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Heterogeneity of trans-callosal structural connectivity and effects on resting state subnetwork integrity may underlie both wanted and unwanted effects of therapeutic corpus callostomy

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ABSTRACT

Background: The corpus callosum (CC) is the primary structure supporting interhemispheric connectivity in the brain. Partial or complete surgical callosotomy may be performed for the palliation of intractable epilepsy. A variety of disconnection syndromes are recognised after injury to or division of the CC however their mechanisms are poorly understood and their occurrence difficult to predict. We use novel high resolution structural connectivity analyses to demonstrate reasons for this poor predictability.

Methods: Diffusion weighted MRI data from five healthy adult controls was subjected to novel high-resolution structural connectivity analysis. We simulated the effects of CC lesions of varying extents on the integrity of resting state subnetworks (RSNs).

Results: There is substantial between-individual variation in patterns of CC connectivity. However in all individuals termination points of callosal connections mostly involve medial and superior sensory-motor areas. Superior temporal and lateral sensory-motor areas were not involved. Resting state networks showed selective vulnerability to simulated callosotomy of progressively greater anterior to posterior extent. The default mode network was most vulnerable followed by, in decreasing order: frontoparietal, limbic, somatomotor, ventral attention, dorsal attention and visual subnetworks.

Conclusion: Consideration of the selective vulnerability of resting state sub-networks, and of between-individual variability in connectivity patterns, sheds new light on the occurrence of both wanted and unwanted effects of callosotomy. We propose that beneficial effects (seizure reduction) relate to disruption of the default mode network, with unwanted "disconnection syndrome" effects due to disruption particularly of the somatomotor and frontoparietal RSNs. Our results may also explain why disconnection syndromes primary reflect lateralised sensory-motor problems (e.g. of limb movement) rather than midline function (e.g. tongue movement). Marked between-subject variation in callosal connectivity may underlie the poor predictability of effects of callosotomy. High resolution structural connectivity studies of this nature may be useful in pre-surgical planning of therapeutic callosotomy for intractable epilepsy.

1. Introduction

The corpus callosum (CC)[1] is the major anatomical structure supporting inter-hemispheric connectivity in the brain. It may be congenitally absent (Benezit et al., 2015), or callosal disconnection can be acquired as a result of traumatic brain injury (Basu et al., 2015). In the latter case the disruption is usually partial (Dennis et al., 2015): the splenium of the CC is a characteristic site for diffuse axonal injury as bio-mechanical factors result in concentration of forces at that site. Callosotomy is also performed therapeutically in the amelioration of intractable epilepsy, particularly for atonic drop seizures.

A range of disconnection syndromes have been described following partial or complete callosotomy. These include the supplementary motor area (SMA) syndrome, the anarchic (or alien) hand syndrome, tactile dysnomia, hemispatial neglect, non-dominant hand agraphia and alexia without agraphia (for review see Jea et al. (2008)). The mechanisms of these at times striking and bizarre phenomena are not well understood and their occurrence is poorly predictable. Several of these syndromes can improve spontaneously over time: again the mechanisms of this improvement are unclear.

In previous work we have demonstrated the value of connectomic perspectives on the occurrence and resolution of disconnection syndromes. In one of the youngest reports of anarchic hand syndrome

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[1] Abbreviations: CC = corpus callosum; fMRI = functional MRI; rs-fMRI = resting state functional MRI; RSN = resting state (sub)network

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(Basu et al., 2015) we described marked reduction in structural connectivity between homologous superior frontal areas and in functional connectivity between homologous posterior cingulate areas; and hypothesized that restoration of interhemispheric connectivity via trans-cerebellar routes may have contributed to resolution. A number of qualitative analyses of the effects of callosotomy in terms of the anatomy of inter-hemispheric white matter tracts as revealed by Diffusion Tensor Imaging (DTI) have been published (Jang et al., 2013; Le et al., 2005; Molko et al., 2002). In Molko et al.'s case study, loss of transcallosal structural connectivity between homologous areas involved in visual word recognition was associated with corresponding impairments in task-related functional MRI (fMRI) activation and clinical alexia (Molko et al., 2002).

Statistical analysis by techniques such as independent component analysis of patterns of spontaneous fluctuation in brain activation (as revealed at low frequencies by Brain Oxygen Level Dependent (BOLD) signal fMRI) identifies groups of brain areas that tend to activate and deactivate in synchrony known as resting state networks (RSNs). RSN models can be derived at different levels of resolution: typically 7 to 20-network models are generated. Within limits the general configuration of these networks is robust and reproducible (Smith et al., 2009; Yeo et al., 2011). Functional interpretations have been assigned to these RSNs based on the functional activation literature (Yeo et al., 2011) (but see Discussion). In this paper we use novel high-resolution techniques to define the relative vulnerabilities of different RSNs to complete and partial in silico "virtual callosotomies" and relate this to subject-specific consequences (desirable and otherwise) of callosotomy.

2. Materials and methods

2.1. Imaging data

Two healthy adult control public-domain datasets were used in this study. The older NKI dataset (Nooner et al., 2012) provides repeated scans on the same individual and was used to verify the within-subject reproducibility of our novel high-resolution connectivity pipeline. One T1 weighted MRI image and two separate diffusion weighted MRI images (scan session 1 and scan session 2) are available for one subject. The T1 scanning protocol parameters are as follows: temporal resolution (TR) = 2500 ms, TE = 3.5 ms, inversion time (TI) = 1200 ms, voxel size of 1 mm isotropic. For diffusion acquisition a multiplexed, multiband echo planar imaging sequence was used (Moeller et al. (2010); Xu et al. (2013)). This included acquisition of 128 direction imaging volumes at a b value of 1500 s/mm^2, along with 9 b = 0 images, TR = 2400 ms, TE = 85 ms with an isotropic voxel size of 2 mm. Further acquisition details are available at http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_ http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/DIff_137.pdf. This data has been used before for assessing scan-rescan reproducibility of network measures (Zhao et al., 2015).

To investigate between subject differences we used the newer HCP dataset (Glasser et al., 2013) which uses a highly customized protocol. T1 weighted images were acquired at 0.7 mm isovoxel resolution with the following parameters: TR = 2400 ms, TE = 2.14 ms, TI = 1000 ms. For diffusion data, a total of 270 diffusion sampling directions were used in three shells of b values 1000, 2000 and 3000 in addition to 18 b0 volumes at a resolution of 1.25 mm isovoxel. Other parameters were as follows: TR = 5520 ms, TE = 89.5 ms. Full details of the acquisition protocols can be found at http://www.humanconnectome.org/documentation/Q1/imaging-protocols.html. Subject characteristics are included in Supplementary Table 1.

2.2. Image processing high resolution pipeline

FreeSurfer recon-all was used to generate the cortical surface mesh of NKI data from the T1 image. The white matter surface mesh was then expanded using mris_expand to generate the cortical mid-surface half way between the grey and white matter (Dale et al., 1999; Fischl et al., 1999; Fischl, 2012). The mid-surface was resampled to 16,000 triangles producing the surfaces shown in Fig. 1 using iso2mesh (Fang and Boas, 2009). For HCP data these steps are preprocessed and available to download at https://db.humanconnectome.org/. For HCP data, resampling was precomputed with Caret software (Van Essen et al., 2001).

HCP diffusion data was downloaded preprocessed (Glasser et al., 2013). NKI data was corrected for eddy current distortions and motion using FSL eddy correct using the first b0 image as reference (Jenkinson and Smith, 2001; Jenkinson et al., 2012). Following eddy correction we rotated the b vectors where appropriate using the dt_rotate_bvecs tool. All diffusion data was reconstructed using generalised q-sampling imaging (Yeh et al., 2010) with a diffusion sampling length ratio of 1.25. The diffusion data and the FreeSurfer processed T1 image were then linearly registered to the same space, and the FreeSurfer segmented corpus callosum (Desikan et al., 2006) used as a seed region for tracking. Grey matter regions were combined into one volume region of interest (ROI) and specified as termination and end point criteria. The registration of the grey matter ROI, the CC ROI, and the diffusion MRI was checked manually in all cases for accuracy. The bottom panels in Fig. 1 demonstrate the CC ROI registration quality. The CC was subdivided into five ROIs which were equally spaced along the primary eigendirection using FreeSurfer.

A deterministic fibre tracking algorithm (Yeh et al., 2013) was used, allowing for crossing fibres within voxels. A total of 1,000,000 tracts were computed with lengths between 10 mm and 300 mm. A fixed step Euler algorithm was used for tracking with the step size set to half the voxel size. Anisotropy and angular thresholds were set to 0.6* Otsu's threshold and 60 degrees respectively.

Once tractography was complete, tract end points were saved in the same space as the FreeSurfer processed T1 image. Tract end points and grey matter midsurfaces were loaded into Matlab and registration quality visually confirmed. To generate connectivity profiles (e.g. top panels in Fig. 1) we looped through each endpoint and assigned it to the closest point (shortest Euclidean distance) on the 16,000 triangles comprising the surface mesh. This gives a list of the number of connections for each point of each triangle. To colour the triangles on the surface plot we show the median value of the three triangle points.

The models of functional resting state network connectivity reported by Yeo et al. (2011) were used. The allocation of the 16,000 triangles to the published anatomical cortical surface boundaries of the subnetworks of the 17-network model was performed using preprocessed data from https://db. humanconnectome.org.

3. Results

The reproducibility of our high-resolution connectivity method was confirmed using scan-rescan DWI data from a single subject in the NKI dataset (Fig. S1). The scan-rescan correlation of traceline counts through the CC from each high-resolution triangle was high (Spearman's $\rho = 0.68$, $p < 0.0001$). Since tractography uses random initial conditions, we also examined the reproducibility of the tractography and subsequent processing, repeating the entire pipeline using the same data. Reproducibility was excellent (Spearman's $\rho = 0.97$, $p < 0.0001$).

3.1. Between-subject variation in connectivity

Between-subject differences in callosal connectivity patterns were examined using the high-resolution HCP data. Five individuals selected at random, with excellent callosal segmentation, were chosen. Fig. 1 shows substantial qualitative between-subject differences in connectivity patterns. For example, subject C has connections involving superior motor areas in both hemispheres, whereas in subject E the connectivity