White matter microstructural organisation of interhemispheric pathways predicts different stages of bimanual coordination learning in young and older adults

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Abstract

The ability to learn new motor skills is crucial for activities of daily living, especially in older adults. Previous work in younger adults has indicated fast and slow stages for motor learning that were associated with changes in functional interactions within and between brain hemispheres. However, the impact of the structural scaffolds of these functional interactions on different stages of motor learning remains elusive. Using diffusion-weighted imaging and probabilistic constrained spherical deconvolution-based tractography, we reconstructed transcallosal white matter pathways between the left and right primary motor cortices (M1–M1), left dorsal premotor cortex and right primary motor cortex (LPMD–RM1) and right dorsal premotor cortex and left primary motor cortex (RPMd–LM1) in younger and older adults trained in a set of bimanual coordination tasks. We used fractional anisotropy (FA) to assess microstructural organisation of the reconstructed white matter pathways. Older adults showed lower behavioural performance than younger adults and improved their performance more in the fast but less in the slow stage of learning. Linear mixed models predicted that individuals with higher FA of M1–M1 pathways improve more in the fast but less in the slow stage of bimanual learning. Individuals with higher FA of RPMd–LM1 improve more in the slow but less in the fast stage of bimanual learning. These predictions did not differ significantly between younger and older adults suggesting that, in both younger and older adults, the M1–M1 and RPMd–LM1 pathways are important for the fast and slow stage of bimanual learning, respectively.

Introduction

With dedicated practice, our ability to perform complex motor skills (e.g. typing on a touch screen mobile) significantly improves. This ability to learn new motor and other skills is crucial at all ages and particularly in older adults (OA). It enables OA to counteract the adverse effects of ageing on sensorimotor control and to maintain functional independence (Swinnen et al., 1998; Seidler et al., 2010).

Behavioural studies have demonstrated that motor learning generally follows two distinct stages: (1) the early, fast learning stage in which improvement in performance is seen within the first training session and (2) the late, slow learning stage in which smaller gains are obtained across subsequent training sessions distributed over a single day, several days or weeks/months (Brashers-Krug et al., 1996; Karni et al., 1998; Doyon et al., 2003). Depending on the task requirements, OA are often able to achieve considerable performance gains with training, similar to younger adults (YA) (Voelcker-Rehage & Willimczik, 2006; King et al., 2013; Maes et al., 2017). However, the question that has remained largely unanswered is the extent to which age modulates behavioural improvements in the fast and slow stages of motor learning.

In addition to learning-related behavioural aspects, functional brain studies have shown the involvement of cerebellar, subcortical...
and cortical (including primary motor (M1), premotor (PM), prefrontal and parietal) structures in motor learning (Jueptner et al., 1997; Doyon et al., 2003; Debaere et al., 2004; Floyer-Lea & Matthews, 2005; Puttemans et al., 2005; Remy et al., 2008; Hardwick et al., 2013; Beets et al., 2015). Aside from cortico-subcortical and cortico-cerebellar circuits involved in different stages of motor learning (Doyon et al., 2003; Dayan & Cohen, 2011), transcallosal cortico-cortical functional interactions within the motor network may also play a relevant role (Kantak et al., 2012). In this regard, previous work reported modulation of interhemispheric coupling between bilateral M1s and between dorsal PM and M1 (PMd–M1) during the fast bimanual learning stage (Andres et al., 1999; Serrien & Brown, 2003; Sun et al., 2007). Whether these results at the level of brain function extend to brain structure, and particularly white matter (WM) microstructural organisation, in YA and OA requires further investigation.

The WM microstructural organisation of the underlying network pathways is critical for the transfer of neuronal information through the network (Fields, 2008). This can be inferred in vivo using diffusion-weighted imaging (DWI). Previous DWI studies in YA have indicated associations between motor learning ability and the WM microstructural organisation of the corpus callosum (CC: containing fibres connecting the two hemispheres) (Sisti et al., 2012), superior cerebellar peduncle (containing fibres connecting the cerebellum with motor and premotor areas) (Della-Maggiore et al., 2009), PM cortex and cerebellum (Tomassini et al., 2011). Of note, except for the study of Sisti et al. (2012), who investigated the slow stage of bimanual learning, the other two studies focused on the fast stage of unimanual motor learning. Two unimanual motor learning DWI studies included both OA and YA groups. Bennett et al. (2011) showed an association between the microstructural organisation of the WM pathway connecting caudate nucleus to dorsolateral prefrontal cortex and the fast and slow stages of unimanual motor learning in both OA and YA. More recently, Schulz et al. (2014) found correlations between the WM microstructural organisation of several cortico-cortical pathways connecting M1 to premotor areas (including PMd) and the slow stage of unimanual motor learning which were present only in OA.

In sum, the extent to which WM microstructural organisation predicts different stages of bimanual coordination learning, particularly in OA, is still unclear. Moving both hands in an organised manner in both space and time is required in many activities of daily living, which support functional independence. Bimanual movements occur twice as often as unimanual movements during activities of daily living (Vega-Gonzalez & Granat, 2005). Furthermore, bimanual (re-)training is frequently discussed in the context of neurorehabilitation in stroke patients (Reinkensmeyer et al., 2016; Kantak et al., 2017). These indications provide a strong impetus for exploring the neural basis of bimanual motor learning in OA.

Here, we investigated the extent to which (1) ageing impacts the fast and slow stages of bimanual motor learning, (2) WM microstructural organisation of transcallosal pathways involving M1 and PMd predicts bimanual motor learning and (3) whether the latter prediction is affected by age. We hypothesised that bimanual coordination performance improves in both stages of learning for both YA and OA (Maes et al., 2017) and that these learning effects are age-dependent, with lower learning rates in OA. Recent studies revealed that WM microstructural organisation of left PMd–right M1 (LPMd–RM1) and M1–M1 pathways predict bimanual performance in OA (Serbruyns et al., 2015; Fujiyama et al., 2016a,b). However, RPMd also appeared to be particularly involved in performing complex bimanual tasks (Sadato et al., 1997; Wenderoth et al., 2004; Aramaki et al., 2006; Van den Berg et al., 2010). Accordingly, we hypothesised that the WM microstructural organisation of the pathways linking M1–M1 and PMd–M1 would predict bimanual motor learning performance. Because previous structural imaging studies have demonstrated age-dependent WM microstructural alterations of the brain (Sullivan & Pfefferbaum, 2006; Giorgio et al., 2010) predicting age-dependent differences in motor tasks performance (Zahr et al., 2009; Sullivan et al., 2010; Voineskos et al., 2012), we hypothesised that age may also modulate the effect of WM microstructural organisation on bimanual motor learning.

### Materials and methods

#### Participants

Twenty-six YA and 25 OA (right-handed; Oldfield, 1971) volunteers participated in the study. Three OA were excluded due to brain lesions and/or extreme atrophy as identified by a trained neuroradiologist. In addition, four YA were excluded: one due to poor DWI quality and presence of artefacts, two due to excessive head movements during DWI acquisition and one dropout. As a result, 22 OA (age: 68.41 ± 5.58 years; 12 females) and 22 YA (age: 21.05 ± 2.48 years; 13 females) were included in the analyses. The groups did not differ significantly with respect to gender ($\chi^2(1) = 0.09$, $P = 0.76$). All participants had normal or corrected-to-normal vision, and none reported neurological, psychiatric or cardiovascular disorders. This study was carried out in accordance with the Declaration of Helsinki (1964) and was approved by the Medical Ethics Committee UZ KU Leuven, Belgium. Participants were financially compensated for participation and provided written informed consent prior to the experiment.

#### Bimanual tracking task

We used a bimanual tracking task in which two dials controlled the direction and speed of a cursor on a computer screen: the right dial controlled displacement along the x-axis and the left dial along the y-axis (Fig. 1A; for details see Sisti et al., 2011; Gooijers et al., 2013; Beets et al., 2015; Chalavi et al., 2016). During each 9-s trial of the task, a white target dot moved over a blue line at a constant speed from start (centre of the screen) to end (Fig. 1B). The participant was instructed to track the target dot as closely as possible by rotating both dials simultaneously. Four coordination patterns imposed by the line direction were tested: both hands rotating inwards, outwards, clockwise or counterclockwise. Each pattern was performed with five distinct interhand frequency ratios, comprising $1 : 1$, $1 : 2$, $1 : 3$, $2 : 1$ and $3 : 1$ (left hand: right hand). Thus, the combination of coordination patterns and frequency ratios resulted in 20 task variations, each being represented by a distinct target line (Fig. 1C). The intertrial interval was 3 s.

#### Experimental set-up and procedure

This study was part of a larger multimodal structural and fMRI project investigating the neural mechanisms underlying bimanual task performance (Beets et al., 2015) and consisted of seven training sessions spread across 14 calendar days. On the first and seventh training session, hereafter referred to as Pre and Post, respectively, participants were trained with the bimanual tracking task in the MRI scanner while lying in a supine position (Fig. 1A), elbows flexed at 45° and forearms resting on pillows. Excessive head movements were prevented by a bite-bar and foam cushions. Visual stimuli were
projected by an LCD projector (Barco 6300, 1280 × 1024 pixels) onto a double mirror placed in front of the participant’s eyes. A non-ferromagnetic apparatus with two dials (diameter = 5 cm) was placed over the participant’s thighs. The participants were required to turn the handle of the dials with the fingers/wrist according to specific coordination patterns. Angular displacements were registered by means of non-ferromagnetic optical shaft encoders (HP, 2048 pulses per revolution, sampling frequency 100 Hz) fixed to the rotation axes of the dials. Version 8.5 of Laboratory Virtual Instrumentation Engineering Workbench (National Instruments) was used for task presentation and recording of the behavioural data.

On the Pre and Post scanning sessions, 96 task trials, divided into 48 trials with concurrent feedback (FB) and 48 trials without feedback (NFB), were performed. The concurrent FB was provided by means of a red cursor displaying the actual tracking trajectory based on the contribution of both limbs. The trials were spread over six fMRI/behavioural runs with inter-run interval of approximately 3 min (total contribution of both limbs). The trials were spread over six fMRI/behavioural runs with inter-run interval of approximately 3 min (total contribution of both limbs). The trials were spread over six fMRI/behavioural runs with inter-run interval of approximately 3 min (total contribution of both limbs). The trials were spread over six fMRI/behavioural runs with inter-run interval of approximately 3 min (total contribution of both limbs).

**Kinematic data analysis**

MATLAB R2011b was used for the offline analyses of the behavioural data. On each trial, the positions (x, y) of the white target dot and the cursor were sampled at 100 Hz. For each trial, the Euclidian distance between the white target dot and the cursor position at each time point was calculated (900 distances in arbitrary units (a.u.)). Subsequently, the ‘trial error score’ was calculated by taking the average of these distances and was used as an indicator of accuracy with higher values reflecting lower bimanual performance.

**Image acquisition**

A Siemens 3-T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 12-channel head coil was used for acquisition of brain images. For anatomical detail, a high-resolution whole brain T1-weighted structural image was obtained using magnetisation-prepared rapid gradient echo (MPRAGE; repetition time (TR)/echo time (TE) = 2300/2.98 ms, voxel size = 1 × 1 × 1.1 mm³, field of view (FOV) = 240 × 256 mm², slices = 160 and flip angle = 9°). Then, a field map image was acquired using a dual gradient echo acquisition (GRE; TR = 1000 ms, TE2/TE1 = 5.69/3.23 ms, voxel size = 3 × 3 × 2.8 mm³, matrix size = 64 × 64, slices = 50; flip angle = 60°). DWIs were acquired prior to the fMRI/behavioural runs in training session Pre using the following parameters: single-shot spin echo planar with spectral attenuated inversion recovery (SPAIR), TR/TE = 10700/82 ms, voxel size = 2.2 × 2.2 × 2.4 mm³, matrix size = 96 × 96, slices = 60, flip angle = 90°, diffusion weighting of b = 1000 mm²/s applied in 64 non-collinear directions and one non-diffusion-weighted image.

**Image processing**

For each subject, first, the DWIs were visually inspected in three orthogonal views using ExploreDTI (Leemans et al., 2009; www.exploredti.com) to identify visible artefacts, such as large signal dropouts and geometric distortions (Tournier et al., 2011). Second, the DWIs were preprocessed using MRtrix3 (J-D Tournier, Brain...
Research Institute, Melbourne, Australia; www.mrtrix.org) which incorporates tools from FSL (Oxford University, Oxford, UK; https://fsl.fmrib.ox.ac.uk) when necessary. The preprocessing steps included the correction of the DWIs for the following: eddy-current-induced distortions and head motion (Andersson & Sotiropoulos, 2016), susceptibility-induced distortions (Jezezard & Balaban, 1995), bias fields (Tustison et al., 2010) and Gibbs ringing (Kellner et al., 2016). Third, the diffusion tensor model was fitted to each voxel of the corrected DWIs with a robust iterative reweighted least squares estimator (Colli et al., 2015) and the fractional anisotropy (FA) map was calculated. Fourth, the warp to the Montreal Neurological Institute (MNI) standard space was obtained by non-linearly registering the FA map to the FMRIB58_FA template using tract-based spatial statistics (TBSS; Smith et al., 2006) algorithm in FSL. The inverse of this warp was also calculated to warp MNI masks to subject’s native space. Fifth, the T1 image was rigidly registered to the corrected DWIs to account for subject motion between the DW and structural scans, using mutual information as a similarity measure. Proper registration was checked visually.

In this study, average FA within the pathway of interest was used as an indicator of WM microstructural organisation to predict learning ability. FA ranges between zero and one with higher values reflecting higher microstructural organisation for the underlying white matter pathway (Beaulieu, 2002). To delineate the pathways of interest and calculate the average FA, the following main steps were performed.

Region of interest (ROI) creation

Using FSL, the bilateral M1 (anterior to the central sulcus) and PMd ROIs of Human Motor Area Template (HMAT; Mayka et al., 2006; http://fsl.fmrib.ox.ac.uk/fsl/2/) were extracted in MNI space. The ROIs were subsequently transformed from MNI to subject’s native space using the inverse warp obtained previously. Of note, HMAT has been created based on 126 functional imaging studies performed with motor tasks. To further refine these masks based on individual anatomy, similar methodology as in Schulz et al. (2014, 2015) was used. First, the registered T1 image of each subject was segmented into grey and white matter (GM and WM) masks using SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/). Second, the GM and WM masks were thresholded at 0.2, non-zero voxels were mean dilated, and the resulting masks were multiplied to create the GM/WM border mask. Third, the GM/WM border mask and each M1 and PMd functional mask were multiplied to obtain the common voxels of these masks. This procedure, thus, integrates both functional and anatomical criteria to better define the ROIs. For each subject, all steps of ROI creation were visually inspected to ensure proper implementation. To restrict tractography (see next section) to the fibre tracts passing only through the CC, the following masks were created for each subject: (1) the CC inclusion mask was created by manual segmentation of the CC in the midsagittal plane and ± 3 slices on each side; (2) the exclusion midline mask was created by drawing the midline in every coronal slice without overlapping with the CC inclusion mask.

Constrained spherical deconvolution (CSD) and probabilistic tractography

Application of CSD to streamline tractography has been shown to increase reliability of tractography throughout the brain (Jeurissen et al., 2011). A compulsory step in CSD is the ‘response function’ (RF) calculation which was made using Tournier’s algorithm (Tournier et al., 2013). Subsequently, CSD (with the maximum harmonic order of 8) was employed to estimate fibre orientation distribution function (fODF) in each brain voxel (Tournier et al., 2007). Probabilistic streamline tractography between ROIs was performed on fODFs, using a second-order integration over fibre orientation distributions (iFOD2) (Tournier et al., 2010) algorithm which treats the fODF as a probability density function from which to sample. The following parameters were used for the tracking algorithm employed in the subject’s native space; number of bidirectional generated streamlines = 10^6, step size = 1 mm, maximum angle between successive steps = 40°, minimum streamline length = 40 mm, maximum streamline length = 250 mm and iFOD cut-off value for initiating and terminating streamlines = 0.1. A symmetric and precise tracking result between two ROIs (for example between bilateral M1s) was obtained by considering both ROIs as ‘seed’ and ‘include’ masks. To guide the tracking algorithm for more accurate reconstruction of transcallosal pathways, the CC inclusion and the exclusion midline mask were also considered. To prevent ‘cross talk’ between the seed areas, the ROIs not involved in the active tracking were used as exclusion masks (Schulz et al., 2014). All previously mentioned procedure was performed in MRtrix3.

Population mask of transcallosal pathways of interest and average FA calculation

To create the population mask for each transcallosal pathway of interest (Fig. 2A), the following procedure was performed in MRtrix3. (1) The tracking result of each subject was warped to MNI space. (2) The tract density image (TDI) was created by calculating the total number of streamlines passing each voxel (Calamante et al., 2010). (3) 0.1% of the total number of successful streamlines with an absolute minimum of 2 per voxel was chosen to threshold the TDI. This threshold was chosen because it eliminated spurious fibre tracts based on visual inspection. (4) Binarised masks were summed across YA and OA to create the population mask which was then thresholded to select only those voxels that were found at least in 68% (N = 30; comparable with Schulz et al., 2014) of the subjects. (5) The thresholded population mask of each pathway of interest was then transformed to the subject's native space to calculate the mean FA value within the subject's mask. The mean FA values and the log_{10} of target error scores were used in the Statistical analysis section.

Statistical analysis

The data set was built with nested (i.e. multiple observations within a single participant) and crossed (i.e. participants observed in multiple bimanual coordination conditions) measurements. Thus, data were analysed using linear mixed models with crossed random factors. Linear mixed models take into account the sampling variability of both participants and conditions, thereby preventing a substantial inflation of false positives (i.e. type 1 error), whereas traditional analyses of variance such as ANOVAs disregard this sampling variability (Boisgontier & Cheval, 2016). Moreover, treating both participants and conditions as random effects allows generalising the results not only to the population of participants, but also to the population of conditions as well (Barr et al., 2013). Finally, linear mixed models prevent information loss due to averaging over observations, as the model accounts for all single trials.

In this study, participants (N = 44) and bimanual coordination patterns (n = 20) served as random factors in the linear mixed models. These models were built using the R language lmerTest package, version 2.0-30 (http://www.r-project.org/). Examination of the statistical assumptions required for linear mixed models revealed
that residuals were not normally distributed and not centred on zero. Therefore, a log10 transformation on target error score was conducted to normalise the distribution of residuals. Of note, for illustration purposes, the non-transformed data were plotted in the figures.

The first model of the series tested the effect of age on the fast (i.e. trial number 1–96 at Pre) or slow (i.e. Pre vs. Post) learning stage (Table 1; Model 1) controlling for the effect of feedback. The second model of the series included the pathways’ FA in interaction with the fast (Table 1; Model 2) or slow learning stage (Table 2; Model 5). The effect of the pathways’ FA on the fast learning stage was assessed based on the interaction with trial number at Pre, and the effect on the slow learning stage was assessed based on the interaction with Pre vs. Post. Including trial as a predictor is only possible using linear mixed models, as traditional ANOVAs require averaging over trials. The third model of the series included a 3-way interaction term (pathways’ FA × learning stage (fast or slow) × age) to investigate the extent to which the effect of FA on the fast (Table 1; Model 3) or slow (Table 2; Models 6a and b) learning stage was dependent on age. The continuous variables were centred on zero. Variance inflation factor (VIF; Belsley, 1991) was used to inspect signs of multicollinearity. Akaike information criterion (AIC; Sakamoto et al., 1986) was used to assess the relative quality of statistical models. The best model of each series (fast and slow stage of learning) was selected based on the following: (1) multicollinearity, with models showing predictors with VIF scores higher than ten being discarded (Hair et al., 1992) and (2) the fit of the models, with model with lower AIC score indicating a more accurate fit for a given set of data (Sakamoto et al., 1986).

Results

Age group differences in WM microstructural organisation

Figure 2A shows the population maps (across YA and OA) of transcallosal pathways connecting bilateral M1s, RPMd–LM1 and LPMd–RM1. In line with our expectation, significant age group differences were observed for all pathways of interest (separate Mann–Whitney U-tests, all P-values < 0.005), with higher FA in YA compared with OA (Fig. 2B).

Model selection

Model 1 (Table 1) investigating the effect of age on the fast learning stage showed an AIC score of 717.2. Model 2 (Table 1) testing the effect of pathways’ FA on the fast stage of learning showed an AIC score of 682.5. Thus, Model 2 predicted the data more accurately than Model 1 (ΔAIC = −34.7, negative ΔAIC means better fit). Model 3 (Table 1) investigating the age-dependent effect of pathways’ FA on the fast stage of learning did not meet the assumptions on the multicollinearity with a VIF score of 20.8. Yet, a sensitive analysis testing each 3-way interaction of Model 3 individually confirmed that none was significant (all P-values > 0.254). Accordingly, Model 2 was the best model of the series testing the fast stage of learning.
Table 1. Predictors of fast stage of bimanual coordination learning. Log10 target error scores (in a.u.) at Pre were used. Model 2 is the best model.

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Model 1</th>
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<th>Model 2</th>
<th></th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>SE</td>
<td>P</td>
<td>b</td>
<td>SE</td>
</tr>
<tr>
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<td>0.045</td>
<td>&lt;2 × 10^{-16} ***</td>
<td>1.308</td>
<td>0.055</td>
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<td>Feedback (vs. no feedback)</td>
<td>0.168</td>
<td>0.008</td>
<td>&lt;2 × 10^{-16} ***</td>
<td>0.168</td>
<td>0.008</td>
</tr>
<tr>
<td>FS learning (trials 1 to 96)</td>
<td>−0.002</td>
<td>3 × 10^{-4}</td>
<td>&lt;2 × 10^{-16} ***</td>
<td>−0.003</td>
<td>3 × 10^{-4}</td>
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<td>Age (OA vs. YA)</td>
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<td>0.056</td>
<td>&lt;8 × 10^{-9} ***</td>
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<td>0.085</td>
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<td>M1–M1 × age</td>
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<td>3 × 10^{-4}</td>
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<td>5 × 10^{-4}</td>
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<td>RPMd–LM1 × FS learning</td>
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<td>LPMd–RM1 × FS learning × age</td>
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<table>
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<td>9.1</td>
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<td>19.0</td>
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<td>AIC</td>
<td>717.2</td>
<td></td>
<td>682.5</td>
<td></td>
<td>679.8</td>
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</tbody>
</table>

FS = fast stage of learning; OA = older adults; YA = younger adults; L = left; R = right; M1 = primary motor cortex; PMd = dorsal premotor cortex; AIC = Akaike information criterion; VIF = variance inflation factor; b = coefficient/estimate; SE = standard error; σ² = variance; *P < 0.05; **P < 0.01; ***P < 0.001. For more details about models see ‘Statistical analysis’ and ‘Model selection’.
Table 2. Predictors of slow stage of bimanual coordination learning. Log₁₀ target error scores (in a.u.) at Pre and Post were used. Model 6b is the best model.

<table>
<thead>
<tr>
<th></th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6a</th>
<th>Model 6b</th>
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<td>b  SE</td>
<td>b  SE</td>
<td>b  SE</td>
<td>b  SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.356 0.039</td>
<td>1.305 0.048</td>
<td>1.222 0.049</td>
<td>1.308 0.048</td>
</tr>
<tr>
<td>Feedback (vs. no feedback)</td>
<td>0.176 0.006</td>
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</tr>
<tr>
<td>FS learning (trials 1 to 96)</td>
<td>-0.002 1×10⁻⁴</td>
<td>-0.002 1×10⁻⁴</td>
<td>-0.002 1×10⁻⁴</td>
<td>-0.002 1×10⁻⁴</td>
</tr>
<tr>
<td>SS learning (Pre vs. Post)</td>
<td>-0.346 0.008</td>
<td>-0.337 0.011</td>
<td>-0.312 0.012</td>
<td>-0.340 0.011</td>
</tr>
<tr>
<td>Age (OA vs. YA)</td>
<td>-0.384 0.046</td>
<td>-0.283 0.074</td>
<td>-0.284 0.069</td>
<td>-0.256 0.077</td>
</tr>
<tr>
<td>RPMd-LM1</td>
<td>2.735 1.899</td>
<td>4.597 2.477</td>
<td>2.938 1.897</td>
<td>2.545 1.214</td>
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<td>RPMd-RM1</td>
<td>-0.125 1.079</td>
<td>2.743 1.365</td>
<td>0.545 1.214</td>
<td>0.656</td>
</tr>
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<td>M1-M1 × age</td>
<td>-4.388 2.247</td>
<td>-11.840 2.878</td>
<td>-4.956 2.286</td>
<td>0.067</td>
</tr>
<tr>
<td>RPMd-LM1 × age</td>
<td>-3.501 3.396</td>
<td>-5.082 1.964</td>
<td>-1.759 1.489</td>
<td>0.243</td>
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<tr>
<td>Age × SS learning</td>
<td>-0.047 0.012</td>
<td>-0.065 0.018</td>
<td>-0.079 0.019</td>
<td>-0.088 0.019</td>
</tr>
<tr>
<td>RPMd-LM1 × SS learning</td>
<td>2.922 0.559</td>
<td>5.016 0.803</td>
<td>3.416 0.571</td>
<td>3.501 0.474</td>
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<td>RPMd-LM1 × SS learning</td>
<td>-3.574 0.472</td>
<td>-3.101 0.692</td>
<td>-3.751 0.474</td>
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<td>RPMd-RM1 × SS learning</td>
<td>0.564 0.268</td>
<td>-1.194 0.381</td>
<td>-0.019 0.303</td>
<td>0.951</td>
</tr>
<tr>
<td>RPMd-LM1 × SS learning</td>
<td>-3.433 1.140</td>
<td>1.075 0.948</td>
<td>3.464 0.548</td>
<td>1.530 0.372</td>
</tr>
<tr>
<td>RPMd-RM1 × SS learning</td>
<td>-3.433 1.140</td>
<td>1.075 0.948</td>
<td>3.464 0.548</td>
<td>1.530 0.372</td>
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Random effects

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<td>Highest VIF</td>
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<td>19.4</td>
<td>9.7</td>
<td>1312.2</td>
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</table>

FS and SS = fast and slow stage of learning; OA = older adults; YA = younger adults; L = left; R = right; M1 = primary motor cortex; PMd = dorsal premotor cortex; AIC = Akaike information criterion; VIF = variance inflation factor; b = coefficient/estimate; SE = standard error; σ² = variance; *P < 0.05; **P < 0.01; ***P < 0.001. For more details about models see 'Statistical analysis' and 'Model selection'.
Model 4 (Table 2) investigating the effect of age on the slow stage of learning showed an AIC score of 1379.4. Model 5 (Table 2) testing the effect of pathways’ FA on the slow learning stage predicted the data more accurately than Model 1 (ΔAIC = -53.8). Model 6a (Table 2) investigating the age-dependent effect of pathways’ FA on the slow stage of learning did not meet the assumptions on the multicollinearity with a VIF score of 19.4. However, sensitive analyses testing each 3-way interaction of Model 6a individually revealed that the 3-way interaction involving the LPMd-RM1 pathway was significant (P < 9 × 10⁻⁴) but not the ones involving M1–M1 (P = 0.087) and RPMd–LM1 (P = 0.130) pathways. Therefore, Model 6b (Table 2) was tested to include the 2-way interactions of Model 5 and the significant 3-way LPMd–RM1 FA × slow-stage learning × age interaction. This model met the multicollinearity assumption with a VIF score of 9.7 and predicted the data more accurately than Model 4 and Model 5 (ΔAIC = -67.2 and -13.4, respectively). Accordingly, Model 6b was the best model of the series testing the slow stage of learning.

Effects of age on the fast and slow stage of learning

Model 2 (Table 2) showed a significant fast-stage learning × age interaction (b = 0.002; P < 7 × 10⁻⁴; Fig. 3A) indicating that the fast stage of learning significantly differs between YA and OA. This effect of age was independent of microstructural organisation of the WM pathways as they were included in this model. Simple slope analysis revealed that target error score decreased more from trial 1 to 96 in OA (b = -0.003; P < 2 × 10⁻¹⁸) than in YA (b = -0.001; P < 3 × 10⁻⁵). Simple effect analysis revealed that target error score was also lower in YA than OA at trial 1 (b = 0.370; P < 2 × 10⁻⁷) and to a smaller extent at trial 96 (b = 0.284; P = 0.002).

Model 6b (Table 2) showed a significant slow-stage learning (i.e. Pre vs. Post) × age interaction (b = -0.088; P < 5 × 10⁻⁶; Fig. 3B) indicating that the slow stage of learning significantly differs between YA and OA. This effect of age was independent of microstructural organisation of the WM pathways as they were included in this model. Simple slope analysis revealed that target error score decreased more from Pre to Post in YA (b = -0.428; P < 2 × 10⁻¹⁵) than in OA (b = -0.340; P < 2 × 10⁻¹⁶). Simple effect analysis revealed that target error score was lower in YA than OA at Pre (b = 0.256; P = 0.002) and to a bigger extent at Post (b = 0.344; P < 5 × 10⁻⁷). Altogether, these results indicated that performance gain was larger in OA compared with YA in the fast stage of bimanual learning. Conversely, the gain in performance was larger in YA compared with OA in the slow stage.

Effects of WM microstructural organisation on the fast stage of learning

Model 2 (Table 1) showed a significant fast-stage learning (i.e. trials 1–96 at Pre) × M1–M1 FA interaction (b = -0.094; P < 4 × 10⁻¹¹; Fig. 4A), indicating that the effect of fast-stage learning significantly varies depending on the level of M1–M1 FA. Simple slope analysis revealed that target error score increased from trial 1 to 96 when M1–M1 FA was low (−1 standard deviation) (b = 0.002; P = 0.009) and decreased when FA was high (+1 standard deviation) (b = -0.004; P < 2 × 10⁻¹⁰). Simple effect analysis revealed that target error score did not significantly differ between low and high M1–M1 FA at trial 1 (b = 0.050; P = 0.985), but was lower at trial 96 for high compared with low M1–M1 FA values (b = -8.826; P = 0.002). In this model, a significant fast-stage learning × RPMd–LM1 FA interaction (b = 0.055; P < 5 × 10⁻⁶; Fig. 4B) also indicated that the fast-stage learning slopes were dependent on RPMd–LM1 FA. Simple slope analysis revealed that target error score decreased from trial 1 to 96 when RPMd–LM1 FA was low (b = -0.003; P < 6 × 10⁻¹²), but not when it was high (b = 6 × 10⁻⁴; P = 0.263). Simple effect analysis revealed that target error score did not significantly differ between low and high RPMd–LM1 FA at trial 1 (b = 0.050; P = 0.985), but was lower at trial 96 for low compared with high RPMd–LM1 FA (b = 5.342; P = 0.022). Model 2 also showed a non-significant fast-stage learning × LPMd–RM1 FA interaction (b = 0.003; P = 0.608) indicating that fast-stage learning slopes were not dependent on LPMd–RM1 FA. In sum, the model predicted higher absolute performance gain in the fast stage of bimanual learning when M1–M1 FA is high or when RPMd–LM1 FA is low, irrespective of age. Furthermore, LPMd–RM1 FA did not affect absolute performance gain in the fast stage of bimanual learning.

Effects of WM microstructural organisation on the slow stage of learning

Model 6b (Table 2) showed a slow-stage learning (i.e. Pre vs. Post) × M1–M1 FA interaction (b = 3.416; P < 3 × 10⁻⁶; Fig. 5A), which indicated that slow-stage learning slopes were dependent on M1–M1 FA. Simple slope analysis revealed that target error score decreased from Pre to Post when M1–M1 FA was low (b = -0.531;
and to a smaller extent when FA was high 

\[ b = \frac{0.550}{0.324} \; (P < 0.001). \]

However, simple effect analysis revealed that target error score did not significantly differ between low and high RPMd–LM1 FA at Pre 

\[ b = \frac{2.938}{0.813} \; (P = 0.129) \] and Post 

\[ b = \frac{0.019}{0.951} \; (P = 0.951). \]

In YA, simple slope analysis revealed that target error score decreased from Pre to Post when RPMd–LM1 FA was low 

\[ b = \frac{-0.306}{0.306} \; (P < 2 \times 10^{-16}) \]

and to a bigger extent when FA was high 

\[ b = \frac{-0.550}{2 \times 10^{-16}}. \]
from Pre to Post when LPMd–RM1 FA was low \( (b = -0.485; P < 2 \times 10^{-15}) \) and to a smaller extent when it was high \( (b = -0.373; P < 2 \times 10^{-16}) \). By contrast, in OA, target error score decreased from Pre to Post to the same extent for low \( (b = -0.339; P < 2 \times 10^{-16}) \) and high \( (b = -0.340; P < 2 \times 10^{-16}) \) LPMd–RM1 FA. Simple effect analysis revealed that target error score did not significantly differ between low and high LPMd–RM1 FA at Pre (YA: \( b = -1.214, P = 0.395 \); OA: \( b = 0.545, P = 0.656 \)) and Post (YA: \( b = 0.297, P = 0.835 \); OA: \( b = 0.526, P = 0.667 \)) in YA and OA. In sum, the model predicted higher absolute performance gain in the slow stage of bimanual learning when RPMd–LM1 FA is high or when M1–M1 FA is low, irrespective of age. Furthermore, lower LPMd–RM1 FA in YA predicted bigger performance gain in the slow stage of bimanual learning.

### Discussion

The present study investigated the extent to which (1) age determined the absolute performance gains in the fast and slow stages of bimanual learning, (2) WM microstructural organisation of the pathway between bilateral M1s and heterotopic pathways between M1 and PMd predicted bimanual motor learning in these stages and (3) the latter predictions were not affected by healthy ageing. DWI and CSD-based probabilistic tractography were used to delineate these transcallosal WM pathways in YA and OA. Behavioural results showed that both OA and YA improved their absolute performance in both fast and slow stages of bimanual learning. However, this improvement was larger during the fast (early) learning stage in OA and during the slow (later) stage in YA. The statistical models predicted that individuals with higher FA of M1–M1 and RPMd–LM1 WM pathways showed larger performance gain in the fast and slow stage of bimanual learning, respectively. These predictions were age-independent.

### Fast and slow stages of learning in YA and OA

Our findings support previous results showing that bimanual performance is lower in OA than YA (Swinnen et al., 1998; Voelcker-Rehage & Willimczik, 2006; Fling et al., 2011; Serbruyns et al., 2015). The lower performance level in OA is generally attributed to the age-related alterations in the central and peripheral nervous system as well as the neuromuscular system (Seidler et al., 2010). In line with previous studies, both age groups showed motor performance improvement during both fast and slow stages of learning (Brashers-Krug et al., 1996; Karni et al., 1998; Doyon et al., 2003). Furthermore, compared with YA, OA showed more gains in performance during the fast but less during the slow stage of bimanual learning. With respect to the fast learning stage, our results seem to be inconsistent with previous work showing higher (Swinnen et al., 1998; Wishart et al., 2002; Perrot & Bertsch, 2007; Cirillo et al., 2010) or similar (Howard & Howard, 1992; Cirillo et al., 2011; Berghuis et al., 2016) absolute performance gain in YA as compared to OA during the first day of practice. However, consistent with our findings, Brown et al. (2009) showed superior capacity of OA over YA to acquire new motor skills in the first session of training. Importantly, our analysis controlled for the level of performance and thereby ruled out this potential confound. Therefore, our results clearly support the fact that the fast learning stage of motor learning is not affected by ageing. With respect to the slow learning stage, our results support previous work showing higher absolute performance gain in YA as compared to OA after 5 days of practice in a demanding bimanual coordination task (Ren et al., 2015) or 4 days of practice in a juggling task (Perrot & Bertsch, 2007). Our findings seem to be in contrast with other juggling (Voelcker-Rehage & Willimczik, 2006) and bimanual coordination (Pauwels et al., 2015) studies indicating, respectively, equal or larger absolute performance gain in OA than YA after several days of practice. However, the results from these latter studies should be considered cautiously as they may be related to a larger window for improvement in OA due to lower initial performance levels.

In sum, our findings showed higher learning rates in OA during the early phase of learning, whereas learning rates were higher in YA during the late phase. This result could be related to previous studies showing that motor tasks learned more quickly are also the ones showing lower retention (Pauwels et al., 2015). Although these previous results were obtained by manipulating task complexity, they may suggest that the learning process we observed here in YA could be more robust over time than the one in OA. This would support previous results showing that retention is higher in YA than in OA (Pauwels et al., 2015). It is worth noting that the diversity of the bimanual tasks and the potential interactions of task-related factors (e.g. task complexity, task difficulty and the presence vs. absence of augmented feedback) and training-related factors (e.g. baseline performance and number of trials) with ageing effects may contribute to inconsistencies in the literature (Maes et al., 2017). In the current study, all these factors were controlled in the models (augmented vs. no augmented feedback, trial number, baseline performance as fixed factors, condition complexity and difficulty as random factors), which makes our findings particularly relevant.

### Microstructural organisation in OA

The spatial configuration of the homotopic transcallosal pathways between M1s was in good agreement with previous reports (Zarei et al., 2006; Wahl et al., 2007; Fling et al., 2013; Schulz et al., 2014). Regarding the heterotopic pathways between PMd and M1, anatomical data in animals have indicated the presence, although sparse, of such direct pathways (Marconi et al., 2003). Using CSD-based probabilistic tractography, we delineated these pathways with a high consistency across subjects and confirmed recent imaging data in humans (Boorman et al., 2007; Schulz et al., 2014; Ruddy et al., 2017). These human imaging data taken together with the animal anatomical data may further support the existence of such direct pathways in humans. We estimated the microstructural organisation of the underlying WM pathway of interest via FA. We found that, for all the reconstructed interhemispheric pathways of interest, the mean FA values were lower in OA than YA, which supports numerous studies indicating reductions in WM microstructural organisation with ageing (Nusbaum et al., 2001; Sullivan & Pfefferbaum, 2006, 2007; Minati et al., 2007; Giorgio et al., 2010; Serbruyns et al., 2015).

### WM pathways, motor learning and ageing

Previous work has indicated the dynamic modulation of activity in a widely distributed network of neocortical structures including, but not limited to, M1 and PMd during the fast and slow stages of bimanual learning (Debaere et al., 2004; Puttemans et al., 2005; Remy et al., 2008; Ronssse et al., 2011; Beets et al., 2015). In addition to intraregional modulation of activity, the alteration of interregional functional connectivity also plays an important role in bimanual learning (Andres et al., 1999; Serrien & Brown, 2003; Sun et al., 2007; Heitger et al., 2012). However, functional
interactions between brain regions may also be contingent upon the structure of the underlying WM pathways (Fields, 2008).

**WM pathways predicting performance in the fast and slow stages of motor learning**

Studies using functional connectivity showed that changes in the coupling of M1–M1 activity occur during the fast stage of bimanual learning (Andres et al., 1999; Serrien & Brown, 2003; Sun et al., 2007). Thus, our results showing that individuals with higher FA in the M1–M1 WM pathway improved more than individuals with lower FA in the fast learning stage support these functional studies and provide a structural foundation for the functional interactions during the fast stage of bimanual learning. Previous work has indicated the role of PMd in premovement cognitive processes such as action selection and planning (Hoshi & Tanji, 2002, 2004; O’Shea et al., 2007), which are important elements for learning of the visuomotor task used in the current study. The PMd is functionally lateralised, such that the LPmd is activated during performance of simple unimanual and bimanual movements, whereas the RPMd is particularly active during complex bimanual movements (Van den Berg et al., 2010). The involvement of PMd in motor learning is also lateralised towards the LPmd during the early stage of learning (for review see Schubotz & Von Cramon, 2003). However, the models from our analyses suggested no effect of LPmd–RM1 FA and an adverse impact of higher RPPMd–LM1 FA on the fast stage of learning. In other words, higher FA between RPPMd and LM1 may suggest that this pathway interferes with the fast learning stage. The absence of effect of the LPmd–RM1 pathway is not in line with previous functional activation findings showing consistent brain activity of LPmd in learning of unimanual motor tasks (Hardwick et al., 2013). This discrepancy suggests that including the less accurate non-dominant limb in the integrated bimanual control structure modifies the predictive value of right and left PMd-related metrics in motor learning.

Our results showed that individuals with lower FA in the M1–M1 WM pathway improved more than individuals with higher FA in the slow learning stage. This result was mainly explained by a difference at Pre but not at Post training session, which suggested that the M1–M1 pathway became less important for the performance in the advanced learning stage. The models also suggested a beneficial impact of higher RPPMd–LM1 FA on the slow stage of learning. In other words, higher FA between RPPMd and LM1 increased the performance gain in the slow learning stage, suggesting that this communication should be maximised at this stage. This results supports previous work showing the involvement of RPPMd during advanced stages of learning and in memory storage (for review see Schubotz & Von Cramon, 2003). However, this result should be cautiously considered as performance gain in the slow stage, and (3) age does not affect the latter predictions. These results suggest that, in both YA and OA, the M1–M1 and RPPMd–LM1 WM pathways are important for the fast and slow stage of bimanual learning, respectively.

Among the strengths of the present study is the use of CSD-based probabilistic tractography which is more reliable in tracking within regions including crossing fibres compared to other multi-fibre methods (Wilkins et al., 2015). However, we note that the acquisition of recently developed multishell DWI could enhance the tracking even more (Jeurissen et al., 2014). Another strength is the use of a statistical approach (i.e. linear mixed models) that limits false-positive rates. Because brain stimulation might alleviate impaired skill acquisition particularly in OA (Zimerman et al., 2013), additional knowledge of age-related structural alterations and their specific associations with motor functions will pave the way for optimising brain stimulation that is propagated via these structural pathways.

**Age does not influence the effect of WM microstructural organisation on learning**

A recent study by Schulz et al. (2014) showed associations between the slow stage of unimanual sequence learning and FA of WM pathways connecting sensorimotor cortical areas, but only in OA. The authors indicated that the lack of associations in YA could be due to the small sample size preventing sufficient statistical power. In the current study, instead of averaging performance across trials which limits the statistical power, we made use of single trials in the linear mixed models. Contrary to Schulz et al. (2014), we reported similar effects for both YA and OA regarding the role of M1–M1 and RPPMd–LM1 WM microstructural organisation in learning. The lack of a significant interaction with age in these pathways is consistent with previous work indicating a link between FA of the WM pathway connecting dorsolateral prefrontal cortex and caudate nucleus during the slow stage of unimanual learning in both YA and OA (Bennett et al., 2011). In our study, we did show an interaction between LPmd–RM1 FA × slow learning stage × age with low LPmd–RM1 FA predicting higher learning rates than high FA in YA. The result suggested an adverse impact of higher LPmd–RM1 FA on the slow stage of learning in YA but not in OA. However, these results in YA should be cautiously considered as performance between individuals with lower and higher LPMd–RM1 FA did not significantly differ at Pre and Post training sessions.

**Conclusion**

Our results showed that (1) age determines the learning gains in the fast and slow learning stages with larger absolute performance improvement in OA during the fast stage and in YA during the slow learning stage, (2) higher FA of the M1–M1 WM pathway predicts larger performance gain in the fast stage of bimanual learning, whereas higher FA of the RPPMd–LM1 WM pathway predicts higher gain in the slow stage, and (3) age does not affect the latter predictions. These results suggest that, in both YA and OA, the M1–M1 and RPPMd–LM1 WM pathways are important for the fast and slow stage of bimanual learning, respectively.

Among the strengths of the present study is the use of CSD-based probabilistic tractography which is more reliable in tracking within regions including crossing fibres compared to other multi-fibre methods (Wilkins et al., 2015). However, we note that the acquisition of recently developed multishell DWI could enhance the tracking even more (Jeurissen et al., 2014). Another strength is the use of a statistical approach (i.e. linear mixed models) that limits false-positive rates. Because brain stimulation might alleviate impaired skill acquisition particularly in OA (Zimerman et al., 2013), additional knowledge of age-related structural alterations and their specific associations with motor functions will pave the way for optimising brain stimulation that is propagated via these structural pathways.

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Conflict of interest
We have no conflict of interest or competing interests to disclose.

Author contributions
HZA, IAMB, MBP and SPS designed the study. IAMB and JG performed the experiment. HZA, SC, IL, QC, JS and BJ contributed in image processing and analysis. MPB and BC performed statistical analyses. HZA and MBP wrote the first draft of the manuscript, but all authors contributed in revising the work and approved the final version of the manuscript.

Data accessibility

Abbreviations
AIC, Akaike information criterion; b, coefficient/estimate; CC, corpus callosum; CSD, constrained spherical deconvolution; DWI, diffusion-weighted imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; FOV, field of view; FS, fast stage; GM, grey matter; GRE, gradient echo; HMAT, human motor area template; L, left; M1, primary motor cortex; MNI, Montreal Neurological Institute; MPRAGE, magnetisation-prepared rapid gradient echo; OA, older adults; ODF, orientation distribution function; PMd, dorsal premotor cortex; ROI, region of interest; R, right; SD, standard deviation; SE, standard error; SPAIR, spectral attenuated inversion recovery; SS, slow stage; TE, echo time; TR, repetition time; VIF, variance inflation factor; WM, white matter; YA, young adults.

References


