

# Fibre orientation dispersion in the corpus callosum relates to interhemispheric functional connectivity

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## Synopsis

Fibre orientation dispersion was previously demonstrated to be higher in midline compared to lateral aspects of the corpus callosum (CC) using microscopy data and diffusion MRI data. We hypothesize that this pattern of dispersion in the CC relates to the degree of heterotopic connections in the brain. In a large cohort of 4903 subjects from the Biobank UK, resting-state functional MRI and diffusion MRI data were compared against each other to find associations between fibre dispersion and interhemispheric functional connectivity.

## Purpose

Linking the anatomy of brain connections to function is fundamental to our understanding of how brain architecture underpins human cognition. A prominent set of brain connections, collectively called the 'corpus callosum' (CC), plays a key role in cross-hemispheric information transfer. Although the CC is generally thought of as a well-organized bundle of axons running parallel to each other and connecting homologous (homotopic) areas, recent studies have demonstrated complex fibre architecture within the CC<sup>1-3</sup>. In particular, fibre orientation 'dispersion' at the midline appears to be greater, compared to the lateral aspects of the CC<sup>4</sup>. This deviation from a well-organized CC might reflect interhemispheric connections of non-homologous (heterotopic) areas. Here we hypothesize that dispersion in the CC is indeed a signature of the degree of heterotopic connectivity. We test this hypothesis in a large cohort of subjects by looking for associations between diffusion MRI (dMRI) estimates of fibre dispersion and resting-state functional MRI (rfMRI) estimates of interhemispheric connectivity.

## Methods

We analyzed dMRI and rfMRI data from 4903 subjects in the UK Biobank project (acquisition parameters and pre-processing steps can be found elsewhere)<sup>5</sup>.

A group-average decomposition of functional connectivity using ICA yielded 55 components corresponding to resting-state networks. These were then split for each hemisphere and possibly further split if a component contained non-contiguous brain areas. To estimate subject-specific connectivity between the resulting brain regions (network 'nodes'), average time-series were generated for every node and correlated with each other using partial correlation. These connectivity values then form a node-by-node matrix of network connectivity. To quantify the balance of homo- to heterotopic interhemispheric connections for a given node, a functional asymmetry index (AI) was defined as the homotopic connection strength minus the mean of the 10% strongest heterotopic connections.

To calculate voxel-wise orientation dispersion (OD), the NODDI model<sup>6</sup> was fit to dMRI data using AMICO<sup>7</sup>. OD values were extracted from the CC after transforming all subjects to the same space and mapping ODs onto a skeleton using TBSS<sup>8</sup>. To estimate which anterior-to-posterior region of CC connects a pair of homotopic areas, structural connectivity probability maps for each node were obtained in the CC using a tractography template. Dispersion was calculated as the mean OD at the center minus the mean OD at the lateral aspects of the CC, referred to as OD hereafter (Figure 1.C).

Associations between OD and AI were calculated, with statistical significance assessed using permutation testing (5000 permutations). Reproducibility was demonstrated by dividing the subjects in two equally sized groups with similar gender and age distribution. For each AI vs OD comparison, the OD values were taken from a region of the CC that connects to the cortical node of interest. A negative control analysis was done by correlating AIs with OD derived from the CC region that is least likely to interconnect the node of interest.

## Results

As reported previously<sup>4</sup>, high dispersion was found in the center of the CC in both dMRI data and polarized light imaging, creating a W-shaped pattern (Figure 1). The splenium, however, exhibited an inverted W-profile. Figure 2 illustrates the group-average functional connectome. For each hemisphere, 81 nodes were defined and homotopic connections exhibited the highest correlations.

Significant associations between AI and OD were primarily found near the midline, with correlation coefficients ranging between  $r=0.05-0.11$  (Figure 3). Of 16 significant associations in the “discovery” in the first group of subjects that survive FDR multiple comparison correction, seven were reproduced in the second group. Highest regression coefficients ( $\beta$ ) were found closer to the CC, and lower regression coefficients distal to the CC (Figure 3.D).

Finally, the negative control analysis yielded a single significant and reproducible association between AI and OD in an implausible CC region (Figure 4), although with a lower regression coefficient ( $\beta=1.55$ ) than the anatomically plausible CC region ( $\beta=1.82$ ).

## Discussion

The W-shaped OD profile was consistently found in the CC of living subjects. Significant associations were found between AI vs OD in regions close the CC, such as the cingulate cortex. In addition, the AI of a particular area appeared to be less associated with OD if the area was more laterally located. We hypothesize that dispersion in the CC is more crucial for midline nodes to project to nearby heterotopic regions, while nodes that are more distant from the CC can form a path to heterotopic areas in other tracts. The negative control analysis yielded one significant node that may be explained by correlation of ODs among different areas of the CC. It may also relate to an indirect association of an alternate biological source.

## References

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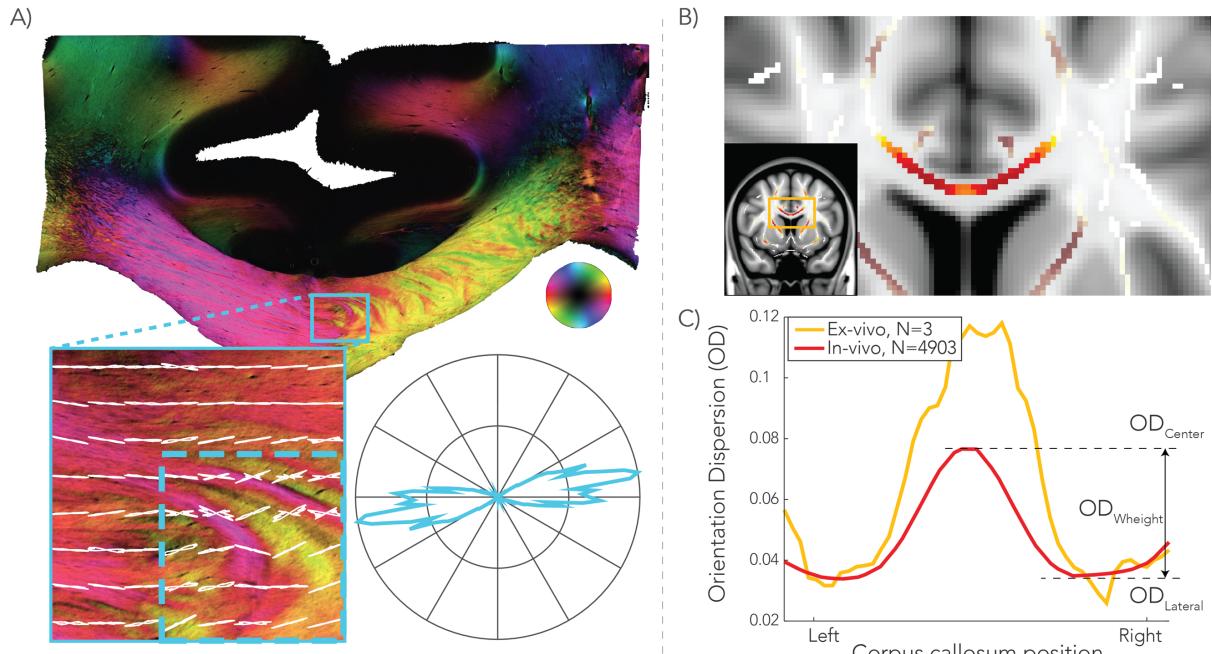


Figure 1. Fibre orientation dispersion in the CC. A) Polarized light imaging (PLI) measures in-plane fibre orientations at microscopic resolution (data described previously<sup>4</sup>). While CC fibres run broadly together, there is significant fibre dispersion, particularly on the midline, as indicated by the angular histogram (polar plot). B) In-vivo OD values projected onto a TBSS skeleton. C) In both the ex-vivo- and in-vivo dMRI data dispersion is characterized by a W-shape. Relative dispersion in the CC was calculated as the height of the W-shape ( $OD_{Wheight}$ ), i.e. the mean OD at the center minus the mean OD at the lateral aspects.

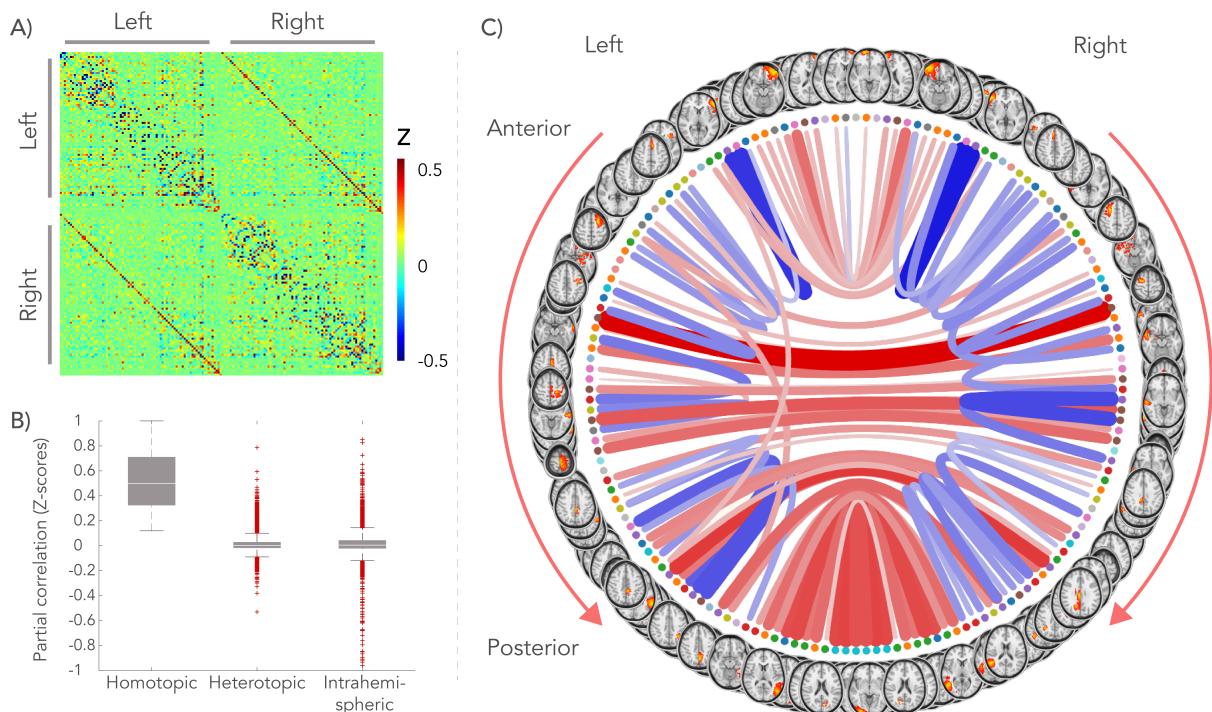


Figure 2. Group-average resting-state networks derived from ICA. A) The partial correlation (using Ridge regression) network matrix depicts intra- and interhemispheric connections represented in four quadrants (i.e. Left-Left, Right-Right, Left-Right and Right-Left). B) Z-score distribution for different types of connections. C) Connectivity visualization across brain regions (nodes). Nodes from the left and right hemisphere are separated and ordered from anterior to posterior (up-down). The lines indicate partial correlations above a certain threshold. Strong positive correlations (red lines) are mostly homotopic areas, while strong negative correlations (blue lines) are primarily intra-hemispheric connections.

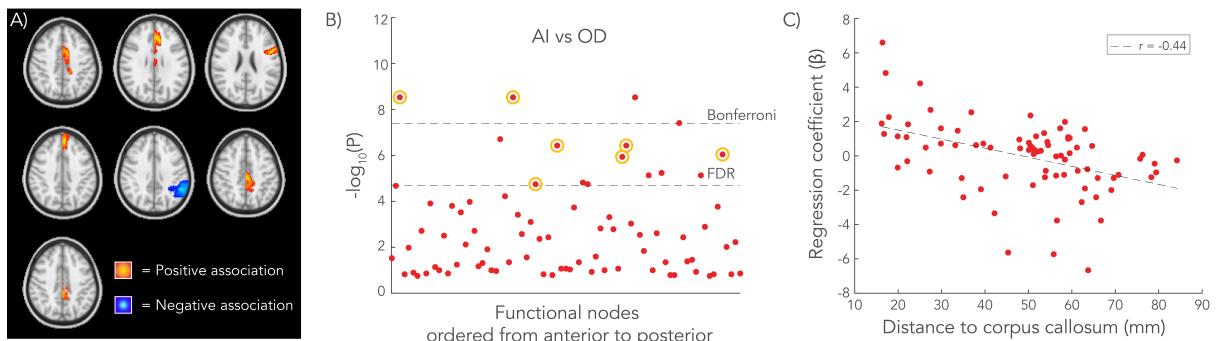


Figure 3. Significant associations between functional AI and OD. **A)** 7 nodes showed significant associations between AI and OD in both groups. The colormaps depict the ICA-weighting of each node. **B)** Scatter plot of all associations ( $-\log_{10}(P)$ ) between the AI of 81 nodes and the OD from the corresponding CC region. Nodes with a yellow circle were reproducible in the second group of subjects (shown in A). **C)** Regression coefficients for the association of each node versus the distance to the CC of that particular node (estimated with tractography). The highest coefficients were located close to the CC.

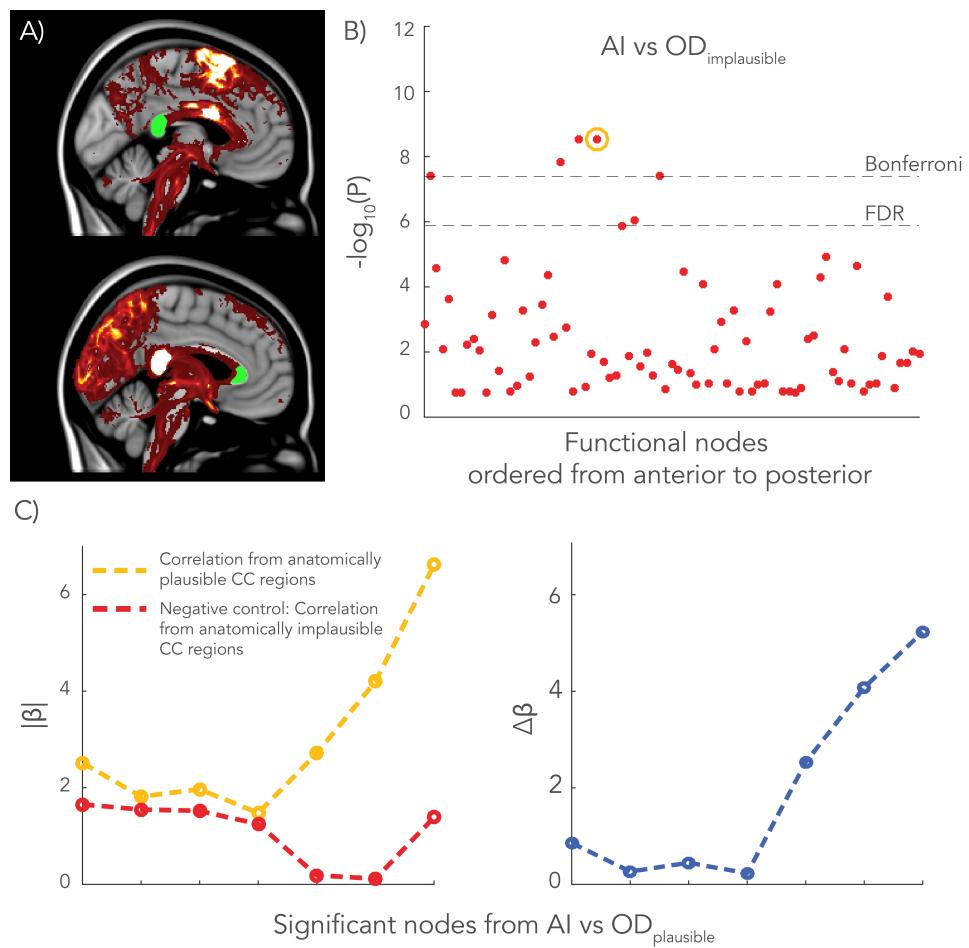


Figure 4. Negative control analysis. **A)** Probability maps (hot-colormap) of tractography data from 2 example nodes indicate the CC region that most likely connects the nodes inter-hemispherically. Negative control analysis was done by extracting OD values from a CC region (green) that is least likely to interconnect the node. **B)** See Figure 3.C for description. One node showed a significant association in both groups. **C)** Regression coefficients from the seven significantly associated nodes from Figure 3 were compared against the negative control analysis in these nodes. Higher regression coefficients were found for all the plausible associations.