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Bimanual motor deficits in older adults predicted by diffusion tensor imaging metrics of corpus callosum subregions

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Abstract Age-related changes in the microstructural organization of the corpus callosum (CC) may explain declines in bimanual motor performance associated with normal aging. We used diffusion tensor imaging in young (n=33) and older (n=33) adults to investigate the microstructural organization of 7 specific CC subregions (prefrontal, premotor, primary motor, primary sensory, parietal, temporal and occipital). A set of bimanual tasks was used to assess various aspects of bimanual motor functioning: the Purdue Pegboard Test, simultaneous and alternating finger tapping, a choice reaction time test and a complex visuomotor tracking task. The older adults showed age-related deficits on all measures of bimanual motor performance. Correlation analyses within the older group showed that white matter fractional anisotropy of the CC occipital region was associated with bimanual fine manipulation skills (Purdue Pegboard Test), whereas better performance on the other bimanual tasks was related to higher fractional anisotropy in the more anterior premotor, primary motor and primary sensory CC subregions. Such associations were less prominent in the younger group. Our findings suggest that structural alterations of subregional callosal fibers may account for bimanual motor declines in normal aging.

Keywords Aging; Bimanual coordination; Corpus callosum; DTI; Fractional anisotropy

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List of abbreviations

AD: Axial diffusivity

CC: Corpus Callosum

DTI: Diffusion Tensor Imaging

FA: Fractional Anisotropy

ISO: Isofrequency ratios

N-ISO: Non-Isofrequency ratios

OA: Older Adults

RD: Radial diffusivity

YA: Young Adults

Introduction

Healthy aging is generally associated with declines in bimanual motor behavior. Since coordinated hand movements are essential in many daily life activities, these changes in bimanual functioning could menace functional independence in elderly. Previous studies found that the execution of bimanual movements slows down as a result of aging (Bernard and Seidler 2012; Desrosiers et al. 1999; Fling and Seidler 2012; Marneweck et al. 2011; Sullivan et al. 2001). Other studies looked at age-related differences in synchronization between the hands during bimanual coordination (Bangert et al. 2010; Fling et al. 2011b; Serrien et al. 2000; Summers et al. 2010; Swinnen et al. 1998; Wishart et al. 2000). This work revealed that older adults were often able to match the performance of young adults during relatively easy coordination patterns, whereas prominent age differences in performance emerged during more complex coordination patterns requiring effortful processing.

Declines in bimanual motor performance may be caused by multiple processes that occur during aging. For instance, the structure of muscles gradually changes during aging, leading to loss of muscle mass and strength in elderly (Doherty 2003; Goodpaster et al. 2006; Hairi et al. 2010; Harris 1997). Age-related declines in sensory acuity and in neural integration of visual (Leibowitz et al. 1980) and proprioceptive feedback (Adamo et al. 2007; Cole and Rotella 2001; Goble et al. 2009; Stelmach and Sirica 1986) might additionally compromise bimanual motor performance. Furthermore, bimanual movements rely on interactions between the hands, and therefore require exchange of information between both hemispheres of the brain. The primary interhemispheric connection is the corpus callosum (CC). The CC is the largest white matter tract in the brain, connecting mostly homotopic but also heterotopic cortical regions (Jarbo et al. 2012). Multiple studies in patients who underwent partial or complete surgical callosotomy have shown that interruption of fibers in a specific CC section leads to specific bilateral synchronization deficits (Berlucchi 2012; Gazzaniga 2005). The current work seeks to determine whether age-related changes in microstructural organization of the CC account for bimanual performance in older adults.

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance technique that enables insight into age-related degenerative changes in white matter brain tissue such as the CC. It provides a quantitative assessment of white matter microstructural organization by quantifying the directionality and rate of diffusion of water within tissue. The most frequently used DTI measure is fractional anisotropy (FA), indicating the degree to which water diffusion is directionally restricted (Basser and Pierpaoli 1996; Tournier et al. 2011). Additionally, the conjoint analysis of axial diffusivity (AD) and radial diffusivity (RD) shows potential to distinguish between diffusivity patterns with different relations to cellular mechanisms of white matter deterioration. AD is assumed to contribute information regarding the integrity of axons or changes in extra-axonal or extracellular space, whereas RD may be selectively sensitive to myelin damage or glial cell morphology (Beaulieu and Allen 1994; Song et al. 2003; Song et al. 2002; Sun et al. 2007; Sun et al. 2006). Previous studies looking at age-

related differences in AD and RD suggest that differences in RD are more prominent than AD differences, tentatively suggesting a predominantly myelin-specific effect in aging (Bhagat and Beaulieu 2004; Davis et al. 2009; Lebel et al. 2012; Madden et al. 2009; Sala et al. 2012; Zhang et al. 2010).

We know from previous DTI studies that microstructural properties of the CC can be linked to performance on a variety of bimanual tasks in healthy young adults (Fling et al. 2011b; Gooijers et al. 2013; Johansen-Berg et al. 2007; Muetzel et al. 2008; Sisti et al. 2012), patients with multiple sclerosis (Bonzano et al. 2008), and patients with traumatic brain injury (Caeyenberghs et al. 2011). In the context of aging however, to the best of our knowledge only two studies have investigated the link between CC microstructure and bimanual performance. Fling et al. (2011b) investigated the association between performance on bimanual tapping tasks and CC microstructure. They found that in the older adults group, higher FA values within the subregion connecting somatosensory cortices was related to better performance on an asynchronous out-of-phase bimanual tapping task. Additionally, in a sample spanning the adult age range (age range = 20-81 years), Sullivan et al. (2001) found a relationship between FA of the splenium of the CC and speed of alternating finger tapping. However, it remains unclear whether structural properties of distinct callosal pathways are associated with age-related performance deficits on different bimanual motor tasks, relying on distinct sensorimotor functions. The present study addressed this issue by exploring relations between microstructural properties of functionally distinct subregions of the CC, and performance on a battery of bimanual tasks in 33 young and 33 older adults.

Four complementary tasks were selected to assess bimanual motor functioning, with all tasks thought to be susceptible to age-related decline and emphasizing partly different sensorimotor functions. First, the Purdue Pegboard Test served as a commonly used clinical measure of fine finger manipulation speed. Secondly, the finger tapping task was used to assess simultaneous and alternating finger tapping speed. Whereas both tasks comprise a motor speed component, exploratory principal component analyses previously showed that they load high on different factors (Takser et al. 2002; Voineskos et al. 2012). Specifically, the Purdue Pegboard Test requires fast visual processing to precisely regulate finger movements, whereas finger tapping depends more on basic motor speed with limited accuracy requirements. Thirdly, a choice reaction time task was used to assess bimanual reaction speed. Besides having a motor speed component, choice reaction time paradigms show sensitivity to deficits in response selection, preparation and generation (Smith 1968). The fourth task was a new visuomotor task, involving complex bimanual coordination patterns relying on intermanual interactions. Rather than focusing on speed of execution as the above-mentioned tasks do, we used the latter task to evaluate accuracy of visually-guided bimanual coordination, represented by tracking accuracy. Based on previous studies, we expected that the older adults would show performance deficits compared to the young adults on all four tasks (Bangert et al. 2010; Bernard and Seidler 2012; Davis et al. 2009; Desrosiers et al. 1999; Fling and Seidler 2012; Fling et al. 2011b; Langan et al.

2010; Madden et al. 2004; Marneweck et al. 2011; Porciatti et al. 1999; Salthouse and Czaja 2000; Sullivan et al. 2001; Summers et al. 2010; Swinnen et al. 1998; Voineskos et al. 2012; Wishart et al. 2000; Zahr et al. 2009).

Our second aim was to compare the white matter microstructural organization of 7 functionally distinct subregions of the CC in the young and older adults using DTI. Accordingly, we subdivided the CC along its anteroposterior axis (Hofer and Frahm 2006; Huang et al. 2005), with the subregions based on their fiber tracts projecting into specific cortical areas, including the (1) prefrontal areas, (2) premotor (and supplementary motor) areas, (3) primary motor areas, (4) primary sensory areas, (5) parietal, (6) temporal, and (7) occipital areas. Employing this classification, previous work of our group has already revealed relations between microstructural organization of specific CC subregions and performance on different bimanual motor tasks in healthy young adults (Gooijers et al. 2013) and in patients with traumatic brain injury (Caeyenberghs et al. 2011).

The ultimate goal of this study was to investigate the pattern of relationships between localized and anatomically specific white matter microstructural organization according to the 7 subregions of the CC, and performance on multiple bimanual motor tasks, emphasizing partly different sensorimotor functions, and susceptible to age-related decline. To the best of our knowledge, we are the first to investigate the specificity of the relationships between all callosal substructures and bimanual performance by employing a battery of bimanual tasks in young and older adults, thereby enabling a thorough examination of the neural correlates of the bimanual performance declines associated with aging.

Materials and Methods

Subjects

After withholding 5 individuals (1 young and 4 older subjects) showing artifacts on their DTI scan that prevented a reliable analysis, 33 young adults (YA, mean \pm SD age = 25.40 ± 4.66 years) and 33 older adults (OA, 69.33 ± 5.56 years) were included in the study. Both groups included 17 females and 16 males. All subjects were right-handed, as verified by the Edinburgh Handedness Inventory (laterality quotient (mean \pm SD): YA: 89 ± 15.12 ; OA: 94.09 ± 12.9) (Oldfield 1971), and had normal or corrected to normal vision. None of the subjects reported a history of neurological or psychiatric disorders. The Montreal Cognitive Assessment scale was used to screen the OA for mild cognitive dysfunction (Nasreddine et al. 2005). All of the OA scored within normal limits (≥ 26). Prior to giving written consent, all subjects received a full explanation of the experimental procedures. The study received approval from the local Ethics Committee for biomedical research, and was performed in accordance with the 1964 Declaration of Helsinki.

Data acquisition

Bimanual tests

Assessment of bimanual motor behavior was achieved using both clinical and instrumented measures. The clinical measure was the Purdue Pegboard Test. The instrumented measures included speeded finger tapping, a choice reaction time test, and a visuomotor task. Outlier detection was performed by transforming all the data per test and per group separately into z-scores. A trial was considered an outlier and discarded from the analysis when the z-score was greater than |3|.

Purdue Pegboard Test

The Purdue Pegboard Test (Lafayette instrument company, USA) is a clinical measure of fine finger manipulation speed relying on fast visual processing. The test consists of manipulating a maximum number of small pins in two vertical columns with pin holes on a board, within a 30-sec time period (Desrosiers et al. 1995; Tiffin and Asher 1948). Previous studies have tested its reliability (Buddenberg and Davis 2000), including one study showing excellent reliability (reliability coefficient of .81) in subjects aged 60 and over (Desrosiers et al. 1995). The test was performed three times with both hands simultaneously. Before starting, the participants were allowed to practice with 3 or 4 pairs of pins. The dependent variable was the average number of pairs inserted during the three trials, with a high score indicating good performance.

Finger tapping test

The finger tapping test is frequently used in studies assessing bimanual motor speed (Muetzel et al. 2008; Njikiktjien et al. 1997; Pelletier et al. 1993; Serrien et al. 2002; Sullivan et al. 2001). In our study, participants had to use the left and right index finger to tap two response buttons on a keyboard (Dell SK-8135) as fast as possible within a 10-sec time period. They were comfortably seated at a table in front of a computer monitor, with lower arms and wrists resting on the table. Two different finger tapping tasks were administered once: (1) tapping simultaneously with the left and right index finger, evaluating in-phase bimanual speed and (2) alternating between tapping with the left and right index finger, evaluating anti-phase bimanual speed. The test was programmed in Hypertext Preprocessor (PHP) 5 and jQuery 1.3 and presented with FireFox on a XAMPP 1.7.3 server.

MATLAB R2008a (Mathworks, Natick, MA) was used to analyze the finger tapping scores, being the sum of correct taps. For simultaneous finger tapping, two taps were considered correct when the intertap interval between the left and right index finger was below 100 msec. For alternating finger tapping, two taps were considered correct when the left and right taps were alternated, accordingly the same button could only be tapped twice if the other button was pressed in between.

Choice reaction time test

Choice reaction time tests are used to evaluate response selection, preparation and movement generation speed (Anstey et al. 2007; Smith 1968; Snodgras et al. 1967; Tuch et al. 2005). In this study, participants were seated with both hands and feet resting on tablets with capacitive proximity switches (Pepperl & Fuchs CBN5-F46-E2, sampling rate 1ms). Four white squares were presented on the screen. The top left and right square represented the left and right hand, respectively. The bottom left and right square represented the left and right foot, respectively. Participants were instructed to keep their hands and feet resting on the tablets, until 1 or maximum 2 squares on the screen turned blue. Upon this visual stimulus, participants had to lift the corresponding limb(s) as fast as possible, releasing the contact with the tablet. Participants were instructed to respond as quickly as possible without sacrificing accuracy. There was a random interval ranging from 1 to 3 seconds between trials, starting from the moment that the subject performed the correct coordination pattern. Ten different limb combinations were administered in a pseudorandom order with each possible combination occurring 3 times, resulting in a block of 30 trials. For each trial, the choice reaction time was obtained by calculating the time interval between the onset of the visual stimulus and the time at which the subject performed the correct coordination pattern. Only the condition in which participants had to lift both hands simultaneously is reported here (Fig. 1A). The dependent variable was the average of the reaction times during the 3 trials of this bimanual condition. Programming and presentation of the task was done using LabView 8.5 (National Instruments, Austin, Texas, USA).

Bimanual visuomotor task

The bimanual visuomotor task is a highly versatile computerized version of the ‘etch-a-sketch’ device (for earlier versions, see Preilowski (1972) and Mueller et al. (2009)). The task enables the evaluation of bimanual coordination accuracy, relying on online control of complex bimanual patterns. The protocol was based on previous studies employing this task in healthy young subjects (Gooijers et al. 2013; Sisti et al. 2011; Sisti et al. 2012). Participants were seated with both lower arms resting on two custom-made adjustable ramps. Direct vision of both hands and forearms was occluded by a horizontal table-top bench, placed over the forearms of the subject. At the end of the ramps, 8 cm below the plane of the ramp, a dial was mounted on a horizontal support consisting of a flat disc (diameter 5 cm) and a vertical peg. The dials could be rotated by holding each peg between the thumb and index finger (Fig. 1B). High precision shaft encoders were aligned with the axis of rotation of the dials to record angular displacement (Avago Technologies, 4096 pulses per revolution, accuracy = $.089^\circ$). Programming and presentation of this task was done using LabView 8.5.

Each trial started with the presentation of a single blue target line with a distinct orientation. At the origin of this line, in the center of the display, a white target dot was presented for 2 seconds, after which it began to move along the target line, towards the peripheral endpoint. The target dot moved at a constant rate and for a total duration of 10 seconds, representing a distance of 162 arbitrary units. Participants were instructed to rotate both dials in order to track the white target dot. The two dials controlled movement of a red subject cursor, namely a dot with a 1 cm long tail, serving as online visual feedback of tracking performance. The gain per rotation of 360 degrees was set to 10 units. The left and right dial controlled the movement of the subject’s cursor along the vertical and horizontal axis, respectively. When the left hand dial was rotated to the right (clockwise), the cursor moved up; when turned to the left (counterclockwise), the cursor moved down. When the right hand dial was rotated to the right (clockwise), the cursor moved to the right; when rotated to the left (counterclockwise), the cursor moved to the left. An auditory stimulus was provided indicating the start and end of each trial. After each trial the screen turned black, regardless of the subject’s location on the screen, and the next target line would appear after an interval of 3 seconds. The goal of each trial was to match the red subject cursor with the white target dot in both space and time, keeping the deviation as small as possible. In other words, participants had to rotate the dials as accurately as possible, generating the correct direction and velocity.

To generate the correct direction, four coordination patterns were introduced: two in which the left and right dial moved in the same direction, either clockwise or counterclockwise, and two in which the left and right dial moved towards or away from each other. The coordination patterns had to be performed at different relative velocities of the hands (frequency ratios), represented by the precise slope (angle) of the target line. We included five frequency ratios (using the convention of referring to the left hand first, and the right hand second): 3:1, 2:1, 1:1, 1:2, 1:3. For example, a 3:1 frequency ratio indicated that the left hand moved three times faster than the right hand. The combination of

coordination patterns (4) and frequency ratios (5) resulted in 20 experimental target pathways (Fig. 1C).

Four blocks of 6 minutes with 3 minutes rest in between were administered. A block consisted of 24 target lines (all 20 distinctive target lines plus the 1:1 frequency ratio repeated in all 4 coordination patterns), presented in a pseudorandom order. Prior to data recording, participants were allowed to practice 12 lines, for a period of 3 minutes, to become familiar with the task variants.

The data were analyzed using both LabView 8.5 software and MATLAB R2008a. The x- and y-positions of the target dot and the subject cursor were sampled at 100Hz. Target deviation per trial was calculated as a measure of accuracy, using the following multistep procedure: (a) Every 10 msec, the difference between the target position and the subject position (d) was calculated, using the Euclidean distance:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$$

where x_2 and y_2 refer to the position of the subject's cursor on the x- and y- axis, respectively, and x_1 and y_1 correspond to the position of the target dot on the x- and y-axis, respectively. (b) At the end of each trial, the average of these distances was computed and defined as the trial's target deviation, expressed in units. A target deviation equal to 0 units would indicate that during the whole trial, the subject cursor was precisely on top of the target dot, representing a perfect performance. Accordingly, larger target deviation scores reflect poorer performance. Based on our previous work, we distinguished between the average target deviation of the trials with isofrequency ratios, with both hands moving at equal speeds (1:1 ratio), and of the trials with non-isofrequency ratios, requiring one hand to move faster than the other (3:1, 2:1, 1:2 and 1:3 ratios).

Image acquisition

Imaging data were acquired on a Siemens 3T Magnetom Trio magnetic resonance imaging (MRI) scanner (Siemens, Erlangen, Germany) with a 12-channel matrix head coil, using a diffusion tensor imaging single-shot spin-echo sequence (repetition time = 10700 msec; echo time = 82 msec; matrix = 96×96 ; $2.2 \times 2.2 \times 2.2$ mm³ voxels; 60 axial slices). Diffusion sensitizing gradients were applied at a b-value of 1000 seconds/mm², along 64 noncollinear directions. One b0 image with no diffusion weighting was acquired.

A 3D magnetization prepared rapid gradient echo (MPRAGE) high resolution T1-weighted structural image (repetition time = 2300 msec; echo time = 2.98 msec; $1 \times 1 \times 1.1$ mm³ voxels; field of view = 240×256 mm²; 160 sagittal slices) was acquired to check for possible abnormalities in gray matter.

Processing

DTI data were analyzed and processed with the same multi-step procedure as employed previously (Caeyenberghs et al. 2011; Gooijers et al. 2013; Sisti et al. 2012): (a) The raw diffusion weighted data and the non-diffusion weighted image were loaded into ExploreDTI (Leemans et al. 2009) and we looped through the separate diffusion weighted imaging volumes 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 (examples shown in Fig. 2A – 2E) to check for any artifacts. Finally, we checked the residual map (as shown in Fig. 2F), reflecting the difference between the modeled and the measured signal (Tournier et al. 2011). With such a residuals map one can detect artifacts that are not always visible on the FA map or on the individual diffusion-weighted images. The 33 young and 33 older subjects included in this study showed sufficiently satisfactory DTI data quality for further analysis. (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. (c) We re-inspected 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 tensor model was fitted to the data using the Levenberg–Marquardt non-linear regression method (Marquardt 1963). The diffusion measures FA, AD and RD were subsequently calculated as described previously by Basser and Pierpaoli (1996). FA values range from 0 to 1, where 0 represents maximal isotropic diffusion (i.e., equal amount of diffusion in all directions), or lack of directional organization, and 1 represents maximal anisotropic diffusion (i.e., only movement parallel to the major axis of a white matter tract), and higher values reflecting ‘more’ organized tissues such as in white matter tracts. AD (the first eigenvalue) represents the diffusivity along the first eigenvector, which is assumed to lie parallel with the fiber pathways. RD (average of the second and third eigenvalues) assesses diffusion perpendicular to the main diffusion direction. Values of AD and RD are always positive, with the AD larger than the RD (for regions with $FA > 0$). (e) DTI data were transformed to MNI space to maximize uniformity in terms of inter-subject brain angulation. In doing so, the subregions of the CC in the subsequent fiber tractography analysis can be defined in a standardized way. An affine, and, subsequently, a high-dimensional non-affine DTI-based co-registration technique were applied to obtain the final DTI data sets in MNI space (Leemans et al. 2005; Van Hecke et al. 2007). In the non-

affine co-registration approach, the images are modeled as a viscous fluid, imposing a constraint on the local deformation field. During normalization, the Jacobian is constrained to reduce the chance of forcing the underlying brain structures in an anatomically non-plausible way. This viscous fluid model was optimized for aligning multiple diffusion tensor components and has been applied successfully in a wide range of applications, where adjusting for morphological inter-subject (and inter-group) differences is considered to be of paramount importance, including work on aging (Hsu et al. 2010; Sage et al. 2009; Van Hecke et al. 2010; Verhoeven et al. 2010). Based on a recently developed simulation framework, the non-affine DTI-based co-registration method, in particular, has been shown to provide highly accurate registration results (Van Hecke et al. 2009).

Fiber tractography

For each individual dataset, estimates of axonal projections of the CC were reconstructed using a deterministic streamline fiber tractography approach (Basser et al. 2000). Fiber pathways were reconstructed by defining seed points distributed uniformly throughout the data at 3 mm isotropic resolution and by following the main diffusion direction (as defined by the principal eigenvector) until the fiber tract entered a voxel with $FA < 0.15$ or made a high angular turn (angle $> 40^\circ$), considered to be not anatomically plausible. The step size was set at 1 mm. The fiber tractography was performed within ExploreDTI (Leemans et al. 2009).

Parcellation of the CC

We arrived at a parcellation of the CC by introducing subdivisions on the midsagittal plane according to the recently described paradigms by Hofer and Frahm (2006) and Huang et al. (2005). The subdivisions were manually defined on color-coded maps of the main diffusion direction within ExploreDTI (Leemans et al. 2009) by the same operator, who was blinded to the group status of the subjects and the findings of the behavioral tests, and according to a priori determined rules that were followed carefully and consistently for each subject (Catani and Thiebaut de Schotten 2008). A geometric partitioning scheme was used to define 7 callosal subregions based on specific arithmetic fractions of the maximum anterior and posterior points of the CC in the midsagittal plane, containing fibers projecting into prefrontal, premotor (and supplementary motor), primary motor, and primary sensory areas as well as into parietal, temporal, and occipital cortical areas.

Definition of the subregions of the CC

CC1 was the most anterior segment covering the first sixth of the CC and containing fibers projecting into the prefrontal cortices. CC2 comprised the remainder of the anterior half of the CC, containing fibers projecting to the premotor (and supplementary motor) cortices. CC3 was defined as the

posterior half minus the posterior third, comprising fibers projecting into the primary motor cortex. CC4, representing the posterior one third minus posterior one fourth, referred to primary sensory fibers. The remaining part of the posterior half of the CC, the splenium, was further divided according to Huang's scheme (2005) based on the fact that, unlike other segments, the splenium is occupied by 3 different populations of fibers that connect three different lobes of the brain. These included fibers connecting the parietal lobes (CC5), temporal lobes (CC6), and occipital lobes (CC7). The parietal subregion occupied 16% of the total CC, the temporal subregion 10% and the occipital subregion 6%. The resulting CC parcellations are shown in figure 3A.

Extraction of diffusion information

In anatomical regions containing multiple fiber orientations, increased microstructural coherence of an individual fiber population can result in a decrease in the overall FA of that region (Basser and Pierpaoli 1996; Tournier et al. 2011; Wiegell et al. 2000). Fibers diverging from the CC and projecting into different cortical areas, cross multiple other major pathways, e.g., superior longitudinal fasciculus, corticospinal tract, corona radiata, and intralobular association fibers (Jeurissen et al. 2012; Vos et al. 2012). Because of these multiple crossings of fibers diverging from the CC, fiber tracking algorithms estimating the continuation of these tracts can fail (Dougherty et al. 2005; Jarbo et al. 2012; Lebel et al. 2010; Wedeen et al. 2008). In the midsagittal part of the CC however, a single and well-defined orientation may be assumed. Therefore, we obtained mean values of FA, AD and RD from the midsagittal segments only, rather than from the entire CC pathways, thereby trying to avoid data contamination originating from crossing fiber areas (or, more generally, partial volume effects), and fulfilling the assumption of the second-rank diffusion tensor model. The boundaries of these segments were defined at 1 cm bilaterally from the midsagittal plane, as shown in figure 3B. Using the fiber tractography approach, we could take full advantage of the orientation information that is captured in the diffusion data to derive the FA, AD and RD values (Cercignani 2010). In other words, we verified that the reconstructed trajectories corresponded with the expected pathway configuration of the CC architecture in that region.

In summary, even though some recent studies have successfully tracked interhemispheric connections between homotopic sensorimotor areas, the current technique has the advantage that white matter microstructural organization of all CC subdivisions can be studied and that the problem of multiple fiber crossing is largely overcome. We believe these advantages weigh up to the potential limitations associated with a predefined geometrical subdivision and that progress in this field can be made by applying different approaches.

Statistical analysis

Unless otherwise stated, statistical analyses were done with the Statistical Package for the Social Sciences, version 19 (SPSS for Windows, 2010). An *alpha* level of 0.05 was used for statistical tests, where applicable correction for multiple comparisons was taken into account by adjusting the *alpha* level based on the number of comparisons according to the Bonferroni correction procedure (Olejnik et al. 1997). Only results surviving Bonferroni correction, i.e. remaining significant at $p < \text{adjusted } \alpha$ level, are reported.

Although all the tasks were used as indicators of bimanual motor functioning, the different tasks emphasize partly different sensorimotor functions. Therefore, we expected subjects to show variation in performance across the tests. To ensure that the tasks yield different aspects of bimanual behavior, we conducted correlation analyses within both groups to explore the relationships between measures.

Next, for the outcome measures of the Purdue Pegboard Test and the choice reaction time test, two-sample *t*-tests were performed comparing the YA with the OA group. Finger tapping scores on the simultaneous and alternating finger tapping task were subjected to a mixed model repeated measures analysis of variance (ANOVA) with between-subjects factor ‘group’ (YA versus OA) and the within-subjects factor ‘tapping condition’ (simultaneous versus alternating finger tapping). A mixed model repeated measures ANOVA was also conducted on the target deviation scores of the bimanual visuomotor task to test for effects of group (between-subjects factor: YA versus OA) and frequency ratio (within-subjects factor: isofrequency ratios (ISO) versus non-isofrequency ratios (N-ISO)).

Subsequently, a multivariate approach to mixed model repeated measures ANOVA was used to estimate microstructural differences among the 7 CC subregions. The between subjects factor was group, enabling the comparison of YA versus OA, and the within subjects factor was CC subregion with 7 levels. In addition, post-hoc planned comparisons were performed to examine between and within group differences using independent and paired *t*-tests respectively. The dependent variables were FA, AD and RD.

Finally, Pearson correlation coefficients were used in both groups to investigate the relations between the FA values of the 7 CC subregions, as a measure of white matter microstructure, and the different bimanual motor scores. Based on the results from previous DTI studies linking microstructural properties of the CC with bimanual performance, as described in the introduction, we expected higher FA values to be related to higher performance levels, and therefore applied directional, one-tailed Pearson correlation tests. For all significant relationships, we applied a Fisher *r*-to-*Z* transformation to compare the strength of correlations between age groups using Statistica, version 10 (StatSoft Inc., 2011).

Results

Bimanual motor behavior

Based on inspection of the z-scores, no outliers were found for the Purdue Pegboard Test. For the finger tapping test, 1.51% (YA) and 3.03% (OA) of the data points was considered as outliers and removed from the analysis. For the choice reaction time test this was 3.03% (YA) and 6.06% (OA), for the visuomotor task 1.04% (YA) and 2.11% (OA). When a subject was excluded from a behavioral task, he/she was also excluded from the correlational analyses of that task with the DTI metrics. For the analyses comprising only DTI metrics, the entire sample was included.

Correlation analyses were conducted to explore the relations between the different measures of bimanual performance. Within the young adults group, the correlation coefficients between the different measures (except for those that are variations of a single task) varied between .0 and .57; within the older adults group between .13 and .52. Not surprisingly, these results suggest that some variation in performance is shared across the tasks since the bimanual aspect is evident in all of them. However, a considerable amount of variance is also unique, and this justifies considering them as partially distinct variables. An overview of the correlation analyses within both groups can be found in Online Resource 1.

Older adults performed significantly worse on all measures of bimanual motor behavior relative to the young adults. For the Purdue Pegboard Test, YA manipulated significantly ($t(63) = 7.750, p < 0.001$) more pegs (12.35 ± 0.25) than OA (9.59 ± 0.25). For the finger tapping test (Fig. 4A), we observed significant main effects of the tapping condition ($F(1,59) = 98.71, p < 0.001$), with more taps during simultaneous finger tapping ($93.45 \text{ taps} \pm 1.97$) than during alternating finger tapping ($73.23 \text{ taps} \pm 1.88$), and of group ($F(1,59) = 60.28, p < 0.001$), with YA performing more taps ($96.03 \text{ taps} \pm 2.29$) than OA ($70.65 \text{ taps} \pm 2.33$). Moreover, there was a significant interaction between condition and group ($F(1,59) = 11.395, p < 0.001$), indicating that the older adults performed disproportionately worse on the alternating versus the simultaneous finger tapping when compared to the young adults. Also on the choice reaction time test, the YA ($657.50 \text{ msec} \pm 20.62$) outperformed the OA ($1072.59 \text{ msec} \pm 65.41$) significantly ($t(33.521) = -6.053, p < 0.001$). Furthermore, mixed model repeated measures ANOVA on the data of the bimanual visuomotor task (Fig. 4B) revealed a main effect of group ($F(1,64) = 63.153, p < 0.001$), indicating that the YA had lower target deviations ($12.49 \text{ units} \pm 0.94$) during this task (indicative of better performance) than the OA ($30.64 \text{ units} \pm 1.43$). In addition, there was a main effect of frequency ratio ($F(1,64) = 81.807, p < 0.001$), with better performance during isofrequency ratios (target deviation = $18.98 \text{ units} \pm 1.13$) than during non-isofrequency ratios ($24.15 \text{ units} \pm 1.23$). There was no significant interaction effect between group and frequency ratio ($F(1,64) = 1.548, \text{ ns}$).

Diffusion Tensor Imaging

DTI measurements of the 7 subregions of the CC are summarized in figure 5.

Repeated-measures ANOVA revealed that FA differed among the 7 CC subregions (main effect of subregion, $F(6,384) = 99.183, p < 0.001$). Post hoc t -tests showed significantly higher FA values in the CC parietal and occipital regions compared to all other subregions within both the YA and the OA group (all p -values < 0.001). There was no significant main effect of group on FA ($F(1,64) = 1.075, ns$). However, a significant group \times subregion interaction was found ($F(6,384) = 8.064, p < 0.001$). Post hoc t -tests revealed that YA had significantly higher FA values compared to OA in the CC prefrontal region ($p < 0.001$). Additionally, in the CC primary motor region, YA showed significantly lower FA values than OA ($p < 0.001$).

The AD, representing diffusivity along the principal diffusion direction, showed main effects of subregion ($F(6,384) = 168.783, p < 0.001$) and group ($F(1,64) = 5.282, p < 0.05$). For both groups, the lowest AD values were observed in the CC prefrontal, parietal and occipital regions. Specifically, the AD of the CC occipital region was significantly lower than in all other subregions in the YA group, and in all other subregions except for the prefrontal subregion in the OA group (all p -values < 0.001). The AD was significantly elevated in the OA group compared to the YA group in the CC temporal ($p < 0.01$) and occipital ($p < 0.01$) region (interaction group \times subregion, $F(6,384) = 3.307, p < 0.01$).

The RD, a measure of diffusivity perpendicular to the main fiber orientation, also showed a main effect of subregion ($F(6,384) = 138.636, p < 0.001$). RD values were significantly lower in the parietal and occipital subregions compared to the other subregions in both groups (all p -values < 0.001). Furthermore, the RD was significantly higher in OA compared to YA (main effect of group, $F(1,64) = 4.370, p < 0.05$), but this effect varied with subregion (group \times subregion interaction, $F(6,384) = 8.499, p < 0.001$). Post hoc t -tests revealed that RD was significantly elevated in the OA versus the YA group in the CC prefrontal ($p < 0.001$) and temporal ($p < 0.01$) region, whereas YA showed elevated RD compared to OA in the CC primary motor region ($p < 0.001$). Consequently, it appears that the group differences in FA were primarily driven by the radial diffusivities.

Relations between microstructural organization of the corpus callosum and bimanual motor behavior

We performed Pearson correlation analyses within both groups to explore age-related associations between the FA values of the 7 CC substructures and performance on the different bimanual tests. An overview of the correlation analyses is shown in table 1.

Within the YA group, FA of the CC primary sensory region correlated with performance on both the ISO and the more difficult N-ISO frequency ratios of the visuomotor task (ISO: $r = -.48, p < 0.01$; N-ISO: $r = -.45, p < 0.01$). In other words, higher FA was associated with lower target

deviations, indicative of a better tracking performance. No other significant correlations were found within the YA group.

Within the OA group, a number of significant correlations were found as shown in figures 6A – 6F. FA of the CC occipital region was associated with performance on the Purdue Pegboard Test ($r = .44$; $p < 0.014$), indicating that better fine bimanual manipulative dexterity is associated with higher FA values within the CC occipital region. Next, the outcome variable of the simultaneous finger tapping task showed a significant relation with FA of the CC premotor region ($r = .45$; $p < 0.014$). Hence, the number of performed finger taps with left and right index finger simultaneously was associated with higher white matter anisotropy in this subregion. FA values of the CC premotor ($r = -.65$; $p < 0.001$) and the primary sensory ($r = -.47$; $p = 0.01$) region were also significantly correlated with performance on the choice reaction time test. In other words, higher FA values in these subregions were associated with faster movements of the hands in reaction to a visual stimulus. Finally, FA of the CC primary motor region was related to performance on both the ISO and N-ISO frequency ratios of the visuomotor task (ISO: $r = -.47$; $p < 0.01$; N-ISO: $r = -.50$; $p < 0.01$).

None of the significant brain-behavior relationships in the older adults were found in the young adults group, and vice versa. Comparing the strength of the correlations between age groups using Fisher r -to- Z transformation further showed significantly different correlation strengths in older and younger adults for the correlations between FA values of CC premotor region and performance on the simultaneous finger tapping task ($p < 0.05$), and performance on the choice reaction time task ($p < 0.01$).

Discussion

In the present study, we used a set of tasks associated with bimanual motor behavior, tapping a range of sensorimotor functions. By subdividing the CC into 7 functionally distinct subregions, we subsequently provided a comprehensive view on location of age-related differences in CC microstructural properties. Finally, relationships between measures of microstructural organization of the CC subregions (FA values) and performance on the different tasks were investigated and age-related correlation differences were assessed. Our results indicated that microstructural variation in particular subregions of the CC is associated with specific bimanual deficits in older adults.

Group differences in bimanual motor behavior

As expected, older adults showed compromised bimanual fine manipulation (Purdue Pegboard Test) and finger tapping speed, compared to the younger adults. Additionally, older adults showed longer reaction times on the choice reaction time test compared to the younger adults, indicating declines in response selection, preparation and generation speed. Finally, older adults showed large deficits in performance on the visuomotor task, with a group average target deviation more than twice as high as in the young adults group. This is consistent with previous literature, showing large age-related performance differences during complex bimanual coordination tasks requiring effortful processing (Bangert et al. 2010; Fling et al. 2011b; Serrien et al. 2000; Summers et al. 2010; Wishart et al. 2000). In accordance with previous studies using the visuomotor task in a young adult sample (Gooijers et al. 2013; Sisti et al. 2011; Sisti et al. 2012), both groups performed worse on the non-isofrequency ratios compared to the isofrequency ratios. No significant interaction between group and frequency ratio was found, indicating that the intergroup difference in performance was similar during both frequency ratio conditions. This implies that adding extra temporal constraints (i.e., non-isofrequency versus isofrequency ratios), did not further magnify the age-related differences in performance.

Group differences in diffusion tensor imaging

Consistent with previous literature, CC parietal and occipital regions showed highest FA values as compared to the other CC subregions within both the young and the older adults group (Caeyenberghs et al. 2011; Chepuri et al. 2002; Gooijers et al. 2013; Hofer and Frahm 2006; Ota et al. 2006).

Our comparison of quantitative fiber tracking measures between the young and older group further revealed lower FA values in the CC prefrontal region in the older adults, whereas differences in the more posterior primary sensory, parietal, temporal and occipital regions of the CC were not significant. Across many studies employing DTI to explore age-related changes in microstructural organization, a general trend has been found towards an anterior to posterior gradient of degradation, as aging is associated with decreased FA in the frontal regions of the brain, including the genu of the

CC, whereas this decline is less pronounced in posterior white matter, including the splenium (Abe et al. 2002; Bennett et al. 2010; Bhagat and Beaulieu 2004; Burzynska et al. 2010; Camara et al. 2007; Coxon et al. 2012; Davis et al. 2009; Hofer and Frahm 2006; Hugenschmidt et al. 2008; Madden et al. 2012; Ota et al. 2006; Raz and Rodrigue 2006; Salat et al. 2005; Sisti et al. 2012; Sullivan et al. 2006; Sullivan and Pfefferbaum 2006; Voineskos et al. 2012; Zahr et al. 2009). Accordingly, our data fit well with the existing literature. Age-related differences in AD and RD did not appear to follow the same pattern of selective vulnerability of anterior CC fibers to normal aging, as additionally to age-related elevations in RD in the CC prefrontal region, pronounced elevations in diffusivity were found in the posterior CC temporal (AD and RD) and occipital (AD) regions as well.

An unexpected finding was that FA in the CC primary motor region was higher in older adults compared to the young adults, which seemed to be primarily driven by the lower RD in this subregion in the older adults. Age-related increases in FA in different white matter regions have previously been reported (Hsu et al. 2010; Inano et al. 2011). However, to the best of our knowledge, this is the first study reporting this counterintuitive difference in the CC primary motor region. In view of the (a) obtained findings in other CC substructures (anterior and posterior to the motor CC) that are consistent with previous work, (b) the detailed quality control of the data, and (c) the relatively large size of our subject pool compared to related literature, we seriously doubt that this deviant finding reflects a mere flaw in data processing or sampling error. Determining the etiology of our results calls for replication and further investigation. Nevertheless, some speculative arguments are discussed next. Looking at FA evolution of the CC over the entire lifespan, Lebel et al. (2012) previously found that the FA peak for the body of the CC -likely to include the CC primary motor region in this study- occurred at around the age of 35 years. The reported increases in FA were driven by decreases in RD, which is presumably indicative of age-related fiber myelination (Janve et al. 2013; Song et al. 2002; Song et al. 2005; Sun et al. 2007; Sun et al. 2006). Using light microscopic examination, Aboitiz et al. (2003; 1992) previously revealed that in the posterior midbody, the highest number of highly myelinated large-diameter fibers in the CC is found, possibly explaining the late FA peak in the body of the CC as described by Lebel et al. (2012). Findings on FA changes at higher ages in the body of the CC have been inconsistent. Some studies report decreases at higher ages (Hasan et al. 2008; Hsu et al. 2010), whereas others report relatively stable FA values (Burzynska et al. 2010; McLaughlin et al. 2007; Michielse et al. 2010; Ota et al. 2006). A closer inspection of the FA values of the CC primary motor region within the older adult group of the current study showed no correlation between age and FA ($r = -.01$, ns), indicating that FA values remained stable after the age of 60. Based on the results of Lebel et al. (2012), it is plausible that the young adults, included in the current study, did not yet reach their FA peak in the CC primary motor region, thereby demonstrating lower FA values as compared to the older adults. In turn, the older adults may have reached their FA peak around midlife and remained relatively stable thereafter. Taken together, the age-related differences in FA in the CC prefrontal

region and in the CC primary motor regions of the current study may possibly be explained in light of changes in CC microstructure across the human lifespan.

Microstructural organization of the corpus callosum and bimanual motor behavior

We explored the relations between DTI-derived FA values of the 7 CC subregions, as a measure of white matter microstructure, and performance on bimanual motor tasks relying on different sensorimotor functions. Applying correlation analyses within the young adults group, we found that higher FA values of the CC primary sensory region were associated with better tracking performance during the isofrequency and non-isofrequency ratios of the visuomotor task. The remaining correlations did not reach significance in this group. Within the older adults group, several correlations were significant. Performance on the Purdue Pegboard Test was associated with FA values of the CC occipital subregion, whereas the other bimanual motor behavior scores correlated with more anterior CC subregions. These relations are discussed in more detail below.

First, whereas Sullivan et al. (2010) and Voineskos et al. (2012) previously found no correlations between unimanual fine finger movement scores and callosal microstructural organization in samples spanning the adult age range, we found a relation between bimanual Purdue Pegboard Test performance and FA in the CC occipital subregion of the older adults. The fibers running through this region are responsible for information transfer between the occipital areas, which are involved in processing of visual information. Noteworthy, the Purdue Pegboard Test was the only task for which a relation with these fibers was found. This may appear somewhat unexpected at first sight, but several potential accounts can be put forward. First, during the execution of the Purdue Pegboard Test, accurate visually-guided movements of the fingers are required under temporal pressure. The pegs precisely fit in the peg holes, leaving no room for error. Moreover, subjects are instructed to exactly synchronize the placement of each pair of pegs in the provided holes. Because of these restrictions, constant on-line monitoring and updating of the different task elements (e.g. the hands, pegs and peg holes) in both visual hemifields is crucial. This probably accounts for the need to transfer information through interconnecting occipital pathways. In the other bimanual motor tasks employed in the present study, this constant fast on-line exchange of visual information might have been less determining for performance. Second, lower FA within the occipital regions of the CC has previously been found to be uniquely related to deficits on the bimanual Purdue Pegboard Test in traumatic brain injury patients (Caeyenberghs et al. 2011). As both elderly and traumatic brain injury patients undergo changes in brain white matter microstructure constraining function, it is not surprising that similar brain-behavior relations are found in both populations.

Next, better performance on the simultaneous finger tapping task was associated with higher FA in the premotor subregion. Fling et al. (2011b) previously found no relations between CC microstructure and performance during a paced simultaneous finger tapping task in which outcome

scores were based on the standard deviation of the imposed 0 msec between-hand lag, with higher scores representing less accuracy. Our finger tapping task assessed in-phase bimanual motor speed whereby participants were instructed to tap as fast as possible. Performance on this task (i.e., the number of taps) was related to microstructural organization of the CC fibers connecting premotor areas.

Further, higher FA values of the premotor and the primary sensory subregion were related to better performance on the choice reaction time test. FA of these CC subregions has previously been linked to upper limb motor outcome in patients suffering from hand motor deficits after subcortical stroke (Wang et al. 2012). Impaired motor response selection has previously been found in healthy subjects undergoing transcranial magnetic stimulation applied to disrupt processing in the lateral premotor cortex (Schluter et al. 1998). Halsband and Lange (2006) suggested that the coding of the association between visuo-spatial information and motor commands can primarily be attributed to the lateral premotor cortex. Picard and Strick (2001) have further shown that the rostral part of the lateral premotor cortex is primarily active during the presentation of external cues, whereas the caudal part plays a role during movement preparation or generation. Involvement of the premotor cortex in choice reaction time tasks has thus previously been demonstrated. Whereas Madden et al. (2004) found no relations between performance on a unimanual choice reaction time task and callosal FA values in older adults, we now found that, for a bimanual version of this task, FA of the premotor and primary sensory subregions of the CC is associated with performance in older adults.

Finally, performance on the computerized visuomotor task was correlated with FA of the primary motor subregion, which equally applied to the isofrequency and the more difficult non-isofrequency ratios. Electroencephalography studies have previously shown that bimanual coordination of skilled finger movements requires an intense interaction between the motor areas of both cerebral hemispheres (Gerloff and Andres 2002). The fibers of the CC primary motor region connect these motor areas, which support the execution of bimanual movements (Swinnen and Wenderoth 2004), and serve as pathways for both facilitatory and inhibitory interactions (Bloom and Hynd 2005; Fling et al. 2011a; Goble et al. 2012; Stinear and Byblow 2002). Although the older adults showed higher FA values in the CC primary motor region as compared to the young adults, they performed worse on this task as a group, indicating that other processes are probably more determining for this age-related performance decline than microstructural changes in the CC. However, the clear relation between FA values in the CC primary motor region and performance within the older adults indicates that lower FA values in this subregion may be related to additional performance deterioration among the older adults.

None of the significant brain-behavior relationships in the older adults were found in the young adults group, and vice versa. Furthermore, correlations between FA values of the CC premotor region and performance on the simultaneous finger tapping task in older and younger adults were

found to differ significantly from each other, indicating explicit age-related differences in the relations between these DTI and performance measures.

Some limitations in our current study must be acknowledged. DTI offers a quantitative method to reduce anatomical information to a tensor and then to a scalar value. However, this implies that, when differences are found in one of these scalar metrics, it is difficult to draw any conclusions about the exact causes at the cellular level (Tournier et al. 2011). FA for example is rather unspecific and can be modulated by changes in myelination, axon density, axon diameter and the layout of the axons within the image (Chepuri et al. 2002). Furthermore, other currently available MRI sequences have improved the detection of white matter damage in older adults, such as T2-weighted imaging and fluid attenuated inversion recovery (FLAIR) scans (for a review, see Gunning-Dixon et al. 2009). Because T2 and FLAIR scans are much more sensitive in detecting white matter hyperintensities, more accurate data can be obtained to objectively assess white matter deterioration in the older adults group. The extent of detected white matter damage can provide long-term neurological and behavioral prognostic information. Additional studies correlating the abnormalities seen on FLAIR with DTI metrics need to be done to better define the neuroimaging correlates of motor performance declines in older adults. Finally, the cross-sectional design used in this study only enabled us to investigate age-related differences in bimanual motor behavior and in microstructural organization of the CC. Individual changes herein over time could not be explored with this design.

Conclusion

We subdivided the CC into 7 functionally distinct regions in both young and older adults and correlated DTI metrics with performance on an expanded set of bimanual tasks. Older adults showed significant bimanual motor deficits on all tasks as compared to young adults. Microstructural organization of several CC subregions showed significant correlations with bimanual performance, particularly in the older adults. More specifically, deficits in bimanual finger manipulation skills, highly depending on on-line visual processing, were associated with white matter FA in the CC occipital subregion in the older adults. The remaining bimanual skills were related to FA of the more anterior premotor, primary motor and primary sensory CC subregions. Understanding these brain-behavior relationships advances our current knowledge on normal brain aging, and may help to identify structural imaging biomarkers of aging that may ultimately serve to provide a foundation for the development of interventions designed to maintain functional independence during aging.

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Disclosure statement for authors

The authors declare that they have no conflict of interest. Participants were informed about the experimental procedures and provided written informed consent. The study was approved by the local Ethics Committee of KU Leuven and was performed in accordance with the 1964 Declaration of Helsinki.

References

- Abe O, Aoki S, Hayashi N, Yamada H, Kunimatsu A, Mori H, Yoshikawa T, Okubo T, Ohtomo K (2002) Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. *Neurobiol Aging* 23(3):433-441
- Aboitiz F, Montiel J (2003) One hundred million years of interhemispheric communication: the history of the corpus callosum. *Braz J Med Biol Res* 36(4):409-420
- Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992) Fiber composition of the human corpus callosum. *Brain Res* 598(1-2):143-153
- Adamo DE, Martin BJ, Brown SH (2007) Age-related differences in upper limb proprioceptive acuity. *Percept Mot Skills* 104(3 Pt 2):1297-1309
- Anstey KJ, Mack HA, Christensen H, Li SC, Reglade-Meslin C, Maller J, Kumar R, Dear K, Eastaer S, Sachdev P (2007) Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia* 45(8):1911-1920
- Bangert AS, Reuter-Lorenz PA, Walsh CM, Schachter AB, Seidler RD (2010) Bimanual coordination and aging: neurobehavioral implications. *Neuropsychologia* 48(4):1165-1170
- Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A (2000) In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine* 44(4):625-632
- Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 111(3):209-219
- Beaulieu C, Allen PS (1994) Determinants of anisotropic water diffusion in nerves. *Magn Reson Med* 31(4):394-400
- Bennett IJ, Madden DJ, Vaidya CJ, Howard DV, Howard JH, Jr. (2010) Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. *Human Brain Mapping* 31(3):378-390
- Berlucchi G (2012) Frontal callosal disconnection syndromes. *Cortex* 48(1):36-45
- Bernard JA, Seidler RD (2012) Hand Dominance and Age Have Interactive Effects on Motor Cortical Representations. *PLoS One* 7(9)
- Bhagat YA, Beaulieu C (2004) Diffusion anisotropy in subcortical white matter and cortical gray matter: changes with aging and the role of CSF-suppression. *J Magn Reson Imaging* 20(2):216-227
- Bloom JS, Hynd GW (2005) The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychol Rev* 15(2):59-71
- Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M (2008) Callosal contributions to simultaneous bimanual finger movements. *J Neurosci* 28(12):3227-3233
- Buddenberg LA, Davis C (2000) Test-retest reliability of the Purdue Pegboard Test. *Am J Occup Ther* 54(5):555-558

- Burzynska AZ, Preuschhof C, Backman L, Nyberg L, Li SC, Lindenberger U, Heekeren HR (2010) Age-related differences in white matter microstructure: region-specific patterns of diffusivity. *Neuroimage* 49(3):2104-2112
- Caeyenberghs K, Leemans A, Coxon J, Leunissen I, Drijkoningen D, Geurts M, Gooijers J, Michiels K, Sunaert S, Swinnen SP (2011) Bimanual coordination and corpus callosum microstructure in young adults with traumatic brain injury: a diffusion tensor imaging study. *J Neurotrauma* 28(6):897-913
- Camara E, Bodammer N, Rodriguez-Fornells A, Tempelmann C (2007) Age-related water diffusion changes in human brain: a voxel-based approach. *Neuroimage* 34(4):1588-1599
- Catani M, Thiebaut de Schotten M (2008) A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex* 44(8):1105-1132
- Cercignani M (2010) Strategies for Patient–Control Comparison of Diffusion MR Data. In: Jones DK, editor *Diffusion MRI*. Oxford University Press, pp 485-499.
- Chepuri NB, Yen YF, Burdette JH, Li H, Moody DM, Maldjian JA (2002) Diffusion anisotropy in the corpus callosum. *AJNR Am J Neuroradiol* 23(5):803-808
- Cole KJ, Rotella DL (2001) Old age affects fingertip forces when restraining an unpredictably loaded object. *Experimental Brain Research* 136(4):535-542
- Coxon JP, Van Impe A, Wenderoth N, Swinnen SP (2012) Aging and inhibitory control of action: cortico-subthalamic connection strength predicts stopping performance. *J Neurosci* 32(24):8401-8412
- Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R (2009) Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage* 46(2):530-541
- Desrosiers J, Hebert R, Bravo G, Dutil E (1995) The Purdue Pegboard Test: normative data for people aged 60 and over. *Disabil Rehabil* 17(5):217-224
- Desrosiers J, Hebert R, Bravo G, Rochette A (1999) Age-related changes in upper extremity performance of elderly people: a longitudinal study. *Exp Gerontol* 34(3):393-405
- Doherty TJ (2003) Aging and sarcopenia. *Journal of Applied Physiology* 95(4):1717-1727
- Dougherty RF, Ben-Shachar M, Bammer R, Brewer AA, Wandell BA (2005) Functional organization of human occipital-callosal fiber tracts. *Proceedings of the National Academy of Sciences of the United States of America* 102(20):7350-7355
- Fling BW, Peltier SJ, Bo J, Welsh RC, Seidler RD (2011a) Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Front Neurosci* 5:38
- Fling BW, Seidler RD (2012) Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. *Cereb Cortex* 22(11):2643-2652

- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD (2011b) Differential callosal contributions to bimanual control in young and older adults. *J Cogn Neurosci* 23(9):2171-2185
- Gazzaniga MS (2005) Forty-five years of split-brain research and still going strong. *Nature Reviews Neuroscience* 6(8):653-659
- Gerloff C, Andres FG (2002) Bimanual coordination and interhemispheric interaction. *Acta Psychologica* 110(2-3):161-186
- Goble DJ, Coxon JP, Van Impe A, Geurts M, Van Hecke W, Sunaert S, Wenderoth N, Swinnen SP (2012) The neural basis of central proprioceptive processing in older versus younger adults: an important sensory role for right putamen. *Human Brain Mapping* 33(4):895-908
- Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP (2009) Proprioceptive sensibility in the elderly: Degeneration, functional consequences and plastic-adaptive processes. *Neuroscience and Biobehavioral Reviews* 33(3):271-278
- Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tyllavsky FA, Visser M, Newman AB (2006) The loss of skeletal muscle strength, mass, and quality in older adults: The health, aging and body composition study. *Journals of Gerontology Series a-Biological Sciences and Medical Sciences* 61(10):1059-1064
- Gooijers J, Caeyenberghs K, Sisti HM, Geurts M, Heitger MH, Leemans A, Swinnen SP (2013) Diffusion tensor imaging metrics of the corpus callosum in relation to bimanual coordination: Effect of task complexity and sensory feedback. *Human Brain Mapping* 34(1):241-252
- Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS (2009) Aging of cerebral white matter: a review of MRI findings. *Int J Geriatr Psychiatry* 24(2):109-117
- Hairi NN, Cumming RG, Naganathan V, Handelsman DJ, Le Couteur DG, Creasey H, Waite LM, Seibel MJ, Sambrook PN (2010) Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. *J Am Geriatr Soc* 58(11):2055-2062
- Halsband U, Lange RK (2006) Motor learning in man: a review of functional and clinical studies. *J Physiol Paris* 99(4-6):414-424
- Harris T (1997) Muscle mass and strength: relation to function in population studies. *J Nutr* 127(5 Suppl):1004S-1006S
- Hasan KM, Kamali A, Kramer LA, Papnicolaou AC, Fletcher JM, Ewing-Cobbs L (2008) Diffusion tensor quantification of the human midsagittal corpus callosum subdivisions across the lifespan. *Brain Res* 1227:52-67
- Hofer S, Frahm J (2006) Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32(3):989-994

- Hsu JL, Van Hecke W, Bai CH, Lee CH, Tsai YF, Chiu HC, Jaw FS, Hsu CY, Leu JG, Chen WH and others (2010) Microstructural white matter changes in normal aging: a diffusion tensor imaging study with higher-order polynomial regression models. *Neuroimage* 49(1):32-43
- Huang H, Zhang JY, Jiang HY, Wakana S, Poetscher L, Miller MI, van Zijl PCM, Hillis AE, Wytik R, Mori S (2005) DTI tractography based parcellation of white matter: Application to the mid-sagittal morphology of corpus callosum. *Neuroimage* 26(1):195-205
- Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, Laurienti PJ (2008) Relating imaging indices of white matter integrity and volume in healthy older adults. *Cereb Cortex* 18(2):433-442
- Inano S, Takao H, Hayashi N, Abe O, Ohtomo K (2011) Effects of Age and Gender on White Matter Integrity. *American Journal of Neuroradiology* 32(11):2103-2109
- Janve VA, Zu ZL, Yao SY, Li K, Zhang FL, Wilson KJ, Ou XW, Does MD, Subramaniam S, Gochberg DF (2013) The radial diffusivity and magnetization transfer pool size ratio are sensitive markers for demyelination in a rat model of type III multiple sclerosis (MS) lesions. *Neuroimage* 74:298-305
- Jarbo K, Verstynen T, Schneider W (2012) In vivo quantification of global connectivity in the human corpus callosum. *Neuroimage* 59(3):1988-1996
- Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J (2012) Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Human Brain Mapping*
- Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, Paus T (2007) Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36 Suppl 2:T16-21
- Klein S, Staring M, Murphy K, Viergever MA, Pluim JP (2010) elastix: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging* 29(1):196-205
- Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD (2010) Functional implications of age differences in motor system connectivity. *Front Syst Neurosci* 4:17
- Lebel C, Caverhill-Godkewitsch S, Beaulieu C (2010) Age-related regional variations of the corpus callosum identified by diffusion tensor tractography. *Neuroimage* 52(1):20-31
- Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C (2012) Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage* 60(1):340-352
- Leemans A, Jeurissen B, Sijbers J, Jones D (2009) ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: 17th Annual Meeting of Intl Soc Mag Reson Med. Hawaii, USA, pp 3537.
- Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med* 61(6):1336-1349

- Leemans A, Sijbers J, De Backer S, Vandervliet E, Parizel PM (2005) Affine coregistration of diffusion tensor magnetic resonance images using mutual information. *Advanced Concepts for Intelligent Vision Systems, Proceedings* 3708:523-530
- Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, Nickerson RJ, Pool J, Colton TL, Ganley JP and others (1980) The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Survey of Ophthalmology* 24(Suppl):335-610
- Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW (2012) Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochim Biophys Acta* 1822(3):386-400
- Madden DJ, Spaniol J, Costello MC, Bucur B, White LE, Cabeza R, Davis SW, Dennis NA, Provenzale JM, Huettel SA (2009) Cerebral White Matter Integrity Mediates Adult Age Differences in Cognitive Performance. *Journal of Cognitive Neuroscience* 21(2):289-302
- Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR, Provenzale JM (2004) Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage* 21(3):1174-1181
- Marneweck M, Loftus A, Hammond G (2011) Short-interval intracortical inhibition and manual dexterity in healthy aging. *Neurosci Res* 70(4):408-414
- Marquardt DW (1963) An Algorithm for Least-Squares Estimation of Nonlinear Parameters. *Journal of the Society for Industrial and Applied Mathematics* 11(2):431-441
- McLaughlin NC, Paul RH, Grieve SM, Williams LM, Laidlaw D, DiCarlo M, Clark CR, Whelihan W, Cohen RA, Whitford TJ and others (2007) Diffusion tensor imaging of the corpus callosum: a cross-sectional study across the lifespan. *Int J Dev Neurosci* 25(4):215-221
- Michielse S, Coupland N, Camicioli R, Carter R, Seres P, Sabino J, Malykhin N (2010) Selective effects of aging on brain white matter microstructure: a diffusion tensor imaging tractography study. *Neuroimage* 52(4):1190-1201
- Mueller KL, Marion SD, Paul LK, Brown WS (2009) Bimanual motor coordination in agenesis of the corpus callosum. *Behav Neurosci* 123(5):1000-1011
- Muetzel RL, Collins PF, Mueller BA, A MS, Lim KO, Luciana M (2008) The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents. *Neuroimage* 39(4):1918-1925
- Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53(4):695-699

- Njiokiktjien C, De Sonneville L, Hessels M, Kurgansky A, Vildavsky V, Vranken M (1997) Unimanual and bimanual simultaneous fingertapping in schoolchildren: developmental aspects and hand preference-related asymmetries. *Laterality* 2(2):117-135
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1):97-113
- Olejnik S, Li JM, Supattathum S, Huberty CJ (1997) Multiple testing and statistical power with modified Bonferroni procedures. *Journal of Educational and Behavioral Statistics* 22(4):389-406
- Ota M, Obata T, Akine Y, Ito H, Ikehira H, Asada T, Suhara T (2006) Age-related degeneration of corpus callosum measured with diffusion tensor imaging. *Neuroimage* 31(4):1445-1452
- Pelletier J, Habib M, Lyoncaen O, Salamon G, Poncet M, Khalil R (1993) Functional and Magnetic-Resonance-Imaging Correlates of Callosal Involvement in Multiple-Sclerosis. *Archives of Neurology* 50(10):1077-1082
- Picard N, Strick PL (2001) Imaging the premotor areas. *Current Opinion in Neurobiology* 11(6):663-672
- Porciatti V, Fiorentini A, Morrone MC, Burr DC (1999) The effects of ageing on reaction times to motion onset. *Vision Research* 39(12):2157-2164
- Preilowski BF (1972) Possible contribution of the anterior forebrain commissures to bilateral motor coordination. *Neuropsychologia* 10(3):267-277
- Raz N, Rodrigue KM (2006) Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev* 30(6):730-748
- Sage CA, Van Hecke W, Peeters R, Sijbers J, Robberecht W, Parizel P, Marchal G, Leemans A, Sunaert S (2009) Quantitative diffusion tensor imaging in amyotrophic lateral sclerosis: revisited. *Human Brain Mapping* 30(11):3657-3675
- Sala S, Agosta F, Pagani E, Copetti M, Comi G, Filippi M (2012) Microstructural changes and atrophy in brain white matter tracts with aging. *Neurobiol Aging* 33(3):488-498 e482
- Salat DH, Tuch DS, Greve DN, van der Kouwe AJW, Hevelone ND, Zaleta AK, Rosen BR, Fischl B, Corkin S, Rosas HD and others (2005) Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of Aging* 26(8):1215-1227
- Salthouse TA, Czaja SJ (2000) Structural constraints on process explanations in cognitive aging. *Psychology and Aging* 15(1):44-55
- Schluter ND, Rushworth MF, Passingham RE, Mills KR (1998) Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain* 121 (5):785-799
- Serrien DJ, Strens LH, Oliviero A, Brown P (2002) Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neurosci Lett* 328(2):89-92

- Serrien DJ, Swinnen SP, Stelmach GE (2000) Age-related deterioration of coordinated interlimb behavior. *J Gerontol B Psychol Sci Soc Sci* 55(5):P295-303
- Sisti HM, Geurts M, Clerckx R, Gooijers J, Coxon JP, Heitger MH, Caeyenberghs K, Beets IA, Serbruyns L, Swinnen SP (2011) Testing multiple coordination constraints with a novel bimanual visuomotor task. *PLoS One* 6(8):e23619
- Sisti HM, Geurts M, Gooijers J, Heitger MH, Caeyenberghs K, Beets IA, Serbruyns L, Leemans A, Swinnen SP (2012) Microstructural organization of corpus callosum projections to prefrontal cortex predicts bimanual motor learning. *Learn Mem* 19(8):351-357
- Smith EE (1968) Choice reaction time: an analysis of the major theoretical positions. *Psychol Bull* 69(2):77-110
- Snodgrass JG, Luce RD, Galanter E (1967) Some Experiments on Simple and Choice Reaction Time. *Journal of Experimental Psychology* 75(1):1-17
- Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH (2003) Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20(3):1714-1722
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002) Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17(3):1429-1436
- Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, Armstrong RC (2005) Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 26(1):132-140
- Stelmach GE, Sirica A (1986) Aging and Proprioception. *Age* 9(4):99-103
- Stinear JW, Byblow WD (2002) Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *Journal of Physiology-London* 543(1):307-316
- Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A (2001) Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *Neuroreport* 12(1):99-104
- Sullivan EV, Adalsteinsson E, Pfefferbaum A (2006) Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. *Cereb Cortex* 16(7):1030-1039
- Sullivan EV, Pfefferbaum A (2006) Diffusion tensor imaging and aging. *Neurosci Biobehav Rev* 30(6):749-761
- Sullivan EV, Rohlfing T, Pfefferbaum A (2010) Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: Relations to timed performance. *Neurobiology of Aging* 31(3):464-481
- Summers JJ, Lewis J, Fujiyama H (2010) Aging effects on event and emergent timing in bimanual coordination. *Hum Mov Sci* 29(5):820-830

- Sun SW, Liang HF, Schmidt RE, Cross AH, Song SK (2007) Selective vulnerability of cerebral white matter in a murine model of multiple sclerosis detected using diffusion tensor imaging. *Neurobiology of Disease* 28(1):30-38
- Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK (2006) Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. *Magn Reson Med* 55(2):302-308
- Swinnen SP, Verschueren SMP, Bogaerts H, Dounskaia N, Lee TD, Stelmach GE, Serrien DJ (1998) Age-related deficits in motor learning and differences in feedback processing during the production of a bimanual coordination pattern. *Cognitive Neuropsychology* 15(5):439-466
- Swinnen SP, Wenderoth N (2004) Two hands, one brain: cognitive neuroscience of bimanual skill. *Trends Cogn Sci* 8(1):18-25
- Takser L, Dellatolas G, Bowler R, Laplante N (2002) Predictive factors of manual dexterity and cognitive performance at 17 years: A 10-year longitudinal study in a rural area of France. *Perceptual and Motor Skills* 95(1):15-26
- Tiffin J, Asher EJ (1948) The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol* 32(3):234-247
- Tournier JD, Mori S, Leemans A (2011) Diffusion tensor imaging and beyond. *Magn Reson Med* 65(6):1532-1556
- Tuch DS, Salat DH, Wisco JJ, Zaleta AK, Hevelone ND, Rosas HD (2005) Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proc Natl Acad Sci U S A* 102(34):12212-12217
- Van Hecke W, Leemans A, D'Agostino E, De Backer S, Vandervliet E, Parizel PM, Sijbers J (2007) Nonrigid coregistration of diffusion tensor images using a viscous fluid model and mutual information. *IEEE Trans Med Imaging* 26(11):1598-1612
- Van Hecke W, Nagels G, Leemans A, Vandervliet E, Sijbers J, Parizel PM (2010) Correlation of cognitive dysfunction and diffusion tensor MRI measures in patients with mild and moderate multiple sclerosis. *J Magn Reson Imaging* 31(6):1492-1498
- Van Hecke W, Sijbers J, De Backer S, Poot D, Parizel PM, Leemans A (2009) On the construction of a ground truth framework for evaluating voxel-based diffusion tensor MRI analysis methods. *Neuroimage* 46(3):692-707
- Verhoeven JS, Sage CA, Leemans A, Van Hecke W, Callaert D, Peeters R, De Cock P, Lagae L, Sunaert S (2010) Construction of a stereotaxic DTI atlas with full diffusion tensor information for studying white matter maturation from childhood to adolescence using tractography-based segmentations. *Human Brain Mapping* 31(3):470-486
- Voineskos AN, Rajji TK, Lobaugh NJ, Miranda D, Shenton ME, Kennedy JL, Pollock BG, Mulsant BH (2012) Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. *Neurobiol Aging* 33(1):21-34

- Vos SB, Jones DK, Jeurissen B, Viergever MA, Leemans A (2012) The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. *Neuroimage* 59(3):2208-2216
- Wang LE, Tittgemeyer M, Imperati D, Diekhoff S, Ameli M, Fink GR, Grefkes C (2012) Degeneration of corpus callosum and recovery of motor function after stroke: A multimodal magnetic resonance imaging study. *Human Brain Mapping* 33(12):2941-2956
- Wedeen VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, Pandya DN, Hagmann P, D'Arceuil H, de Crespigny AJ (2008) Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage* 41(4):1267-1277
- Wiegell MR, Larsson HB, Wedeen VJ (2000) Fiber crossing in human brain depicted with diffusion tensor MR imaging. *Radiology* 217(3):897-903
- Wishart LR, Lee TD, Murdoch JE, Hodges NJ (2000) Effects of aging on automatic and effortful processes in bimanual coordination. *J Gerontol B Psychol Sci Soc Sci* 55(2):P85-94
- Zahr NM, Rohlfing T, Pfefferbaum A, Sullivan EV (2009) Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage* 44(3):1050-1062
- Zhang Y, Du AT, Hayasaka S, Jahng GH, Hlavin J, Zhan W, Weiner MW, Schuff N (2010) Patterns of age-related water diffusion changes in human brain by concordance and discordance analysis. *Neurobiol Aging* 31(11):1991-2001

Table 1. Correlations between FA of the CC subregions and bimanual motor performance within the young and the older adults group.

Young adults	Prefrontal CC1	Premotor CC2	Primary motor CC3	Primary sensory CC4	Parietal CC5	Temporal CC6	Occipital CC7
Purdue Pegboard	-.19	-.22	.01	-.10	-.17	.08	.13
Simultaneous finger tapping	.11	-.17	.00	.01	-.22	-.04	.09
Alternating finger tapping	.20	.20	.06	.33	-.03	.35	.04
† Choice reaction time test	.34	.09	.00	-.09	.21	-.28	-.15
† Visuomotor task ISO	-.15	-.10	-.15	-.48**	.05	-.07	.15
† Visuomotor task N-ISO	-.11	-.13	-.17	-.45**	.05	-.12	.10
Older adults	Prefrontal CC1	Premotor CC2	Primary motor CC3	Primary sensory CC4	Parietal CC5	Temporal CC6	Occipital CC7
Purdue Pegboard	-.02	.06	.04	.17	.33	.10	.44**
Simultaneous finger tapping	.38	.45**	.39	.39	.38	.18	.27
Alternating finger tapping	.34	.26	.36	.24	.17	.25	-.14
† Choice reaction time test	-.31	-.65***	-.44	-.47**	-.38	.00	-.18
† Visuomotor task ISO	-.06	-.04	-.47**	-.26	-.24	-.29	.00
† Visuomotor task N-ISO	.04	-.08	-.50***	-.21	-.13	-.10	.09

FA, fractional anisotropy; CC, corpus callosum; ISO, isofrequency ratios; N-ISO, non-isofrequency ratios.

Results reported as being significant survived Bonferroni correction for 7 comparisons.

**. Correlation is significant at the 0.01 level (one-tailed).

***. Correlation is significant at the 0.001 level (one-tailed).

†. For these tasks, lower scores reflect better performance.

Online Resource 1: Relationships between the different bimanual test scores within the young and the older adults group.

		Young adults					
		Purdue Pegboard	Simultaneous finger tapping	Alternating finger tapping	† Choice reaction time test	† Visuomotor task isofrequency ratios	† Visuomotor task non-isofrequency ratios
Purdue Pegboard	Pearson <i>Sig.</i>	1	.47 <i>0.008</i>	.08 <i>0.66</i>	-.22 <i>0.252</i>	.00 <i>0.999</i>	-.00 <i>0.989</i>
Simultaneous finger tapping	Pearson <i>Sig.</i>		1	.39 <i>0.031</i>	-.14 <i>0.471</i>	-.04 <i>0.842</i>	-.06 <i>0.737</i>
Alternating finger tapping	Pearson <i>Sig.</i>			1	-.51 <i>0.005</i>	-.45 <i>0.01</i>	-.57*** <i>0.001</i>
† Choice reaction time test	Pearson <i>Sig.</i>				1	.41 <i>0.025</i>	.42 <i>0.02</i>
† Visuomotor task isofrequency ratios	Pearson <i>Sig.</i>					1	.85*** <i>0.000</i>
† Visuomotor task non-isofrequency ratios	Pearson <i>Sig.</i>						1

Results reported as being significant survived Bonferroni correction for 15 comparisons.

**. Correlation is significant at the 0.01 level (two-tailed).

***. Correlation is significant at the 0.001 level (two-tailed).

†. For these tasks, lower scores reflect better performance.

Scores in light grey represent correlations between subscores of the same task.

		Older adults					
		Purdue Pegboard	Simultaneous finger tapping	Alternating finger tapping	† Choice reaction time test	†Visuomotor task isofrequency ratios	†Visuomotor task non- isofrequency ratios
Purdue Pegboard	Pearson <i>Sig.</i>	1	.21 <i>0.256</i>	-.13 <i>0.486</i>	-.26 <i>0.179</i>	-.37 <i>0.039</i>	-.38 <i>0.03</i>
Simultaneous finger tapping	Pearson <i>Sig.</i>		1	.60 ^{***} <i>0.000</i>	-.2 <i>0.316</i>	-.34 <i>0.061</i>	-.34 <i>0.058</i>
Alternating finger tapping	Pearson <i>Sig.</i>			1	-.27 <i>0.157</i>	-.52 ^{**} <i>0.002</i>	-.52 ^{**} <i>0.002</i>
† Choice reaction time test	Pearson <i>Sig.</i>				1	.36 <i>0.057</i>	.36 <i>0.054</i>
† Visuomotor task isofrequency ratios	Pearson <i>Sig.</i>					1	.92 ^{***} <i>0.000</i>
† Visuomotor task non-isofrequency ratios	Pearson <i>Sig.</i>						1

Results reported as being significant survived Bonferroni correction for 15 comparisons.

**. Correlation is significant at the 0.01 level (two-tailed).

***. Correlation is significant at the 0.001 level (two-tailed).

†. For these tasks, lower scores reflect better performance.

Scores in light grey represent correlations between subscores of the same task.

Figures

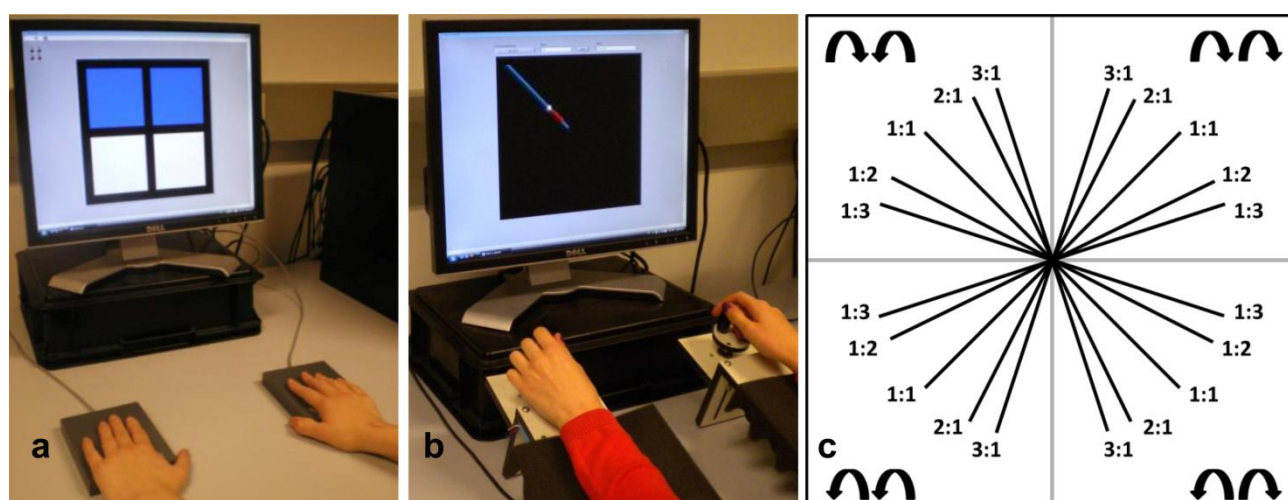


Fig. 1 Experimental setup. (a) Choice reaction time test. The condition in which participants had to lift both hands simultaneously is displayed on the computer screen. (b) Bimanual visuomotor task. Please note that during the experiment, both hands were covered with a horizontal table-top bench (c) Schematic representation of the bimanual visuomotor task. The 20 target pathways are represented: 4 different coordination patterns and 5 frequency ratios (3:1, 2:1, 1:1, 1:2, 1:3) between the left and right hand

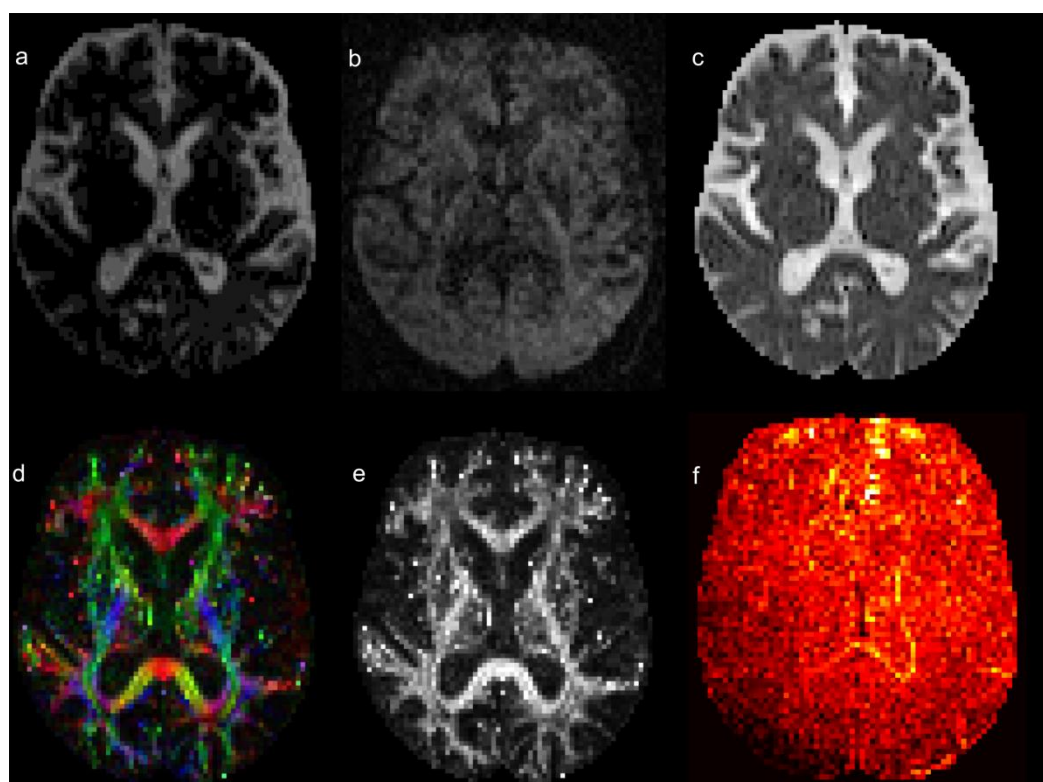


Fig. 2 Inspection of the raw data. Axial view of a representative dataset of an older subject, before correction for subject motion and eddy current induced geometric distortions. (a) Non-diffusion weighted image. (b) Diffusion weighted image. (c) Mean diffusivity. (d) Color-coded fractional anisotropy. (e) Fractional anisotropy. (f) Diffusion tensor residual map (yellow = high residuals; red = low residuals)

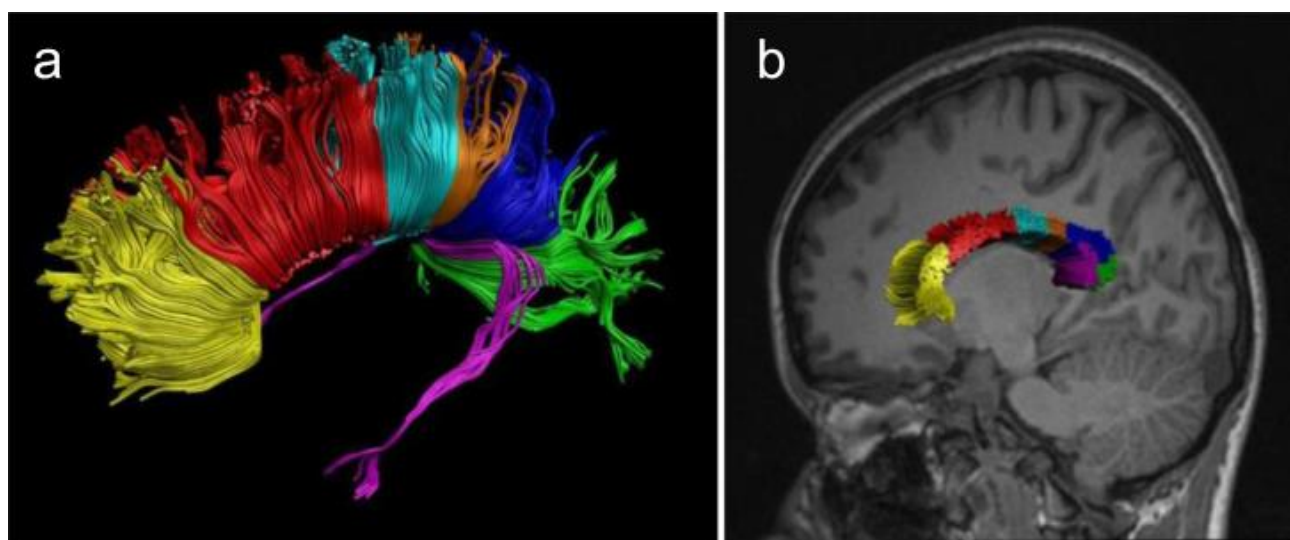


Fig. 3 The corpus callosum (CC) of a sample subject divided into seven subregions: prefrontal (yellow), premotor (red), primary motor (light blue), primary sensory (orange), parietal (dark blue), temporal (purple) and occipital (green). (a) All reconstructed callosal fibers comprising bundles projecting into the 7 subregions. (b) Midsagittal fiber bundle segments for each CC subregion, displayed on a T1 image. Mean values of fractional anisotropy, axial diffusivity and radial diffusivity were obtained from these midsagittal segments only

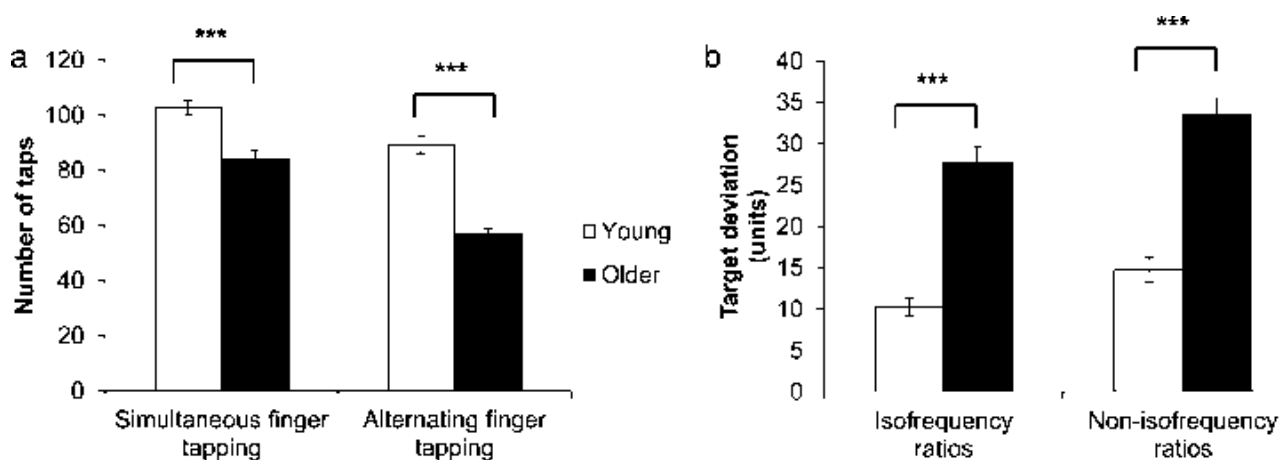


Fig. 4 Bimanual motor performance means \pm standard error. (a) Number of taps on the simultaneous and alternating finger tapping test. (b) Target deviation on the isofrequency and non-

isofrequency ratios of the visuomotor task, lower target deviations represent better performance. *** $p < 0.001$, for comparisons between the young and older adults

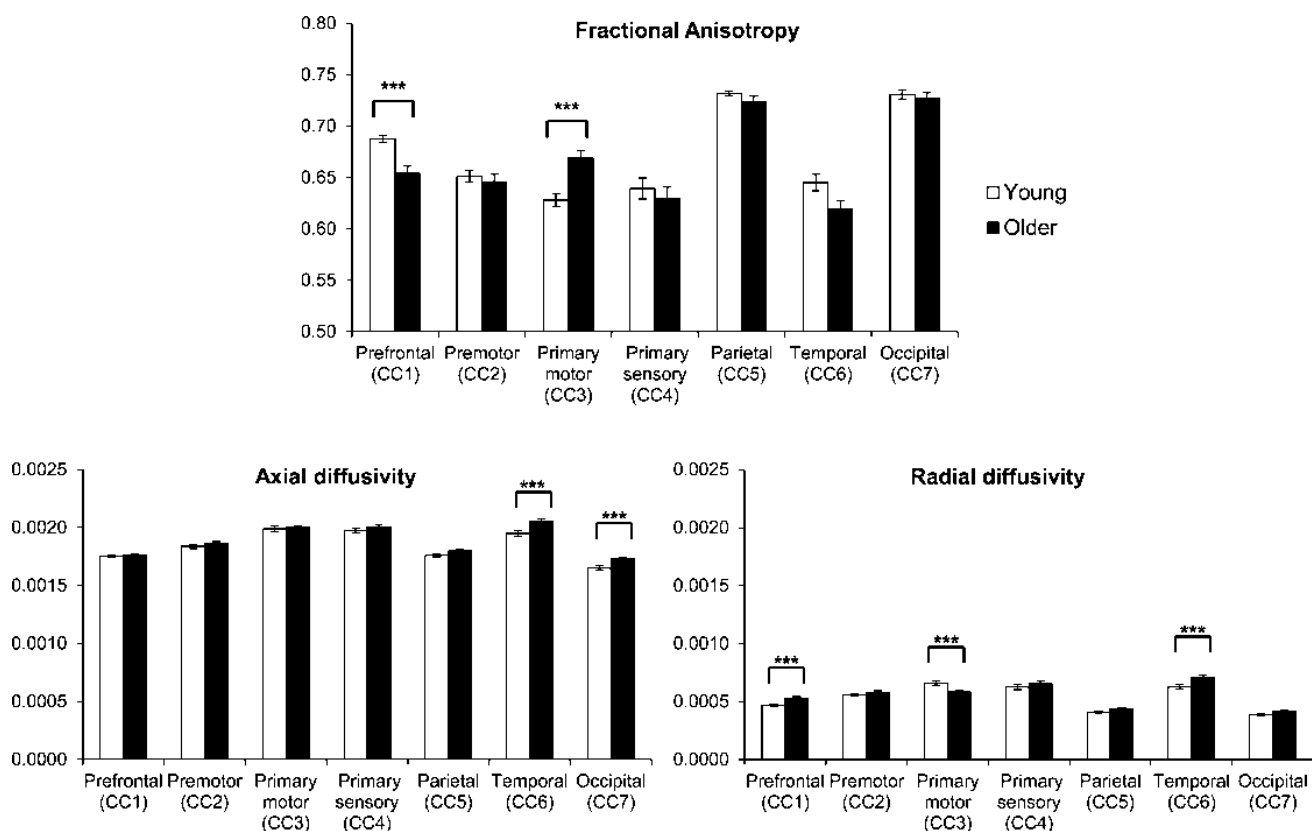


Fig. 5 Diffusion parameter means \pm standard error as a function of age group and corpus callosum (CC) subregion. Results reported as being significant survived Bonferroni correction for 7 comparisons. *** $p < 0.001$, for comparisons between the young and older adults

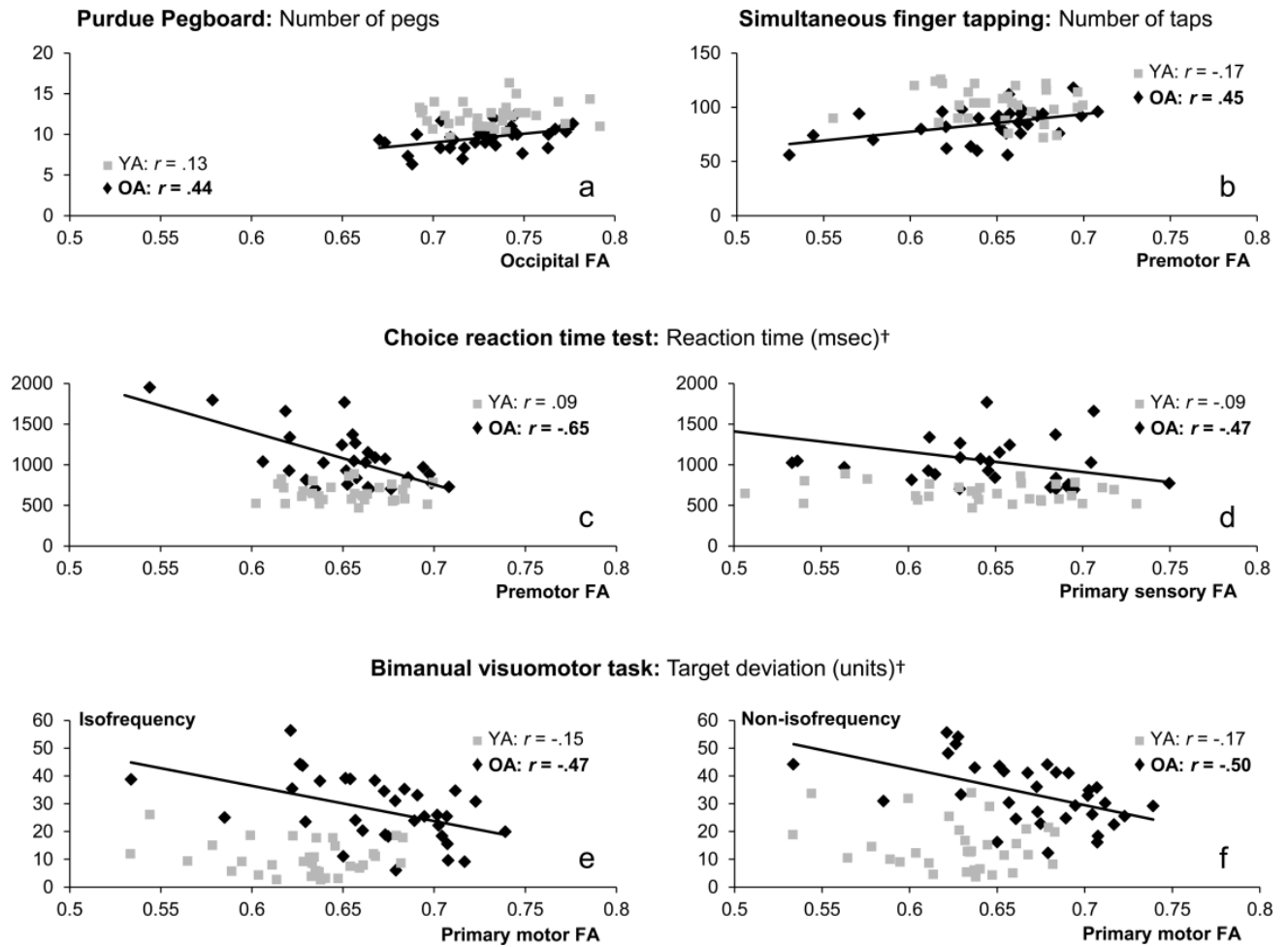


Fig. 6 Plots indicating the relationships between fractional anisotropy (FA) of specific corpus callosum subregions and the bimanual motor task scores in young adults (YA, grey) and older adults (OA, black). Only correlations that were significant in the older adults group, surviving family-wise Bonferroni correction, are shown. [†]For these tasks, lower scores reflect better performance