Alterations in Brain White Matter Contributing to Age-Related Slowing of Task Switching Performance: The Role of Radial Diffusivity and Magnetization Transfer Ratio

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Abstract: Successfully switching between tasks is critical in many daily activities. Age-related slowing of this switching behavior has been documented extensively, but the underlying neural mechanisms remain unclear. Here, we investigated the contribution of brain white matter changes associated with myelin alterations to age-related slowing of switching performance. Diffusion tensor imaging derived radial diffusivity (RD) and magnetization transfer imaging derived magnetization transfer ratio (MTR) were selected as myelin sensitive measures. These metrics were studied in relation to mixing cost (i.e., the increase in reaction time during task blocks that require task switching) on a local-global switching task in young ($n = 24$) and older ($n = 22$) adults. Results showed that higher age was associated with widespread increases in RD and decreases in MTR, indicative of white matter deterioration, possibly due to demyelination. Older adults also showed a higher mixing cost, implying slowing of switching performance. Finally, mediation analyses demonstrated that decreases in MTR of the bilateral superior corona radiata contributed to the observed slowing of switching performance with increasing age.

Additional Supporting Information may be found in the online version of this article.

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Key words: aging; mixing cost; switch cost; diffusion tensor imaging; magnetization transfer imaging; mediation

INTRODUCTION

We are confronted with a constant stream of incoming stimuli. Flexibly switching between different responses to these stimuli, depending on the context, is essential for successful behavior. This skill, called “task switching,” generally comes with a “performance cost.” That is, switching between tasks is slower and more error-prone than repeating a task [Monsell, 2003]. In older adults, increases in performance cost have been documented extensively [for a review, see Wasylshyn et al., 2011]. This performance deterioration may jeopardize their functional independence, as switching between tasks is an essential component of daily functioning.

Functional imaging studies have shown that successful task switching heavily depends on a distributed frontoparietal network, which is thought to be involved in top-down processes to bias attention to the selection of task-relevant information [Banich et al., 2000]. During task switching, older adults (compared with young adults) have previously shown a decreased ability to activate these areas [DiGirolamo et al., 2001; Gold et al., 2010; Jimura and Braver, 2010] together with a reduced functional connectivity among these areas [Madden et al., 2010], but also hyperactivation has been observed in older adults in specific frontal areas [Coxon et al., 2010; Hakun et al., 2015; Zhu et al., 2014]. In addition to frontoparietal interactions, also corticosubcortical interactions are considered crucial for flexible behavior. Particularly, the subthalamic

nucleus and the striatum (both being input zones of the basal ganglia) have been shown to interact closely with the middle frontal gyrus and the medial frontal cortex to mediate behavioral switching [Coxon et al., 2010; Hikosaka and Isoda, 2010; Leunissen et al., 2013; Neubert et al., 2010; van Schouwenburg et al., 2015]. Coxon et al. [2010] specifically investigated subcortical changes in activation in older adults during task switching, with a marked reduction in basal ganglia function as main result.

It is possible that age-related alterations in the white matter tracts, interconnecting these cortical and subcortical regions, affect their functioning. Accordingly, previous aging studies have revealed a relation between general measures of microstructural organization (i.e., fractional anisotropy and/or mean diffusivity) of different white matter tracts and task switching performance [Gold et al., 2010; Hakun et al., 2015; Kennedy and Raz, 2009; Madden et al., 2009; Zhu et al., 2014].

In this article, we aimed to specifically investigate the contribution of age-related alterations in white matter myelination to task switching performance in older adults. Myelin promotes fast information transfer and changes in myelination have been shown to alter conduction speed [Fields, 2008]. However, previous work has shown that aging is accompanied by degeneration of myelin [Albert, 1993; Marner et al., 2003; Peters, 2002; Tang et al., 1997]. Since successful task switching depends on fast interactions between a large network of brain regions, we hypothesize that myelin degeneration plays a key role in age-related slowing of switching behavior. To this end, we selected two magnetic resonance imaging (MRI) measures that have both been proposed to be sensitive to myelin changes, i.e., the diffusion tensor imaging (DTI)-derived measure radial diffusivity (RD) and the magnetization transfer imaging (MTI) derived measure magnetization transfer ratio (MTR).

DTI assesses white matter microstructural organization by using a tensor model to quantify the directionality and rate of diffusion of water within tissue [Basser and Pierpaoli, 1996]. Our first selected measure, RD, reflects diffusion perpendicular to the main diffusion direction and has been suggested to be sensitive to myelin, with higher RD being indicative of less myelin [Janve et al., 2013; Song et al., 2002, 2005; Sun et al., 2006, 2007]. Additionally, in a study by Janve et al. [2013] RD demonstrated better specificity as compared with other DTI measures in detecting the presence of white matter demyelination.

Although the aforementioned studies—using mainly rodents—indicate that white matter myelin modulates RD,

Abbreviations

ALIC	anterior limb of the internal capsule
CING	dorsal cingulum
DTI	diffusion tensor imaging
FA	fractional anisotropy
GEN	genu of the corpus callosum
MRI	magnetic resonance imaging
MTI	magnetization transfer imaging
MTR	magnetization transfer ratio
RD	radial diffusivity
ROI	region of interest
RT	reaction time
SCR	superior corona radiata
SE	standard error
SLF	superior longitudinal fasciculus
SPLE	splenium of the corpus callosum
SS	sagittal stratum
UNC	uncinate fasciculus

recent evidence shows that in fiber systems with more complex architecture this relation between myelin content and RD can be attenuated and is more ambiguous [De Santis et al., 2014; Madler et al., 2008; Vos et al., 2012]. Our second selected measure, MTR, depends less on architectural complexity as compared with RD, and is therefore suggested to capture changes in myelination more directly [Wolff and Balaban, 1989]. Additionally, MTR has shown sensitivity to white matter alterations that do not affect the diffusion MRI signal [Mandl et al., 2015]. Accordingly, we used MTR to complement our RD measures. It represents the relative change in MR signal intensity caused by fast exchange of magnetization between protons bound to macromolecules and protons in neighboring free water when applying an off-resonance radio frequency pulse. MTR has been correlated with histological measures of myelin in animals [Deloire-Grassin et al., 2000; Dousset et al., 1992, 1995; Rausch et al., 2009], and human postmortem brains [Barkhof et al., 2003; Schmierer et al., 2004; van Waesberghe et al., 1999]. As such, decreases in MTR are thought to reflect a loss of macromolecular content, typically myelin.

The main aim of this study was to explore whether white matter alterations account for slowing of switching performance with increasing age, using myelin sensitive measures. Our hypotheses were twofold: (a) older adults show more slowing of performance in task blocks during which they have to switch between tasks, i.e., a higher mixing cost, as compared with the young adults, and (b) this effect is mediated by age-related alterations in white matter as observed using RD and MTR.

MATERIALS AND METHODS

Participants

Young (range 18–30 years) and older participants (range 60–80 years) were recruited from the general population by means of advertisements and active recruitment. Potential participants were screened and excluded if they had diabetes or contraindication to MRI, or a current or past history of psychiatric illness, of neurological illness, of use of anti-epileptic medication or of drug or alcohol abuse. Additionally, older participants were excluded when they scored below 26/30 on the Montreal Cognitive Assessment scale [Nasreddine et al., 2005]. After further excluding participants showing artifacts on their DTI or MTI scan that prevented a reliable analysis, the final sample consisted of 24 young adults (mean age $\pm$ standard error (SE) = 23.7 $\pm$ 0.7 years, 10 males) and 22 older adults (mean age $\pm$ SE = 67.5 $\pm$ 0.9 years, 11 males). All participants were right-handed, as verified by the Edinburgh Handedness Inventory (laterality quotient, mean $\pm$ SE: young adults: 87.9 $\pm$ 3.2; older adults: 95 $\pm$ 2.2), and had normal or corrected to normal vision. Prior to giving written consent, all participants received full explanation of the experimental

procedures. The study received approval from the local Ethics Committee for Biomedical Research at KU Leuven, and was performed in accordance with the 1964 Declaration of Helsinki and its amendments [World Medical Association, 1964].

Experimental Design

Local-global switching task

Task switching performance was assessed using a computerized task switching paradigm, i.e., the local-global switching task, which has previously been employed by our group [Caeyenberghs et al., 2014; Leunissen et al., 2014]. Participants were comfortably seated with lower arms and wrists resting on a table. The task was presented on a 54.6 cm computer monitor, located on the table, at a distance between 100 and 120 cm in front of the participant at eye level.

The paradigm involved two-shape recognition tasks performed under either single-block or switch-block conditions. Figure 1a shows the four possible stimuli: big squares or rectangles (contour) composed of multiple smaller squares or rectangles (building blocks). The “global” task required a decision as to whether the stimulus’ contour is either a square or a rectangle. The “local” task required a decision as to whether the stimulus’ building blocks are either squares or rectangles.

For both tasks, a cue appeared between 400 and 600 ms prior to presentation of the stimulus (interval randomly varying), indicating which task needed to be performed. The global task was cued by a big square and rectangle appearing left and right of the location where the stimulus was next presented, respectively. The local task was cued by a small square and rectangle (Fig. 1b).

Participants had to respond as fast as possible without sacrificing accuracy by pressing “1” with their right index finger for squares and “2” with their right middle finger for rectangles on a standard computer keyboard. Both the cue and the stimulus remained on the screen until the participant responded, or until 2,500 ms had elapsed. The interval between a response and the presentation of the next trial varied randomly between 900 and 1,100 ms.

First, two single-blocks were presented, one in which only the global task had to be performed during the entire block, and one with only the local task. The order of these two single-blocks was counterbalanced across participants. The third block was always a switch-block, in which the task alternated every other trial (i.e., two global task trials, followed by two local task trials, etc.). Hence, this block included both task-repetition and task-switch trials. The experiment consisted of 24 trials in each single-block, and 49 trials in the switch-block. Before the experiment, participants practiced four trials for each single-block, and 8 to 16 trials for the switch-block.

To verify whether the older adults understood the general task instructions, we first assessed percent accuracy

Figure 1.

Local-global switching task. (a) Possible stimuli of the local-global switching task. There were four possible stimuli, each comprising a big square or rectangle (contour) composed of multiple smaller squares or rectangles (building blocks). (b) Example of a global and a local task trial. Each trial started with a cue indicating which task to perform. The global task (shown on the left side of the figure) was cued by a big square and rectangle appearing left and right and required a decision as to whether

the stimulus' contour is either a square or a rectangle. The local task (shown on the right side of the figure) was cued by a small square and rectangle and required a decision as to whether the stimulus' building blocks are either squares or rectangles. Following this cue a stimulus was presented, and participants had to rapidly press key "1" with their right index finger for squares and key "2" with their right middle finger for rectangles.

during the single-blocks. Next, reaction times of the correct trials (RTs) were used to evaluate two types of performance cost: mixing cost and switch cost. Mixing cost refers to the increase in RTs when comparing switch-blocks with single-blocks (i.e., RT switch block – RT single blocks). Switch cost refers to the increase in RTs when comparing task-switch with task-repetition trials within the switch-block (i.e., RT task-switch trials – RT task-repetition trials). Outlier detection was performed by transforming the scores per dependent variable and per group separately into z-scores, scores with an absolute value of $z \geq 3$ were considered as outlying and were removed.

Image acquisition

Imaging data were acquired on a Siemens 3T Magnetom Trio magnetic resonance imaging scanner (Siemens, Erlangen, Germany) with 12-channel matrix head coil. DTI of the brain was performed using a single-shot spin-echo sequence (TR = 10,700 ms; TE = 82 ms; matrix size = 96×96 ; 2.2 mm isotropic voxels; 60 axial slices). Diffusion sensitizing gradients were applied at a b -value of 1,000 s/mm², along 64 noncollinear directions. One b_0 image with no diffusion weighting was acquired. A three-dimensional (3D) gradient-echo pulse MTI sequence was subsequently performed with the following parameters: TR = 50 ms; TE = 4.59 ms; field of view = 230×173 mm²; voxel size = $2.2 \times 1.8 \times 2.4$ mm³; 60 axial slices. Two consecutive imaging sets were acquired, one with and one without an off-resonance saturation pulse. To check for possible abnormalities in gray matter, a 3D magnetization prepared rapid gradient echo (MPRAGE) high-resolution T1-weighted structural image was acquired, with the following parameter settings: TR = 2,300 ms; TE = 2.98 ms; field of

view = 240×256 mm²; voxel size = $1 \times 1 \times 1.1$ mm³; 160 sagittal slices.

Image Processing

DTI processing

DTI data were processed with a similar multi-step procedure as described previously [Serbruyns et al., 2015]: (a) The raw diffusion weighted data and the nondiffusion weighted image were loaded into ExploreDTI version 4.8.1 [Leemans et al., 2009] and the separate diffusion weighted imaging volumes were looped at a high frame rate to check for any obvious artifacts in the data, such as large signal dropouts and geometric distortions. We also toggled between the views of the first and last acquired diffusion weighted image to observe subtle system drifts. Next, we inspected the images in different orthogonal views to check for any interslice and intravolume instabilities, and visualized various image maps to check for artifacts. Finally, we checked the residual map, reflecting the difference between the modeled and the measured signal [Tournier et al., 2011]. Using a residuals map, artifacts can be detected that are not always visible on the fractional anisotropy (FA) map or on the individual diffusion-weighted images. (b) The DTI data sets were corrected for subject motion and eddy current induced geometric distortions [Leemans and Jones, 2009]. In summary, the diffusion weighted images were realigned to the non-diffusion weighted image using an affine co-registration method based on mutual information with cubic interpolation to resample the images [Klein et al., 2010]. During this correction procedure, the b -matrix was adjusted for the rotational component of subject motion to ensure correct

diffusion tensor estimates. Rotations were on average 0.35° with a SE of 0.03° for the young adults and 0.34° with a SE of 0.05° for the older adults. Translational motions did not exceed 1 voxel (mean $\pm$ SE: young adults: 0.55 ± 0.03 mm; older adults 0.68 ± 0.02 mm). (c) We reinspected the data in three orthogonal planes in a loop format to ensure that the motion/distortion correction was performed correctly and that no additional artifacts were introduced into the data. (d) The diffusion tensors and subsequently RD were calculated using a non-linear regression procedure [Basser and Pierpaoli, 1996; Jones and Basser, 2004]. (e) The DTI data were transformed to MNI space by applying an affine and, subsequently, a high-dimensional non-affine DTI-based registration technique [Leemans et al., 2005; Van Hecke et al., 2007].

MTI processing

The MTI data were analyzed and processed using the following multistep procedure: (a) The raw data were visually inspected to check for any artifacts using MRIcron [Rorden and Brett, 2000]. (b) The raw data were loaded into FMRIB Software Library (FSL) 4.1.9. For each subject, volumes with and without the off-resonance radio frequency saturation pulse were co-registered, using the linear image registration tool (FSL FLIRT) [Jenkinson et al., 2002; Jenkinson and Smith, 2001]. This procedure was used to remove possible tilts in the brain due to the participant's between scan head movements. (c) Non-brain tissue was removed from the images using the Brain Extraction Tool [Smith, 2002]. (d) The MTR for each voxel was then calculated using the following equation: $MTR = (S_0 - S_1)/S_0$ whereby S_0 is the signal intensity without saturation pulse and S_1 is the signal intensity with saturation pulse. The MTR is expressed as a ratio where 0 represents no signal reduction and 1 represents total signal reduction due to magnetization transfer. (e) The MTI data were transformed to MNI space by applying FSL FLIRT.

Spatial alignment between DTI and MTI data and masking

For the spatial alignment between the DTI and MTI data, FA was chosen as registration contrast because of its relative high effective signal-to-noise ratio. Accordingly, for each subject, the normalized MTI images were spatially aligned to the FA map of the normalized DTI scans using rigid transformations. In doing so, it was assured that the images in both modalities were in the same orientation, enabling the comparison of the DTI and MTI results. We then visually reinspected the different image maps in three orthogonal planes to ensure that the registration was performed correctly. Finally, the DTI and MTI data were masked on a voxel by voxel basis by applying a threshold at the participant level (minimum FA of 0.20) to minimize the effect of residual misalignments between the MTI and DTI data sets due to differences in acquisition geometry

and to reduce potential partial volume effects from cerebrospinal fluid and gray matter.

Parcellation of the white matter regions of interest

The ICBM-DTI-81 white-matter labels atlas [Mori et al., 2008] was used for parcellation of the regions of interest (ROIs). Eight ROIs were selected based on previous neuroimaging studies investigating task switching in older adults as referred to in the introduction. For visualization purposes, masks of these ROIs are displayed on FA maps of the white-matter atlas of Mori et al. [2008] in Figure 2. The ROIs included: two corticosubcortical tracts, i.e., bilateral anterior limb of the internal capsule (ALIC) containing frontopontine fibers and thalamic projections to the frontal, and cingulate cortex and bilateral superior corona radiata (SCR) containing both descending and ascending axons connecting the internal capsule with frontal and (pre)motor regions; four long association tracts, i.e., bilateral superior longitudinal fasciculus (SLF) connecting frontal, occipital, parietal, and temporal cortices; bilateral sagittal stratum (SS) containing the inferior longitudinal fasciculus, which connects the occipital and temporal cortices, and the inferior fronto-occipital fasciculus, which connects the orbitofrontal and occipital cortices; bilateral uncinate fasciculus (UNC) connecting the orbitofrontal cortex with temporopolar and limbic regions; and bilateral dorsal cingulum (CING), extending longitudinally above the callosum and connecting portions of the cingulate gyrus; and finally two commissural fibers, i.e., the genu of the corpus callosum (GEN) connecting left and right frontal cortices, and the splenium of the corpus callosum (SPLE) connecting left and right occipital, parietal, and temporal cortices. Average RD and MTR values were computed in all eight ROIs for each subject. Given the number of regions involved and the lack of a priori hypotheses regarding laterality differences, average RD and MTR values for left and right hemisphere were used for the bilateral fibers (ALIC, SCR, SLF, SS, UNC, and CING).

Statistical Analyses

Statistical analyses were done with the Statistical Package for the Social Sciences, version 22 (SPSS for Windows, 2010). Unless otherwise stated, an α level of 0.05 was used for statistical tests, where applicable correction for multiple comparisons was performed by using a modified Bonferroni correction [Holm, 1979]. Only results surviving this Bonferroni correction are reported.

First, a multivariate approach to repeated measures analysis of variance (ANOVA) was used to test for age-related differences in RD and MTR among the selected ROIs. The between subjects factor was age group (young adults, older adults), and the within subjects factor was ROI with eight levels (ALIC, SCR, SLF, SS, UNC, CING, GEN, SPLE). The dependent variables were RD and MTR.

Figure 2.

Region of interest masks. Regions are depicted on fractional anisotropy maps of the white-matter atlas of Mori et al. [2008]. (a) Coronal view of bilateral anterior limb of the internal capsule (ALIC, green) and bilateral superior corona radiata (SCR, purple). (b) Axial view of bilateral dorsal cingulum (CING, dark blue). (c) Axial view of bilateral superior longitudinal fasciculus

(SLF, red). (d) Axial view of bilateral sagittal stratum (SS, pink). (e) Axial view of bilateral uncinate fasciculus (UNC, orange). (f) Axial view of the genu (GEN, yellow) and splenium (SPLE, light blue) of the corpus callosum. [Color figure can be viewed at wileyonlinelibrary.com]

Significant main effects and interactions were further explored with post hoc *t*-tests.

Next, to exclude the possibility that differences in RTs between young and older adults are confounded by a difference in understanding of the general task instructions, age-related differences in percent accuracy during the single-blocks were tested using an independent *t*-test.

Further, RTs were subjected to repeated measures ANOVA with age group (young adults, older adults) as between-subjects factor and Condition (single-blocks versus switch-block) as within-subjects factor. A significant interaction effect between these two factors would be indicative of a difference in mixing cost (i.e., RT switch block – RT single blocks) between the two age groups.

Furthermore, literature shows that mainly the mixing cost is affected by age, whereas differences in switch cost (i.e., RT task-switch trials – RT task-repetition trials within the switch-block) are relatively small [Wasylyshyn et al., 2011]. To check whether this trend is confirmed by our data, we performed an additional repeated measures ANOVA with age group (young adults, older adults) as between-subjects factor and switch-block trial type (task-switch trials versus task-repetition trials) as within-subjects factor. Here, a significant interaction effect between these two factors would be indicative of a difference in switch cost.

Finally, PROCESS, a SPSS macro developed by Hayes [2013] was used to determine whether age-related RD

Figure 3.

Model used to determine whether age-related slowing of task switching performance is mediated by alterations in white matter as observed using radial diffusivity (RD) and magnetization transfer ratio (MTR). c = *total effect* of age group on mixing cost. This total effect was, per region of interest (ROI), separated into two distinct pathways: an *indirect* (mediation) effect ($a*b$,

dashed arrows) with a = the effect of age group on the mediator variable RD or MTR of this particular ROI and b = the effect of the mediator variable on mixing cost while controlling for age group; and a *direct effect* (c' , dotted arrow) of age group on mixing cost, i.e., the effect of age group on mixing cost independent of its effect through the mediator variable.

and/or MTR alterations partially accounted for the effect of age group on mixing cost.

The first step in this procedure was the evaluation of the overall effect of age group on mixing cost. This effect, further termed the *total effect* (c), quantifies the average difference between young and older adults in mixing cost (see top panel of Fig. 3) and is expressed in units (here: ms).

Next, it was evaluated if part of this total effect of age group on mixing cost can be explained through its effects on white matter RD and MTR. Accordingly, per ROI two separate mediation models were tested: one model using RD of this ROI as a mediator variable, and another model using MTR. In each of these mediation models, the total effect was partitioned in two distinct pathways that were evaluated using ordinary least squares path analysis (see bottom panel of Fig. 3).

The first pathway, termed the *indirect* pathway (dashed arrows), represents how age group contributes to differences in the used mediator variable, and how this in turn contributes to differences in mixing cost. *Indirect effects* are estimated as $a*b$, meaning the product of (a) which represents the effect of age group on the mediator variable, and (b) which represents the effect of the mediator variable on mixing cost while controlling for the effect of age group. We were particularly interested in these indirect effects, as a significant indirect effect would indicate significant mediation by the mediator variable used in the model.

Although not critical for the evaluation of the significance of mediation by the mediator variable being tested, we also investigated the second pathway, termed the *direct* pathway (dotted arrow). This pathway represents the

residual influence of age group on mixing cost, i.e., the effect of age group on mixing cost independent of its effect via the mediator variable used. This *direct effect* is estimated with c' , and corresponds exactly to the difference between the total and the indirect effect of age group on mixing cost in the model.

One of the main advantages of this approach is that it enables direct testing of the significance of the indirect effect and thus of mediation. Here, this was accomplished using 10,000 stratified bootstrap samples to determine bias-corrected confidence intervals for the indirect effects. To correct for multiple comparisons, 99% confidence intervals were used. Accordingly, indirect effects with 99% confidence intervals entirely above zero were regarded as significantly mediating the relation between age group and mixing cost.

As a last step in the mediation analyses, R^2_{med} was calculated for each significant indirect effect of age group on mixing cost through the mediator variable as a measure of effect size, representing the proportion of variance in mixing cost attributable to this indirect effect.

RESULTS

Age-Related White Matter Alterations

RD (mm^2/s) and MTR values of the eight ROIs are summarized in Figure 4.

RD differed between the age groups (main effect of age group: $F_{(1,44)} = 20.79$, $P < 0.001$), and among the eight ROIs (main effect of ROI: $F_{(7,308)} = 29.73$, $P < 0.001$).

Figure 4.

Radial diffusivity (mm^2/s) and magnetization transfer ratio means $\pm$ standard error as a function of age group and region of interest. ALIC = anterior limb of the internal capsule; SCR = superior corona radiata; SLF = superior longitudinal fasciculus; SS = sagittal stratum; UNC = uncinate fasciculus; CING = dorsal

cingulum; GEN = genu; SPLE = splenium. Results reported as being significant survived a modified Bonferroni correction for eight comparisons [Holm, 1979]; *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, for comparisons between the young and older adults.

Additionally, a significant age group $\times$ ROI interaction was found ($F_{(7,308)} = 9.09$, $P < 0.001$). Post hoc t -tests were performed to investigate which specific structures showed age-related deterioration. It was found that relative to the young adults group, RD was significantly elevated in the older adults group in all ROIs, except the UNC (GEN, SLF, and ALIC $P < 0.001$; SCR and SPLE $P < 0.01$; CING and SS $P < 0.05$).

MTR also showed main effects of age group ($F_{(1,44)} = 40.37$, $P < 0.001$) and ROI ($F_{(7,308)} = 47.48$, $P < 0.001$), and a significant age group $\times$ ROI interaction ($F_{(7,308)} = 9.27$, $P < 0.001$). Older adults showed lower MTR values in all ROIs, except the UNC (SS and CING $P < 0.01$, all other $P < 0.001$).

Age-Related Slowing of Switching Performance

Detailed results of the performance of young and older adults on the local-global task, including accuracy and reaction times on the different trial types/blocks are offered in Table I of the Supporting Information. Based on inspection of the z -scores within the groups, no outlying scores were identified. There was no difference between young and older adults in percentage accuracy in the single-blocks (older adults = $98.91\% \pm 0.39$; young adults = $98.19\% \pm 0.48$; $t_{(44)} = -1.14$, ns), indicating that both groups understood the task requirements equally well.

RTs in the switch-block were significantly longer than RTs in the single-blocks (main effect of condition: $F_{(1,44)} = 144.19$, $P < 0.001$; switch-block: $869.52 \text{ ms} \pm 44.74$; single-blocks: $536.55 \text{ ms} \pm 15.23$). There was also a significant main effect of age group on RT ($F_{(1,44)} = 48.36$,

$P < 0.001$), with older adults responding slower ($846.61 \text{ ms} \pm 28.62$) compared with young adults ($571.42 \text{ ms} \pm 27.33$). As depicted in Figure 5, there was a significant interaction effect between these two factors ($F_{(1,44)} = 27.11$, $P < 0.001$), which indicated that the older adults demonstrated a significantly higher mixing cost (RT switch block – RT single blocks) as compared with young adults (older adults $486.51 \text{ ms} \pm 43.34$; young adults $192.22 \text{ ms} \pm 36.75$).

RTs within the switch-block showed a significant main effect of age group (older adults = $1,089.87 \text{ ms} \pm 46.54$; young adults = $667.53 \text{ ms} \pm 44.56$; $F_{(1,44)} = 42.97$, $P < 0.001$) and switch-block trial type (task-repetition trial = $864.81 \text{ ms} \pm 32.8$; task-switch trial = $892.59 \text{ ms} \pm 34.94$; $F_{(1,44)} = 1.741$, $P < 0.05$). However, no significant difference in switch cost (RT task-switch trials – RT task-repetition trials within the switch-block) was found between the young and older adults (older adults = $60.45 \text{ ms} \pm 41.73$; young adults = $-4.91 \text{ ms} \pm 12.82$; $F_{(1,44)} = 2.411$, interaction effect n.s.).

Behavioral Significance of Age-Related Alterations in Brain White Matter

The total effect of age group on mixing cost ($c \pm \text{SE}$) was 294.28 ± 56.52 . This implies that, similar to what is stated above, older adults showed a mixing cost that was on average 294.28 ms higher as compared with the young adults. Next, we conducted mediation analyses to determine whether this effect of age group on mixing cost could be explained by age-related differences in RD or MTR of any of the ROIs. Accordingly, we used mediation models that take into account the total effect of age group on mixing cost (c) and next, depending on the mediator

TABLE I. Overview of the mediation analyses

White matter tract	Indirect effect of age <i>ab</i> (99% bootCI)	Mediation effect size (99% bootCI)	Direct effect of age <i>c'</i> (SE)
Radial diffusivity			
Anterior limb of internal capsule	NS	NS	280.42*** (66.27)
Superior corona radiata	NS	NS	313.83*** (64.25)
Superior longitudinal fasciculus	NS	NS	308.34*** (68.31)
Sagittal stratum	NS	NS	304.96*** (61.69)
Uncinate fasciculus	NS	NS	307.81*** (59.42)
Dorsal cingulum	NS	NS	286.25*** (62.12)
Genu of corpus callosum	NS	NS	271.90*** (75.17)
Splenium of corpus callosum	NS	NS	292.20*** (63.21)
Magnetization transfer ratio			
Anterior limb of internal capsule	NS	NS	294.28*** (56.52)
Superior corona radiata	98.73 (24.09–214.52)	0.27 (0.11–0.48)	195.55** (66.06)
Superior longitudinal fasciculus	NS	NS	269.31*** (67.76)
Sagittal stratum	NS	NS	290.61*** (60.86)
Uncinate fasciculus	NS	NS	278.20*** (57.2)
Dorsal cingulum	NS	NS	269.89*** (59.64)
Genu of corpus callosum	NS	NS	300.13*** (74.63)
Splenium of corpus callosum	NS	NS	241.20*** (65.43)

ab = indirect effect of age group on mixing cost through the mediator; 99% bootCI = 99% bias-corrected bootstrap confidence interval; R^2_{med} = the proportion of variance in mixing cost attributable to the mediation effect; *c'* = direct effect of age group on mixing cost; SE = standard error. ****P* < 0.001, ***P* < 0.01; ns not significant.

variable used in a specific model, separated this total effect into direct (*c'*) and indirect (*a*b*) effects. An overview of the results of these mediation analyses is shown in Table I.

Using RD of the different ROIs as mediator variables in separate models, no significant indirect effects of age group were found, indicating that alterations in RD did

Local-global switching task: reaction time (ms)

Figure 5.

Local-global switching task reaction time means $\pm$ standard error as a function of age group and single- or switch-blocks. Mixing cost corresponds to the difference between the average reaction time during the switch-block and the single-blocks (switch – single). ****P* < 0.001, for comparison of mixing cost between the young and older adults (interaction effect).

Figure 6.

Model showing significant mediation of the relation between age group and mixing cost through the magnetization transfer ratio (MTR) of the superior corona radiata (SCR). c = total effect of age group on mixing cost; $a*b$ (99% bias-corrected bootstrap confidence interval) = indirect effect (dashed arrows) with

a = the effect of age group on MTR of the SCR and b = the effect of MTR of the SCR on mixing cost while controlling for age group; c' = direct effect (dotted arrow) of age group on mixing cost. $***p < 0.001$, $**p < 0.01$.

not significantly contribute to the age-related declines in switching performance.

Using MTR of the different ROIs as mediator variables, the effect of age group on mixing cost was shown to be partly mediated by the MTR of the SCR ($R^2_{\text{med}} = 0.27$) as shown in Figure 6: older adults showed lower MTR values in the SCR as compared with the young adults group ($a = -0.0091$), and these lower MTR values partly accounted for the increase in mixing cost observed in this older adults group ($b = -10,880.56$).

DISCUSSION

The main aim of this study was to determine whether white matter alterations related to demyelination account for slowing of task switching performance with aging. Alterations with advancing age were demonstrated for both selected metrics, i.e., RD and MTR. Further, older adults showed higher mixing costs, indicative of slower switching performance. Finally, age-related alterations in MTR values of the bilateral superior corona radiata were found to contribute to these increased mixing costs in older adults.

Age-Related White Matter Alterations

In line with current literature, we observed widespread RD increases in older adults compared with young adults [Bhagat and Beaulieu, 2004; Davis et al., 2009; Hasan et al., 2009; Hsu et al., 2010; Kumar et al., 2013; Lebel et al., 2012; Madden et al., 2012; Sala et al., 2012; Zhang et al., 2010].

Findings with respect to age-related MTR changes have been less consistent. In the current study, we observed lower MTR values in all regions of interest in older compared with young adults, except for the uncinate fasciculus. Such widespread age-related decline in MTR is in line with several previous studies [Callaghan et al., 2014; Fazekas et al., 2005; Ge et al., 2002; Hofman et al., 1999; Schiavone et al., 2009; Silver et al., 1997; Spilt et al., 2005; Tanabe et al., 1997], but in contrast to others reporting no age effects [Armstrong et al., 2004; Benedetti et al., 2006; Mehta et al., 1995]. Possible explanations for the inconsistent results of these studies may be the large heterogeneity in methodological approaches of data acquisition or analysis used.

Slowing of Task Switching Performance in Older Adults

Older adults showed a significantly higher mixing cost compared with young adults. Mixing cost refers to the increase in reaction time during switch-blocks as compared with single-blocks, and reflects the extra time needed for “sustained” executive processes during a switch-block. These sustained processes reflect the engagement of monitoring processes to uphold high sensitivity to environmental cues, and the active maintenance of multiple task sets in working memory [Sakai, 2008]. On the other hand, switch cost did not differ between the groups. Switch cost refers to the difference between task-switch and task-repetition trials within a switch-block, and is thought to reflect the extra time needed for “transient” control processes during task-switch trials. These transient

processes relate to the detection of a required switch, followed by the active configuration of an alternative task set [Rogers and Monsell, 1995].

It can be concluded that in this study, the sustained executive control processes during task switching were affected in older adults, but not the transient. This difference in the effect of age on mixing and switch costs is consistent with the conclusions of a review on aging and task switching by Wasylyshyn et al. [2011].

The Role of White Matter Alterations in Age-Related Slowing of Task Switching Performance

Our study is the first to explore the contribution of white matter alterations in age-related slowing of task switching performance using multiple myelin sensitive measures (i.e., RD and MTR). Accordingly, the current results complement the results of previous aging studies which mainly focused on general DTI measures (i.e., fractional anisotropy and/or mean diffusivity) for the investigation of the relation between white matter and task switching performance in older adults [Gold et al., 2010; Hakun et al., 2015; Kennedy and Raz, 2009; Madden et al., 2009; Zhu et al., 2014].

The main result of this study was that decreases in MTR of the superior corona radiata contributed to the observed slowing of switching performance with increasing age. This tract contains both descending and ascending axons that connect the frontal and (pre)motor regions with the basal ganglia [Davis, 1910; Mori et al., 2008], which have long been known to interact closely to enable motivated action selection [Alexander et al., 1986; Deniau and Chevalier, 1985]. That is, initially, the basal ganglia were assigned a selective gating function in the context of motor control, which comprised selecting and “releasing the brakes” on the appropriate motor action plan among multiple competing plans offered by the frontal cortex [Chevalier and Deniau, 1990].

More recently, it has been shown that these cortico-subcortical interactions are also crucial for the guidance of motivated action selection during cognitive tasks, including task switching. That is, in addition to the aforementioned selective gating function of the basal ganglia during task switching [Frank and Badre, 2012; Hazy et al., 2007], they have been shown to guide the rapid and selective updating of frontal task-relevant representations that is crucial during switching tasks by combining enhancement of task-relevant with suppression of task-irrelevant information processing [van Schouwenburg et al., 2015]. However, in the context of aging specifically, Coxon et al. [2010] previously found that, relative to young adults, older adults show reduced basal ganglia activation during motor task switching. Based on our results and the aforementioned literature, we tentatively hypothesize that this reduced subcortical functioning in older adults is, at least

in part, related to the deterioration of cortico-subcortical information transfer that was found in the current study.

Our finding that alterations in the superior corona radiata contribute to age-related slowing of task switching performance is in line with the results of previous studies using different task switching paradigms. That is, relations between the structural properties (fractional anisotropy) of this tract and performance scores of different switching tasks have previously been observed in healthy young adults [Seghete et al., 2013] and in patient groups [Leunissen et al., 2013, 2014; van Schouwenburg et al., 2014]. From this pattern of results, it appears that the superior corona radiata may support a function that is important for task switching in general, possibly reflecting cognitive flexibility.

On the other hand, our study did not replicate the results of some previous aging studies reporting relations between structural properties (fractional anisotropy) of specific tracts and task switching performance [Gold et al., 2010; Kennedy and Raz, 2009; Madden et al., 2009; Zhu et al., 2014]. Of note, this does not necessarily imply that RD or MTR of these tracts was not related to performance in general in our study, but alternatively indicates that alterations in RD and MTR of these tracts during aging were not driving the observed slowing of task switching performance. It appears from these findings that there are many different study design characteristics that can cause variation in the results of different neuroimaging studies. These potentially include variation in studied population, in switching task characteristics, in switching task performance scores, in white matter measures (FA vs. RD/MTR) and in statistical analysis approaches.

Interestingly, only MTR (and not RD) changes were found to mediate the relation between age and slowing of task switching performance. As myelin and speed of performance are strongly related [Bartzokis et al., 2010], a potential explanation could be that MTR has been proposed as a more direct measure of myelin than RD. That is, RD can also be highly influenced by architectural complexity [De Santis et al., 2014]. For example, crossing fibers are likely to influence RD (but not MTR) of the fibers of the superior corona radiata crossing between the transversely oriented commissural fibers that converge to the corpus callosum [Naidich et al., 2012]. Accordingly, although there is no doubt that RD is a powerful metric for the assessment of brain-behavior relations [Davis et al., 2009; Mella et al., 2013; Sullivan et al., 2010], results of the current study indicate that MTR shows complementary potential for the determination of relations between white matter and performance on tasks requiring high execution speed.

Finally, in the current study we used DTI and MTI because of their well-established utility in the determination of brain-behavior relations [Davis et al., 2009; Mella et al., 2013; Schiavone et al., 2009; Sullivan et al., 2010]. It is important to note however that due to the limitations of

the techniques, neither RD nor MTR can be interpreted as absolute measures of myelin. We recommend future research to make use of the recently developed models that can provide more specific measures of white matter properties, such as bitensor (free-water) diffusion modeling [Planetta et al., 2016], quantitative magnetization transfer (qMT) imaging [Alexander et al., 2011], or multicomponent relaxation measurements [De Santis et al., 2014; Madler et al., 2008].

CONCLUSIONS

We explored the relations among age, task switching performance, and white matter characteristics of several major white matter tracts, using DTI-derived RD, and MTI-derived MTR. Consistent with previous studies, we found that advancing age was associated with increases in RD and decreases in MTR in a number of preselected white matter tracts, and with a higher mixing cost. Furthermore, we showed that age-related decreases in MTR of the bilateral superior corona radiata contributed to slowing of switching performance in older adults. Our findings underline the contribution of white matter changes, reflecting altered communication between cortical and subcortical brain regions, to age-related declines in switching performance. Furthermore, they highlight the potential of MTI in the determination of distinct age-related brain-behavior associations.

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