Fiber-specific variations in anterior transcallosal white matter structure contribute to age-related differences in motor performance

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\textbf{ABSTRACT}

Age-related differences in bimanual motor performance have been extensively documented, but their underlying neural mechanisms remain less clear. Studies applying diffusion MRI in the aging population have revealed evidence for age-related white matter variations in the corpus callosum (CC) which are related to bimanual motor performance. However, the diffusion tensor model used in those studies is confounded by partial volume effects in voxels with complex fiber geometries which are present in up to 90% of white matter voxels, including the bilateral projections of the CC. A recently developed whole-brain analysis framework, known as fixel-based analysis (FBA), enables comprehensive statistical analyses of white matter quantitative measures in the presence of such complex fiber geometries. To investigate the contribution of age-related fiber-specific white matter variations to age-related differences in bimanual performance, a cross-sectional lifespan sample of healthy human adults (N = 95; 20–75 years of age) performed a bimanual tracking task. Furthermore, diffusion MRI data were acquired and the FBA metrics associated with fiber density, cross-section, and combined fiber density and cross-section were estimated. Whole-brain FBA revealed significant negative associations between age and fiber density, cross-section, and combined metrics of multiple white matter tracts, including the bilateral projections of the CC, indicative of white matter micro- and macrostructural degradation with age. More importantly, mediation analyses demonstrated that age-related variations in the combined (fiber density and cross-section) metric of the genu, but not splenium, of the CC contributed to the observed age-related differences in bimanual coordination performance. These findings highlight the contribution of variations in interhemispheric communication between prefrontal (non-motor) cortices to age-related differences in motor performance.

1. Introduction

Bimanual coordination, which is the ability to move the two hands in an organized manner in space and time, is required for many fine and gross motor activities of daily living, such as driving a car, typing an email, and tying shoelaces (for reviews, see Maes et al., 2017; Swinnen, 2002; Swinnen and Wenderoth, 2004). Previous behavioral research has identified age-related declines in bimanual coordination performance, especially when the task at hand becomes more complex (for reviews, see Krehbiel et al., 2017; Maes et al., 2017). Such behavioral declines have adverse consequences in the context of functional independence and quality of life in aging. Besides musculoskeletal changes (Faulkner et al., 2007; Hairi et al., 2010), other important factors may underlie these age-related declines in bimanual performance, including alterations in the brain white matter (for a review, see Seidler et al., 2010). Therefore, investigations into the white matter structures underlying compromised bimanual coordination in aging are critical for our efforts to counteract these movement difficulties and prolong the functional independence in older adults.

Successful bimanual coordination requires the optimal exchange of neuronal signals between the two brain hemispheres (Gooijers and Swinnen, 2014). The primary conduit for neuronal communication...
between the two hemispheres is the corpus callosum (CC). Previous work in patients submitted to partial or complete surgical callosotomy has shown that interruption of fibers in a specific CC section results in specific bilateral synchronization deficits (Berlucchi, 2012; Gazzaniga, 2005). In particular, it has been demonstrated that sectioning the anterior part of the CC in epileptic (Pereilowski, 1972) or non-epileptic (Caille et al., 2005) patients leads to slower and less accurate bimanual performance. With respect to aging, previous preclinical and post-mortem studies have demonstrated age-related degeneration of the axons and sheaths of myelinated fibers in numerous white matter tracts, including the CC (Bowley et al., 2010; Marner et al., 2003; Meier-Ruge et al., 1992; Peters and Rosene, 2003). Similar to the clinical cases, these degenerative alterations in the properties of transcallosal white matter pathways may contribute to the bimanual performance deficits observed in aging.

Diffusion magnetic resonance imaging (dMRI) can provide information about the underlying microstructure of brain white matter tissue in vivo. Previous dMRI work has shown a widespread pattern of age-related decline in white matter microstructural properties, which is more pronounced in anterior than posterior brain areas (for reviews, see Bennett and Madden, 2014; Sullivan et al., 2010). However, evidence on the association between microstructural properties of the CC and bimanual coordination performance in older adults is scarce. Fling and colleagues demonstrated that lower degree of white matter microstructural organization in the somatosensory and primary motor mid-sagittal subregions of the CC were, respectively, related to lower bimanual tapping and force production performance in older adults (Fling et al., 2011; Fling and Seidler, 2012). Furthermore, in a lifespan sample of healthy adults, Sullivan et al. (2001) reported that a lower degree of microstructural organization in the splenium of the CC was associated with decreased bimanual alternating tapping performance with aging. In another study, administering a battery of bimanual tasks, Serbruyns et al. (2015) found that a lower degree of microstructural organization in the occipital mid-sagittal subregion of the CC was associated with inferior bimanual visuo-manual manipulation skills in older adults, whereas lower performance on other bimanual tasks was related to a lower degree of microstructural organization in the more anterior premotor, primary motor and primary sensory mid-sagittal subregions of the CC. More recently, Fujiyama et al. (2016) extended the observed brain-behavior associations for the homotopic CC connections to non-homotopic CC connections by showing positive correlations between bimanual coordination performance and microstructural organization of white matter tracts connecting prefrontal and premotor cortices to contralateral primary motor cortex in older adults.

Although results of the abovementioned dMRI studies are informative, they face methodological limitations as the diffusion tensor (DT) showing positive correlations between bimanual coordination performance on other bimanual tasks was related to a lower degree of microstructural organization (e.g., fractional anisotropy: FA) which are less straightforward to endow with underlying biological processes in crossing-fiber regions. To overcome this limitation, a whole-brain analysis framework, known as Fixel-Based Analysis (FBA) (Raffelt et al., 2017), has recently been developed. This framework enables comprehensive statistical analyses of white matter quantitative measures in the presence of complex fiber geometries. Within this framework, specific scalar quantitative measures are provided for individual fiber populations within a voxel, i.e., ‘fixels’ (Raffelt et al., 2015). Therefore, by applying FBA it is possible to go beyond whole-voxel FA estimations and to provide more accurate and anatomically specific information about properties of white matter populations, particularly in crossing-fiber regions (Grazioplene et al., 2018; Mito et al., 2018).

The FBA framework offers microstructural measures sensitized to the total intra-axonal volume of white matter axons for individual tracts and can thus be used to detect microstructural alterations within specific white matter tracts. More importantly, because aging is associated with substantial white matter atrophy (Giorgio et al., 2010; Salat, 2011), it is important to account for the potential macrostructural, morphological changes that may contribute to the observed microstructural changes in white matter properties. In this regard, relative to the widely applied DT approach, FBA is a more accurate and specific approach to assess age-related variations in white matter properties. Particularly, aside from estimating microstructural differences in the density of fibers (FD) within a fiber bundle, it estimates macrostructural differences in the fiber-bundle cross-section (FC), and differences arising from a combination of both of these features (FDC) (Raffelt et al., 2017).

The overarching objective of this study was to examine whether age-related variations in the white matter macro- and microstructural properties account for age-related differences in bimanual performance. To this end, dMRI data of a cross-sectional lifespan (20–75 years) sample of 95 healthy adults were acquired to investigate age-related variations in white matter FBA metrics. To probe age-related differences in motor behavior, a bimanual coordination task (BCT) was administered. Mediation analysis was applied to investigate inter-relations between age, white matter tissue properties, and bimanual coordination performance. We hypothesized that the age-related differences in bimanual performance would be mediated by age-related white matter variations in bilateral projections of the CC, as observed using FBA metrics.

2. Methods

2.1. Participants

A cohort of 106 right-handed (Oldfield, 1971) adults aged between 18 and 80 years was recruited from Leuven and the surrounding region to take part in this study. All participants had normal or corrected-to-normal vision, reported no known psychological, psychiatric or neurological disorders, were taking no psychoactive medication, and did not present any MRI contra-indications. Out of the 106 screened participants, 11 were excluded: 2 participants voluntarily withdrew from the study before completion of the protocol, 6 participants were excluded due to technical issues during acquisition of the dMRI data, 1 presented a brain lesion, and 2 participants did not reach the cut-off score of 24 on the Montreal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005). Thus, the final analyses were performed on 95 participants (mean ± std = 48.3 ± 17.6; range = 20.2–74.5 years; 51 males). The experiment was approved by the local ethical committee of KU Leuven and all participants provided written informed consent.

2.2. Experimental procedure

This study was part of a larger multimodal neuroimaging project investigating the neural mechanisms underlying motor performance in aging. The full experimental protocol consisted of 3 sessions. In the first session, participants completed screening-related questionnaires and assessments (e.g., health status, MRI contra-indications, MoCA) and were familiarized with the task by executing blocks of bimanual coordination tasks (BCT) while positioned supine in a mock MRI scanner. In the second session, in addition to a high resolution T1-weighted structural image, a series of MRI scans in the absence of a task were acquired for which the results are unrelated to the ones presented in the present article and are published elsewhere (Hermans et al., 2018; King et al., 2018). In the third session, while lying supine in the actual MR scanner, participants executed 8 blocks of the BCT during which functional MRI (fMRI) and subsequently dMRI scans were acquired. Here, we present the results obtained by analysis of the dMRI data in relation to motor performance obtained during the MRI scans in the third session.
2.3. Bimanual coordination task (BCT)

2.3.1. Task setup and procedures

Participants performed multiple blocks of the BCT analogous to the task previously employed in our laboratory, but including different task variations (Boisgontier et al., 2018; Chalavi et al., 2016, 2018; Gooijers et al., 2016; Sisti et al., 2011; Zivari Adab et al., 2018). Using an LCD projector (Barco 6300, 1280 x 1024 pixels), visual stimuli were projected onto a double mirror placed in front of the participant’s eyes. A custom-made non-ferromagnetic device with 2 dials (5 cm diameter) was placed above the participant’s lap (Fig. 1A). Rotation of the dials with the 2 hands controlled the movement direction and speed of a cursor presented on the computer screen. Clockwise (CW) and counter-clockwise (CCW) rotations of the right-hand dial moved the cursor towards the right and left side of the screen (along X-axis), respectively. CW and CCW movements of the left-hand dial moved the cursor upward and downward (along Y-axis), respectively. Angular displacements of the dials were recorded with non-ferromagnetic high precision optical shaft encoders (HP, 2048 pulses per revolution, 100 samples per sec, accuracy = 0.088°) and were processed online using LabView 8.5 (National Instruments, Austin, Texas, USA).

Each BCT trial started by presenting the desired target trajectory (blue line) and a target (white circle) (Fig. 1B). This information remained on the screen for 2 s and the participants were instructed to not move during this time epoch (i.e., planning phase). Subsequently, the target dot started moving along the target trajectory at a constant speed for a total duration of 10 s. During this time, participants were instructed to closely track the target dot by rotating both hand dials simultaneously (i.e., execution phase). During the execution phase, online visual feedback of the participants’ performance was provided via a red cursor, which depicted the current position as well as the positions corresponding to the preceding second. After the execution period, the screen turned black for 3 s (inter-trial interval), after which the next BCT trial began.

The BCT was divided into four conditions to modulate task complexity, i.e., rotating both hands with the same or at different speeds and directions (Fig. 1C). In the first, simplest condition, participants were instructed to rotate the left hand and the right hand dial at a constant and matching speed, resulting in a diagonal line trajectory on the screen. The direction of movement was either from the bottom-right of the screen towards the top-left of the screen, or vice versa. The slope of the line in this case was 1, which meant that both hands were moving at the same speed (3 trials/block/direction of movement; hereafter referred to as the

![Image of BCT setup](image-url)
‘Line iso’ condition). In the second condition, participants were instructed to rotate the dials at different speeds resulting in a line trajectory with a slope of either 2.5 or 0.4. The direction of movement was from the bottom-right of the screen to the top-left (3 trials/block/slope; hereafter referred to as the ‘Line noniso’ condition). In the third condition, participants were instructed to rotate the dials at a constant and matching speed (slope = 1), but a change in direction was required after 5 s, resulting in a V- or inverted V-shaped pattern. The movement initiated from the left side of the screen in case of V-shaped pattern, and from the right side of the screen in case of an inverted V-shaped pattern (3 trials/block/direction of movement; hereafter referred to as the ‘Angle’ condition). Basicly, this condition required the participant to change rotation direction (switch) in one hand while continuing the movement with the other hand. In the fourth, most challenging condition, participants were instructed to rotate the dials at a constant and matching speed (slope = 1), but after every 2 s a change in direction was required, resulting in a zig-zag pattern. This zig-zag pattern was either oriented horizontally or vertically with the movement initiated from the right or bottom side of the screen, respectively (3 trials/block/direction of movement; hereafter referred to as the ‘Multi-angle’ condition).

In total, 192 BCT trials were performed. These trials were distributed over eight 6-min blocks, each consisting of 24 trials, presented in sub-blocks of 6 trials per condition. The order of sub-blocks was pseudorandomized across blocks. Between blocks 4 and 5, a passive/rest BCT block was included in which an exemplary performance was presented but no actual movement was executed. Neither data from this block nor from the familiarization session were analyzed in this study.

2.3.2. Behavioral analysis

For each trial, the x and y positions of the white target dot and the subject’s cursor were sampled at 100 Hz and recorded for subsequent offline behavioral analysis conducted in MATLAB R2016b (The MathWorks Inc., Natick, MA). The BCT performance was defined as the percentage of the target pattern ‘covered’ by the participants’ hand movements. Thus, for each sample (i.e., every 10 ms) of the subject’s trajectory, a point on the target pattern with minimum Euclidean distance from the subject’s trajectory was identified and marked as ‘covered’ (Fig. 1D).

The final performance score was calculated as the total number of unique ‘covered’ points divided by the total number of points forming the target pattern (i.e., 1000), multiplied by 100. Consequently, using this procedure, moving on top or parallel to the target line with a correct inter-hand speed would result in a high performance score. However, moving away from the target pattern, moving too slow or too fast with respect to the target speed, cutting corners and/or turning in the wrong direction (in conditions Angle and Multi-angle) would result in a lower performance score. A non-parametric Friedman ANOVA with ‘task condition’ as a within-subjects factor was implemented in Statistica 13.1 to analyze the effect of task complexity on performance. The association between performance in different task conditions and age was calculated using Pearson’s, Spearman’s, and 10% Winsorized correlation coefficients. The age-performance correlations were further compared across task conditions using Steiger’s Z-test (Steiger, 1980).

2.4. Brain imaging

2.4.1. Acquisition parameters

dMRI data were acquired using a Philips Achieva 3T scanner with a 32-channel head coil, located at the University Hospital of Leuven, Belgium. Multishell data were acquired using a spin-echo echo-planar imaging sequence with the following parameters: b = 700 s/mm² (16 directions); b = 1200 s/mm² (30 directions); b = 2800 s/mm² (50 directions); 6 interleaved volumes without diffusion weighting (b = 0 s/mm²); voxel size = 2.5 × 2.5 × 2.5 mm³, echo-time/repetition time (TE/TR) = 74/9000 ms; SENSE = 2; matrix size = 96 × 96; and number of slices = 50. In addition, 1 b = 0 s/mm² image was acquired with reversed phase encoding, for the purpose of susceptibility-induced distortion correction. The total acquisition time was 17.5 min. Furthermore, a high-resolution three-dimensional T1-weighted structural image was acquired (three-dimensional transient field echo (TFE); repetition time = 9.6 ms; echo time = 4.6 ms; inversion time = 900 ms; flip angle = 8°; voxel size = 0.98 × 0.98 × 1.2 mm³; field of view = 250 × 250 × 192; 160 coronal slices, total scan time = 6 min).

2.4.2. Fixed-based analysis (FBA)

All the dMRI processing steps for FBA, which are described below, were conducted either using commands implemented within MRtrix3 (Tournier et al., 2019) or using MRtrix3 scripts that interfaced with external software packages such as FSL (Jenkinson et al., 2012) or ANTs (Avants et al., 2014). In brief, dMRI data were denoised (Veraart et al., 2016) and corrected for eddy, motion, and susceptibility induced distortions (Andersson et al., 2003, 2016; Andersson and Sotiropoulos, 2016). Afterward, 3-tissue response functions representing single-fiber white matter, grey matter and CSF were obtained from the data themselves using an unsupervised approach (Dhollander et al., 2016). Subsequently, dMRI data was unsampled to an isotropic voxel size of 1.3 mm³ (to improve downstream fiber orientation distribution registration and statistics (Derby et al., 2014; Raffelt et al., 2012b)) and a brain mask was estimated. Next, 3-tissue constrained spherical deconvolution (CSD) was performed for each subject, using averaged (across all subjects) response functions for each tissue type with the multi-shell multi-tissue CSD algorithm (Jeurissen et al., 2014), resulting in the white matter fiber orientation distribution function (FOD) for each voxel. Joint bias field correction and global intensity normalization of the 3-tissue parameters was performed in the log-domain. To achieve spatial correspondence, the FOD images of 48 subjects (16 within 20–40 age interval, 16 within 40–60 age interval, 16 above 60 years of age; gender matched in each interval) were entered to an iterative registration and averaging approach to generate a study-specific population template to which all 95 subjects’ FODs were registered (Raffelt et al., 2011, 2012a).

The metrics of fiber density (FD), fiber-bundle cross-section (FC), and a combined measure of fiber density and cross-section (FDC) were calculated for each subject across whole-brain white matter fissels. These metrics and their interpretations have been fully described by Raffelt et al. (2017) and are briefly summarized here. FD relates to the volume of the intra-axonal compartment of fibers oriented in a particular direction and is specifically sensitive to microstructural alterations within a voxel. A reduction in fiber density could be due to a loss of axons, such as in multiple sclerosis (Gajamange et al., 2018), whereas an increase in FD could result from an increase in axon diameter, or the number of axons occupying a given space, such as in developmental processes (Genc et al., 2018). FC relates to the volume perpendicular to the fiber bundle orientation and is sensitive to macrostructural, morphological changes in the cross-sectional area of a fiber bundle. A reduction in FC has been observed in Alzheimer’s disease (Mito et al., 2018), whereas an increase in FC has been reported during development (Genc et al., 2018). FDC is a combined measure that incorporates both the micro- and macrostructural effects described above, thus providing overall sensitivity to any differences related to white matter’s capacity to transmit information.

Total intracranial volume (TIV) was obtained from T1-weighted images using the standard pipeline of FreeSurfer (Fischl, 2012), and the average subject head movement across dMRI volumes was computed from the restricted root-mean-square movement output by the FSL General Linear Model (GLM). dMRI and fMRI were used to investigate associations between age or BCT performance with FD, FC, and FDC across whole-brain white matter fissels. Notably, age and BCT performance were not included in the same GLM because the two variables were highly correlated (see section 3.1). Gender, TIV, and the average subject movement across dMRI volumes were included as nuisance covariates in the GLMs. Connectivity-based smoothing and statistical inference were performed with the connectivity-based fixed enhancement (CFE) approach using a 2-million template-based tractogram (Raffelt et al., 2011, 2012a).
2.5. Mediation analysis

To investigate whether age-related variations in transcallosal white matter pathways contribute to age-related differences in bimanual performance, mediation analyses were performed (Mackinnon et al., 2007). In these analyses, mediation of the age–bimanual performance relation by white matter is conceptually defined as age negatively affecting white matter measures, and white matter measures positively affecting bimanual performance. Thus, a data-driven approach was adopted whereby a whole-brain map of tracts exhibiting both a statistically significant negative association with age and a positive association with BCT performance for the FDC metric was generated. The transcallosal tracts of this map were further selected and categorized into two major CC tracts of interest (see section 3.4). For each participant, mean FDC was computed across the tracts within each of the transcallosal tracts of interest. The FDC metric was used in these analyses since it is a measure of total intra-axonal volume occupied by white matter fibers and can be denoted as the marker of total capacity of a particular white matter tract for information transmission (Raffelt et al., 2017), i.e., a relevant measure in the context of behavior.

The commonly-used mediation approach (Baron and Kenny, 1986), implemented in the M3 mediation toolbox (Wager et al., 2008, 2009), was used. The first step in this approach was the evaluation of the overall effect of age on BCT performance (see Fig. 2). This effect, hereafter referred to as total effect (c), represents the total effect of age on BCT performance. Next, we evaluated whether part of this total effect of age on BCT performance was explained by the effect of age on FDC of a specific white matter tract (i.e., mediator). Accordingly, for each tract of interest a mediation model was tested in which the total effect was partitioned into two distinct pathways that were evaluated using ordinary least-squares path analysis. The first pathway, hereafter referred to as indirect pathway (ab), represents how age contributes to differences in the candidate mediator variable, and how this in turn contributes to differences in BCT performance. The indirect effect was estimated as ab, meaning the product of path a, which represents the effect of age on the mediator variable, and path b, which represents the effect of the mediator variable on BCT performance while controlling for the effect of age. Of particular interest was the indirect effect, since 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, the second pathway, hereafter referred to as direct pathway (c'), was also investigated. This pathway represents the residual influence of age on BCT performance, i.e., the effect of age on BCT performance independent of its effect via the mediator variable (i.e., tract FDC) used. This direct effect was estimated with c', and corresponds exactly to the difference between the total and the indirect effect of age on BCT performance in the model. One of the main advantages of this method is that it enables direct testing of the significance of the indirect effect and therefore mediation. Here, this was accomplished using 10,000 bootstrap samples to determine bias-corrected 95% confidence intervals for the indirect effects. Accordingly, indirect effects with 95% confidence intervals entirely below zero (one-tailed test based on the clearly directional hypotheses) were regarded as significantly mediating the relation between age and BCT performance. For comparative reasons, the conventional diffusion tensor-derived metrics of white matter microstructural organization, namely fractional anisotropy (FA) and mean diffusivity (MD), were also obtained for the transcallosal tracts of interest (see Supplementary Materials and Fig. S1 for detailed methodology) and were entered into the separate mediation models.

3. Results

3.1. Bimanual coordination performance and age

Results of the Friedman ANOVA revealed that the median BCT performance differed significantly between task conditions ($\chi^2 (3) = 251.7; p < 0.0001$). Post-hoc Wilcoxon matched paired tests using the Bonferroni correction revealed that BCT performance was significantly lower in the Multi-angle (median [interquartile range]: 68.7 [16.4]) as compared with the Angle (79.4 [10.7]), Line noniso (87.8 [5.3]), and Line iso (88.1 [4.9]) conditions (all ps < 0.0001). The performance in the Angle condition was lower when compared to both Line noniso and Line iso conditions (both ps < 0.0001). However, the BCT performance in Line noniso and Line iso conditions were not statistically different (p > 0.05). These findings indicate a decline in BCT performance as the task becomes more complex.

We further investigated how BCT performance in different task conditions varied as a function of age (Fig. 3). Results of these correlation analyses revealed a strong negative association between age and performance in each BCT condition (Line iso/Line noniso/Angle/Multi-angle: $r_{\text{Pearson}} = -0.6/$–0.59/$–0.72/$–0.77; $r_{\text{Spearman}} = -0.64/$–0.68/$–0.74/$–0.79; $r_{\text{Winsorized}} = -0.63/$–0.67/$–0.73/$–0.78; All ps < 0.0001), indicating that in this cross-sectional sample lower BCT performance is associated with higher age. The Steiger’s Z-test using Pearson’s correlation revealed that although the strength of these correlations with age did not differ between the simpler Line iso and Line noniso conditions ($Z = -0.2; p > 0.05$), they were less strong when compared to the more complex Angle and Multi-angle conditions (All $Zs > 2.66; all ps < 0.01$). Furthermore, it was observed that the strength of the negative correlation with age tended to be less strong in the Angle than in the Multi-angle condition ($Z = 1.75; p = 0.04$). These results were also confirmed using more robust Spearman’s and Winsorized correlations (see Supplementary Table 1). Interestingly, it also became apparent that the negative age-performance associations, particularly in the more complex task conditions, already emerged from an early age and showed a gradual linear pattern. Overall, these findings indicate that the negative age-BCT performance association became more pronounced when task complexity increased. As the age-related differences in bimanual performance were most pronounced in the Multi-angle condition and all task conditions were also highly correlated (All $rs > 0.72; All ps < 0.0001$), the
performance scores in this condition were chosen to serve as the primary motor performance-related variable of interest in the analyses presented in the subsequent sections.

3.2. Whole-brain FBA: association between aging and white matter

To investigate the association between age and brain structure, separate non-parametric permutation GLM analyses with age as dependent variable and FD, FC, or FDC as independent variables were run. Gender, TIV and mean subject head movement were added to the model as covariates of no interest. Fig. 4 shows an example axial brain slice with fixels showing a significant negative association between age and the FDC metric ($p < 0.05$, FWE-corrected). As demonstrated by a zoomed-in crossing-fiber region (see the inset), FBA enables fiber tract-specific inference by assigning an individual p-value to each fixel, rather than to each voxel.

Fig. 5 illustrates streamline segments associated with fixels that showed a significantly negative association with age for fiber density (FD), fiber bundle cross-section (FC), and both measures combined (FDC) ($p < 0.05$, FWE-corrected). Streamlines are colored according to their direction. Fixels showing a negative age-microstructural FD association were mainly found in bilateral projections of the genu (G1/G2/G3), midbody (B1/B2), isthmus, and splenium (S1/S2) of the corpus callosum (CC), bilateral fornix, bilateral anterior thalamic radiations (ATR), anterior commissure (AC), bilateral cingulum, bilateral inferior fronto-occipital fasciculus (IFOF), and bilateral corticospinal tract (CST). Fixels showing a negative age-macrostructural FC association were found in the bilateral projections of the genu (G1/G2/G3) of the CC, bilateral cingulum, left superior longitudinal fasciculus (LSLF), right inferior longitudinal fasciculus (RILF), bilateral ATR, AC, and bilateral IFOF.

While some fiber pathways, most notably bilateral fornices, midbody (B1/B2), isthmus, and splenium (S1/S2) of the CC, and LSLF only exhibited a negative association between age and the FD or the FC metric, some others, most notably genu of the CC (G1/G2/G3), showed negative associations between age and both metrics. When macro- and microstructural fiber differences were combined using the FDC metric, negative associations with age were observed in fixels of the genu (G1/G2/G3), midbody (B1), and splenium (S1) of the CC, bilateral cingulum, AC, bilateral fornix, bilateral ATR, bilateral CST, RILF, and bilateral IFOF. Important to note, the fixels showing negative associations with age appeared more in anterior relative to posterior white matter regions of the brain.

3.3. Whole-brain FBA: association between bimanual performance and white matter

To investigate the association between bimanual performance and brain structure, separate GLM analyses were run using BCT performance as the dependent variable, FD, FC, or FDC as independent variables and gender, TIV and mean subject movement as covariates of no interest (Fig. 6). A direct visual comparison of Figs. 5 and 6 for the corresponding maps revealed a high similarity between maps. The vast majority of tracts...
with positive performance-related associations (i.e., higher FC/FD/FDC metrics were associated with better BCT performance) also exhibited negative associations with age (i.e., lower FC/FD/FDC metrics associated with higher age). However, despite these commonalities, there were some differences between these maps. For instance, the FC of the LSLF tract showed a significant association with age, but no significant association with BCT performance (see row 2 column 1 of Figs. 5B and 6B). It is also noteworthy that FDC of the genu (G1/G2/G3) and splenium (S1), and not midbody and isthmus, of the CC was significantly correlated with BCT performance.

3.4. Inter-relation between age, white matter, and bimanual performance

Mediation analyses were performed to investigate whether the observed age-related differences in BCT performance were mediated by age-related variations in the CC. To that end, fixes exhibiting both a significant negative association with age and a positive association with BCT performance in the Multi-angle condition for the FDC metric were selected as a mask (Fig. 7A). The performance in the Multi-angle condition was opted since it showed the strongest age-related differences among all BCT conditions. The FDC metric was chosen as it combines
both FD and FC and thus can be used as a structural marker for total information transmission capacity of a white matter tract. As illustrated in Fig. 7B, the transcallosal fixels of this mask formed two major tracts. The first tract connected mainly left and right prefrontal cortices via the genu (G1/G2/G3), and the second tract connected mainly left and right parietal cortices via the splenium (S1) of the CC. As expected based on the results of whole-brain analyses, the average FDC of the genu and splenium tracts positively correlated with BCT performance ($r_{\text{genu}} = 0.6; r_{\text{spleum}} = 0.38; \text{both } p < 0.001$; Fig. S2) and negatively with age ($r_{\text{genu}} = -0.68; r_{\text{spleum}} = -0.44; \text{both } p < 0.001$).

We included age as the independent variable, mean FDC of the genu or the splenium tract as the mediator, and BCT performance in the Multi-angle condition as the outcome variable in the mediation analysis. This analysis revealed that the FDC value of the genu tract mediated the effect of age on BCT performance ($\beta = -0.06 \pm 0.03, p = 0.03; c = -0.48 \pm 0.04, p < 0.001; c' = -0.42 \pm 0.05, p < 0.001$). Of note, given the significance of the direct path coefficient $c'$, this mediation effect is ‘partial’ and not ‘complete’. As illustrated in Fig. 7C left, higher age was significantly associated with lower FDC in the genu tract ($\alpha = -0.0028 \pm 0.0003, p < 0.001$), and this lower FDC was significantly associated with lower BCT performance ($b = 22.76 \pm 10.64, p = 0.03$). Including splenium as the mediator variable in the model (Fig. 7C right), no significant...
indirect effect of age was found on BCT performance \((ab = -0.02 \pm 0.02, p = 0.46; c = -0.48 \pm 0.04, p < 0.001; c' = -0.46 \pm 0.05, p < 0.001)\). Thus, higher age was significantly associated with lower FDC in the splenium tract \((a = -0.0024 \pm 0.0005, p < 0.001)\), but this lower FDC was not significantly associated with lower BCT performance \((b = 6.79 \pm 8.25, p = 0.4)\). Altogether, these results indicate that the age-related variations in the fiber-specific FDC metric of the genu, but not splenium, of the CC contributed to the observed age-related variations in bimanual coordination performance. It is noteworthy that conducting identical analyses on the conventional FA or MD measures showed no significant mediation effects for either the genu or splenium tract (see Supplementary Materials for more details).

4. Discussion

The current study is the first application of the recently developed voxel-based analysis (FBA) of dMRI data to investigate age-related variations in white matter fiber-specific metrics and their links with age-related differences in bimanual motor performance. At the behavioral level, higher age was associated with lower bimanual performance, and this negative association was more pronounced with increasing task complexity. At the neural level, higher age was associated with lower white matter microstructural (assessed by fiber density metric, FD), macrostructural (assessed by cross-section metric, FC), and the combined FD & FC (i.e., FDC) fiber-specific metrics. These negative associations were more apparent in the anterior relative to the posterior parts of brain white matter. Importantly, age-related variations in FDC of the tract connecting bilateral prefrontal cortices via the genu of the corpus callosum (CC) partially mediated the age-related differences in bimanual coordination performance.

4.1. Age-related differences in bimanual motor behavior

Aging is generally associated with a reduced ability to perform motor (including bimanual coordination) tasks, especially the more complex ones, which require effortful processing (Fling et al., 2011; Fujiyama et al., 2016; Krebbiel et al., 2017; Maes et al., 2017; Serbruyns et al., 2015; Serrien et al., 2000; Slesio-Jofre et al., 2014; Swanen et al., 1998; Wishart et al., 2000). Here, we studied a cross-sectional lifespan sample of adult participants performing simple and more complex continuous bimanual coordination tasks and confirmed previous findings by reporting: (i) negative correlations between age and bimanual coordination performance across all task complexity levels, and (ii) an increase in the strength of the negative correlation between age and bimanual performance as a function of increased task complexity. However, our findings of gradual negative age-bimanual performance associations in the more difficult conditions prompt questions about the reasons underlying these negative associations to start at a relatively early age.

4.2. Age-related variations in FBA metrics of white matter

The FBA pipeline was employed in a cross-sectional lifespan sample of human adults for the first time. Unlike previous aging studies mostly performing voxel-based analyses of non-fiber specific measures of white matter microstructural organization (e.g., FA) (for reviews, see Bennett and Madden, 2014; Sullivan et al., 2010), the presently applied voxel-based analyses allows sub-voxel fiber-specific investigation of measures related to white matter microstructure, local macrostructure, and the combination of micro- and macrostructure. This approach thus provides a more accurate and meaningful interpretation of white matter changes in aging, since different fibers in a voxel can be differently affected by the aging process.
Our findings demonstrated that higher age is associated with lower FD, FC, and FDC for white matter tracts. The lower values of FD/FC/FDC are indicative of a lower intra-axonal volume fraction, whereby, for any hypothetical voxel, the fraction of space occupied by axons is smaller. This suggests that either the axons are decreasing in diameter, or that a lower number of axons is occupying this space (i.e., axonal deletion), in a region-specific manner with age. Both of these mechanisms have been observed in post-mortem aging studies (Bowley et al., 2010; Marner et al., 2003; Meier-Ruge et al., 1992; Peters and Rose, 2003), and can lead to a decreased capacity of fiber tracts to ‘transfer information’ across brain regions. It is important to mention that even though it is possible from a biological perspective that the loss of total intra-axonal volume, either via a decrease in axonal diameter or loss of the entire axons, can be a consequence of demyelination, we cannot make a direct link to the demyelination process here as myelination is not what is directly assessed or measured by the FBA metrics.

The negative associations between age and FD, FC and FDC were observed across a number of white matter tracts. The spatial extent of these negative associations is broadly in line with findings from previous dMRI studies reporting greater age-related declines in white matter microstructural properties (such as FA or MD) in the anterior than posterior regions of the brain (Abe et al., 2002; Head et al., 2004; Ota et al., 2006; Pfefferbaum et al., 2005; Sullivan et al., 2006, 2010; Sullivan and Pfefferbaum, 2006). While the diffusion metrics extracted in the previous dMRI studies quantify different properties of white matter structure as compared to those used in the present work, the combined evidence lends support to the white matter retrogenesis hypothesis that later developed axons in the anterior brain regions are more susceptible to age-related differences than earlier developed axons in more posterior brain regions (Bennett and Madden, 2014; Cox et al., 2016).

4.3. Age-related variations in white matter partially mediate the age-related differences in bimanual coordination behavior

For the first time, we explored the contribution of age-related white matter variations to age-related differences in bimanual coordination performance using a pixel-based metric. As described by Raffelt et al. (2017), the combined FDC measure is an accurate and sensitive metric to detect an effect of interest in case both FD and FC measures decrease. Therefore, the FDC metric was used as a potential structural marker of the motor cortices, it was significantly associated with the FDC of the more posterior CC tract (i.e., splenium) in our study does not necessarily imply that the FDC of this tract was not related to bimanual performance in general. It rather indicates that the negative age-FDC association for this tract was not driving the observed age-related differences in performance on the present bimanual coordination task. Additionally, the lack of structure-behavior relation for the CC genu tract in those studies could be due to methodological differences. For example, to avoid data contamination originating from crossing fibers, the latter studies obtained the estimation of the microstructural metrics from the mid-sagittal segments of the CC only, rather than from the entire CC pathways extending more laterally into the grey matter. Using the more advanced FBA framework, we were able to go beyond the CC mid-sagittal plane and obtained fiber-specific structural metrics for the more lateral projections of the CC, also in crossing fiber regions. Other possible factors contributing to variations between our and previous findings include variations in the sample studied, the type of bimanual task used, structural metrics (i.e., FDC vs FA), and statistical analysis methods.

4.4. Cross-sectional designs and cohort effects

In this study, we utilized a cross-sectional design to investigate the link between motor performance and age-related variations in the quality of white matter tracts. It is important to note that cross-sectional aging studies may suffer from ‘cohort effects’, confounding the interpretation of the findings. More specifically, people belonging to the same age group are exposed to the same historical events, social situations, and nutritional availability. This distinguishes them from other age groups. Therefore, longitudinal study designs are often proposed. Nonetheless, in the study of brain structure/behavior associations such as ours, longitudinal studies also carry inherent limitations because the repeated measurements of task performance may give rise to practice effects, masking true performance capability. Additionally, previous longitudinal studies addressing age-related white matter changes (across time spans from a few months to several years) have lent support to the results of the cross-sectional aging studies by reporting aging-induced white matter deterioration (Charlton et al., 2016; Engvig et al., 2012). Accordingly, it appears that both approaches may provide valuable information about the aging brain and associated behavioral changes.

4.5. Methodological considerations

Mediation analysis is a powerful statistical tool to analyze the inter-relationship among variables, however, it is important to be aware of its limitations. Although there is enough empirical evidence to believe that white matter is indeed one of many mediators of age-related variations in motor behavior, the mediation analysis toolset provides information about, in the simplest case, three-way relationships between variables and does not provide any method to test whether white matter is truly a mediator (Fiedler et al., 2011). The results must, therefore, be interpreted with care. Additionally, widespread changes in the central and peripheral nervous system, as well as the neuromuscular system take place in older age (Seidler et al., 2010). There is a strong interplay among those changes, and between them and motor behavior changes in older adults (Maes et al., 2017). Consequently, our results must be interpreted conservatively in terms of how much it explains the age-related differences in motor performance. Nonetheless, our findings still provide valuable information linking age-related variations in white matter characteristics and their impact on bimanual motor performance.

5. Future directions and conclusion

In this study, we used a uni-modal approach to explore the relations between age, bimanual coordination performance, and structural white
matter characteristics, using recently developed fixed-based analysis (FBA) of dMRI data. However, future work could employ multi-modal approaches and combine fixed-based structural metrics with, for example, functional or neurochemical metrics to provide a more complete understanding of the aging effects on bimanual performance.

In summary, our findings indicated that advancing age was associated with inferior bimanual coordination performance and more so in complex as compared to simple tasks. Furthermore, negative associations of age with fiber-specific FBA metrics were observed more in anterior than posterior brain white matter, pointing to compromised fiber density and/or cross-section with advancing age. More importantly, age-related variations in FDC of the transcallosal tracts connecting prefrontal cortices contributed to age-related differences in bimanual coordination performance. These findings underscore the contribution of micro- and macrostructural white matter variations, reflecting differences in interhemispheric communication between prefrontal (non-motor) cortices, in compromised bimanual coordination performance with advancing age. Furthermore, they highlight the potential of FBA in the determination of distinct brain-behavior associations in an ever-increasing aging society.

Declaration of competing interest

The authors have no conflict of interest or competing interests to disclose.

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Appendix A. Supplementary data

Supplementary to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116530.

Author contributions

HZA, DM, and SPS designed the study. HZA, SC, TSM, JG, and TD contributed in image processing and analysis. HZA and SC performed statistical analyses. HZA and SC wrote the first draft of the manuscript. All authors contributed in revising the work and approved the final version of the manuscript.

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