Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age

Martin Lövdén a,b,⁎, Ylva Köhncke a, Erika J. Laukka a, Grégoria Kalpouzos a, Alireza Salami a,d, Tie-Qiang Li c, Laura Fratiglioni a,e, Lars Bäckman a

© 2014 Elsevier Inc. All rights reserved.

ARTICLE INFO

Article history:
Accepted 9 August 2014
Available online xxx

Keywords:
Cognitive performance
Longitudinal
Structural equation modeling
White matter microstructure
Cognitive aging

ABSTRACT

The integrity of the brain’s white matter is important for neural processing and displays age-related differences, but the contribution of changes in white matter to cognitive aging is unclear. We used latent change modeling to investigate this issue in a sample of very old adults (aged 81–103 years) assessed twice with a retest interval of 2.3 years. Using diffusion-tensor imaging, we probed white matter microstructure by quantifying mean fractional anisotropy and mean diffusivity of six major white matter tracts. Measures of perceptual speed, episodic memory, letter fluency, category fluency, and semantic memory were collected. Across time, alterations of white matter microstructure in the corticospinal tract were associated with decreases of perceptual speed. This association remained significant after statistically controlling for changes in white matter microstructure in the entire brain, in the other demarcated tracts, and in the other cognitive abilities. Changes in brain volume also did not account for the association. We conclude that white matter microstructure is a potent correlate of changes in sensorimotor aspects of behavior in very old age, but that it is unclear whether its impact extends to higher-order cognition.

Introduction

Cognitive performance declines in aging (Rönnlund et al., 2005; Schaie, 2005). The neuroanatomical substrates of these decreases are not completely charted (Salthouse, 2011). Various neuroimaging probes of the brain’s white matter display pronounced age-related differences (Madden et al., 2012; O’Sullivan et al., 2001; Salthouse, 2011; Sullivan and Pfefferbaum, 2006; Westlye et al., 2010). Intact white matter is important for neural information transmission and synchronous processing in large-scale neural networks (Andrews-Hanna et al., 2007; Fields, 2008). We can therefore hypothesize that age-related changes in white matter contribute to decrements in cognitive performance (O’Sullivan et al., 2001). As a corollary of this hypothesis, we must assume that within-person changes of cognitive performance and white matter integrity proceed together. Cross-sectional studies, using a single occasion, between-person comparison as a substitution for longitudinal, within-person assessment, have revealed a link between white matter integrity and various aspects of cognitive performance (Madden et al., 2012; O’Sullivan et al., 2001; Salami et al., 2012; Salthouse, 2011). However, such studies cannot directly estimate change and can therefore not investigate the critical prediction of an association between inter-individual differences in changes of white matter and cognition in aging.

To our knowledge, only one longitudinal study (Charlton et al., 2010) has linked changes in cognition to changes in white matter microstructure measured with diffusion-tensor imaging (DTI). DTI is a magnetic resonance (MR) technique that probes white matter by quantifying the diffusion of water molecules in tissue, and is often used to compute directional specificity (fractional anisotropy; FA) and average rate (mean diffusivity; MD) of diffusivity in a voxel. Higher FA reflects higher fiber density and coherence within a voxel, and is typically assumed to signify better white matter integrity. Higher MD denotes less dense tissue in a voxel and is often taken to indicate poorer white matter integrity. The study by Charlton et al. (2010) observed significant 2-year whole-brain decreases of FA and increases of MD in a sample of adults aged 50–90 years (see also Barrick et al., 2010). Changes in indices of whole brain MD were significantly related to changes in working memory performance, but not to changes in perceptual speed and executive functioning. Regional differences of white matter change were not investigated, which is a limitation given the functional
specificity of several white matter tracts (Catani and Ffytche, 2005), the presence of substantial tract specificity of between-person differences (Lövdén et al., 2013), and cross-sectional evidence of heterogeneous regional mean decline (Sullivan and Pfefferbaum, 2006).

We report analyses of 2.3-year changes in white matter microstructure and cognitive performance in a sample of very old individuals, aged between 81 and 103 years. We used structural equation modeling (SEM) to analyze longitudinal changes in region-of-interest variables extracted from the core of six major tracts. One major advantage of SEM is that latent factors can be formed. A factor represents the shared variance among its observed indicators. Measurement error is separately estimated. When change is estimated from latent factors, the influence of error, which is especially challenging to deal with in longitudinal data, is therefore attenuated. We have previously reported analyses from the baseline assessment of this sample (Laukka et al., 2013b; Lövdén et al., 2013). In these studies, we formed factors representing between-person differences that are common across hemispheres for a given tract. This model was based on the principle of tract-based organization of connections among gray-matter areas (Catani and Ffytche, 2005; Filley, 2010) and evidence of high correlations between FA in homologous tracts in the two hemispheres (Wahl et al., 2010). Results showed good validity for models forming tract factors of mean FA or MD. In contrast, a model assuming only a general factor of white matter microstructure did not fully represent the individual differences (Lövdén et al., 2013). Age-related differences in FA and MD of the tract factors were sizable. In addition, white matter microstructure in several of the tracts was associated with perceptual speed, but not with verbal fluency, category fluency, episodic memory, and semantic memory (Laukka et al., 2013b).

Here, we include follow-up data to estimate changes in FA and MD and directly investigate whether white matter microstructure displays average change over 2.3 years in very old age and whether there are reliable between-person differences in these changes. We also examine whether changes generally go together across tracts, which informs the discourse on the prominence of general and region-specific individual differences in aging of white matter (Lövdén et al., 2013; Penke et al., 2010). Finally, and most importantly, we investigate whether white matter changes are associated with changes in factors representing perceptual speed, verbal fluency, category fluency, episodic memory, and semantic memory.

Materials and methods

Participants

Subjects participated in a population-based longitudinal study, the Swedish National study on Aging and Care in Kungsholmen (SNAC-K). A sample of 3363 individuals, stratified on age (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99+ years), took part in a first data collection assessing medical, psychological, and social status through interviews and clinical examinations. A follow-up assessment including individuals 81 years or older was completed three years later. A second follow-up was completed five to six years after the first assessment. Identical DTI protocols were used in a subsample at the first and the second follow-up. We therefore focused on data from these two assessments, hereafter referred to as time 1 and 2. At time 1, 764 individuals took part in the assessment of cognitive performance. Of these, 112 individuals underwent DTI and had acceptable quality of the images (e.g., no movement artifacts). From this sample, we excluded participants with dementia diagnosis (n = 196), Parkinson's disease (n = 2), stroke (n = 2), or Guillain–Barré syndrome (n = 1), at time 1 or time 2. The remaining sample consisted of 563 individuals that had taken part in the cognitive assessments and 77 individuals of these participated in DTI. At time 2, 378 individuals returned for cognitive testing (on average 2.7 years after time 1; SD = 0.3) and 40 individuals returned for DTI (on average 2.3 years after time 1; SD = 0.2).

Table 1 summarizes background variables for the total sample and for the subsample with DTI data at time 1. As expected based on the concomitancies for MR imaging, the DTI sample tended to be positively selected on these background variables, but these effects [(Mbaseline sample − Mtotal sample) / SDtotal sample] were generally small (range = 0.15–0.29 SD). Selectivity of the DTI sample was relatively restricted (range = 0.00–0.48 SD; median = 0.22 SD) also for the cognitive variables (see description below). Longitudinal mean selectivity [(Mbaseline sample − Mtotal sample) / SDtotal sample] for the background and cognitive variables, indicating the magnitude to which individuals who survived and participated at time 2 differed from the original sample at time 1, was small for both the total and the DTI sample (0.05–0.18 SD; median = 0.14 SD).

MR imaging

All MR images were acquired using a single 1.5 T scanner (Philips Intera, Netherlands). At both time points and for all subjects, DTI data were acquired using a single-shot diffusion-weighted echoplanar imaging sequence with the following parameters: FOV = 230 × 138 mm2; 128 × 77 matrix; TE = 104 ms; TR = 5368 ms; and slice thickness = 5 mm with 1 mm gap. One volume of non-diffusion-weighted images (b = 0) and 6 volumes of diffusion-weighted images at a b-value of 600 s/mm2 were acquired. The DTI scheme was composed of 6 non-collinear gradient directions. T1-weighted images were acquired using the 3D FFE (fast field echo) sequence. The acquisition parameters were: TR = 15 ms, TE = 7 ms, flip angle = 15°, number of slices (axial) = 128, slice thickness = 1.5 mm, in-plane resolution = 0.9375 × 0.9375 mm, no gap, FOV = 240 × 240, and matrix = 196 × 256.

Preprocessing of DTI images

DTI data for all subjects from all assessments were corrected for eddy current artifacts and motion, and the tensor elements were calculated. MD and FA were then derived on a voxel-by-voxel basis (see Lövdén et al., 2013, for details). The FA data were further processed using tract-based spatial statistics (TBSS; Smith et al., 2006), which is part of FSL (Smith et al., 2004). All available images were normalized, using nonlinear registration 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. The mean skeleton was thresholded and binarized at FA > 0.2. This resulted in a skeleton that included 101466 voxels. Each participant’s normalized FA data were then projected onto this skeleton, which results in individual skeleton images. The MD images were projected onto the skeleton in the same way, based on the results of the processing of the FA images. We refrained from any specific processing of the longitudinal data, such as coregistering the images across time points (Engvig et al., 2012), because the validity of preprocessing streams with longitudinal coregistration is currently not clearly established. In addition, we...
wanted to use all available data (including those individuals with data at only one time point) in the analyses.

From the resulting individual skeleton images, we extracted mean FA and MD for six regions of interest (ROI) in each hemisphere using the procedures validated by Lövdén et al. (2013). Specifically, we selected probabilistic template masks for the cingulum gyrus part of cingulum (CCG), the corticospinal tract (CS), the forceps major (FMAJ), the forceps minor (FMIN), the inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF). Five masks were based on the JHU white-matter tractography atlas (Wakana et al., 2004), but the CS mask from the Catani tractography atlas (Catani and Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2011) was selected for the CS, because it fitted the skeleton better. The callosal tracts 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. The resulting binary masks were then combined with the skeleton mask. To avoid overlap with the callosal tracts, the CCG mask was then 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. We additionally edited the masks manually, with a focus on excluding overlap between the tracts and restricting the ROI to the core of the tract. Note that the skeleton mask is identical for all subjects, so that these procedures do not introduce any source of between-subject error, but rather increases the anatomical validity of the ROIs. The resulting ROIs are depicted in Fig. 1.

The ROIs were then used to extract mean FA and MD data from the individual skeletons. This procedure resulted in 24 FA and 24 MD variables (6 tracts × 2 hemispheres × 2 time points) for the analyses. Table 2 summarizes descriptive statistics of the resulting measures. In reading this table, note that the number of individuals with DTI data is 77 at time 1 and 40 at time 2, so that the estimates cannot be directly compared over time because they come from a partially different sample. CCG = cingulum cingulate gyrus; CS = corticospinal tract; FMAJ = forceps major; FMIN = forceps minor; IFOF = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; L = left; R = right.

Table 2: Descriptive statistics of mean FA and MD from the white matter regions of interest.

| Tract        | n váxe|x | FA     | MD     | FA     | MD     | FA     | MD     |
|--------------|-------|-------|--------|--------|--------|--------|--------|
| CCG_L        | 214   | 0.490 | 0.039  | 0.486  | 0.045  | 0.853  | 0.043  | 0.865  | 0.053  |
| CCG_R        | 257   | 0.487 | 0.036  | 0.495  | 0.042  | 0.833  | 0.033  | 0.857  | 0.046  |
| CS_L         | 3774  | 0.609 | 0.024  | 0.607  | 0.024  | 0.768  | 0.035  | 0.792  | 0.034  |
| CS_R         | 3170  | 0.651 | 0.010  | 0.652  | 0.032  | 0.776  | 0.040  | 0.784  | 0.039  |
| FMAJ_L       | 682   | 0.681 | 0.037  | 0.677  | 0.036  | 0.775  | 0.054  | 0.786  | 0.052  |
| FMAJ_R       | 726   | 0.665 | 0.039  | 0.657  | 0.041  | 0.789  | 0.040  | 0.803  | 0.047  |
| FMIN_L       | 2143  | 0.497 | 0.035  | 0.488  | 0.035  | 0.893  | 0.053  | 0.913  | 0.055  |
| FMIN_R       | 2139  | 0.477 | 0.034  | 0.469  | 0.029  | 0.903  | 0.053  | 0.919  | 0.055  |
| IFOF_L       | 2886  | 0.507 | 0.035  | 0.500  | 0.037  | 0.872  | 0.042  | 0.887  | 0.042  |
| IFOF_R       | 2690  | 0.501 | 0.034  | 0.495  | 0.039  | 0.861  | 0.043  | 0.872  | 0.043  |
| SLF_L        | 952   | 0.480 | 0.040  | 0.478  | 0.047  | 0.816  | 0.048  | 0.826  | 0.052  |
| SLF_R        | 925   | 0.466 | 0.037  | 0.465  | 0.040  | 0.811  | 0.050  | 0.825  | 0.052  |

Note: Note that the number of individuals with DTI data is 77 at time 1 and 40 at time 2, so that the estimates cannot be directly compared over time because they come from a partially different sample. CCG = cingulum cingulate gyrus; CS = corticospinal tract; FMAJ = forceps major; FMIN = forceps minor; IFOF = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; L = left; R = right.

Longitudinal mean selectivity for these variables was small (0.01–0.14 SD; median = 0.07 SD). Note that, initially, data for more tracts (e.g., fornix, the hippocampal segment of the cingulum, and the anterior thalamic radiation) were extracted, but preliminary analyses showed low test–retest correlations for these variables (all rs < .50), suggesting poor reliability, perhaps because these tracts are smaller or more complex in their structure than the reported major tracts.

Preprocessing of T1-weighted images

Preprocessing of the T1-weighted images was performed in SPM12b (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA, US). Segmentation of the T1 images into gray matter, white matter, and cerebrospinal fluid was performed using the improved unified segmentation approach as

Fig. 1. Regions of interests from which mean fractional anisotropy and mean diffusivity were extracted for each individual. Red = cingulum cingulate gyrus; blue = corticospinal tract; green = forceps major; violet = forceps minor; yellow = inferior fronto-occipital fasciculus; cyan = superior longitudinal fasciculus. The backdrop image is the MNI ICBM template.
implemented in SPM12b, which enhances registration and uses an extended set of tissue probability maps (Ashburner and Friston, 2005).

The “light cleanup” option was used to further remove odd voxels from the segments. All segments were visually verified. Total brain tissue volume was obtained by adding gray matter and white matter volumes.

Cognitive assessment

Trained psychologists administered the cognitive test battery according to a standardized procedure (see Laukka et al., 2013a, for details). Five cognitive abilities were measured by two tests each. Perceptual speed was measured with digit cancellation (Zazzo, 1974) and pattern comparison (Salthouse and Babcock, 1991). In the digit cancellation task, participants sequentially go through rows of digits (1–9 in random order) and cross out every “4” as quickly as possible. The score used for this task was the number of correctly crossed 4s in 30 s. For pattern comparison, participants sequentially go through pairs of line-segment patterns and mark whether the patterns are “same” or “different.” The task consisted of two pages with 30 patterns for each page. Participants were given 30 s per page and the score used was mean number of correct classifications across the two pages.

Episodic memory was measured by free recall and recognition (hits–false alarms) of 16 unrelated concrete nouns that were presented orally and visually for 5 s during encoding. The recognition task, for which the 16 target words were presented randomly intermixed with 16 distractors, was administered following free recall. Only items described as being “remembered” (Tulving, 1985) by the participant were included in the recognition (D) score. Semantic memory was indexed by a measure of vocabulary (Durman, 1960) and a measure of general knowledge (Dahl et al., 2009). Letter fluency was indexed by two letter fluency tasks, for which participants were asked to orally generate as many words as possible in 60 s, beginning with the letters F and A, respectively. Category fluency was also indexed by two tasks. Participants were asked to orally generate as many words as possible in 60 s, belonging to the categories animals and professions, respectively.

Skewness and kurtosis were acceptable for all cognitive measures (skewness = −0.92–0.55; kurtosis = −0.19–0.90), indicating normally distributed variables. The test–retest correlations were low for the measures of recognition (r = .32) and general knowledge (r = .13), suggesting possible problems with the reliability of these measures. Our SEM approach to the statistical analyses attenuates the influence of error (see Statistical procedures), but poor reliability may negatively influence standard errors. The results for the semantic and episodic memory abilities should be interpreted in light of this fact. The test–retest correlations were fairly high for the other measures (rs = .51–.80; median = .69), indicating acceptable lower boundaries of reliability.

Statistical procedures

We used a latent change model (LCM; McArdle and Nesselroade, 1994; see Fig. 2), to estimate initial level and longitudinal change (i.e., the difference between time 1 and time 2) in the DTI and cognitive variables (see also Raz et al., 2005; Raz et al., 2013). In the model, we assumed a latent unobserved factor at time 1 (t1) and one analogous factor (i.e., the difference between time 1 and time 2) in the DTI and cognitive variables (see also Laukka et al., 2013a). For the cognitive variables, the respective indicators of each ability formed factors of perceptual speed, letter fluency, category fluency, episodic memory, and semantic memory (Laukka et al., 2013a). In our LCM, the t2 factor is defined as the unit-weighted sum of the t1 factor plus a latent difference score (diff), so that the diff factor is interpreted as the latent change from t1 to t2. This latent change approach attenuates problems related to unreliability of raw difference scores by estimating the mean (μt1) and variance (σ²t1) of longitudinal change separately from the freely estimated error variances (σ²ex1, σ²ey1, σ²ex2, & σ²ey2). In addition, this model allows for simultaneously estimating the initial mean (μt1), between-person differences in this initial level (σ²t1), and the covariance between initial level and change (ρt1, diff). In all models, we included chronological age, years of education, sex as predictors of the level (t1) and change (diff), and pattern comparison (Salthouse and Babcock, 1991). The estimates involving the latent difference score (i.e., longitudinal change) are thus not influenced by cross-sectional age heterogeneity, or individual differences in education, and sex. The predictors were centered so that the reported estimates of level and change pertain to the mean of the sample on these demographic factors.

Finally, we estimated one of the loadings (11) of the two indicators on the factors and the mean differences between the indicators of the factors (μdiff). To interpret the results at the latent level, it must be possible to constrain these two parameters to be equal over time (i.e., to assume strong measurement invariance; Meredith, 1993; Meredith and Teresi, 2006) without losing model fit against the unconstrained model in which the parameters are allowed to vary over time. If strong measurement invariance is refuted, then the two indicators of a construct (e.g., FA in left and right CCG) are changing differently, so that it does not make sense to interpret results at the latent level of their common variance.

We first analyzed the DTI data, estimating 12 different univariate models, one for each of the white matter tracts and index of white matter microstructure (i.e., FA and MD). Of main interest here is the magnitude of the mean (μdiff) and variance (σ²diff) of the difference

Please cite this article as: Lövdén, M., et al., Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age, Neuroimage (2014), http://dx.doi.org/10.1016/j.neuroimage.2014.08.020
score (diff), addressing the questions of whether mean change in FA and MD can be observed over 2.3 years, and whether there are between-person differences in the amount of change. The estimate of the variance in change ($\sigma^2_{\text{diff}}$) must be significant to allow for investigating associations between changes in the DTI metrics and other variables.

That is, a constant (i.e., non-significant variance) cannot correlate with anything. Only acceptable univariate models (i.e., those being measurement invariant and showing significant variance in change) were then included in bivariate LCMs of each pairwise combination of the tract factors. Here, the correlations among the latent difference factors (diff) were of primary interest, because they address the question of the extent to which changes in white matter integrity go together across the tracts of the brain.

Next, we analyzed the cognitive variables with the same statistical procedures. The abilities displaying strong measurement invariance and significant variance in change were taken to a final step, which estimated bivariate models of each pairwise combination of cognitive and white matter factors. Here, the estimates of the correlations between changes in white matter and cognitive performance were of primary interest, because they address the question of whether aging-related change of white matter is associated with cognitive decline. If we detected a significant association between changes in cognitive performance and white matter, then we also examined whether changes in total brain volume (gray + white matter volume) could account for this association, by regressing the latent change variable of change in brain volume (time 2 − time 1).

Handling missing values

Missing data was handled by estimating the models with full information maximum likelihood (FIML; Finkelstein, 1979; Schafer and Graham, 2002). This state-of-the-art method uses all available information in a model for estimating parameters that involve missing values. Hence, individuals with partial missing data (e.g., time 1 but not time 2 data) can be included without imputing missing data. This method generates less biased population estimates than other widespread procedures dealing with missing values (e.g., listwise deletion, regression imputation, mean imputation; e.g., Schafer and Graham, 2002). For example, though longitudinal mean selectivity was fairly small in this study (0.01–0.18 SD), restricting the sample to returnees at time 2 would have resulted in more positively biased estimates of the initial means compared to the FIML approach. The FIML approach also comes with higher power for those parameters that are based on a larger sample.

The FIML algorithm works under the assumption of missing-at-random (MAR; Rubin, 1976; see Schafer and Graham, 2002 for a non-technical treatment), meaning that the probability that a score on variable X is missing can rely on other variables in the model, but not on X per se. The FIML algorithm as applied here is enhanced by our inclusion of variables that are likely to be powerful predictors of missingness, such as time 1 data on the measures of interest, two complementary variables of each factor, chronological age, years of education, and sex.

In addition to using the attractive features of the FIML method to deal with longitudinal dropout, we used it to enhance the estimation of the association between changes in white matter microstructure and cognitive performance. Specifically, we included the total sample with cognitive data in these models. This approach results in a large proportion of individuals with missing values on the white matter variables (around 85%) in these analyses. This is nevertheless preferred over restricting analyses to the sample with DTI data, because the parameters for the cognitive abilities are estimated with much better precision when the full sample is included. The subsample with DTI data was not severely selected on the cognitive variables ($\text{median} = 0.22$ SD) and the variables included in the models (i.e., cognitive performance and demographics) are likely to predict most of the non-random missingness in the white matter variables (e.g., due to contraindications for MR). Therefore, the parameter estimates are likely to be more precise and less biased than estimates from models restricted to the sample with DTI data.

However, to further probe the findings that this approach generated, we also report analyses of the associations between changes in cognitive performance and white matter that are restricted to the select individuals with DTI data from both time 1 and time 2 ($n = 40$). To assure comparability with the LCM results, we averaged the left and right sides of each tract. We also formed unit-weighted composites of the two indicators of each cognitive ability, by first standardizing the individual measures (using mean and standard deviation at time 1 as reference values) and then averaging the two measures representing an ability. Raw difference scores computed on the unit-weighted composites (time 2 − time 1) were used as measures of change. Partial correlations, controlling for education, sex, and age, among level (time 1) and change in these variables were then computed. We further used this sample to investigate whether any significant associations between a white matter tract and cognitive performance were unique for that tract. To this end, we used multiple regression to examine whether the tract in question significantly predicted cognitive performance also after accounting for changes in the other tracts and whole-skeleton white matter integrity. In addition, with the same approach we investigated whether any association with a cognitive ability remained after controlling for other abilities. The reason for doing this on the raw difference scores, rather than with LCM, was that these analyses require including many variables in the models, and an LCM approach would therefore need a larger sample size than available in this study.

Results

Changes in white matter microstructure

To analyze longitudinal change of white matter microstructure, we first estimated univariate LCMs (see Fig. 2) separately for the FA and MD variables of each of the six tracts in the sample with DTI data at time 1 ($n = 77$). With exception of the model of MD in the CCG, which had unacceptable fit, $\chi^2(7, N = 77) = 14.41, \text{CFI} = .962$, RMSEA = .117, and may therefore not deliver trustworthy estimates, the models assuming intercepts ($H_{\text{asym}}$) and unstandardized loadings (11) on the tract factors to be equal over time all had reasonable fit, all $\chi^2(7, N = 77) < 10.16, \text{CFI} > .986, \text{RMSEA} < .077$. These models did not fit significantly worse than models allowing these parameters to freely vary, all $\Delta \chi^2(2) < 5.89, p > .05$. Thus, strong measurement invariance over time is an acceptable assumption for all these tracts.
Among levels of MD and FA were generally significant differences. These results are displayed in Table 4. Note that these correlations are controlled for the effect of age, education, and sex. With the exception of FA in the CCG and SLF, these estimates reached significance ($p < .05$). Across most tracts, the estimates of longitudinal change tended to be somewhat larger than the cross-sectional age differences. After controlling for years of education and sex, age differences ranged from $-0.011$ (SLF) to $-0.002$ (CS) to $-0.002$ (CS). FD decayed in MD over the 2.3 years were observed for all tracts. Annual mean change ($\mu_{\text{annual}}$) for MD and FA for the CCG and SLF, indicating that increases in MD over time were not pronounced for the oldest old. Such age-based nonlinear change was not observed for FA in any of the tracts. Years of education was neither consistently related to level nor change in white matter, with only one effect on initial level (FA in FMAJ) and one effect on change (FA in FMIN) reaching conventional significance ($p < .05$). Women demonstrated lower initial level of FA in FMIN, IFOF, and SLF than men, but showed less negative changes in FA of FMIN. Significant between-person differences in change over time ($\sigma_{\text{diff}}^2$) were observed for FA in the CCG, CS, FMAJ, IFOF, and SLF for MD in the CS, FMAJ, and FMIN. Further analyses targeting associations between individual differences in change were therefore restricted to these tracts. These analyses were pursued with bivariate LCMs of each pairwise combination of the tract factors.

Correlations among level and change in the modeled tracts are displayed in Table 4. Note that these correlations are controlled for the influence of age, education, and sex, so that heterogeneity emanating from these variables is not influencing the associations. Correlations among levels of MD and FA were generally significant and relatively high. Changes in FA were in general associated across tracts ($r = .28$–.77). In contrast, changes in MD were weakly associated among tracts, and also correlated weakly with changes in FA. Based on the sizable associations among levels of FA and MD in the tracts, we also attempted to estimate general models (one for MD and one for FA) in which all tracts loaded on a common factor (Lövdén et al., 2013), but the fit of these models was unacceptable, both $\chi^2(328, N = 77) = 718.80, CI < .793, RMSEA = .123$, indicating that a general factor alone was not an adequate representation of between-person differences in white matter microstructure (see also Lövdén et al., 2013). In addition, strong measurement invariance over time was not an acceptable assumption for these models, indicating that the different tracts displayed distinct patterns of change.

Changes in cognitive performance

Next, we modeled the cognitive data in the same way as the DTI data, but using the full sample with cognitive data at time 1 ($n = 498$).

Table 4

Partial correlations, controlling for chronological age, years of education, and sex, among inter-individual differences in level (time 1; above diagonal) and change (below diagonal) in FA and MD in the tracts of interest that displayed significant variance in change ($n = 37$).

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FA in CCG</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>2. FA in CS</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>3. FA in IFOF</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>4. FA in FMIN</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>5. FA in SLF</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>6. MD in CS</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>7. MD in IFOF</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
<tr>
<td>8. MD in FMIN</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
<td>$t_4$</td>
</tr>
</tbody>
</table>

Note: FA = fractional anisotropy; MD = mean diffusivity; CCG = cingulum cingulate gyrus; CS = corticospinal tract; FMAJ = forceps major; FMIN = forceps minor; IFOF = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus. * $p < .05$. ** $p < .01$.

Please cite this article as: Lövdén, M., et al. Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age, NeuroImage (2014), http://dx.doi.org/10.1016/j.neuroimage.2014.08.020
563). Strong measurement invariance over time was an acceptable assumption for all of the cognitive abilities, all χ²(7, N = 563) < 17.65, CFI > .989, RMSEA < .052, all Δχ²(2) < 2.84, p > .24. This allowed us to interpret results at the cognitive ability level (see Table 5). All five abilities displayed significant negative mean change. Despite the possible influence of retest effects, the estimates of annual longitudinal change (p = 2.7 years) tended to be larger than the cross-sectional age effect (controlled for influences of years of education and sex). Chronological age did not influence change, indicating linearity of changes as a function of age. Years of education was positively associated with level of performance on all five abilities, but did not influence change. Women performed significantly better than men on perceptual speed and episodic memory, but changes in cognitive performance were unrelated to sex. Between-person differences in change were not significant for semantic memory, but reached significance for perceptual speed, letter fluency, category fluency, and episodic memory.

The analyses targeting associations between changes in white matter integrity and cognition were therefore restricted to these four cognitive abilities.

### Associations between white matter microstructure and cognitive performance

Using the full sample (n = 563), we estimated the associations between white matter microstructure and cognitive ability with bivariate LCMs of each pairwise combination of the tract factors and cognitive abilities. Correlations between initial levels of white matter microstructure and cognitive ability, and the limits for significance at an alpha level of p = .01 (dashed lines) and p = .05 (thick lines), are displayed in Fig. 3. Using the more conservative threshold of p = .01, the correlation between perceptual speed and FA in the CS reached significance, Δχ²(1) < 12.04, p < .001.

Correlations between changes in white matter microstructure and changes in cognitive abilities are displayed in Fig. 4. Critically, the relationships of changes in perceptual speed to changes in both FA and MD in CS reached significance, Δχ²(1) < 7.74, p < .01 and Δχ²(1) < 8.37, p < .01, respectively. Note that these correlations are controlled for the influence of chronological age, education, and sex, so that heterogeneity emaning from these variables is not influencing these associations. To further probe the associations, we also included change (time 2 − time 1) in total brain volume as a covariate. The correlations between changes in CS and perceptual speed remained significant after controlling for change in total brain volume, Δχ²(1) < 7.53, p < .01 for FA and Δχ²(1) < 7.93, p < .01 for MD. Generally, change in total brain volume was not significantly associated with change in FA or MD in any of the tracts (all ps > .09).

Follow-up analyses on the sample with complete DTI data at time 1 and time 2 (n = 40)

The results reported above were throughout similar in the select sample with complete DTI data (see Supplementary Table 1), which was analyzed using partial correlations, controlling for education, age, and sex, among level (time 1) and change in the unit-weighted composites forming each cognitive ability and the tract measures formed by averaging left and right hemispheres. Most importantly, the correlations were trustworthy.

---

**Table 5** Results from univariate LCMs of initial level (time 1) and change (diff) in cognitive abilities (n = 563).

<table>
<thead>
<tr>
<th>Cognitive Ability</th>
<th>Mean (μ)</th>
<th>Variance (σ²)</th>
<th>Unstandardized effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level (time 1)</td>
<td>Change (diff)</td>
<td>Age</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>15.66*</td>
<td>−0.83*</td>
<td>4.92*</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>14.68*</td>
<td>−0.56*</td>
<td>16.45*</td>
</tr>
<tr>
<td>Category fluency</td>
<td>18.59*</td>
<td>−0.56*</td>
<td>12.98*</td>
</tr>
<tr>
<td>Episodic frequency</td>
<td>5.92*</td>
<td>−0.27*</td>
<td>3.03*</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>21.45*</td>
<td>−0.71*</td>
<td>9.81*</td>
</tr>
</tbody>
</table>

* Note. Edu = years of education. Men are coded 0 and women 1.

**Q2**

* p < .05.

**Q1**

Please cite this article as: Lövdén, M., et al., Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age, NeuroImage (2014), http://dx.doi.org/10.1016/j.neuroimage.2014.08.020
between changes in the CS and perceptual speed reached significance for both FA, \( r = .47, p = .004 \), and MD, \( r = -.47, p = .004 \). Note that the magnitude of these correlations that are based on the raw difference scores is reduced by error, so that they cannot be directly compared to the estimates from the structural equation models that attenuated this influence.

Finally, we addressed whether changes in FA and MD in the CS predicted variance in change of perceptual speed after controlling for changes in the other tracts, which it did, \( \Delta R^2 = .189, \Delta F (1) = 9.28, p < .005 \) for FA and \( \Delta R^2 = .198, \Delta F (1) = 8.76, p < .006 \) for MD. Changes in FA and MD in the CS also remained significant predictors after controlling for average change across the entire white-matter skeleton, \( \Delta R^2 = .096, \Delta F (1) = 4.34, p < .045 \) for FA and \( \Delta R^2 = .187, \Delta F (1) = 8.47, p < .007 \) for MD. Similarly, changes in perceptual speed remained a significant predictor of changes in FA, \( \Delta R^2 = .169, \Delta F (1) = 6.70, p < .015 \), and MD, \( \Delta R^2 = .133, \Delta F (1) = 6.01, p < .020 \), after controlling for change in episodic memory, letter fluency, and category fluency.

Thus, the associations between changes in perceptual speed and changes in FA and MD were to a significant degree not shared with the other tracts or the other cognitive abilities.

Discussion

We report mean change in FA and MD in major white matter tracts over an average of 2.3 years in a sample of very old adults. Between-person differences in change of FA were significant for five of the examined six tracts. For MD, such differences were significant for three of the tracts. The individual differences in change of FA were associated across tracts. In contrast, changes of MD were weakly associated among tracts, and generally also correlated weakly with changes in FA. Mean longitudinal decline was also observed for the investigated cognitive abilities.

Importantly, decreases of perceptual speed were significantly associated with changes in both FA and MD in the CS tract.

Mean changes in MD and FA over time were significant for most tracts. For MD, these changes decelerated with higher age, but because the density of observations was low in the higher ages, interpretation of this finding must await replication. The general magnitude of the mean changes is much in line with those reported by Barrick et al. (2010) in their study of 2-year longitudinal changes in a sample of individuals with a mean age of 69 years. For example, their estimates of annual mean changes in FA of the genu (\(-.004\)) and splenium (\(-.003\)) of the corpus callosum correspond well to the present estimates of changes of FA in FMIN (\(-.004\)), which passes through the anterior part (genu) of the corpus callosum, and FMAJ (\(-.004\)), which crosses the posterior part (splenium) of the corpus callosum.

For most of the tracts, longitudinal mean changes were numerically larger than the cross-sectional age differences, after controlling for years of education and sex. The magnitude of the cross-sectional age differences (see also Lövdén et al., 2013) is in line with earlier reports (Madden et al., 2012; O'Sullivan et al., 2001; Saltuske, 2011), and the pattern of larger changes than age differences corroborates the results from analyses of whole-brain changes in FA reported by Charlton et al. (2010). The pattern is also in line with studies of changes in gray matter volume (Raz et al., 2005). Age-differential selectivity in cross-sectional studies, such that individuals eligible for and willing to take part in longitudinal studies are more likely to be positively selected the older they are, likely accounts for these different magnitudes. This is especially likely when proxies for cohort effects, such as education (Ronnland et al., 2005), have been statistically accounted for, and when longitudinal selectivity is small and has been optimally handled with appropriate statistical techniques.

The major strength of longitudinal studies is that between-person differences in within-person change can be directly estimated. Estimates of these individual differences in FA reached significance for five of the six tracts examined. For MD, the differences were significant for three of the tracts. The presence of significant individual differences in change is a requirement for appropriate investigation of associations between changes in different factors. If this estimate is not significant, true changes are constant across individuals, so that changes cannot correlate with other variables. The separate estimation of this parameter from error is a major strength of this study. Without this feature, it is difficult to resolve whether a low correlation is due to an absence of an association or to a low "signal" in the variables.

Importantly, between-person differences in changes of FA were substantially associated among tracts that displayed significant variance in change. In contrast, changes in MD were weakly associated among tracts. Changes in MD also correlated weakly with changes in FA, the only exception being the correlation between FA and MD in the CS. These are novel results, which are not predicted from the uniformly significant and relatively high correlations among level of MD and FA.

The substantial correlations among levels of FA and levels of MD indicate shared between-person differences among tracts in very old age. This finding is consistent with previous work reporting that a general factor accounts for a substantial portion of between-person differences in white matter microstructure of a manifold of regions and tracts (Lövdén et al., 2013; Penke et al., 2010). Nevertheless, and also consistent with past reports (Lövdén et al., 2013), a general factor alone did not adequately capture individual differences in FA and MD. In addition, strong measurement invariance over time was not an acceptable assumption for models postulating a general factor only, indicating that the different tracts showed partly different patterns of change. However, the pronounced associations among changes of FA in the different tracts indicate that a substantial portion of between-person...
differences in change in very old age is also shared among tracts. This was not predicted from our previously reported cross-sectional evidence, which showed that the magnitude of correlations among level of FA in different tracts did not increase with age (Lövdén et al., 2013). Such an increase would have been predicted if changes were associated (Hofer and Sliwinski, 2001; Hofer et al., 2006; Van Petten, 2004), but this prediction assumes an absence of age-differential selectivity, which, is probably an untenable assumption in most cross-sectional work. Thus, the longitudinal data deliver the novel finding that changes of FA in a tract often go together with changes in other tracts, although tract-specific changes are also present, as indicated by the non-perfect correlations.

In contrast, changes in MD were weakly associated among each other, indicating that MD in different tracts decline relatively independent of each other, and independent of FA, in old and very old age. Together, these distinct dimensionalities of changes in MD and FA show that FA and MD capture different changes of white matter in aging. These findings also suggest the presence of effects (e.g., environmental and genetic) that impact white matter at the level of tracts and that these effects are to a varying degree shared by different groups or pairs of tracts. The presence of unique individual differences in change in the tracts calls for investigating the association between white matter microstructure and cognitive performance at the level of tracts, and not only for general, whole-brain, indices.

A key finding was that changes of FA and MD in the CS tract were associated with decreases in perceptual speed. This association was evident both in the smaller sample with DTI data at time 1 and time 2 and in the SEM analyses using all available data to estimate the association. The correlations between changes in perceptual speed and changes in the other tracts, and between changes in CS and changes in the other cognitive abilities, were numerically lower and did not reach significance. The CS tract contains mostly axons originating in the motor cortex, and to some extent in the somatosensory and parietal cortices, and transfers information from these regions to the spinal cord. This pathway is used for cortical modulation of spinal cord activity and is critical for most sensorimotor functions, such as the precise and voluntary hand and finger movements involved in the tasks used in this study to index perceptual speed (Lemon and Griffiths, 2005). This is an important finding in light of the commonly found association between white matter microstructure and level of performance on perceptual speed tasks (Madden et al., 2012; Penke et al., 2010; Salami et al., 2012; Salthouse, 2011). Using the baseline data from the present sample, we also reported that perceptual speed, and not the other cognitive abilities, was significantly associated with FA and MD in old age (Laukka et al., 2013b).

In the present report, using data from the two follow-up waves, we corroborate these results with the observation of a significant association between level of perceptual speed and white matter microstructure in the CS tract. This finding is in line with previous links between white matter microstructure and motor speed (Vernooij et al., 2009), though others have found associations between white matter and perceptual speed after controlling for motor function (Sasson et al., 2012). The lack of speed task without a motor component is a limitation of our study. That said, the relative confinement of our longitudinal results to an association between changes in CS and perceptual speed suggests that age-related changes on typical perceptual speed tasks may partly reflect sensorimotor changes, at least in very old age. The paper-and-pencil tasks we used as markers of perceptual speed are widely used in cognitive aging research (Hoyer et al., 2004; Verhaeghen and Salthouse, 1997) and have been instrumental in studies of the influential processing-speed hypothesis of cognitive aging (Salthouse, 1996). Thus, the white matter correlates of changes in performance on these tasks should be of major interest.

The current study could not detect a significant contribution of decline in white-matter-microstructure to our measures of higher-order cognition (i.e., episodic memory, letter fluency, and category fluency). However, we also note that the estimated limits for significance of the correlation between changes in CS and perceptual speed include the estimates of some of the other associations (see Fig. 4). This indicates that the CS-speed link is not significantly higher than that for many of the other correlations. Generally, the point estimates of correlations between latent variables are higher than raw correlations, because the influence of error is attenuated. However, this comes at the cost of higher standard errors. The high point estimates for some of the associations must be interpreted with this in mind.

Considering the presence of shared-between-person differences across white matter tracts (Lövdén et al., 2013; Penke et al., 2010) and cognitive abilities (Carroll, 1993), we did, however, show that the association between white-matter changes in the CS and perceptual speed remained after controlling for changes in the other tracts, changes in the entire white matter skeleton, and changes in episodic memory, letter fluency, and category fluency. These results suggest that the association between changes in perceptual speed and changes in the CS tract was quite specific, but we can of course not exclude that change in unmeasured tracts or cognitive abilities may share variance with the observed association. Note that these analyses were performed on the smaller subsample with complete DTI data at both time 1 and time 2. A latent-variable approach would have been more attractive in this context, because the problem with differential influences of error on the associations (e.g., highly reliable whole brain measure versus less reliable individual tract measures) can be attenuated with this approach. Unfortunately, such an approach requires including many variables in the models and therefore a larger sample size than was available in the present study.

Together, the present results suggest that changes in white-matter microstructure contribute to changes in sensorimotor aspects of behavior in very old age, but that it remains unclear whether changes in white matter contribute to aging of higher-order cognitive functions. The findings add specificity to previous longitudinal studies using whole-brain indices of white matter microstructure (Charlton et al., 2010). Most importantly, by explicitly estimating between-person differences in within-person change, the study takes this field beyond the reliance on mean cross-sectional age differences as a proxy of aging. Considering repeated critiques of the use of cross-sectional data to estimate developmental associations between different variables (Hofer and Sliwinski, 2001; Hofer et al., 2006; Lindenberger and Pöttér, 1998; Lindenberger et al., 2011; Maxwell and Cole, 2007), this is a significant advancement. However, a few limitations of the present work should be noted.

It must be underscored that generalization of the present results is restricted to very old age. Many changes in white matter microstructure may already have occurred before very old age. Furthermore, individual differences in the group of old-old individuals may partly be of a different nature than those present in groups of younger old individuals. For example, differences in cognitive performance between individuals may be higher, at least in crystallized abilities such as semantic memory (de Frias et al., 2007; Hagberg et al., 2001), in very old age and these differences may in turn be related to proximity to death (Small and Bäckman, 1999). Thus, it is possible that the association between perceptual speed and white matter microstructure is select for this group of the oldest old. However, the focus on very old age is also a strength of the paper, considering the rising population in this age range and the lack of knowledge concerning neural correlates of cognitive aging in late senescence. We also note that the lack of a significant correlation between white matter microstructure and episodic memory should be interpreted cautiously. The recognition task complementing the recall task to index episodic memory suffers from low reliability. This likely contributes to the more imprecise estimates of the associations involving the episodic memory factor (see Figs. 3 & 4). Also, our approach to extract mean FA and MD in the tracts of interest assumes that between-person differences are homogenous within the demarcated tracts. Data-driven approaches suggest that correlations among voxels are highest within anatomically defined tracts (Li et al., 2012), which partly supports this assumption. Nevertheless, due to variations in the...
degree of crossing fibers (Jeurens et al., 2012) and other histological properties within a tract, and perhaps individual differences in such irregularities, this assumption may not be valid for the entire tracts. These problems may be aggravated by the relatively low quality of the DTI images (1.5 T, 6 directions, and low b-value), which is a reflection of the time point of starting the data collection for this longitudinal study.

Though it comes with the cost of missing out on potential hemisphere-specific associations, forming latent variables comes with the great advantage of attenuating problems related to suboptimal signal-to-noise ratio. However, this approach does not eliminate the possibility that the large voxels may have increased partial volume effects. The TBSS processing reduces the impact of such effects, but does not completely eliminate them. We therefore focused on the core parts of major tracts to minimize these problems, although this approach comes with the cost of missing out on finer parts of white matter that may be important for higher-order cognition. We also note that some major tracts that are highly interesting as cognitive correlates, such as the fornix and the anterior thalamic radiation, could not be reliably measured, perhaps because of their smaller or more complex nature, and were therefore not included. Having noted these limitations, we emphasize that we have reported, based on measures extracted in the same way as in this study, good fit of a model postulating tract factors, with high correlations within a specific tract across hemispheres (Lövén et al., 2013). This indicates high reliability and validity of the measures, and of the approach to preprocessing the images and demarcating the tracts of interest.

We conclude that change in white matter microstructure is a potent neural correlate of decline in sensorimotor aspects of perceptual speed in very old age, but it remains unclear whether aging of white-matter microstructure contributes to decline in higher-order cognition. Future research should investigate the influences of vascular risk (Burgmans et al., 2010) and white-matter lesions (Vernooij et al., 2008) on the observed associations. It is also important to pitch different potential antecedents of cognitive aging, including for example changes in gray matter (Raz et al., 2005) and changes in neurotransmitters such as dopamine (Bäckman et al., 2010), against each other, and assess their relative timing, to further chart the biological underpinnings of cognitive aging.

Funding

The Swedish National study on Aging and Care, SNAC (www.svac.org) is financially supported by the Ministry of Health and Social Affairs, Sweden, the participating County Councils and Municipalities, and the Swedish Research Council. In addition, specific grants were obtained from the Swedish Council for Working Life and Social Research (LB, LF, EJL, ML), the Swedish Research Council (LB, LF, EJL, ML), Swedish Brain Power (LB, LF), the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet (LB), an Alexander von Humboldt Research Award (LB), and a donation from the af Jochim Foundation (LB).

Acknowledgments

This research has made use of the SMILE medical imaging laboratory at Karolinska University Hospital, Stockholm, Sweden. We thank all staff involved in the data collection in SNAC-K.

References


Please cite this article as: Lövén, M., et al., Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age, Neuroimage (2014), http://dx.doi.org/10.1016/j.neuroimage.2014.08.020.


