Prediction of functional connectivity from structural brain connectivity

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Introduction: Studies that examine the relationship of functional and structural connectivity are important in interpreting neurophysiological data. Although, the relationship between functional and structural connectivity has been explored with a number of statistical tools [*1, 2*], there is no explicit attempt to quantitatively measure how well functional data can be predicted from structural data. Here, we predict functional connectivity from structural connectivity by utilizing a predictive model based on principal component analysis (PCA) and canonical correlation analysis (CCA).

Methods: Whole brain resting-state fMRI, diffusion weighted images (DWI) and T1-weighted images (3T) were obtained for eight healthy adults. fMRI imaging protocol: T2*-weighted gradient EPI sequence, TR/TE = 2000/30, 31 ascending slices with thickness 3.25 mm, gap 0.75 mm, voxel size 2.5×2.5×4 mm, flip angle 90°, FOV 280×220×123 mm, matrix 112×87. DWI were acquired in 16 non-collinear directions in each of four imaging runs, resulting in a total of 64 directions. Images were obtained in 72 slices, slice thickness 2 mm, FOV 224 mm, matrix 128 x 128, voxel size 1.75 x 1.75 x 2 mm^3, b value 1000 s/mm^2.

Preprocessing: Eddy current correction of DWI, motion correction and spatial smoothing of fMRI as well as brain extraction was performed with FSL. Bias correction was applied to T1 and B0 images [*3*] to improve the robustness of the non-rigid registration tools.

Regions of interest (ROI): Brain network construction was carried out only for connections between cortical regions. A cortical parcellation was obtained by a multi-atlas segmentation technique. Firstly, label propagation based on multiple atlases was used to segment each T1 image into 83 cortical and subcortical regions [*4*]. The robustness of the segmentation was further enhanced by incorporating decision fusion to select the manual segmented images with the highest similarity to the new subject [*5*]. Probabilistic tissue segmentation was performed to distinguish gray matter, white matter and CSF with SPM. Atlas-based and tissue-based segmentation was fused to provide the final ROI. Segmentations were transformed to both the diffusion and fMRI space by using non-rigid registration [*6*].

Extraction of Structural and Functional Networks: Tracts between regions are identified using a standard probabilistic algorithm available in FSL. However, measurements of connection probability are difficult to interpret as the probability measure reflects uncertainty in the data rather than likelihood of connection. Instead, we estimate the local diffusion anisotropy by determining the diffusive transfer between voxels using the orientation distribution function (ODF) [*7, 8*]. Diffusion anisotropy is related to changes in myelination, fiber density and packing. Therefore, connectional strength can be compared across subjects and it is, inherently, associated to functional connectivity. To construct corresponding functional networks the fMRI signal was averaged across voxels within each area. Partial correlation was used to compute functional connectivity accounting for the whole brain mean signal. Correlations were transformed to z-statistics using the Fisher r-to-z transform.

Reduction of dimensionality and predictive model: Each brain's connection is treated as variable with a number of observations equal to the number of subjects for both functional and structural data. To reduce dimensionality PCA is applied to each connectivity matrix. CCA is applied to the reduced variables in order to find two basis vectors, one for each variable, so that the projections of these variables onto the basis vectors are maximally linearly correlated. Since the canonical coefficients convert an individual's multivariate observation to two univariate quantities, prediction can be obtained by means of regression analysis. Therefore, a new observation of anatomical connectivity is projected to PCA coordinate system and the regression coefficients estimated from a training set are applied to predict the corresponding functional connectivity. Finally, the predicted values are transformed from PCA to the Cartesian coordinate system.

Results and Discussion: A leave-one-out approach was adapted to test the robustness of the suggested methodology. Therefore, prediction was performed eight times, each with seven subjects in the training set and one used for prediction. Fig.1 demonstrates a qualitative view of the results for one of the subjects. ROIs are plotted by cerebral hemispheres, with right-hemispheric ROIs in the lower left quadrant, left-hemispheric ROIs in the top right quadrant, and inter-hemispheric connections in the upper left and lower right quadrants. The coefficient of determination for each prediction/subject is shown in Table 1. The results demonstrate that the combination of PCA and CCA is a promising approach in capturing intrinsic characteristics of both functional and structural brain connectivity. The model succeeds in distinguishing connections between left and right hemisphere, even when inter-hemispheric connections are underestimated with tractography techniques. The explained variance shown in Table 1 indicates that prediction can be used as a tool to investigate the relationship among anatomical and functional connectivity, and it will assist in gaining a deeper understanding of the underlying mechanisms. It is also evident that a monosynaptic model of structural connectivity cannot totally explain functional connectivity. In other words, functional connectivity is also triggered and influenced by indirect connections, suggesting that a polysynaptic model of structural connectivity may enhance the performance of the prediction.

Conclusions: A multivariate statistical technique based on PCA and CCA was exploited to predict functional connectivity from structural connectivity. We demonstrated that the suggested methodology is capable of capturing subtle details of brain network characteristics. Future work would aim to use a larger sample of data to improve the performance of the prediction and investigate the influence of indirect connections and distance between ROIs.

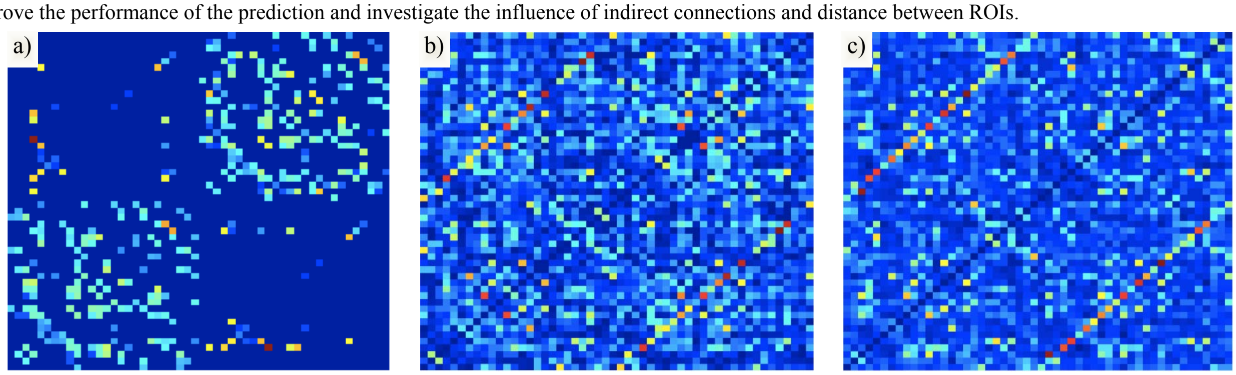

Fig. 1: Inference of functional connectivity from structural connectivity. a) The anatomical connectivity matrix, b) The original functional connectivity matrix, c) The predicted functional connectivity matrix in a one left-out fashion.

Sub1	Sub2	Sub3	Sub4	Sub5	Sub6	Sub7	Sub8
0.46	0.58	0.75	0.77	0.47	0.89	0.63	0.58

Table 1: Coefficients of Determination. (Leave-one-out methodology)

Acknowledgements: MRC Special Research Fellowship in Biomedical Informatics

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