



Brief communication

Differential relationships between transcallosal structural and functional connectivity in young and older adults

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Abstract

Numerous studies have identified age differences in brain structure and function that correlate with declines in motor performance. While these investigations have typically focused on activity in isolated regions of the brain, resting state functional connectivity magnetic resonance imaging (MRI) and diffusion tensor imaging allow for more integrative assessments of spatially disparate neural networks. The novel contribution of the current study is to combine both resting state functional connectivity and diffusion tensor imaging to examine motor corticocortical circuits in young and older adults. We find that relatively greater functional connectivity between the primary motor cortices was strongly associated with decreased structural connectivity and poorer motor performance solely in older adults. We suggest that greater functional connectivity in older adults may be reflective of a release from the normally predominantly inhibitory interhemispheric communication associated with the primary motor cortices.

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1. Introduction

Numerous studies have identified age differences in brain structure, function, and biochemistry that correlate with declines in motor (Seidler et al., 2010) and cognitive (Reuter-Lorenz and Lustig, 2005) performance. However, these investigations have typically focused on isolated regions of interest. In contrast, recent approaches in resting state functional connectivity magnetic resonance imaging (fcMRI) and diffusion tensor imaging (DTI) have been used to assess brain functional (fcMRI) and structural (DTI) network connectivity, allowing for more integrative assessments of distributed neural systems. There is currently scant information about whether structural and functional connec-

tivity are affected by age in a parallel fashion and whether the 2 are related to motor behavior in unique or overlapping ways.

FcMRI studies have shown that brain regions with similar functions and known anatomical connections exhibit strong correlations in the low-frequency blood oxygen level dependent (BOLD) signal when individuals are at rest (Biswal et al., 1995; Fox and Raichle, 2007; Vincent et al., 2007). Intriguingly, while most patient groups exhibit reduced functional network connectivity (Jelsone-Swain et al., 2010), recent work provides compelling evidence that older adults demonstrate increased connectivity of interhemispheric motor cortical networks compared with young adults (Langan et al., 2010; Zuo et al., 2010). Furthermore, older adults with greater functional connectivity between the motor cortices exhibit less ipsilateral sensorimotor cortex activation during a unimanual motor task (Langan et al., 2010). One notable limitation of fcMRI is that correlated

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activity between 2 structures can reflect both direct and indirect connections (Fox and Raichle, 2007). Moreover, a change in coupling as measured with fcMRI may also reflect changes in signal-to-noise ratio within a given structure (Donahue et al., 2011). Thus integrating fcMRI with measures of structural connectivity can provide additional insight.

In organized tissue such as white matter in the brain and muscle, diffusion of water is anisotropic, i.e., direction-dependent (Chanraud et al., 2010). DTI has been used to map and assess structural integrity of motor cortical network tracts (Fling et al., 2011a; Hofer and Frahm, 2006). A growing body of literature indicates that not only is the quantity of white matter reduced in older adults, but the quality of remaining white matter is compromised as well (reviewed in Seidler et al., 2010). Specifically, older adults demonstrate a marked loss of myelinated fibers (Marnier et al., 2003), which can be assessed with radial diffusivity (measured with DTI; Gulani et al., 2001) a sensitive measure of white matter microstructural decline with age. Recent work from our laboratory has demonstrated that the microstructural integrity of callosal regions connecting sensorimotor cortical targets is related to motor performance in a differential fashion for young and older adults. Specifically, on a unimanual tapping task greater callosal microstructure was related to better performance solely in older adults (Fling et al., 2011b).

There is a gap in understanding how brain structural and functional network connectivity are interrelated, how they change with age, and how such changes contribute to older adults' sensorimotor deficits. The goal of the current study was to integrate across measures of functional and structural connectivity to determine how they relate to motor function in young and older adults. We hypothesized that advanced age would be associated with decreased integrity of inter-hemispheric structural connectivity (DTI) and a concomitant increase in the strength of resting state functional connectivity (fcMRI) between primary motor cortices. Further, we predicted that relatively poorer structural corticocortical fiber tract integrity would be associated with greater functional connectivity solely in older adults, reflective of an age-related shift towards greater interhemispheric facilitatory communication between motor cortices. Finally, based upon previous work (Fling et al., 2011b; Langan et al., 2010) we predicted that both poorer structural and greater functional connectivity would be negatively related to motor performance in older but not young adults.

2. Methods

2.1. Participants

Twelve young adults (7 males; mean age 22.1 ± 2.8 years; range 18–28 years) were recruited from the student population at the University of Michigan (average education: 14.9 years). Fifteen community-dwelling older adults

(8 males; 67.2 ± 5.2 years; range 65–76 years) also participated in this study (average education: 15.3 years). Participants were strongly right-handed as determined by the Edinburgh Handedness Inventory (young adults (YAs): 0.87; older adults (OAs): 0.9) (Oldfield, 1971).

2.2. Motor paradigm (unimanual tapping)

Thirty minutes prior to their magnetic resonance imaging (MRI) scan, participants performed a finger tapping task consisting of four 30-second tapping trials, with 20 seconds of visual fixation at the start and end of each of these trials (Fling et al., 2011b). Participants were asked to focus on a fixation cross hair in the center of a computer monitor (LabVIEW 6.1; National Instruments, Austin, TX, USA). Red circles (13-mm diameter) flashed 2 cm from the right side of fixation at 1 Hz to pace participants. Participants tapped with their right (dominant) index finger at 1 Hz and were instructed not to use the circle appearance as a cue to tap; instead they were to tap in synchrony with its onset.

2.3. Image acquisition

We collected whole brain high-resolution structural magnetic resonance images on a 3T MRI scanner (General Electric; Waukesha, WI, USA) using a spoiled gradient echo sequence (124 slices, field-of-view: 24 cm, voxel size: $0.94 \times 0.94 \times 1.4$ mm, repetition time (TR): 10.2 ms, and echo time (TE): 3.4 ms).

2.3.1. Functional connectivity (fcMRI)

Two hundred forty T2*-weighted BOLD images (TR = 2 seconds, TE = 30 ms, flip angle = 90° , field-of-view = 220×220 mm, voxel size = $3.4 \times 3.4 \times 3.2$ mm, 40 axial slices) were collected using a single-shot gradient-echo reverse spiral pulse sequence. A visual fixation cross was presented using a rear projection visual display. Participants were instructed to keep their eyes centered on the cross and to not think about anything in particular. A pressure belt was placed around the abdomen of each participant to monitor the respiratory signal. A pulse oximeter was placed on the participant's finger to monitor the cardiac signal. The respiratory, cardiac, and functional MRI (fMRI) data collection were synchronized.

2.3.2. Structural connectivity (DTI)

Diffusion weighted (DW) images were collected using a single shot echo-planar sequence in the axial plane (39 slices; TE/TR: 82.8 ms/9000 ms; image field of view: $220 \text{ mm} \times 220 \text{ mm}$; voxel size $3 \times 3 \times 3$ mm; b-value = 800 seconds/mm²; 15 diffusion-sensitizing directions). Images were motion and eddy-current corrected. Using the averaged images with b = 0 and b = 800 seconds/mm², the diffusion tensor was calculated and fractional anisotropy (FA) images were constructed off-line using ExploreDTI (v4.8.1, Utrecht, The Netherlands) (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 ($\lambda_1 > \lambda_2 > \lambda_3$) 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.

2.3.3. Fiber tractography

Interhemispheric fiber tractography between bilateral primary motor cortices (M1s) was performed using a previously described technique (Fling et al., 2011a). Briefly, each participant's FA map was normalized into Montreal Neurological Institute (MNI) space, aligned along the anterior/posterior commissure line with the coordinate 0, 0, 0 placed at the brain's center of mass, and voxel size was resampled to $2 \times 2 \times 2$ mm through the use of ExploreDTI (Tournier et al., 2011). The human motor area template (HMAT; Mayka et al., 2006) was coregistered to each individual's MNI-normalized FA image and subsequently used as a mask of the M1. Interhemispheric fiber tracts were identified by placing seed and target regions of interest (ROIs) in homologous M1 regions (e.g., right and left) as identified by the HMAT. Fiber tracts were constructed based upon deterministic streamline tractography (Mori and van Zijl, 2002).

2.4. Data analysis

2.4.1. Motor performance

Motor performance was defined as the standard deviation of the intertap interval. This is a typical measure used to describe tapping consistency for visually paced unimanual tapping (Bangert et al., 2010; Fling et al., 2011b; Helmuth and Ivry, 1996) where a lower value is indicative of better performance.

2.4.2. Functional connectivity (fcMRI)

The preprocessed data were normalized to MNI space using SPM5 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk) and low-pass filtered with a 0.08-Hz cutoff frequency in order to examine the frequency band of interest, and to exclude higher frequency sources of noise such as heart rate and respiration (Biswal et al., 1995). The HMAT (Mayka et al., 2006) was coregistered to each individual's MNI-normalized functional magnetic resonance image and subsequently used as a mask of the M1. To create the individual interhemispheric M1 fcMRI map, the following procedures were taken: for each voxel within the left (or right) M1, correlation coefficients with the time course from all the other voxels in the contralateral M1 were averaged. The average correlation value was Z transformed and assigned to the left (or right) M1 voxel. Thus each voxel of the interhemispheric fcMRI map indicates how strongly a particular voxel is connected to the contralateral M1. The left and right interhemispheric fcMRI maps (restricted to the HMAT-defined M1s) were entered into the group-level random effects analyses, which

were carried out in SPM5 (Wellcome Department of Cognitive Neurology) using a threshold of $p < 0.05$ family-wise error (FWE) correction and an extent voxel threshold of 10. Interhemispheric M1 connectivity was determined by placing a spherical ROI with a radius of 5 mm, centered on the peak voxel identified in the group-level random effects analyses (Nichols and Hayasaka, 2003). Z scores averaged across all voxels within the ROI were used as an index of interhemispheric M1 connectivity for the left and the right M1.

2.4.3. Structural connectivity (DTI)

Descriptive metrics were calculated for the microstructure of fiber tracts connecting homologous M1s, specifically fractional anisotropy, mean diffusivity, longitudinal diffusivity (λ_1), and radial diffusivity ($[\lambda_2 + \lambda_3]/2$). Radial diffusivity describes water diffusion along the off-principle eigenvalues; therefore lower radial diffusivity is interpreted as being indicative of better tract microstructural integrity (Basser et al., 2000).

2.5. Statistical analysis

Independent *t* tests were performed to compare between-group measures of tapping variability, functional connectivity strength and fiber tract microstructure. Additionally within each group we performed linear regression to investigate the relationship between motor performance (assessed by tapping variability), fiber tract microstructure, and functional connectivity strength while correcting for multiple comparisons. For all significant relationships we used a Fisher *r*-to-*Z* transformation to identify differences in the strength of correlations between age groups. All data are presented as mean \pm standard deviation unless otherwise noted.

3. Results

3.1. Motor performance

Young adults had significantly less ($p < 0.05$) unimanual tapping variability (79.0 ± 12.1 ms) than older adults (89.6 ± 19.8 ms).

3.2. Functional connectivity (fcMRI)

Comparable peak coordinates of M1 functional connectivity were found within the left M1 for the young ($-28, -28, 46$) and older adults ($-26, -28, 48$), whereas in the right M1 the young adult hotspot was more lateral ($44, -20, 60$) than that of the older participants ($24, -32, 72$). In both right and left M1, the young adults' hotspot was located more inferiorly. No differences in functional connectivity strength were observed when performing a between group contrast of either YA > OA or the converse, OA > YA, using a corrected family-wise error 0.05 threshold. When performing exploratory analysis with the threshold relaxed to an uncorrected 0.001, older adults display significantly stronger functional connectivity than young adults in both the right and left M1. With this less stringent threshold,

young adults still show no areas of greater functional connectivity than their older counterparts in either M1.

3.3. Structural connectivity (DTI)

A significant age group difference was noted for radial diffusivity ($p < 0.001$) with lower radial diffusivity of fiber tracts connecting bilateral M1s in the young (0.54×10^{-3} mm²/second) versus older adults (0.58×10^{-3} mm²/second), indicative of better fiber tract microstructure for the young adults. Significantly greater fractional anisotropy ($p < 0.001$) was observed in young adults as well. Finally, no group differences were found for mean or longitudinal diffusivity ($p > 0.10$ for both).

3.4. Relationships between behavior and metrics of connectivity

No relationship ($p > 0.1$) was observed between fiber tract microstructure and motor performance in either young or older adults. Nor was any association found between functional connectivity and performance in young adults ($p > 0.2$). Conversely, greater right ($r = 0.56$; $p < 0.02$) and left M1 ($r = 0.59$; $p < 0.01$) functional connectivity was significantly correlated with tapping variability in older adults. The strength of these correlations was significantly different between age groups for both the right ($Z = 2.4$; $p < 0.01$) and left M1 ($Z = 1.9$; $p < 0.04$). Thus, more functional connectivity between primary motor cortices was predictive of poorer performance in older, but not young, adults (Fig. 1).

Radial diffusivity of fiber tracts connecting the primary motor cortices was significantly and positively correlated with functional connectivity of the right ($r = 0.64$; $p < 0.01$) and left M1 ($r = 0.52$; $p < 0.03$) in older but not young ($p > 0.1$) adults. The strength of these correlations was significantly different between age groups for both the right ($Z = 3.07$; $p < 0.001$) and left M1 ($Z = 2.3$; $p < 0.02$). That is to say, poorer structural connectivity was related to greater functional connectivity between motor cortices solely in older adults (Fig. 2). Finally, we report no relationships between metrics of

structural connectivity (FA, mean, radial, or longitudinal diffusivity) and motor behavior.

4. Discussion

This is the first study to combine structural and functional connectivity to provide a comprehensive description of the effects of age on the neuromotor system. We report that stronger functional connectivity between the primary motor cortices is related to poorer structural connectivity and poorer motor performance in older adults. None of these relationships were observed in young adults.

The goals of the current study were to integrate across neuroimaging techniques to begin to elucidate the complex relationships between patterns of functional and structural connectivity. Poorer structural connectivity was related to stronger functional connectivity between motor cortices in older adults. While it is not possible to disambiguate the BOLD signal to identify inhibitory or excitatory processes, recent studies indicate that both inter- and intrahemispheric inhibition are decreased in the aging cortex (Peinemann et al., 2001; Talelli et al., 2008). There has yet to be definitive evidence indicating how the aging process affects interhemispheric facilitation; however, multiple studies have documented age differences in brain recruitment patterns during motor task performance.

Older adults exhibit overrecruitment of bilateral motor cortices relative to young adults, even when performing unimanual movements (Riecker et al., 2006; Ward and Frackowiak, 2003). This has oft been posited to be the result of nonselective recruitment, suggesting that brain structure-function relationships become less precise with age, resulting in older adults inefficiently recruiting additional regions of the brain compared with young adults (Logan et al., 2002; Riecker et al., 2006). Further, the extent of brain activation in the ipsilateral sensorimotor cortex during unimanual actions (“motor overflow”) is associated with the degree of change in interhemispheric inhibition from rest to muscle contraction in older adults (Talelli et al., 2008). Taken together with the current results, these findings suggest that increased connectivity in older adults may be reflective of a release from the

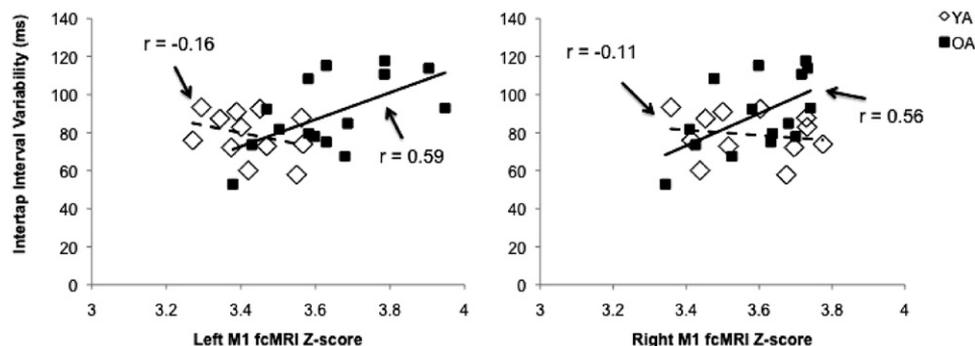


Fig. 1. Stronger functional connectivity of both the right and left primary motor cortex (M1) was significantly associated with poorer unimanual motor performance in older (solid lines), but not young adults (dashed lines).

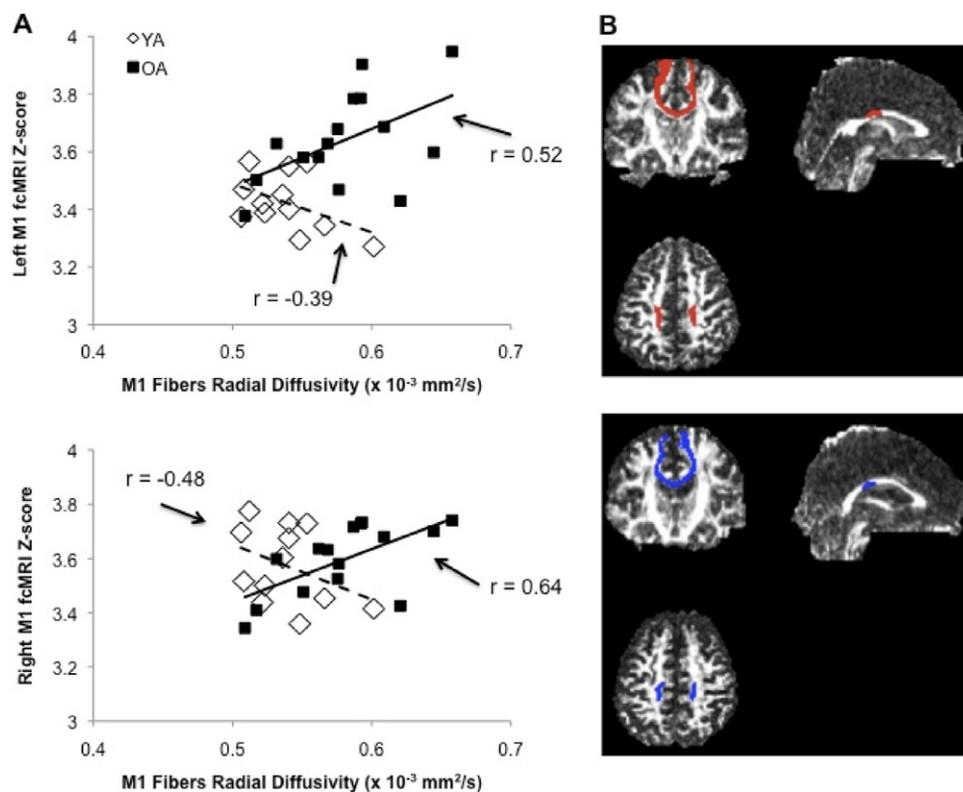


Fig. 2. Poorer fiber tract microstructure (i.e., higher radial diffusivity) was positively correlated with the strength of functional connectivity for both the right and left motor cortex (M1) in older (solid lines), but not young (dashed lines) adults (A). Interhemispheric fiber tracts connecting bilateral 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 Montreal Neurological Institute (MNI) space (B).

normally predominantly inhibitory interhemispheric communication associated with the primary motor cortices (Lenzi et al., 2007; Netz, 1999), and signify a shift toward more facilitatory interhemispheric communication. Future work would benefit from investigating these relationships during the performance of bimanual tasks where interhemispheric communication demands are increased.

Finally, our previous work has shown that unimanual motor performance is positively associated with callosal microstructural integrity in older adults (Fling et al., 2011b). It is worth noting the lack of such a relationship in either young or older adults in the current report. While our previous work focused solely on microstructural integrity of the corpus callosum from a single midsagittal slice, the current work uses a more comprehensive fiber tractography approach. The methodological differences may explain the lack of structure-behavior correlations observed here, but this remains unclear.

Disclosure statement

The authors disclose no conflicts of interest.

The Medical Institutional Review Board (IRBMED) of the University of Michigan approved all procedures and human participant involvement in this study.

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