Fundamental Differences in Callosal Structure, Neurophysiologic Function, and Bimanual Control in Young and Older Adults

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Bimanual actions involve coordinated motion but often rely on the movements performed with each hand to be different. Older adults exhibit differentially greater variability for bimanual actions in which each hand has an independent movement goal. Such actions rely on interhemispheric communication via the corpus callosum, including both facilitatory and inhibitory interactions. Here, we investigated whether age differences in callosal structure and interhemispheric function contribute to this selective movement difficulty. Participants performed 3 force production tasks: 1) unimanual, 2) bimanual simultaneous, and 3) bimanual independent. Older adults had significantly greater interhemispheric facilitation during voluntary muscle activation. We also report a fundamental shift with age in the relationship between callosal tract microstructural integrity and interhemispheric inhibition (IHI). Specifically, older adults with relatively greater callosal tract microstructural integrity have less IHI. Furthermore, greater IHI was related to poorer bimanual performance (assessed by dominant hand force variability) in older adults on all tasks, whereas this relationship was only observed in young adults for the bimanual independent condition. These findings indicate changes in interhemispheric communication with advancing age such that older adults may rely on bilateral cortical cooperation to a greater extent than young adults for manual actions.

Introduction

For many bimanual activities (e.g., shirt buttoning), each hand works independently to accomplish a mutual goal. Such movements not only involve coordinated motion in time and space but also rely on independent control of each hand (cf., Swinnen 2002; Carson 2005). Older adults demonstrate specific difficulties with motor tasks where the 2 hands are moving along independent spatial–temporal paths (Bangert et al. 2009; Fling, Walsh, et al. 2011), which we refer to as bimanual independent movements. Interhemispheric transfer via the corpus callosum plays a key role in the production of such coherently integrated behavior, assuring the appropriate balance of excitatory and inhibitory transcallosal communication between the primary motor cortices.

Transcallosal fibers primarily connect homologous cortical regions of the right and left hemispheres; thus, the corpus callosum mediates the transfer and integration of the lateralized cognitive, motor, and sensory information between the cortices (Aboitiz 1992). Numerous studies utilizing diffusion tensor imaging (DTI)-based fiber tractography have demonstrated the relationships between interhemispheric motor fiber tract microstructural integrity and task performance in both healthy participants (Johansen-Berg et al. 2007) and those with white matter dysfunction (Bartels et al. 2008; Bonzano et al. 2008; Kern et al. 2011). While individual differences in callosal quantity and quality have shown to be behaviorally relevant in both young and older adults, it appears there may be a fundamental shift with age in these relationships. For example, recent work from our lab has demonstrated that the size and microstructural integrity of callosal regions connecting these sensorimotor cortical targets are related to motor performance in a differential fashion for young and older adults. Specifically, on an asynchronous bimanual tapping task greater callosal microstructural integrity was related to “poorer” performance in young adults, yet “better” performance in older adults (Fling, Walsh, et al. 2011). As a result of poorer callosal tract structure, an alteration in the balance of interhemispheric excitation and inhibition may be one potential mechanism underlying the differential age relationships we previously observed (Fling, Walsh, et al. 2011).

Interhemispheric communication can have either net facilitatory or inhibitory effects (Chen et al. 2003); however, multiple lines of research indicate that callosal connections between the 2 motor cortices have primarily inhibitory effects (Netz 1999; De Gennaro et al. 2004; Lenzi et al. 2007). Structural integrity of callosal tracts connecting the primary motor cortices is predictive of interhemispheric inhibition (IHI) in young adults (Wahl et al. 2007; Fling, Benson, et al. 2011), whereas relationships between inhibition and callosal structure have yet to be described in older adults. Multiple studies have documented increased bilateral cortical recruitment in older adults during both cognitive and motor tasks (cf., Reuter-Lorenz and Lustig 2005; Seidler et al. 2010) suggestive of an age-related shift toward increased excitatory communication. Thus, a converging body of literature indicates decline in both IHI and callosal tract microstructural integrity with advancing age, coupled with an increase in interhemispheric facilitation. The interrelationships between transcallosal motor tract microstructural integrity and neurophysiologic function, and their combined impact on motor control, have yet to be studied.

In the present study, participants performed behavioral tasks to assess manual dexterity, including the Purdue Pegboard and timed shoelace tying and shirt buttoning. We used DTI to quantify the microstructural integrity of transcallosal fiber tracts connecting the primary motor cortices. Furthermore, participant’s motor control was assessed on 3 force production tasks: 1) unimanual, 2) bimanual simultaneous, and 3) bimanual independent. Finally, we used transcranial magnetic stimulation (TMS) to assess interhemispheric facilitation (via contralateral motor evoked potentials [MEPs]) and inhibition (via ipsilateral...
silent period [iSP]) in young and older adults during unimanual force production. We hypothesized that better microstructural integrity of the callosal fiber tracts connecting the 2 primary motor cortices would be positively related to bimanual task performance in older adults, but negatively related to performance in young adults. Furthermore, we hypothesized that lower IHI would be related to better bimanual independent task performance in both young and older adults. Finally, we expected to find less IHI and greater interhemispheric facilitation in older adults. This pattern of results would provide support for the notion that callosal structure-function relationships, as well as the balance of IHI and interhemispheric facilitation, undergo a fundamental shift with age.

Materials and Methods

Participants

Twenty-one young adults (10 men; mean age 22.1 ± 2.8 years; range 18-28 years) were recruited from the student population at the University of Michigan (average education: 15.0 years). Eighteen community-dwelling older adults (8 men; 67.2 ± 5.2 years; range 65–76 years) also participated in this study (average education: 15.3 years). This experiment was approved by the Medical Institutional Review Board of the University of Michigan. Participants gave their informed written consent prior to beginning the experiment and were compensated for their time.

We performed testing on 2 days, separated by <1 week. On the first day of testing, we acquired structural magnetic resonance (MR) and diffusion weighted (DW) images (detailed in the following section). We also administered the Edinburgh Handedness Inventory (Oldfield 1971); all participants were strongly right handed, (mean = 0.89) and the Montreal Cognitive Assessment (MoCA) to assess general cognitive function. All participants completed the unimanual (dominant and nondominant hand), bimanual, and assembly components of the Purdue Pegboard as well as timed tasks of shoelace tying and buttoning a dress shirt. On the second day of testing, we assessed IHI through the use of the iSP technique and interhemispheric facilitation assessed by the contralateral MEP amplitude. Both measures were assessed during the unimanual force production task described below.

Image Acquisition

On day 1, we collected whole brain high-resolution structural MR images on a 3T MR imaging (MRI) scanner (General Electric, Waukesha, WI) using a spoiled gradient echo sequence (124 slices, field of view: 24 cm, voxel size: 0.94 × 0.94 × 1.4 mm, time repetition [TR]: 10.2 ms, and time echo [TE]: 3.4 ms). DW images were collected using a single shot echo-planar sequence in the axial plane (39 slices; TE/TR: 82.8 ms/9000 ms; field of view: 220 × 220 mm; voxel size 0.9 × 0.9 × 3.1 mm; b-value = 800 s/mm²; 15 diffusion-sensitizing directions). Images were motion and eddy-current corrected to account for drifts in scanner acquisition. Using the averaged images with b = 0 and b = 800 s/mm², the diffusion tensor was calculated and fractional anisotropy (FA) images were constructed off-line using ExploreDTI (Tournier et al. 2011). Diffusion tensors were calculated from the 15 DW images based upon a simple least squares fit of the tensor model to the diffusion data (Basser et al. 2000). Diagonalization of the tensor yields 3 voxel-specific eigenvalues (λ₁ > λ₂ > λ₃) representing diffusivities along the 3 principle directions of the tensor. The 3 eigenvectors were then used to construct fiber tracts and the resultant diffusion properties as described below.

Fiber Tractography

Interhemispheric fiber tractography between sensorimotor regions of interest was performed using a previously described technique (Fling, Benson, et al. 2011). Briefly, each participant’s FA map was normalized into an Montreal Neurological Institute (MNI) space via a rigid-body transformation, and voxel size was resampled to 2 × 2 × 2 mm through the use of ExploreDTI (Tournier et al. 2011). The Human Motor Area Template (HMAT; Mayka et al. 2006) was also rigid-body transformed into MNI space, coregistered to each individual’s normalized FA image, and subsequently used as a mask of the primary motor cortex (M1). Interhemispheric fiber tracts were identified by placing seed and target regions of interests in the homologous M1 regions as identified by the HMAT. Fiber tracts were constructed based upon deterministic streamline tractography using the method of Mori et al. (cf., Mori and van Zijl 2002).

IHI and Interhemispheric Facilitation

Five young adults and 3 older adults from the first day of testing were unable to undergo the TMS procedure based on screening (6 individuals were taking prescription medication with possible contraindications and 2 individuals had a familial history of epilepsy). Thus, on day 2 a subset of 16 young adults and 15 older adults from the initial imaging session underwent a TMS procedure to assess IHI and interhemispheric facilitation.

Experimental Task

Participants were seated in a chair with both their dominant and nondominant forearms resting on a table. The shoulders were abducted at approximately 45°, the elbows were flexed at approximately 90°, and the forearms were pronated with the palms of the hand lying flat on the custom apparatus. The wrist, third, fourth, and fifth fingers were constrained from moving, isolating force production to the index finger. A preamplified force transducer (OMEGA LC509-015 Beam Load Cell) was positioned at the lateral aspect of the proximal interphalangeal joint of the isolated index finger to record compressive isometric force (output: 0.5–9.5 Vdc; excitation: 24 ± 4 Vdc).

Surface electromyography (EMG) and MEPs were recorded from the first dorsal interosseous (FDI) muscle of both hands using 4 mm Ag/AgCl electrodes. Surface EMG and MEP data were recorded using Biopac hardware and AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA). The EMG signal was collected and digitized at 2000 Hz, amplified and band pass filtered (10–1000 Hz). To assess maximal voluntary contractile (MVC) force of the FDI, participants were instructed to press as hard as possible on the load cell using the index finger abduction of the dominant or nondominant hand for 3 consecutive 6 s trials per hand. The highest force sample in each trial was averaged across 3 MVC trials providing an estimate of the participants’ MVC. A minimum 90-s rest period was provided in between each MVC trial.

Participants performed 3 different force production tasks: 1) unimanual isometric force of the dominant hand at a constant force target level; 2) bimanual simultaneous isometric force with both hands producing the same constant force target level (bimanual simultaneous task); and 3) dominant hand isometric force at a constant force target level while the nondominant hand matched a 1 Hz sine wave (bimanual independent task; Fig. 1). The order of conditions was counter balanced across the participants. For all conditions, the force target levels used in the experiment were scaled to 20% of each individual subject’s MVC (during the bimanual independent task, the peak force of the nondominant sine wave-matching hand was also 20% MVC), visual feedback of the target force and the produced force were provided. Each trial lasted 35 s and force output was sampled at 200 Hz. Participants were provided rest breaks of 5 min in between each trial (a total of 9 trials) in an attempt to minimize fatigue.

 Ipsilateral Silent Period

IHI was measured by evoking an iSP in the dominant hand FDI. The iSP is elicited by focal TMS of the M1 ipsilateral to the hand making a voluntary contraction, leading to a brief suppression of voluntary activity in the electromyogram signal of this muscle (Meyer et al. 1995). The iSP reflects inhibition of volitional motor activity and thus is particularly well suited to investigate interhemispheric control of voluntary cortical motor output (Giovannelli et al. 2009).

Prior to performing the experimental paradigm, we used a Magstim Rapid magnetic stimulator (The Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, UK) and a focal figure of 8 coil (diameter of each wing 70 mm) to identify the right hemisphere M1 hotspot for the left FDI. The coil was placed tangential to the scalp with the handle
The optimum site in the right M1 (hotspot) for eliciting motor responses in the left FDI was identified at suprathreshold intensity. This location was marked on the scalp and subsequently utilized to elicit iSPs from the right FDI as it has previously been shown that the topography of the contralateral MEP and the iSP correspond closely (Wassermann et al. 1991). Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output. Using standard protocol, the RMT was defined as the minimum stimulus intensity that elicited MEPs of 50 μV in at least 5 out of 10 consecutive trials (Triggs et al. 1994).

Once participants reached the target force level during the unimanual task, we applied stimulation at 120% of RMT to the right motor cortex to elicit dominant hand iSPs. A minimum of 5 iSPs were evoked per trial with an interstimulus interval jittered between 5 and 8 s (Garvey et al. 2001; Jung and Ziemann 2006). During the unimanual condition, EMG data were also collected and monitored from the nondominant hand to ensure full relaxation and that the TMS coil was always in the appropriate location over the right M1.

**Interhemispheric Facilitation**

Interhemispheric facilitation was assessed by measuring the motor-evoked potential in the resting nondominant hand during unimanual isometric contraction. Ongoing activity of 1 motor cortex has previously been shown to transcallosally facilitate the contralateral M1 (Sohn et al. 2003; Carson et al. 2004), which is reflected by an increase in the size of the contralateral MEP (i.e., the nondominant resting hand in this context).

**Data Analysis**

**Fiber Tractography**

Descriptive metrics were calculated for the microstructural integrity of M1 fiber tracts, including FA and radial diffusivity \( \left( \frac{\gamma_2 + \gamma_3}{2} \right) \). FA, a rotationally invariant index that ranges from 0 (isotropic) to 1 (anisotropic), is a measure of the magnitude and orientation of diffusion derived from the tensor’s eigenvalues on an intravoxel basis (Sullivan et al. 2010). Therefore, higher FA values are interpreted as reflecting better white matter microstructural integrity (Basser and Pierpaoli 1996). Conversely, "lower" radial diffusivity is interpreted as being indicative of better tract microstructural integrity (Basser et al. 2000).
Interhemispheric Facilitation

Peak-to-peak amplitude was quantified for each MEP elicited from the nondominant hand during the unimanual force production task (15 in total per participant). Because MEPs were standardized to 50 μV when identifying the RMT, those elicited during the task result in a normalized value comparable across participants.

Statistical Analysis

Independent t-tests were performed to compare between-group performance on the MoCA, timed shoelace tying and shirt buttoning, contralateral MEP amplitude (interhemispheric facilitation), and all metrics of IHE: ISP onset, ISP duration, dISP, and dISP-max. A mixed-model repeated measures analysis of variance (ANOVA) was used to analyze measures of fiber tract microstructural integrity, manual dexterity, and dominant hand force production. Significance was set at an alpha of 0.05 (SPSS 18.0) and the Huyn-Feldt epsilon was computed to test for sphericity; we interpreted corrected P values in cases of violation. Significant main effects were subjected to post hoc paired t-tests and Bonferroni corrected for multiple comparisons. We have previously shown a fiber-tract-specific relationship between the microstructural integrity and inhibition (Fling, Benson, et al. 2011); thus, within each age group, we performed linear regression to investigate the relationship(s) between microstructural integrity of fiber tracts connecting the primary motor cortices, dISP, and dominant hand variability (RMSE) on the 3 different force production tasks. Therefore, M1 fiber tract microstructural integrity was used as a predictor of dISP and behavioral performance, and dISP was also used separately as a predictor of behavioral performance. We also used linear regression to investigate the association between the interhemispheric facilitation and motor overflow. All correlation analyses using either fiber microstructural integrity or dISP as a predictor were Bonferroni corrected for multiple comparisons (α = 0.05/4). Finally, for all significant relationships, we used a Fisher r-to-Z transformation to compare the strength of correlations between age groups. All data are presented as mean ± SD, unless otherwise noted.

Results

Behavioral Testing

Descriptive metrics of cognitive performance (MoCA), manual dexterity (Purdue Pegboard), and functional manual control tasks (timed shoelace tying and shirt buttoning) can be viewed in Table 1. While both groups demonstrated similar MoCA scores and performance on the shoelace-tying task, young adults were significantly better at all manual dexterity tasks assessed with the Purdue Pegboard (a significant group and condition main effect, but no group × condition interaction; P < 0.001 for all comparisons), as well as significantly faster on the timed shirt-buttoning task (P < 0.01).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Group performance on tasks assessing general cognitive performance, manual dexterity, and manual performance of daily functional tasks</th>
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<tbody>
<tr>
<td></td>
<td>Young adults</td>
</tr>
<tr>
<td>MoCA</td>
<td>28.8 (1.3)</td>
</tr>
<tr>
<td>Purdue Pegboard (number of pegs)</td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>16.0 (1.9)*</td>
</tr>
<tr>
<td>Nondominant</td>
<td>14.9 (2.1)*</td>
</tr>
<tr>
<td>Bimanual</td>
<td>12.6 (1.0)*</td>
</tr>
<tr>
<td>Assembly</td>
<td>39.8 (8.2)*</td>
</tr>
<tr>
<td>Shirt buttoning (s)</td>
<td>13.9 (2.3)*</td>
</tr>
<tr>
<td>Shoelace tying (s)</td>
<td>4.7 (0.9)</td>
</tr>
</tbody>
</table>

Note: For the MoCA and Purdue Pegboard, higher values are indicative of better performance. For timed shoelace tying and shirt buttoning, lower times are indicative of faster performance. Young adults demonstrated significantly better performance on all components of the Purdue Pegboard and were significantly faster on the shirt-buttoning task. No group differences were noted for the MoCA or in timed shoelace tying. Data are mean (SD). *P < 0.05.

Interhemispheric Sensorimotor Fiber Tracts

A significant age group difference was noted for FA (F1,30 = 21.5, P < 0.001) and radial diffusivity (F1,30 = 11.1, P < 0.001) with a higher FA and lower radial diffusivity in young adults, both indicative of better fiber tract microstructural integrity. FA and radial diffusivity were highly correlated across individuals (r = 0.7); therefore, we use FA as our sole measure of fiber tract microstructural integrity for the remainder of the current manuscript.

Force Production Performance

MVC force was quite similar between groups for both the dominant (YA: 4.3 lbF; OA: 4.6 lbF) and nondominant (YA: 3.9 lbF; OA: 4.3 lbF) FDI with no statistical differences noted. As a result, during the force production tasks, both groups were producing not only the same relative forces but also similar absolute forces. A repeated measures ANOVA of dominant hand force variability across the 3 conditions revealed a significant main effect of RMSE for condition (F2,50 = 303.8, P < 0.001) and for group, such that older adults had significantly more variability (F1,29 = 23.7, P < 0.001). Post hoc paired-sample t tests showed that dominant hand variability was significantly lower during the unimanual condition than for either bimanual condition (t > 6.6, P < 0.001 for both comparisons). When comparing the 2 bimanual conditions (simultaneous and independent), dominant hand variability was significantly lower during the simultaneous condition (t1,30 = 8.5; P < 0.001). Finally, we found a significant condition × group interaction for RMSE (F1,29 = 75.4, P < 0.001), such that variability was differentially greater in older adults during the bimanual independent condition (t1,29 = 7.9; P < 0.001; Fig. 2). No differences were noted between the groups for either the unimanual or bimanual simultaneous conditions (t1,29 < 0.7; P > 0.5 for both comparisons).

For dominant hand force accuracy (mean force output normalized to the target goal), we report a significant main effect of condition (F2,56 = 16.7, P < 0.001) but no group main effect (F1,28 = 0.9; P > 0.35) or group × condition interaction (F2,56 = 1.3; P > 0.26). No difference in accuracy
was found between the unimanual (91.9%) and bimanual simultaneous (91.5%) force conditions. Dominant hand accuracy on both these conditions was significantly better than during the bimanual independent task (77.6%; \( t_{1,29} = 4.0; P < 0.001 \) for both comparisons).

Two additional behavioral metrics demonstrate that participants were able to adhere to each bimanual force condition. During the bimanual simultaneous condition, nondominant hand variability (RMSE = 0.057) and accuracy (89.06%) were similar to the dominant hand during the same task (RMSE = 0.054; accuracy = 91.5%). Furthermore, during the bimanual independent force condition, both groups were able to approximate a 1 Hz sine wave with the nondominant hand (mean frequency YA: 0.93 Hz; OA mean: 0.89 Hz).

### IHI and Interhemispheric Facilitation

All TMS measures can be viewed in Table 2. Briefly, no difference in RMT was noted between groups (\( P > 0.4 \)); thus, stimulation intensity to elicit iSPs (120% RMT) was similar for young (76% of maximal stimulator output) and older adults (78% of maximal stimulator output). To elicit the 15 iSPs necessary for analysis, an average of 15.3 stimulations and 15.5 stimulations were required for the young and older groups, respectively. Although not significant, we report a trend for stimulations were required for the young and older groups, respectively. Although not significant, we observed a trend such that FA was negatively correlated with the variability for older adults on both the unimanual (\( r = -0.33; P < 0.1 \)) and bimanual simultaneous (\( r = -0.34; P < 0.1 \)) condition. Finally, we found that during the bimanual independent condition FA was positively associated with dominant hand variability (\( r = 0.41; P < 0.06 \)) in young adults at a level trending toward significance, but negatively associated with variability in older adults (\( r = -0.57; P < 0.01 \)). The strength of these correlations was also significantly different between groups when assessed using a Fisher r-to-Z transformation (\( Z = 2.7; P < 0.01 \); Fig. 6). Therefore, we show that structural integrity of interhemispheric fiber tracts is related to complex bimanual motor performance in a differential fashion for young and older adults.

Similar to the observed structural relationships, IHI was not related to performance in young adults during either the unimanual (\( r = -0.13 \)) or bimanual simultaneous (\( r = -0.19 \)) conditions. Conversely, in older adults greater IHI was significantly related to poorer performance of both the unimanual (\( r = 0.59; P < 0.01 \)) and the bimanual simultaneous (\( r = 0.55; P < 0.01 \)) condition. We also report that greater IHI is correlated with more dominant hand variability during the bimanual independent condition for both age groups (YA: \( r = 0.59; OA: r = 0.63 \)). Thus, higher IHI is associated with poorer performance on only the most difficult bimanual condition in young adults. Conversely, greater IHI is related to poorer performance across all conditions in our older adult contingent. Finally, no relationship was observed in young or older adults between interhemispheric facilitation and motor performance (\( P > 0.1 \)), nor between facilitation and fiber tract microstructural integrity (\( P > 0.1 \)).

### Discussion

To our knowledge, this is the first study to simultaneously investigate the effects of age on interhemispheric microstructural integrity and physiologic function along fiber tracts connecting the primary motor cortices. We employed a comprehensive approach to investigate callosal sensorimotor fiber tract structure, IHI, facilitation, and their combined impact on motor control in young and older adults. We report that older adults exhibit disproportionately greater variability for

#### Table 2

<table>
<thead>
<tr>
<th>Measures evoked using TMS</th>
<th>Young adults</th>
<th>Older adults</th>
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<tbody>
<tr>
<td>RMT, %</td>
<td>63.6 (2.3)</td>
<td>64.9 (3.1)</td>
</tr>
<tr>
<td>Prestimulus EMG, mV</td>
<td>1.03 (0.14)</td>
<td>0.93 (0.13)</td>
</tr>
<tr>
<td>iSP onset, ms</td>
<td>38.6 (0.8)</td>
<td>29.8 (0.9)</td>
</tr>
<tr>
<td>iSP duration, ms</td>
<td>27.4 (2.2)</td>
<td>27.9 (1.8)</td>
</tr>
<tr>
<td>dSP, %</td>
<td>73.6 (1.6)</td>
<td>68.9 (2.3)</td>
</tr>
<tr>
<td>dSP maximum, %</td>
<td>91.9 (1.1)</td>
<td>91.5 (1.3)</td>
</tr>
<tr>
<td>Contralateral MEP, mV</td>
<td>3.98 (1.7)</td>
<td>10.3 (4.8)*</td>
</tr>
</tbody>
</table>

Note: No age group differences were noted for any measure, although a trend was observed toward a decreased IHI (assessed by dSP) in older adults (\( P < 0.08 \)). Older adults had significantly greater interhemispheric facilitation (assessed by contralateral MEP). Values are mean (SD). *\( P < 0.001 \).
Figure 3. Age-related differences in IHI (A) and interhemispheric facilitation (B). There was a trend for greater IHI in young adults ($P < 0.08$) and significantly greater facilitation in older adults ($P < 0.001$). For both age groups, a representative example of the iSP (mean of 15 stimulations) and contralateral MEP (one stimulation) are provided. For each instance, the young adult example is the top panel and the older adult example is the bottom panel. In each of these instances, stimulation is applied at time point 0. $***P < 0.001$. 
Figure 4. (A) Rectified EMG activity during a unimanual force production trial from 1 representative young (top 2 panels) and older adult (bottom 2 panels) illustrating motor overflow for the older adult. For each participant, the top panel reflects EMG activity from the nondominant resting hand’s FDI, whereas the bottom panel is EMG from the dominant, force producing hand’s FDI. Observable spikes in each participant’s nondominant hand, EMG activity profile reflect stimulator artifact during SP elicitation. Note that different scales are used on the y-axis for nondominant as opposed to dominant hand EMG activity to better illustrate motor overflow. (B) Average EMG during the unimanual force production task from the nondominant FDI normalized to baseline EMG activity. Older adults had significantly greater motor overflow than young adults. *P < 0.02. LH = left hand (nondominant); RH = right hand (dominant).

Figure 5. (A) Age differences in the relationship between the microstructure of interhemispheric fiber tracts connecting primary motor cortices and IHI. While young adults demonstrate a significant linear relationship \( r = 0.76; P < 0.001; \) red), older adults show an inverse relationship \( r = -0.72; P < 0.002; \) blue). Using a Fisher r-to-Z transform, the strength of correlation is also significantly different between groups \( P < 0.001 \). The dashed line represents linear regression fit for older adults. (B) Interhemispheric fiber tracts connecting bilateral primary motor cortices in a representative young (red) and older (blue) adult. Coordinates for both images are \( x = 0, y = -2, z = 30 \) in normalized MNI space.
bimanual actions when the 2 hands have independent force production goals. Additionally, we have shown that IHI is negatively associated with performance on the bimanual independent condition in both age groups; however, interhemispheric fiber tract structural integrity is related to performance in a differential fashion for young and older adults. A novel finding of the current study is that lower FA (i.e., poorer microstructural integrity) is strongly correlated with higher levels of IHI in older adults. This is the opposite of what has previously been reported in young adults (Fling, Benson, et al. 2011; Wahl et al. 2007). Thus this is the first work to report a quantitative shift in the relationship between sensori-motor fiber tract microstructural integrity and IHI with age.

A significant body of literature has identified transcallosal connections between the homologous M1 regions, both within human and non-human models. While dense connections between M1 trunk and face representations have reliably been identified; M1 forelimb and hand representations typically have relatively scant callosal connections (Rouiller et al. 1994; Fang et al. 2008). The current study demonstrates relatively dense M1 callosal connections, and although we do not identify the specific cortical target of these fiber tracts (e.g., hand or face regions of the precentral gyrus), the relationships with physiological function discussed below provide strong evidence that the M1 fiber pathways we have identified play a significant role in the interhemispheric communication during volitional motor output.

Structural MRI has demonstrated that there is substantial interindividual variability in callosal size and morphology for both young and older adults (Stancak et al. 2003; Raz et al. 2010; Sullivan et al. 2010; Fling, Chapekis, et al. 2011; Fling, Walsh, et al. 2011). Recent neuroimaging literature indicates that not only is the quantity of white matter reduced in older adults but also the quality of remaining white matter is compromised as well (reviewed in Seidler et al. 2010). Multiple studies report declines in callosal microstructural integrity with advancing age (cf., Seidler et al. 2010), which are associated with significant behavioral deficits. For example, less lateralized task processing during both cognitive (Muller-Oehring et al. 2007) and motor (Langan et al. 2010) tasks is associated with smaller callosal size in older adults. In the current study, we found that older adults exhibit differentially greater variability for bimanual tasks when the 2 hands have independent movement goals. This was evidenced by greater dominant hand variability during the bimanual independent force production task, as well as poorer performance on clinical (Purdue Pegboard) and functional (timed shirt buttoning) tasks of manual dexterity in older adults. On the other hand, older adults demonstrated comparable performance to young adults during the unimanual and bimanual simultaneous force conditions. Although previous studies report that increased callosal microstructural integrity is beneficial to speeded synchronous bimanual tasks in young adults (Johansen-Berg et al. 2007) and individuals with multiple sclerosis (Bonzano et al. 2008), recent work from our lab demonstrates that this relationship is task specific. Specifically, “asynchronous” bimanual performance and callosal microstructural integrity are negatively related in young adults, whereas they are positively correlated in older adults (Fling, Walsh, et al. 2011). These findings strongly implicate age differences in size and integrity of callosal microstructural fibers as key contributors to the bimanual control deficits, potentially due to a reduced ability to inhibit motor overflow to the contralateral sensorimotor cortex.

The current findings suggest a shift in the balance of IHI and interhemispheric facilitation with advanced age. IHI is mediated by the transcallosal glutamatergic pathways that synapse onto pyramidal tract neurons through gamma-aminobutyric acid inhibitory interneurons (Werhahn et al. 1999). A converging body of literature indicates there are reductions in cortical inhibition with advancing age. Declines in both intrahemispheric (Peinemann et al. 2001; Sale and Semmler 2005) and interhemispheric (Talelli et al. 2008) inhibition have been reported in older adults, as well as a reduced ability to modulate intracortical inhibition to meet task demands (Fujiyama et al. 2009). Age differences in IHI have not previously been investigated using the iSP technique nor have there been reports of age differences in interhemispheric facilitation. We found that older adults had significantly greater interhemispheric facilitation, coupled with a trend for less IHI. Furthermore, although stronger inhibition was predictive of decreased facilitation in the young adults, no such relationship existed in the older adults. Multiple studies have previously indicated that older adults have increased bilateral cortical activity (Ward and Frackowiak 2003; Ward et al. 2008) and interhemispheric motor network connectivity (Langan et al. 2010; Zuo et al. 2010) potentially reflective of an increased excitability within these motor regions, and a release from their typically inhibitory interactions. This study provides physiological evidence supporting this hypothesis; however, the underlying mechanisms resulting in this potential shift in interhemispheric communication have yet to be fully elucidated.

Interindividual variability in motor control is frequently treated as a source of "noise" and discarded by averaging data from a group of participants. Kanai and Rees (2011) recently proposed that interindividual differences can be used as a source of information to link human behavior to brain anatomy. Indeed, we report that greater IHI was related to...
poorer performance across all force production tasks in older adults, whereas higher levels of IHI was only related to poorer performance during the bimanual independent task in young adults. Similarly, previous work has shown that older adults benefit from bihemispheric processing across all levels of task complexity on a divided visual field letter-matching task, whereas young adults only demonstrate similar benefits on the most complex tasks (Reuter-Lorenz et al. 1999). Taken together, these results suggest that older adults benefit from bilateral cortical cooperation (less IHI) across all tasks, whereas young adults only benefit from such cooperation during the bimanual independent task.

While IHI is necessary to prevent interference of control processes between the 2 cortices (cf., Bloom and Hynd 2005; Carson 2005), emerging work demonstrates that reduced IHI is beneficial for performance of asynchronous bimanual tasks (Shim et al. 2005). For example, musicians have decreased IHI compared with nonmusicians (Ridding et al. 2000). Conversely, individuals with the demyelinating disease multiple sclerosis have greater levels of IHI (Boroojerdi et al. 1998). The fact that IHI and fiber tract microstructural integrity are related to performance in a differential fashion for young and older adults strongly supports our finding of an age-related shift in the relationship between interhemispheric fiber tract structure and IHI.

Studies combining DTI and TMS have previously shown that fiber tract microstructural integrity is a strong predictor of IHI capacity in young adults (Fling, Benson, et al. 2011; Wahl et al. 2007); however, we are unaware of any studies that have assessed this relationship in older adults. Here, we report a fundamental shift with age in the relationship between microstructural integrity of fiber tracts connecting bilateral primary motor cortices and IHI. Specifically, older adults with relatively higher FA of these fiber tracts have less IHI. We suggest that these results implicate a change in the balance of interhemispheric excitatory and inhibitory communication with age. Such a change may be a (nonconscious) strategic shift; that is to say, older adults who are able to maintain interhemispheric fiber tract integrity may rely more on interhemispheric facilitation and less on IHI in order to facilitate improved motor control. It remains unclear whether these lower levels of IHI represent an adaptive change related to better motor control across the lifetime, or an explicit neural strategy adopted at a later point in life to facilitate improved performance. Either explanation is plausible, however, it is important to note that even in those older adults with relatively low levels of IHI, motor performance was still notably poorer than young adults. Thus, this strategy alone would not insulate older adults from experiencing decline in performance.

Interhemispheric interactions between additional sensorimotor cortices (both homologous and nonhomologous) were beyond the scope of the current paper but are clearly worthy of further investigation. For example, movement-related facilitation from the right PMd to the left M1 has recently been shown to predict performance during antiphase bimanual movements, suggesting that these connections contribute to independent yet coordinated control of the 2 hands (van den Berg et al. 2010; Liuzzi et al. 2011).

Conclusions

We report a qualitative shift in the balance of interhemispheric communication with age. This is evidenced by greater interhemispheric facilitation, greater motor overflow, and less IHI in older adults relative to their younger counterparts. Furthermore, we report that older adults have significantly reduced microstructural integrity of interhemispheric fiber tracts connecting primary motor cortices. Relatively higher FA of fiber tracts connecting primary motor cortices was related to “better” performance on the bimanual independent force production task in older adults but “poorer” performance in young adults on the same task. Additionally, greater IHI was related to poorer performance on all force production tasks in older adults, but only on the bimanual independent task in young adults. Finally, we report an age-related shift in the relationship between IHI and callosal fiber tract microstructural integrity connecting bilateral primary motor cortices. Better structural integrity was positively associated with IHI in young adults, whereas the relationship was negative in older adults. These findings suggest changes in interhemispheric communication with advancing age such that older adults rely on the bilateral cortical cooperation to a greater extent than young adults on both unimanual and bimanual motor tasks.

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References


