Published in final edited form as:

Neuroimage. 2007 ; 36(Suppl 2): T16–T21. doi:10.1016/j.neuroimage.2007.03.041.

Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills

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Abstract

Variation in brain structure may reflect variation in functional properties of specific brain systems. Structural variation may therefore reflect variation in behavioural performance. Here, we use diffusion-weighted magnetic resonance imaging to show that variation in white matter integrity in a specific region in the body of the corpus callosum is associated with variation in performance of a bimanual co-ordination task. When the callosal region showing this association is used as a seed for probabilistic tractography, inter-hemispheric pathways are generated to the supplementary motor area and caudal cingulate motor area. This provides further evidence for the role of medial wall motor areas in bimanual co-ordination and supports the idea that variation in brain structure reflects inter-individual differences in skilled performance.

Introduction

Variations in sensory and motor experience are associated with variations in brain structure. In non-human animals, differences in the size and number of cells and synapses in specific brain systems have been observed following manipulation of environmental complexity and sensorimotor activity (Beaulieu and Colonnier, 1987; Ichikawa et al., 1993; Turner and Greenough, 1985). These cellular effects may be reflected in gross morphological changes detectable by brain imaging techniques and, therefore, open to investigation in human subjects. There is growing evidence, for example, that structural variations in specific brain regions are associated with relevant forms of expertise in populations of professional musicians (Gaser and Schlaug, 2003; Sluming et al., 2002), taxi drivers (Maguire et al., 2000), or bilingual individuals (Mechelli et al., 2004).

Many of the previous studies on structural plasticity, both in the human brain and in animal models, have focussed on experience-dependent morphological changes in grey matter, potentially reflecting local plastic changes such as increases in dendritic arborisation or synaptogenesis. It is possible, however, that experience-dependent structural changes also occur along the white matter pathways inter-connecting particular functional networks and, perhaps, reflecting changes in myelination or axonal architecture (Markham and Greenough, 2004).

This idea is supported by findings that inter-individual variation in specific white matter pathways relate to variation in performance of tasks that should employ those pathways

(Deutsch et al., 2005; Madden et al., 2004; Schulte et al., 2005; Tuch et al., 2005; Wolbers et al., 2006). The microstructure of white matter pathways can be interrogated *in vivo* using diffusion imaging to calculate voxel-wise estimates of fractional anisotropy (FA), a measure of the directional dependence of water diffusion (Basser et al., 1994). FA is a complex measure reflecting various structural properties of the white matter including axonal density and diameter, myelination, and fibre complexity (Beaulieu, 2002).

Here, we wished to test whether variation in bimanual co-ordination skill is related to variation in the structural properties of the corpus callosum in a non-expert population of healthy adult subjects who have not received any particular training regime. The corpus callosum (CC) provides the major white matter link between the hemispheres, connecting both homotopic and heterotopic cortical regions (Pandya and Seltzer, 1986). Agenesis of the corpus callosum, or acquired damage to transcallosal pathways, impairs bimanual motor performance (Larson et al., 2002; Serrien et al., 2001), especially for tasks requiring asynchronous co-ordinated bilateral movements (Geffen et al., 1994; Zaidel and Sperry, 1977). Although direct callosal connections between the motor cortices are relatively sparse (Innocenti et al., 1995), there are strong inter-hemispheric connections between hand representations in the two supplementary motor areas (SMA) (Rouiller et al., 1994) and transcallosal connections between the cingulate cortices (Locke and Yakovlev, 1965). Evidence for a role for SMA and cingulate motor areas in bimanual motor control is strong: single cells in SMA in monkeys respond to bimanual movements (Brinkman, 1984); functional imaging studies in human report increased activity in medial wall motor areas during motor tasks requiring bimanual co-ordination (Sadato et al., 1997; Stephan et al., 1999); lesions to midline motor areas in human, even in the absence of callosal damage, impair bimanual co-ordination (Laplane et al., 1977; Stephan et al., 1999). Together, this evidence suggests that inter-hemispheric callosal connections between midline motor areas are critical for bimanual motor tasks requiring asynchronous control of the hands.

In this study, we tested whether inter-individual variation in callosal pathways relates to variability in performance of a bimanual task. The structure of callosal fibres was measured using voxel-wise estimates of fractional anisotropy calculated from diffusion imaging.

Materials and methods

Subjects

Ten healthy right-handed adults (5 male, 5 female; aged 21-45 years) were studied.

Bimanual co-ordination

We adapted a bimanual co-ordination task introduced by Stephan et al. (1999). The subject was asked to produce asynchronous bimanual finger-thumb opposition movements paced by a metronome at 10 different frequencies (range: 1 to 3.3 Hz). Pilot studies demonstrated that, for most healthy subjects, this range includes frequencies at which subjects perform the task extremely well, frequencies at which they produce moderate performance, and frequencies at which their performance breaks down. This range therefore captured performance variation across subjects. The maximal aperture of one hand matched temporally the minimal aperture of the other side hand. Movements were recorded with goniometers, attached along the metacarpophalangeal joint of the index fingers, during a 12-second interval for each metronome frequency; the sampling rate was 130 Hz. We calculated the correlation between the angle time series for both hands and determined two summary frequencies which usefully captured performance variation across subjects: (1) the 'best performance frequency', i.e., frequency at which this correlation was closest to -1; (2) the 'standard performance frequency', i.e., frequency at which performance was about 80% (+/-

10 %) (correlation ranged between -0.72 and -0.88). The ratio between the standard and best-performance frequency was taken as a relative measure of bimanual co-ordination and used as a regressor in subsequent image analysis.

Diffusion MRI acquisition and analysis

Diffusion-weighted (3 acquisitions of 60 directions, b-value 1000mm^{-2} , $2.2 \times 2.2 \times 2.2\text{mm}$ voxels, 60 slices) and T1-weighted data were acquired using a 1.5T Siemens Sonata. FA values were calculated using FDT (<http://www.fmrib.ox.ac.uk/fsl>). We used TBSS, a method for statistical comparison of FA values between individuals (Smith et al., 2006), to test for local correlations between bimanual co-ordination scores and FA within the corpus callosum. First, individual FA maps are non-linearly aligned using a method based on free form deformations and B-splines (Rueckert et al., 1999) (implemented in the Image Registration Toolkit, www.doc.ic.ac.uk/~dr). The mean FA image across subjects is calculated and used to generate a white matter tract 'skeleton'. Individual subject FA values are warped onto this group skeleton for statistical comparisons by searching perpendicular from the skeleton for maximum FA values. Note that no spatial smoothing is applied to the FA maps or skeleton values. We tested for correlation between bimanual co-ordination score and FA after co-varying for age, which has significant effects on FA (Pfefferbaum et al., 2000). As we restricted our initial search to voxels on the skeleton within the corpus callosum on the mid-sagittal plane ($n=114$), we used a statistical threshold of $t>3$ and did not correct for multiple comparisons. Voxels identified in this way were used as seed masks for probabilistic tractography (Behrens et al., 2003). A multi-fibre model was fit to diffusion data at each voxel to allow tracing of fibres through regions of fibre crossing or complexity (Behrens et al., submitted). These methods are fully described elsewhere (Behrens et al., submitted; Behrens et al., 2003). Briefly, at each voxel, we estimate a probability distribution (pdf) on each fibre direction. Tractography then proceeds by drawing multiple (in this case 25,000) streamline samples through these pdfs from each seed voxel to build up an estimate of the distribution of connections from each seed voxel. When these streamlines reach a voxel in which more than one direction is estimated they follow the direction that is closest to parallel with the direction at which the streamline arrives.

Generated pathways are volumes in which values at each voxel represent the number of samples passing through that voxel and, therefore, the probability of connection to the seed voxel. To remove spurious connections, pathways in individual subjects were thresholded to include only voxels which had at least 25 samples passing through them (out of 25,000 generated from each seed voxel). This low threshold should allow us to be sensitive to weak paths. Pathways in each subject were then binarised and overlaid to produce population probability maps for each pathway, in which voxel values represent the number of subjects in whom a pathway is present.

Results and Discussion

We found a high correlation between FA and bimanual co-ordination scores in the body of the corpus callosum (Figure 1). The voxels on the mid-sagittal plane formed part of a cluster of supra-threshold voxels spanning the corpus callosum (43 voxels, mean $t\text{-stat}=3.4$, max $t\text{-stat}=4.8$).

When this cluster was used as a seed mask for probabilistic tractography, we found paths connecting the seed with the supplementary motor area and the caudal cingulate motor area (Figure 2). The same approach did not reveal paths connecting the seed callosal area with the (lateral) primary motor cortex, except for in one individual subject (Figure 3).

This suggests that inter-individual variations in bimanual co-ordination reflect variability in white matter integrity in callosal pathways - most strongly in paths connecting the supplementary motor areas. The high spatial specificity of the region of high correlation suggests that variation between individuals differs across functional systems. Although there are some suggestions that inter-individual variation in brain structure can be captured by a general IQ marker (Colom et al., 2006), there is also abundant evidence for regional variations in brain structure and function reflecting specific patterns of skill and experience (Bengtsson et al., 2005; Gaser and Schlaug, 2003; Maguire et al., 2000; Sluming et al., 2002).

Previous studies have suggested that normal variation in white matter fractional anisotropy (FA) in specific brain pathways is related to varying performance in related visuospatial and cognitive tasks (Deutsch et al., 2005; Madden et al., 2004; Schulte et al., 2005; Tuch et al., 2005; Wolbers et al., 2006). For example, increased FA in white matter underlying the inferior parietal cortex is associated with higher efficiency in mental rotation (Wolbers et al., 2006); FA along the optic radiations correlates with response time in a choice reaction-time task but in this case the correlation is positive: increasing (i.e. slower) response times correlate with higher FA (Tuch et al., 2005). This relationship is less intuitive, as a simple-minded interpretation of FA suggests that higher FA should indicate higher 'integrity', for example reflecting increased packing density or myelination. FA is, however, a complex measure that will be influenced not only by myelination, axon size, and axon density (Beaulieu, 2002), but also by path geometry and the presence of crossing fibre pathways. In the current study, we tested the relationship between FA and behaviour in a strongly coherent, parallel fibre system, namely the corpus callosum, and therefore expected to find increasing FA associated with improving behavioural performance.

Inter-individual variation in callosal size has previously been shown to correlate with fMRI activation in medial motor areas during performance of a bimanual motor task (Stancak et al., 2003). *In vivo* measures of callosal size have been shown to relate to the number of myelinated and non-myelinated fibres (Aboitiz et al., 1992) both in the healthy brain and in disease states such as multiple sclerosis (MS), where axonal degeneration plays a role in accumulating disability (Evangelou et al., 2000). Further, in MS, reduced callosal size correlates with reduced FA within the normal appearing white matter of the callosum, suggesting that measures of FA within the callosum reflect local axonal density (Cader et al, unpublished observations). Previous studies have shown that visuomotor inter-hemispheric transfer correlates with FA in the splenium and genu of the corpus callosum in healthy control subjects, suggesting that structural variation has functional consequences (Schulte et al., 2005). Here, we tested the relationship between callosal FA and performance on a purely motor inter-hemispheric task and were particularly interested in the spatial specificity of correlations with FA within the callosum. By using sites of local FA correlation as seeds for probabilistic tractography we were able not only to identify the sites of local FA change, but also to implicate specific cortico-cortical connections in task performance.

We found that the callosal region where FA correlated with bimanual co-ordination performance gave rise to pathways connecting the supplementary motor areas and caudal cingulate areas in the two hemispheres. Tracer studies in macaque demonstrate that the hand area of SMA has dense homotopic transcallosal connections, in contrast to the modest transcallosal connections between primary motor hand areas (Rouiller et al., 1994). SMA also has heterotopic transcallosal connections that are dense with cingulate motor areas, moderate with lateral premotor cortex, and sparse with M1 in the opposite hemisphere (Rouiller et al., 1994). The cingulate motor areas also have dense homotopic transcallosal projections (R.J. Morecraft, personal communication). The relative strength of transcallosal connectivity between SMAs and CMAs has not yet been systematically studied using

anatomical tracers. Damage to these medial motor areas impairs bimanual co-ordination (Geffen et al., 1994; Larson et al., 2002; Serrien et al., 2001; Zaidel and Sperry, 1977). The correlation between callosal size and movement-related fMRI activity is much stronger for medial wall motor areas than for lateral motor areas (Stancak et al., 2003). Our finding is therefore consistent with previous work suggesting that callosal connections between medial wall motor areas are most critical in bimanual co-ordination. It is also the case, however, that diffusion tractography tends to be most sensitive to medial fibres when seeds are placed in the corpus callosum, as the presence of longitudinal fibres, such as the superior longitudinal fasciculus make tracking to lateral areas less likely. In an attempt to reduce this problem we used a tractography approach that can model multiple fibre directions at each voxel (Behrens et al., in press). Even with this model, connections to lateral motor areas were rarely seen from the region of CC showing high correlation with bimanual performance (Figures 2,3). To test whether lateral connections could be traced from other regions in the CC we seeded all voxels within the CC on the mid-sagittal plane. In addition to strong connections with medial wall areas, we also found lateral connections in prefrontal, premotor and parietal cortices in some subjects but a striking absence of lateral connections to the primary sensorimotor cortices (Figure 4). The absence of lateral connections was found not only for the levels of the motor cortex corresponding to the hand representation, but also for more ventral portions of primary motor cortex where the face representation would be found. By contrast, medial parts of M1, including lower limb representations, showed strong inter-hemispheric connectivity using tractography (Figure 4).

It is tempting to interpret this as human evidence for the anatomical finding in macaque monkey of sparse connectivity between lateral motor areas (Rouiller et al., 1994), but it is also possible that this reflects limitations of the tractography technique. Callosal connections to lateral motor areas would have to cross not only the longitudinally oriented SLF, but also the superior-inferiorly oriented cortico-spinal tract. Therefore, it is likely that there are voxels along this route that contain at least three major fibre directions. We have previously shown although diffusion data such as the type acquired here (60 diffusion encoding directions, b-value of 1000 smm^{-2}) provides sufficient evidence to allow for fitting of two fibre directions at many white matter voxels, such data does not provide evidence for three or more directions at any white matter voxels (Behrens et al., in press). It is likely that diffusion data with greater angular resolution and higher b-values, which could enable modelling of three or more directions when they are present, may help to establish the relative strength of transcallosal connections to lateral motor cortices.

We have demonstrated a specific association between integrity of white matter pathways and a functional skill in a healthy adult population. This suggests that inter-individual variability in brain structure has functional consequences. The current study provides us with a snapshot that makes it impossible to establish the direction of causality between structure and function: it is possible that innate variation in brain structure influences subsequent skill levels. It has recently been demonstrated, for example, that genotype not only influences brain structure (Bueller et al., 2006), but also influences the degree of functional plasticity in the motor system (Kleim et al., 2006). It is likely that, in addition to any innate influences on brain structure, differences in experience, manifest as variable activity along specific brain pathways, result in plastic changes that could be reflected in local measures of fractional anisotropy. Piano training, for example, results in different patterns of FA change depending on the age at which training is given (Bengtsson et al., 2005), suggesting that environmental influences at specific developmental stages trigger long lasting structural changes that are reflected in FA measures along those pathways. FA reflects numerous structural properties of the white matter (Beaulieu, 2002), some of which may be subject to experience-dependent changes. Exposure to an enriched environment in rats, for example, results in increases in the size or number of axons in the corpus callosum

(Juraska and Kopeck, 1988). Future longitudinal studies using diffusion MRI should test whether alterations in experience, such as intensive skill training, result in observable changes in white matter structure in the adult human brain.

Acknowledgments

We are grateful for financial support from the Wellcome Trust (HJB), Canadian Institutes for Health Research (TP), UK Medical Research Council (TEJB), UK Engineering and Physical Sciences Research Council (SMS). We thank Jennifer Campbell for providing the diffusion imaging pulse sequence and David Flitney for help with figures.

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Figure 1. Region of corpus callosum showing correlation between FA and bimanual co-ordination skill

A) Midsagittal section of mean fractional anisotropy (FA) map. Corpus callosum is visible as a bright structure with high FA. Pale blue line indicates location of skeleton used in TBSS analysis. Red-yellow voxels indicate those showing significant ($t > 3$) correlation with behaviour. These significant voxels formed part of a cluster of voxels spanning the callosum and seen in axial (B) and coronal (C) sections above. The correlation across individual subjects between mean FA across this cluster and the bimanual co-ordination score can be seen in D. Females are shown by open circles, males by closed circles.

Figure 2. Paths from callosal region where FA correlates with bimanual co-ordination performance

Paths were generated that appear to connect the seed cluster in the mid callosum with the medial-wall motor areas including supplementary motor area and posterior cingulate motor area as shown in coronal (A), sagittal (B), and axial (C) sections. Paths are group probability maps, where colour coding reflects the proportion of the population in which a tract is present from dark (3/10) to light (10/10) blue. Tracts have been thresholded to show only those present in at least 3/10 of subjects. (D) shows 3D renderings of the pathway (blue), the white matter skeleton used in the TBSS analysis (beige), and the callosal region of significant correlation between FA and bimanual co-ordination score (red, visible in left view only).

Figure 3. Effects of thresholding on pathways

Paths are shown as in Figure 2 but thresholded to show only those pathways present in different proportions of the population from >0% to >70%. Top row shows coronal images and bottom row shows axial images. When paths from all subjects are displayed (>0%) connections to lateral motor cortices are visible in one subject. Note that the weakening of the pathways at higher population thresholds will partly reflect inter-subject registration error and anatomical variability. Transcallosal connections to medial motor areas were generated from the seed region in all subjects.

Figure 4. Connections from the whole callosum

When we seeded from all voxels within the callosum visible on the mid-sagittal plane the strongest connections were found to the medial wall areas. Lateral connections to prefrontal, parietal, and temporal cortices were stronger than those to primary sensorimotor areas.