Microstructural organization of corpus callosum projections to prefrontal cortex predicts bimanual motor learning

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The corpus callosum (CC) is the largest white matter tract in the brain. It enables interhemispheric communication, particularly with respect to bimanual coordination. Here, we use diffusion tensor imaging (DTI) in healthy humans to determine the extent to which structural organization of subregions within the CC would predict how well subjects learn a novel bimanual task. A single DTI scan was taken prior to training. Participants then practiced a bimanual visuomotor task over the course of 2 wk, consisting of multiple coordination patterns. Findings revealed that the predictive power of fractional anisotropy (FA) was a function of CC subregion and practice. That is, FA of the anterior CC, which projects to the prefrontal cortex, predicted bimanual learning rather than the middle CC regions, which connect primary motor cortex. This correlation was specific in that FA correlated significantly with performance of the most difficult frequency ratios tested and not the innately preferred, isochronous frequency ratio. Moreover, the effect was only evident after training and not at initiation of practice. This is the first DTI study in healthy adults which demonstrates that white matter organization of the interhemispheric connections between the prefrontal structures is strongly correlated with motor learning capability.

Successful coordination of the left and right hands is an essential activity of daily living. The marvelous interaction between the hands to accomplish a variety of goal-directed actions is taken for granted, but an ingenious brain architecture underlies this function (Swinnen 2002; Swinnen and Wenderoth 2004). The corpus callosum (CC) connects homotopic and heterotopic cortical regions to allow interhemispheric communication and has been implicated in bimanual performance, such as in finger tapping tasks (Gerlof and Andres 2002; Muetzel et al. 2008; Bennett et al. 2011; Fling et al. 2011). Patients who have undergone partial or complete callosotomy demonstrate significant bimanual coordination deficits (Eliassen et al. 2000; Serrien et al. 2001; Kennerley et al. 2002; Sternad et al. 2007). In patients with multiple sclerosis who have damage to the CC, white matter organization of the anterior callosal portions has been correlated with impairments of bimanual coordination (Schulte et al. 2005; Johansen-Berg et al. 2007; Bonzano et al. 2008, 2011a,b; Della-Maggiore et al. 2009; Tomassini et al. 2011). However, these studies only examined short-term motor performance. The role of the CC in learning new motor skills across time remains to be investigated.

While several studies have revealed the importance of the CC in bimanual coordination, findings on the specificity of CC subregions for predicting bimanual performance are mixed (Sullivan et al. 2001; Johansen-Berg et al. 2007; Bonzano et al. 2008; Muetzel et al. 2008; Gooijers et al. 2011). For instance, asynchronous bimanual finger-thumb opposition movements have been correlated with structural organization of the midbody (Johansen-Berg et al. 2007), alternate finger tapping with the splenium (Sullivan et al. 2001; Muetzel et al. 2008) and performance on a repetitive finger tapping task with fractional anisotropy (FA) of anterior regions (Bonzano et al. 2008). Recently, we used a novel bimanual dial rotation task and found that the motor and occipital regions of the CC correlated with bimanual performance (Gooijers et al. 2011).

Most of the aforementioned diffusion tensor imaging (DTI) studies have analyzed brain-behavior relationships using diseased populations, using primarily general CC classifications, i.e., genu, midbody, and splenium, or the Witelson classification (1989). However, the Witelson classification is based on nonhuman pri-mates and does not accurately capture the functionally distinct regions of the human CC. Furthermore, with the exception of our recent report, no DTI studies have yet included a broader umbrella of complex bimanual task conditions, thereby varying the degree and nature of interhemispheric communication required (Gooijers et al. 2011).

Here, we used a tractography-based parcelation method that approximates the heterogeneous anatomic and functional distribution of information transmitted along the CC (Huang et al. 2005; Hofer and Frahm 2006; Caeyenberghs et al. 2011; Gooijers et al. 2011). We partitioned the CC into seven subregions based on its connections to the (1) prefrontal regions, (2) premotor and supplementary motor areas, (3) primary motor cortex, (4) primary sensory cortex, and (5) occipital, (6) parietal, and (7) temporal cortex, as we have done previously (Caeyenberghs et al. 2011; Gooijers et al. 2011). We investigated the organization of the seven CC subregions in healthy young adults in relation to performance on a bimanual visuomotor task, which is a computerized version of the “Etch-a-sketch” device (for earlier versions, see Preilowski 1972; Jeeves et al. 1988; Mueller et al. 2009). The novelty of the present task is that we systematically manipulated the following parameters collectively: hand dominance allocation, frequency ratio (FR), and whether the FR was an integer or
noninteger ratio, an element that is critical in the timing of finger-tapping movements (Summers et al. 1993).

The objective of this study was to determine whether structural organization of the CC—measured at a single time point prior to training—would predict how well healthy subjects learn a novel bimanual coordination task. Specifically, we hypothesized that the anterior region of the CC would be most critical for learning this bimanual task. Our hypothesis was predicated on the collective work of Preilowski (1972), Ellassen et al. (2000), and Bonzano et al. (2008) in conjunction with functional magnetic resonance imaging (fMRI) studies that point to the prefrontal cortex (PFC) as a critical structure for the acquisition of novel (including bimanual) skills (Doyon et al. 1996; Shadmehr and Holcomb 1999; Doyon and Ungerleider 2002; Debaere et al. 2004a; Puttermans et al. 2005; Remy et al. 2008, 2010). Several studies using fMRI have demonstrated that PFC activation is strong early in motor learning. Furthermore, damage to the PFC often impairs new learning (for review, see Miller 2000). Therefore, we also predicted that the relationship between learning and anterior regions of the CC would hold well for newly acquired, nonpreferred coordination patterns but less for preexistent, preferred coordination patterns that are part of the intrinsic motor repertoire of the performer and do not demand new learning. This hypothesis was tested in healthy young adult participants who practiced the task across several days.

Results

Behavioral data

Training across 6 d

Change in performance across days was determined using a 6 × 7 (Day × Frequency Ratio) repeated measures ANOVA of absolute deviation (AbDv). There was a significant main effect of day, indicating a decrease in AbDv with practice across Days 1–6 [F(5,85) = 224.47, P < 0.0001] (Fig. 1). Tukey post-hoc tests revealed that there was a significant decrease (P < 0.01) between each consecutive day with the exception of the last two time points. The main effect of frequency ratio was also significant [F(6,102) = 24.85, P < 0.001], which indicated that error increased as the interlimb difference in movement frequency became higher.

The interaction effect was also significant and was further explored with respect to intertask differences at pre- and post-test and changes with practice [F(30,510) = 2.57, P < 0.001]. Within the pre-test, the error score for the 1:1 frequency ratio was significantly lower than for all remaining frequency ratios tested (P < 0.05 for all pairs). In view of our specific interest in those subtasks showing the highest and lowest error score (see below), we found that error scores during 3:1 and 1:3 performance were significantly greater than the 1:1 ratio at pre-test (P < 0.05). No significant differences remained across any frequency ratio comparisons at post-test, except for 3:1 and 1:3, which showed significantly larger error scores than 1:1 (P < 0.01). Further, Tukey post-hoc tests revealed that between pre- and post-test, the reduction in error scores was much greater for the 3:1 and 1:3 patterns compared with the 1:1 pattern (P < 0.05). To reduce the likelihood of Type 1 errors and to preserve the broad spectrum of task complexity, subsequent DTI analysis included the frequency ratios that resulted in the smallest AbDv (1:1) and the largest AbDv (1:3 and 3:1) at the time of the pre- and post-test.

Diffusion tensor imaging data

Regional effects of fractional anisotropy

A repeated measures ANOVA on the FA values of the seven CC subregions revealed a significant main effect of region [F(6,90) = 4.41, P < 0.001] (see Fig. 2C). Post-hoc Tukey demonstrated that FA values were higher in the parietal (CC5) and occipital (CC6) regions of the CC compared to the other regions (P < 0.001).

Multiple linear regression

Forward stepwise regression was used to determine which of the seven CC subregions accounted for the greatest amount of variance at post-test. The independent variables in our model included the seven CC subregions. The dependent variable was the performance at post-test for each of the frequency ratios tested. The greatest amount of variance in performance was accounted for by CC1 at the post-test for the most difficult frequency ratios (3:1 and 1:3).

Correlation analysis of pre- and post-test performance with CCI

Based on the results from our regression models, we correlated CC1 with AbDv of 1:1, 3:1, and 1:3, at both pre- and post-test. Negative correlations indicate that a higher FA is predictive of lower performance error. CC1 correlated significantly with performance of the 1:3 frequency ratio at post-test (r = −0.70, P = 0.001) but not at pre-test (r = −0.35, P = 0.16). For the converse 3:1 frequency ratio, CC1 also predicted performance at post-test (r = −0.54, P = 0.02) but not at pre-test (r = −0.21, P = 0.39). For the 1:1 coordination task, no significant correlations were observed (r = −0.05 [P = 0.84]) at pre-test and r = −0.22 [P = 0.39] at post-test.

We tested more directly if there was a significant difference between the correlation coefficient at pre- and post-test for each of the frequency ratios, following transformation to Fisher Z-scores. The correlation difference between 1:3 performance and the FA of CC1 at post-test compared to pre-test reached significance (P = 0.04). The remaining comparisons did not reach statistical significance, despite a similar trend for 3:1.

Naturally crossing fibers in the brain represent one of the major challenges of DTI metrics. One advantage of obtaining white matter integrity metrics of the mid-sagittal tract structure is that the potential impact of crossing fibers on the FA score is limited (for a similar approach, see Rohlffing et al. 2010). To verify whether the previously obtained correlations would be affected when the length of

Figure 1. (A) Changes in error score across training. (B) The 1:1 frequency ratios result in the least error and the 1:3 and 3:1 frequency ratios in the greatest error.
the whole tract was analyzed, the FA of the entire bilateral tract pathways projecting into the prefrontal cortex was also determined. In this case, there was a statistically significant correlation between the FA of associated fibers and the most difficult 1:3 frequency ratio at post-test ($r = 0.67, P = 0.002$) but not at pre-test ($r = -0.35, P = 0.15$). The correlation between CC1-associated fibers and the AbDv of 3:1 at post-test was significant ($r = -0.49, P = 0.03$) and was nonsignificant at pre-test ($r = -0.04, P = 0.86$). For the 1:1 ratio, $r = -0.37$ ($P = 0.12$) at post-test and $-0.12$ ($P = 0.61$) at pre-test.

Partial correlations to assess performance change

Finally, we computed partial correlations to determine whether the changes in performance as a result of training were predicted by the CC1 and associated fibers. The variance in post-test performance accounted for by pre-test performance was partitioned out to arrive at a cleaner metric of performance change with practice. The remaining residuals were then correlated with the FA of CC1 and associated fibers, as was done above. For the CC1, the $r$ value was highest for 1:3 ($r = -0.72, P = 0.001$) (Fig. 3), second highest for 3:1 ($r = -0.52, P = 0.03$), and lowest for 1:1 ($r = -0.29, P = 0.23$). The correlation coefficient between CC1 and 1:1 was significantly lower than the $r$ value for CC1 and 1:3 performance (two-directional) $P < 0.05$. When correlations were computed for the CC1 associated fibers, the results were similar: 1:3 ($r = -0.70, P = 0.002$) (Fig. 4), 3:1 ($r = -0.49, P = 0.04$), and 1:1 ($r = -0.35, P = 0.16$). These results suggest that CC1 predicted post-test performance significantly following removal of the variance accounted for by pre-test performance. Together with the significant correlation difference (as reported in the previous paragraph), the present partial correlation analysis provides additional confirmation in the sense that CC1 predicts post-test performance on the complex coordination task when the variance accounted for by pre-test performance is extracted from post-test performance.

For completeness, we also report the $r$ values between the FA of CC1 and the remaining task variants located between the 1:1 and 3:1 frequency ratios: for 2:3 and 3:2 and CC1, $r = -0.36$ and $r = -0.44$, respectively; for 1:2 and 2:1, $r = -0.64 (P < 0.05)$ and $r = -0.46$, respectively.

Discussion

Several decades ago, seminal work on split brain subjects already indicated that the anterior CC is critical for bimanual performance (Preilowski 1972; Jeesee et al. 1988). The role of the CC in bimanual learning has received much less attention. Here, we trained healthy young adults for several days on a bimanual task with varying degrees of complexity and found that the predictive power of FA for the CC was specific to subregion and practice. Significant correlations were detected for the most difficult frequency ratios after training and not at initiation of practice or for the intrinsically favorable iso-frequency rhythms, adding specificity to the obtained effect. These data are novel in that previous studies examining the role of the CC in bimanual tasks primarily looked at single session motor performance instead of the learning-related dynamics (Johansen-Berg et al. 2007; Bonzano et al. 2008; Muetzel et al. 2008; Gooijers et al. 2011). Here, we compared correlation coefficients at pre- and post-test and made use of a partial correlation analysis to investigate the association between CC structural integrity and bimanual coordination learning, as discussed further below.

We used a tractography-based segmentation of the CC into seven subregions. We chose to do this because the CC is not a homogeneously tract from a functional and structural perspective. In fact, the CC has a topographical organization varying along the length of the A-P axis. Lower FA values are found in the anterior and middle regions compared to the posterior regions (Sullivan et al. 2001; Chepurii et al. 2002; Pfefferbaum and Sullivan 2003; Hasan et al. 2005, 2009). Consistent with this, we also found that the parietal and occipital regions of the CC had higher FA values compared to anterior and middle regions (Caeyenberghs et al. 2011; Gooijers et al. 2011). Regional differences of the FA have been attributed to varying degrees of permeability of the myelin sheaths, changes in orientation of axons, differences in axon-packing density, and...
thickening of myelin and axonal caliber, where a higher FA value is indicative of more densely packed CC fibers (Chepuri et al. 2002; Hofer and Frahm 2006). These interpretations are supported by microscopic examination of the CC (Aboitiz et al. 1992).

Subjects with higher FA values in CC1 performed better on the most difficult frequency ratios following practice. These results were confirmed when we analyzed the FA along the entire length of the fibers that project into the outer prefrontal cortex. This indirectly suggests that demands on attention and working memory were important for learning progress. Error was higher for 3:1 and 1:3 compared to 1:1 patterns at both pre- and post-test, indicating that the former were more difficult to perform both before and after practice (Semjen and Summers 2002; Summers 2002; Gooijers et al. 2011; Sisti et al. 2011). Furthermore, the degree to which interhemispheric communication is necessary for bimanual tasks is dependent upon whether or not the task is novel or familiar (Franz et al. 2000). For example, callosumy patients can successfully perform familiar tasks that require two hands, such as tying shoes; however, they are unable to learn novel tasks that require coordination of the two hands, such as threading a needle (Franz et al. 2000). We also hypothesized that correlations between bimanual learning and the FA of the CC would depend on task complexity. Consistent with this, partial correlation coefficients of CC1 and the 1:1 and CC1 and the 1:3 task revealed a significant difference. Interestingly, Ullen et al. (2003) used fMRI to map active neural networks during intrinsically favorable in-phase patterns compared with more difficult anti-phase patterns and found that the former was characterized by strong activation in subcortical activity and the latter, asynchronous pattern was characterized by activation in the frontal lobe among other cortical regions.

When error was high and subjects had not yet learned the appropriate bimanual coordination patterns, there was no clear evidence of a structure-function relationship between FA values and performance under the augmented visual feedback conditions studied here. After the subjects practiced the task, a significant correlation emerged such that a higher FA in CC1 predicted lower performance error. Furthermore, we also computed the partial correlation coefficients to account for any variance in post-test performance due to pre-test performance. The FA values of CC1 predicted performance for the most difficult frequency ratios, and not intrinsically favorable 1:1 patterns.

These novel structural data may complement a consistent finding with fMRI studies reporting increased activation in the PFC early in motor learning (Thoenissen et al. 2002; Debaere et al. 2004a; Poldrack et al. 2005; Puttemans et al. 2005; Mars et al. 2008; Remy et al. 2008). It is difficult to match the timeline of our study with fMRI studies; however, our data are consistent with the general view that acquisition of skill evolves from a cognitive, attention-demanding stage, dependent on prefrontal cortical activity, to an autonomous stage characterized by automaticity and dependent on other cortical and subcortical areas (Fitts and Posner 1967). Reaching automaticity can take days, weeks, or even years. There are several possibilities which may explain the involvement of PFC in learning, including attention-demanding sensory processing, suppression of preferred isochronous tendencies, and the necessity to continuously update the movement plan based on error processing (Doyon et al. 1996; Richer et al. 1999; Shadmehr and Holcomb 1999; Thoenissen et al. 2002; Puttemans et al. 2005; Mars et al. 2008; Remy et al. 2010).

A significant difference between partial correlation coefficients was found when the FA of CC1 and 1:1 performance was compared with the FA of CC1 and 1:3 performance ($P < 0.05$). Previous work has demonstrated that the neural resource demands for a complex coordination mode are much higher than for an intrinsically favorable coordination mode that can often be performed without much prior practice (Ullen et al. 2003; Debaere et al. 2004a, b). For example, Debaere et al. (2004a) demonstrated that the PFC was activated during initial practice of a more complex, $90^\circ$ out-of-phase coordination mode but not during practice of the easy in-phase mode. We suggest that structural quality of the tracts is less critical during performance of easier coordination modes because even low structural quality is sufficiently adequate for the reduced signal transmission requirement under such circumstances. However, the more difficult frequency ratios place greater demands on neural transmission to support information processing. Hence, structural organization of white matter tracts becomes more critical.

In sum, the predictive power of the FA of the anterior CC segment was a function of practice on the more complex coordination modes. This result complements fMRI studies demonstrating that the PFC is a critical structure in motor learning (Debaere et al. 2004a; Floyer-Lea and Matthews 2004; Steele and Pehnune 2010). It provides a strong case for considering the role of structural brain metrics in predicting behavioral change as a result of learning, one of the most intriguing abilities of biological systems.

**Materials and Methods**

**Participants**

Eighteen healthy, right-handed adults (16 females and 2 males, mean age = 22.3 years, SD = 3.6) were included in the experiment. Subjects were recruited locally and many were students or graduate students at the university or its affiliates. Informed consent was signed prior to testing. The experiment was approved by the local Ethics Committee of Katholieke Universiteit Leuven.
Task and procedure

We used a recently established behavioral protocol (Gooijers et al. 2011; Sisti et al. 2011) consisting of a bimanual tracking task where two dials controlled the direction and speed of a cursor on the PC monitor (see Fig. 5). When both dials were turned simultaneously, the cursor moved at an angle that was dependent on both the direction and frequency of dial rotation. We tested seven frequency ratios: 3:1, 2:1, 3:2, 1:1, 2:3, 1:2, and 1:3 (by convention, left hand is referred to first, L1H2R1). Four combinations of movement directions (leftward, rightward, inward, and outward) and seven frequency ratios resulted in 28 experimental target pathways. A trial included presentation of a single target line with a distinct angle representing a unique coordination pattern and lasted 7 sec. Time between trials varied between 4 and 6 sec. One trial block included 28 randomized trials. This was repeated six times with 1–3 min of rest between each block.

Absolute deviation of each trial was calculated by averaging the orthogonal distance between the target line and the subject cursor at each time point (100 Hz). A higher AbDv reflected greater error, hence worse performance. Subject means were calculated for each frequency ratio and collapsed across directions for each day. Procedures for pre-test, four practice sessions, and post-test were identical.

Augmented visual feedback was provided. Here, two displacements, left and right dials, are represented by a single moving cursor on the screen. The augmented visual feedback refers to feedback that is added to the normally available information feedback sources. In the present case, it specifically refers to online information about the cursor position on the PC screen.

Image acquisition

A Siemens 3 T Magnetom Trio MRI scanner (Siemens) with standard head coil was used with the following parameters (Jones and Leemans 2011): single-shot spin-echo; slice thickness = 2.5 mm, TR = 8300 msec, TE = 111 msec, number of diffusion directions = 150, b values were 700, 1000, and 2800 sec/mm², 58 sagittal slices, voxel size = 2.5 × 2.5 × 2.5 mm³. The DTI sequence lasted 22 min. All subjects were young, healthy adults, and a skilled technician walked them through the procedure. Foam cushions and bite bars were used to further minimize movement artifacts.

DTI processing and regions of interest

DTI data were analyzed with ExploreDTI (http://www.exploredti.com) (Leemans et al. 2009) and with the same set of procedures as described previously (for details, see Caeyenberghs et al. 2011; Gooijers et al. 2011). The diffusion weighted imaging volumes were first checked for artifacts (Tournier et al. 2011). Motion artifacts were realigned using affine coregistration with the appropriate b-matrix rotation (Leemans and Jones 2009; Klein et al. 2010). The diffusion tensor model was fitted to the data using nonlinear regression, and the FA was calculated as described previously (Basser and Pierpaoli 1996). The FA values ranged from 0 to 1, where 0 represents maximal isotropic diffusion, i.e., an equal amount of diffusion in all directions, and 1 represents maximal anisotropic diffusion, with higher values reflecting “more organized” tissue organization. The DTI data were transformed to MNI space (Leemans et al. 2005; Van Hecke et al. 2007). Deterministic streamline tractography of the CC was performed for each subject by manually drawing regions of interest (Leemans et al. 2009). The FA thresholds to initiate and continue tracking were 0.15. The maximum angle threshold was 40° (step size = 1 mm). ROIs were drawn within the CC of each participant on the mid-sagittal plane using ExploreDTI as described previously (Fig. 2A,B; Leemans et al. 2009; Caeyenberghs et al. 2011; Gooijers et al. 2011; Vos et al. 2011). Whole brain tractography was performed and two-dimensional selection (“AND”) ROIs were drawn according to specific anatomical landmarks and a priori determined rules that were followed consistently for each subject (Catani and Thiebaut de Schotten 2008). Specifically, the AND function was used to connect the left and right hemispheric bidders along the horizontal plane. Briefly, seven subregions of the CC were defined corresponding to: CC1 (prefrontal), CC2 (pre- and supplementary motor areas), CC3 and CC4 (primary motor and sensory cortices), CC5 (parietal), CC6 (occipital), and CC7 (temporal) regions. Mean FA for each subregion of the CC was calculated. Specifically for the prefrontal CC segment (CC1), we included an additional analysis, in which the FA was calculated for the fiber bundle that traverses the genu, that is, the entire bilateral tract pathways projecting into the prefrontal cortex.

Statistical analysis

To determine the change in performance across days, a 6 × 7 (Day × Frequency Ratio) repeated measures ANOVA of the AbDv was performed. The seven levels of frequency ratio were: 3:1, 2:1, 3:2, 1:1, 2:3, 1:2, and 1:3. Day consisted of six levels including, pre-test, four practice days, and post-test. Significant main and interaction effects were explored by post-hoc tests using Tukey correction. To examine the microstructural differences among the seven CC subregions, a one-way repeated measures ANOVA was conducted. Forward stepwise regression models were used to test whether the FA in specific CC subregions is predictive of bimanual performance. The “F-to-enter” was 0.05 and “F-to-remove” was 0.45. Based on the results of the models, Pearson correlations and partial correlations were also computed. All statistical analyses were performed with Statistica (StatSoft, Inc.) using an α-level of 0.05 or lower when applying Bonferroni correction for multiple comparisons.
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