracts of interest (Fig. 2) in each hemisphere. These 14 masks (7 tracts $\times$ 2 hemispheres) were used to extract mean FA and MD data from each individual's skeleton image. Specifically, we initially selected probabilistic template masks for the seven tracts of interest: the cingulate gyrus part of cingulum (CCG), the portion of cingulum that extends to the hippocampus (CHC), the corticospinal tract (CS), the forceps major (FMAJ), the forceps minor (FMIN), the inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF). The CS mask emanated from the Catani tractography atlas [Catani and Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2011], and the remaining masks were based on the JHU white-matter tractography atlas [Hua et al., 2008; Wakana et al., 2004]. The callosal tracts, which were not already separated across hemispheres, were split into separate masks for each hemisphere. Next, we visually inspected the fit of each mask to the skeleton mask and thresholded each mask individually to optimize fit. Note that the skeleton mask is identical for all subjects, so that this procedure does not introduce any source of between-subject error, but rather increases the anatomical validity of the mask. The resulting binary masks were then combined with the skeleton mask. Further work was focused on ensuring that there were clear separations between the masks: To avoid overlap with the callosal tracts, the CCG was combined with an exclusive corpus callosum mask. The IFOF was defined as the part not included in FMAJ or FMIN, and posterior to MNI $y = 24$. SLF was defined as the part not overlapping with IFOF. After these steps, all masks were inspected together to ensure that there were no overlap among them. Finally, the masks were used to extract the mean FA and MD data from the individual skeletons.

Table II reports the descriptive statistics of the resulting 14 FA and 14 MD variables. All variables displayed acceptable skewness and kurtosis [Kline, 1998]. The size of the masks was generally similar across hemispheres, and so were the mean FA and MD values. Preliminary analyses showed that Pearson correlations between the same

TABLE II. Descriptive statistics of the tracts in the total sample

		FA				MD			
Tract	n_{voxels}	*M*	SD	Skew	Kurt	*M*	SD	Skew	Kurt
CCG_L	732	0.42	0.03	0.03	−0.30	0.83	0.05	0.47	0.23
CCG_R	661	0.39	0.03	0.20	−0.32	0.82	0.05	0.45	0.07
CHC_L	849	0.39	0.03	0.11	−0.16	1.00	0.09	0.38	−0.13
CHC_R	823	0.40	0.03	0.37	−0.07	1.01	0.11	0.45	−0.12
CS_L	4,599	0.56	0.02	−0.06	−0.13	0.75	0.03	0.88	0.80
CS_R	4,517	0.56	0.02	0.07	−0.36	0.76	0.03	0.85	0.95
FMAJ_L	1,085	0.59	0.03	−0.39	−0.06	0.78	0.06	1.16	1.82
FMAJ_R	1,277	0.56	0.03	−0.27	−0.34	0.79	0.06	1.11	1.70
FMIN_L	2,117	0.51	0.03	−0.27	−0.18	0.81	0.06	0.63	0.38
FMIN_R	1,995	0.52	0.04	−0.22	−0.30	0.83	0.06	0.55	0.33
IFOF_L	3,794	0.47	0.03	−0.14	−0.35	0.85	0.05	0.81	0.55
IFOF_R	3,851	0.46	0.02	−0.27	−0.14	0.84	0.05	0.90	1.13
SLF_L	3,462	0.41	0.02	−0.25	−0.26	0.78	0.05	0.85	0.88
SLF_R	2,789	0.42	0.03	−0.12	−0.29	0.77	0.04	1.09	1.94

Note: CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; L, left; R, right.

tract across hemispheres were generally significant and high, and higher than correlations between different tracts, supporting the reliability and validity of these variables.

SEM Analyses

We first estimated the measurement model (Fig. 1A), specifying tract-factors that represent individual differences common across the hemispheres for a given tract. One model was estimated for FA and one for MD. To standardize the tract factors, one unstandardized loading on each factor was fixed to 1. We estimated the model as a multiple group model, with one age group of 60–72 years and one age group of 78–87 years. We included chronological age as a predictor of the tract factors to covary out the effect that age heterogeneity within age groups may have on variances and covariances. Measurement equivalence of this model over age groups was then investigated by comparing it to a nested model that assumes the unstandardized loadings on the tract factors to be equal across groups. A nonsignificant difference in fit between these models indicates that the loadings are equivalent across age groups, which is an important methodological prerequisite for using the same model for different age groups [Meredith, 1993]. Finally, we inspected the correlations among the tract factors as a function of age group and examined the confidence intervals around the correlations to detect potential age-group differences (to arrive at 95% confidence intervals around the correlations, we used bootstrapping, 500 iterations, bias-corrected percentile method).

Next, we fitted the alternative model positing that between-person differences generalize across the tracts of interest (Fig. 1B) as a multiple group model and inspected the fit of this model. Chronological age was included as a predictor of the general factor. Note that this model and the tract-based model depicted in Figure 1A are not nested, and therefore cannot be directly compared in a straightforward manner. Rather, whether the two models provide acceptable representations of the data are evaluated separately for each model using fit indices that take model complexity into account.

Finally, we collapsed the multiple groups and estimated a model positing specific tract factors (Fig. 1A) to the data from the total sample. Chronological age was included in this model and was allowed to covary with the tract factors. In this way, we can estimate age-related differences in each of the tract factors by inspecting the bivariate correlation between chronological age and a tract factor.

To estimate these models, we used AMOS (IBM SPSS 19) and maximum likelihood estimation. Model fit was evaluated with the comparative fit index (CFI) and the root-mean-square error of approximation (RMSEA). A CFI above 0.95 and an RMSEA below 0.08 was regarded as indicating acceptably fitting models [e.g., Kline, 1998]. The difference in chi-square fit statistics was used to compare nested models. The threshold for statistical significance was $P < 0.05$.

RESULTS

The measurement model (Fig. 1A) estimated as a two-group model (62–72 and 78–87 years) of the FA data showed a good fit, χ^2 (126, $N = 260$) = 131.28, CFI = 0.998, RMSEA = 0.013. Fixing the unstandardized loadings on the tract factors to be equal across age groups did not significantly reduce the fit, χ^2 (133, $N = 260$) = 138.52, CFI = 0.998, RMSEA = 0.013; $\Delta\chi^2$ (7) = 7.24, $P > 0.404$. The

TABLE III. Correlations among tract factors for fractional anisotropy in the age group of 62–72 years (below the diagonal) and the age group of 78–87 years (above the diagonal)

Factor	CCG	CHC	CS	FMAJ	FMIN	IFOF	SLF
CCG	—	0.34	0.73*	0.74*	**0.93***	**0.78***	0.85*
CHC	0.57*	—	0.41*	0.12	0.30	0.50*	0.53*
CS	0.67*	0.33*	—	0.45*	0.67*	0.61*	0.81*
FMAJ	0.72*	0.36*	0.58*	—	0.67*	0.65*	0.51*
FMIN	**0.73***	0.37*	0.67*	0.64*	—	0.76*	0.77*
IFOF	**0.66***	0.48*	0.61*	0.67*	0.73*	—	0.75*
SLF	0.80*	0.49*	0.80*	0.69*	0.72*	0.80*	—

Note: CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus.
*Significant correlation at $P < 0.05$. Bold typeface indicates significant age-group differences for a correlation.

same model for MD also showed an acceptable fit, χ^2 (126, $N = 260$) = 277.49, CFI = 0.953, RMSEA = 0.068, and a model with the unstandardized loadings on the tract factors estimated to be equal across age groups again did not worsen the fit, χ^2 (133, $N = 260$) = 284.28, CFI = 0.953, RMSEA = 0.066; $\Delta\chi^2$ (7) = 6.79, $P > 0.451$. Thus, the model is an acceptable representation of both the FA and MD data, and metric measurement invariance across age is an acceptable assumption.

With these preconditions fulfilled, we inspected the correlations among the tract factors (Tables III and IV). These correlations were mostly significant in both age groups for both FA and MD, indicating shared individual differences in white matter microstructure among the tracts. However, the correlations were generally lower than the significant and high loadings of the observed measures on the tract factors (Table V). This pattern is in line with the acceptable fit of this model and indicates convergent and discriminant validity of the tract factors. In other words, an organization of individual differences in the observed measures into tracts is a valid representation of the data. The magnitude of the correlations was not generally higher in the older group, neither for FA nor for MD (see Fig. 3). However, a few individual correlations displayed significant age-group differences (Tables III and IV). For FA, the correlations between CCG and FMIN and between CCG and IFOF were higher in the group of 78–87 than in the age group of 62–72 years. For MD, the correlation between FMAJ and FMIN was lower in the group of 78–87 than in the age group of 62–72 years.

An alternative to the model organizing the individual differences at the tract level is a model that postulates only a general factor (Fig. 1B), which extracts the common variance across the 14 variables. We estimated such a general-factor model as a multiple group model (62–72 and 78–87 years), with loadings constrained across age groups. The general factor accounted for a significant proportion of the variance in all observed measures (Table V), indicating the presence of such a general factor in the data. However, this model was clearly an inadequate representation of the data, χ^2 (193, $N = 260$) = 983.60, CFI = 0.750, RMSEA = 0.126 for FA and χ^2 (193, $N = 260$) = 1006.63, CFI = 0.747, RMSEA = 0.128 for MD. This model apparently fails to represent important between-subject variances and covariances at the tract level.

Finally, to report age-related mean trends in the white matter microstructure of the tracts, we collapsed the multiple group model and estimated the model positing specific tract factors (Fig. 1A) to the data from the total sample while allowing chronological age to covary with the tract factors. Table VI reports the estimates of age-related mean differences (i.e., correlations between age and the tract factors) in white matter microstructure. As expected, these trends were substantial for both FA ($r = -0.35$ to -0.59) and MD ($r = 0.57$–0.69). Widespread significant age-related decreases in FA and increases in MD were also detected in voxelwise analyses (Fig. 4). No voxels displayed significant additional nonlinear age relations. No significant increases in FA or decreases in MD were observed.

DISCUSSION

Results showed good fit of a model positing that individual differences in white matter microstructure among older adults are organized according to tracts. Correlations between tracts were generally sizable, but lower than the loadings of the left and right hemisphere measures on the tract factors, supporting the validity of the tract factors. A model postulating a general factor, which extracts the variance shared among the observed tracts in the left and right hemisphere, is clearly an insufficient representation of the individual differences in white matter microstructure in

TABLE IV. Correlations among tract factors for mean diffusivity in the age group of 62–72 years (below the diagonal) and the age group of 78–87 years (above the diagonal)

Factor	CCG	CHC	CS	FMAJ	FMIN	IFOF	SLF
CCG	—	0.37*	0.51*	0.46*	0.76*	0.56*	0.66*
CHC	0.45*	—	0.41*	0.71*	0.44*	0.61*	0.33*
CS	0.54*	0.29*	—	0.65*	0.66*	0.79*	0.82*
FMAJ	0.60*	0.75*	0.61*	—	**0.62***	0.93*	0.68*
FMIN	0.68*	0.42*	0.62*	**0.75***	—	0.76*	0.75*
IFOF	0.69*	0.55*	0.75*	0.91*	0.79*	—	0.87*
SLF	0.74*	0.30*	0.80*	0.66*	0.77*	0.89*	—

Note: CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus.
*Significant correlation at $P < 0.05$. Bold typeface indicates significant age-group differences for a correlation.

TABLE V. Standardized loadings on the tract factors in the models of fractional anisotropy (FA) and mean diffusivity (MD) across age groups

		Model tract-factors (Fig. 1A)				Model general (Fig. 1B)			
		FA		MD		FA		MD	
Factor	Indicator	60–72 years	78–87 years	60–72 years	78–87 years	60–72 years	78–87 years	60–72 years	78–87 years
CCG	Left	0.85	0.86	0.84	0.83	0.76	0.85	0.62	0.62
	Right	0.92	0.88	0.86	0.81	0.80	0.86	0.69	0.70
CHC	Left	0.67	0.57	0.65	0.69	0.33	0.32	0.32	0.42
	Right	0.72	0.68	0.81	0.80	0.36	0.40	0.44	0.50
CS	Left	0.96	0.94	0.94	0.96	0.76	0.77	0.81	0.79
	Right	0.95	0.93	0.87	0.92	0.77	0.77	0.77	0.77
FMAJ	Left	0.91	0.90	0.82	0.82	0.73	0.65	0.74	0.67
	Right	0.85	0.88	0.82	0.89	0.68	0.64	0.72	0.70
FMIN	Left	0.92	0.95	0.92	0.90	0.83	0.84	0.80	0.80
	Right	0.91	0.95	0.95	0.91	0.81	0.85	0.81	0.79
IFOF	Left	0.91	0.90	0.88	0.88	0.78	0.77	0.85	0.82
	Right	0.97	0.90	0.89	0.90	0.84	0.80	0.87	0.87
SLF	Left	0.94	0.92	0.98	0.94	0.88	0.82	0.92	0.87
	Right	0.92	0.88	0.92	0.89	0.85	0.80	0.86	0.81

Note: CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus. All loadings were significant at $P < 0.05$. The standardized loadings, which are interpreted as correlations, may differ somewhat between age groups although the unstandardized loadings were fixed over age group.

this sample of older adults. However, the general factor accounted for a significant portion of the variance in all of the observed measures [see also Penke et al., 2010], indicating the presence of generalizable portions of individual differences. White matter microstructure displayed pronounced age-related differences in old age. However, the correlations among the tract factors did generally not increase as a function of age group. This finding provides no support for the notion that individual differences in aging of white matter microstructure play out in a similar manner across the investigated tracts.

Between-person differences in white matter microstructure were strongly associated across the left and right hemisphere of a specific tract, and in part structured differently for distinct tracts. These findings suggest that the diverse genetic and environmental effects that operate over the life course partly impact individual differences in white matter microstructure differently for distinct tracts, and more similarly for the same tract across hemispheres

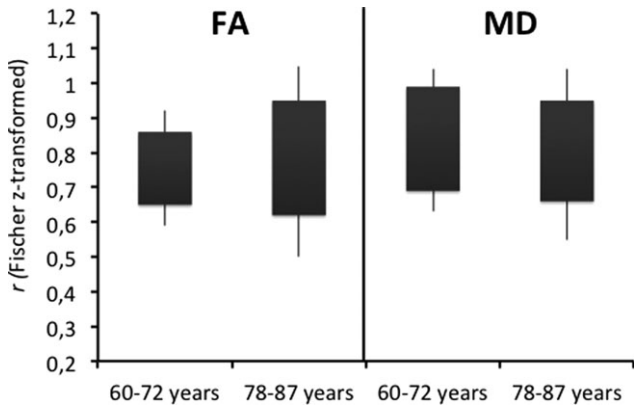

Figure 3.

Box plot (interquartile range, 95% confidence intervals) of the 21 correlations (Fischer z-transformed) between the tract factors (see Fig. 1A) for fractional anisotropy (FA) and mean diffusivity (MD) as a function of age group (60–72 vs. 78–87 years).

TABLE VI. Age-related differences in white matter microstructure for the total sample: Correlations between chronological age and the tract factors

	r with chronological age	
Tract	Fractional anisotropy	Mean diffusivity
CCG	−0.57	0.68
CHC	−0.54	0.69
CS	−0.38	0.62
FMAJ	−0.49	0.64
FMIN	−0.59	0.63
IFOF	−0.55	0.63
SLF	−0.35	0.57

Note: CCG, cingulum cingulate gyrus; CHC, cingulum hippocampus; CS, corticospinal tract; FMAJ, forceps major; FMIN, forceps minor; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus. All correlations were significant at $P < 0.05$.

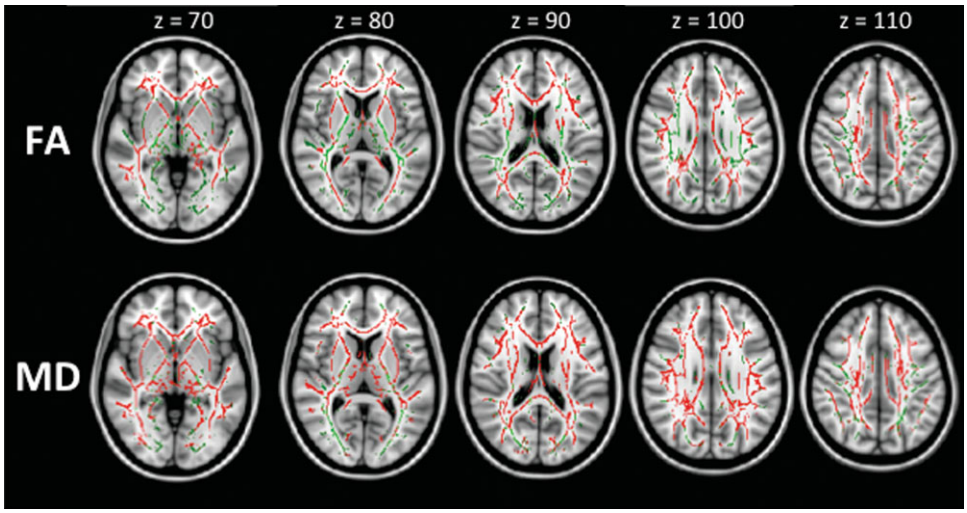

Figure 4.

Linear influences of chronological age on FA (upper row) and MD (bottom row) in the TBSS skeleton superimposed on transverse slices of a template T_1 image (MNI 152). Red areas indicate significant voxels ($P < 0.001$, corrected for multiple comparisons across space and with threshold-free cluster enhancement). Green voxels are the nonsignificant remains of the skeleton. No voxels displaying significant additional nonlinear age relations were detected. Age was always associated with decreases of FA and increases of MD.

than for distinct tracts within and between hemispheres. This finding is in line with recent results from data-driven analytical techniques used to explore correlations among white matter microstructure in different tracts [Wahl et al., 2010] and across individual voxels [Li et al., in press]. For example, Wahl et al. [2010] observed generally stronger correlations between mean FA of homologous pairs of tracts than between nonhomologous pairs. Our findings are also in line with reports of varying heritability estimates of white matter microstructure across tracts [Chiang et al., 2009; Kochunov et al., 2010]. This study extends these findings by demonstrating acceptable fit of a model postulating that individual differences in white matter microstructure in old age are organized at the tract level. This provides formal support for the convergent and discriminant validity of the tract factors, and thus for the organization of white matter microstructure at the tract level. This finding is predictable from known anatomical and functional principles [e.g., Catani and Ffytche, 2005; Filley, 2010]. Homologous tracts obviously share localization between the left and the right hemisphere. Different white matter tracts also interconnect distinct functional systems [e.g., Damoiseaux and Greicius, 2009]. Homologous tracts are to a varying degree sharing functions between hemispheres, and different tracts do not share function to the same extent. Genetic and environmental effects on white matter microstructure should therefore play out in a similar manner for homologous tracts [Li et al., in press; Wahl et al., 2010].

The finding that the tract concept is a valid organizational principle for white matter microstructure is nontrivial, especially when dealing with individual differences among older adults. It is easy to imagine that age-related differences in white matter integrity are stochastically hemisphere-specific, caused by effects that are of regional and hemisphere-specific, rather than tract-specific, nature (e.g., microbleeds). If such effects are pronounced in aging, one should expect an organization according to tracts to be a weaker model of individual differences in white matter microstructure in more advanced stages of old age. We found no evidence of such a pattern, as indicated by the equivalence of the left and right hemisphere loadings on the tract factors across the age groups of 60–72 and 78–87 years.

With few exceptions, correlations among tract factors were significant, indicating shared individual differences among tracts in this sample of older adults. However, a general factor alone was clearly insufficient for capturing the dimensionality of individual differences in white matter microstructure. This suggests that a substantial amount of environmental and genetic effects impact white matter microstructure at the level of tracts and that these effects are to a varying degree shared between pairs and groups of tracts. The heterogeneity of the correlations between tracts (ranging from 0.12 to 0.93) supports this notion [see also Wahl et al., 2010]. Different tracts may to varying extent share factors such as regional localization and genetic determinants. Different individuals also invest different amounts of time and effort into distinct functions during the life course. Shared involvement of different tracts in functions, such as language and sensorimotor skills, may produce shared individual differences in white

matter microstructure of tracts involved in such functions through experience-dependent plasticity in childhood [Bengtsson et al., 2005], younger adulthood [Scholz et al., 2009], and older adulthood [Lövden et al., 2010]. That said, it is important to note that a general factor accounted for a significant portion of the variance in the observed measures. This finding is in line with previous findings [Penke et al., 2010] and indicates the additional presence of effects on white matter integrity that influence the brain globally.

Thus, an important message from this study is that individual differences in white matter microstructure are multidimensional and organized according to multiple principles, such as tract-specific, common effects across pairs or groups of tracts, and brain-general effects. Any given observed measure contains a varying amount of all these influences. Although we think that this empirical message matches the mental model of most researchers, the point has important implications that need to be explicitly considered. For example, it is common to study whether between-person differences in the integrity of a selected brain region are related to outcomes such as functional brain activity or cognitive performance. If such correlations reach significance, then interpretations tend to focus on the functional relevance of the specific brain region. Without statistical control of the presence of shared variance across white matter regions, which sometimes, but not always, is applied in the literature, such accounts run the risk of misinterpreting an association that is driven by shared individual differences across regions, some of which may generalize across the entire brain. This problem is likely to be present also in investigations of gray matter integrity and volume [Salthouse, 2011; Wu et al., in press]. On the other hand, investigations of whole brain indices of white matter microstructure fail to represent the existing tract-specific individual differences as well as individual differences that are shared between pairs and groups of tracts. That is, specific relations between individual tracts or regions and the outcome of interest are often not investigated. Further, when specific tracts are investigated in addition to global measures [e.g., Penke et al., 2010], researchers should be aware that specific measures are likely to suffer from lower reliabilities than more global measures, which benefit from aggregation or factor-analytic extraction techniques. Such reliability differences will bias the results against finding associations with the more specific measure. Regardless of the outcome of interest (e.g., age, sex, education, cognition, and disease), it is important to empirically resolve these interpretational ambiguities stemming from the presence of both general and specific individual differences in measures of white matter microstructure.

Here, we investigated the evidence in favor of the notion that aging has general influences on the integrity of distinct white matter tracts. The mean age trends were quite consistent with previous findings [Madden et al., 2009; Sullivan et al., 2006]: Age differences in FA and MD were pronounced in the examined tracts and in the voxel-wise analyses. For FA, the FMIN showed the strongest association with age, and the association with age tended to be weaker for FMAJ, consistent with past reports of larger age differences in FA of the genu than the splenium [Sullivan et al., 2006]. Age associations for MD tended to be somewhat higher and somewhat more uniform (r = 0.57–0.69) than those for FA (r = −0.35 to −0.59). The novel findings on the dimensionality of age differences are to be found in the pattern of correlations among the tract factors as a function of age. Interestingly, the correlation between MD in the FMAJ and the FMIN was lower in the group of 78–87 than in the age group of 62–72 years, indicating that aging affects the rank ordering of individuals differently for these two regions. This finding suggests that different mechanism may cause age-related decline in these two tracts. Such findings go unnoticed if one inspects mean age trends, which were very similar for MD in the FMAJ and the FMIN. Two correlations (CCG with FMIN and IFOF, respectively) for FA were higher in the older age group. These findings suggest that individual differences in aging of FA in these tracts are associated. That is, assuming that individual differences in aging are present, rank ordering of individuals' white matter integrity should be more strongly determined by aging-related influences with increasing age. Thus, the correlations among between-person differences in integrity of different tracts should increase as a function of age if individual differences in aging of different tracts are associated [see also Hertzog, 1985; Hofer and Sliwinski, 2001; Hofer et al., 2006; Van Petten, 2004]. Nevertheless, a general age-related increase of the correlations among the tracts was not found. Thus, the general pattern of results provided no support for the notion that aging is a process with homogenous effects on white matter microstructure across the brain. Note, however, that this conclusion is based on the assumption of between-person differences in aging of white matter microstructure and on the typical assumptions of cross-sectional research, such as the absence of cohort effects and age-differential selection effects [Hofer and Sliwinski, 2001; Hofer et al., 2006]. Thus, longitudinal work is needed for addressing the dimensionality of white matter changes in aging more directly [Lindenberger et al., 2011].

Some limitations and assumptions of the present work should be noted. First, we note that between-person differences in white matter microstructure may be organized according to several principles (e.g., general, tract-based, functional, regional, and hemisphere-specific), some of which could not be directly modeled with the present approach (e.g., hemisphere-specific and regional). Future studies should address the importance of such factors. In this vein, we also note that our way of extracting mean measures of white matter microstructure with atlas-based templates assumes homogeneity of individual differences across the voxels within the anatomically defined tracts. Data-driven approaches to detect covariation among

voxels suggest that the strongest FA correlations are found among voxels in anatomically discernible tracts and tract segments [Li et al., in press]. These findings partly support the homogeneity assumption. Nevertheless, due to variation in the degree of crossing fibers, histological properties within a tract, and potential individual and age-related differences in such variability, this assumption may not be valid across an entire anatomically-defined tract. Data-driven approaches to define white matter regions with homogeneity of individual differences [Groves et al., 2011; Li et al., in press] are promising future avenues for avoiding this assumption. On the other hand, the good fit of the model postulating tract factors and the high correlations within a specific tract across hemispheres indicate high reliability and validity of the measures, and of the way, we preprocessed the data and extracted the tracts of interest. Thus, whereas our approach may not capture important sub-variability within the tracts, it does capture systematic variability at the level of tracts, indicating that this is one important dimension of between-person differences in white matter microstructure.

Second, we note that the DTI measurements were not of more modern quality, which is a reflection of the time point of collecting the data. The quality of the images may have resulted in suboptimal signal-to-noise ratio and made it impossible to apply tractography. Although forming latent variables attenuated the influence of error variance, the large and anisotropic voxels may have introduced partial volume effects (gray/white mixture) that could not be completely accounted for by the TBSS processing. This may have introduced partial volume influences on the measures of white matter microstructure that may systematically vary across age and tracts. Regardless of the quality of the DTI, future studies may need to take volume differences into account to arrive at better estimates of age differences in white matter microstructure [e.g., Bastin et al., 2010; Vernooij et al., 2008]. That said, the effect of partial volume averaging across tracts was however minimized in this study by ensuring that there was no voxel overlap among tracts and by selecting tracts of interest that were well separated.

Finally, we note that generalization of the present results is restricted to old age. In addition, the lack of a young comparison group may limit the conclusion related to the dimensionality of individual differences in the aging of white matter microstructure. However, age-related differences in white matter microstructure were pronounced in our sample of older adults. Moreover, previous studies [e.g., Westlye et al., 2010] show that age-related differences in white matter microstructure accelerate after the age of 60. Thus, this study captures well the period of the adult lifespan where most of the age-related action in white matter microstructure occurs. Nevertheless, future studies should include a lifespan sample to extend the generality of the current findings. Future studies should also examine the potentially moderating influences of vascular risk [Burgmans et al., 2010; Kennedy and Raz, 2009], atrophy [Bastin et al., 2010; Vernooij et al., 2008], and lesion formation [Vernooij et al., 2008] on the dimensionality of between-person differences in white matter microstructure.

We conclude that individual differences in white matter microstructure among older adults are organized according to multiple principles. For any given measure, several components of individual differences will be present. Future research may profit from applying methods suitable for disentangling general and specific influences, such as those used in intelligence [Carroll, 1993] and cognitive-aging research [e.g., Hofer and Sliwinski, 2001; Hofer et al., 2006; Lindenberger and Ghisletta, 2009; Salthouse, 2011]. SEM offers one attractive route, which enables the formation of latent factors that attenuate the influence of error and forces the researcher to explicate the measurement model of individual differences. Under optimal situations, SEM may also be used for simultaneously extracting general and specific variance components at the latent level [Schmiedek and Li, 2004]. When SEM is combined with multiple regression approaches, predicted relations between white matter microstructure and outcomes of interest can be empirically examined to bolster specific interpretations of findings. For any given outcome (e.g., education, cognition, and disease), it is an empirical issue whether relations are specific to certain white matter tracts or rather reflect general influences. Here, we reported the novel finding that correlations among white matter microstructure in distinct tracts do not generally increase from early to late phases of older adulthood. This finding provides indirect evidence suggesting that aging of white matter microstructure is not a process that plays out in a similar manner across the brain. Longitudinal work is needed to corroborate these findings.

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