INFERENCE OF FUNCTIONAL CONNECTIVITY FROM STRUCTURAL BRAIN CONNECTIVITY

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ABSTRACT

Studies that examine the relationship of functional and structural connectivity are tremendously 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, explicitly, by utilizing a predictive model based on PCA and CCA. The combination of these techniques allowed the reduction of dimensionality and modeling of inter-correlations, successfully. We provide both qualitative and quantitative results based on a leave-one-out validation.

Index Terms— Brain connectivity, fMRI, tractography, functional connectivity, structural connectivity

1. INTRODUCTION

Functional specialization/segregation and functional integration/ connectivity are major factors influencing the brain's computational power and stability. Functional specialization investigates how different brain areas are consistently engaged in some aspects of cognitive or motor processing. However, it has become evident that it is not meaningful to investigate functional specialization without considering how different brain areas interact. In practice, different types of functional imaging data, such as PET, fMRI and EEG, which exhibit varying spatiotemporal properties and represent various neural activities, are used to characterise brain connectivity. In the absence of precise information about the anatomical relationship between a neuronal pair whose functional interactivity is being accessed, the research community has started to converge on Friston's definition of functional connectivity [3]. According to it, functional connectivity is defined as the temporal correlation between spatially remote neurophysiological events.

However, the relationship between functional connectivity and its underlying neural substrate is obscure [4]. Advances in diffusion weighted MR imaging allow the inference of microscopic tissue properties, such as water diffusion, *in vivo*. Water diffusion, also called diffusion anisotropy, is higher in the direction of the fiber tract within an oriented tissue. Various tractography techniques have been developed to exploit this voxel-based measure and extract neuronal tracts [5, 6]. This allowed the modeling of dense networks of macroscopic fiber bundles within the brain.

As a consequence, significant research effort has been directed recently towards the understanding of brain connectivity with both functional and structural data [1, 2]. A linear relationship between structural and functional data has been demonstrated in [1, 2]. However, strong functional connectivity was also observed in areas without direct structural links and inter-regional distance accounted for only some of the variance in functional connectivity.

In this work, we are interested in inferring functional from structural connectivity. Prediction is a popular tool in statistics. Here, the ultimate goal is not the prediction itself but investigating the relationship among the variables, which will assist in gaining a deeper understanding of the underlying mechanisms. We estimate functional and structural networks based on regions of interest (ROI) derived from a combined atlas-tissue segmentation approach. Weights of structural connections are calculated with a newly developed technique that uses a probabilistic framework to detect tracts but the connection weights are a measure of mean anisotropy [7]. Principal component analysis (PCA) and Canonical correlation analysis (CCA) are combined to deal with the vast dimensionality of connections and infer functional connectivity from structural connectivity. A leave-one-out approach is used to validate our model.

2. MATERIALS

2.1. Data acquisition

Brain connectivity analysis was performed in eight adult volunteers (average age: 30.8; range: 20-52). Scanning was performed on a Philips 3T Achieva scanner (Philips Medical Systems, Netherlands). The scanner uses Nova Dual gradients, a phased array head coil, and sensitivity encoding (SENSE) with an undersampling factor of two.

Functional MRI images were obtained using a T2*-weighted gradient-echo echoplanar imaging (EPI) sequence with whole-brain coverage (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°,

field of view 280×220×123 mm, matrix 112×87). Quadratic shim gradients were used to correct for magnetic field inhomogeneities within the brain.

Diffusion weighted images were acquired in 16 non-collinear directions in each of the four imaging runs, resulting in a total of 64 directions. The following parameters were used: 72 slices, slice thickness 2 mm, field of view (FOV) 224 mm, matrix 128 x 128 (voxel size 1.75 x 1.75 x 2 mm^3), b value 1000 s/mm^2 (one image with non weighted diffusion), and total acquisition time 20 minutes.

High resolution T1-weighted whole-brain structural images were also obtained in all subjects.

2.2. Preprocessing

FSL was the main tool for image pre-processing of both diffusion weighted (DWI) and fMRI images [8]. This involved eddy current correction of DWI and motion correction as well as spatial smoothing of fMRI images. Brain extraction was performed originally with FSL and it was manually refined later. Bias correction was applied to T1 and B0 images to improve the robustness of the non-rigid registration tools.

3. METHODS

Brain network construction was carried out only for connections between cortical regions. A cortical parcelation 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 [9]. This is a highly accurate, automated approach that uses anatomical correspondence to propagate segmentation from manually segmented images to new individuals. 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 [10].

BOLD fluctuations are profound in gray matter, while DTI is more reliable in delineating white matter fibers [11]. Hence, probabilistic tissue segmentation was performed with SPM to classify gray matter, white matter and cerebrospinal fluid (CSF) [12]. Subsequently, 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 [13], Fig.1.

3.1. Extraction of Structural and Functional Networks

Tracts between regions are identified using a standard probabilistic algorithm available as part of FSL [5, 8]. However, measurements of connection probability are difficult to interpret as the probability measure reflects uncertainty in the data rather than likelihood of connection [7, 14]. Instead, we estimate the local diffusion anisotropy by determining the diffusive transfer between voxels using the orientation distribution function (ODF) [7, 15]. Note that the local diffusion anisotropy reflects changes in myelination, fiber density and packing [16]. Therefore, connectional strength can be compared across subjects and it is inherently related 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.

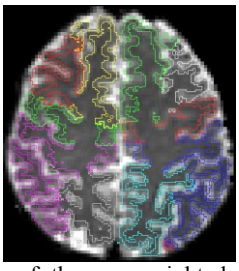

Fig 1. Segmentation of the non-weighted diffusion image via multi-atlas segmentation of the corresponding T1 image.

This strategy has applied in a number of previous works [1, 2]. The fisher's transform was used to obtain the corresponding z-scores. This produces normal random variables with variance one and allow inter-subjects comparisons.

3.2. Reduction of Dimensionality with PCA

The aim of the predictive model is to use structural connectivity across subjects to predict functional connectivity and vice-versa. Each brain's connection is treated as a variable, which results in a total of $N(N-1)/2$ variables, where N is the number of ROI. Therefore, structural and functional connectivity are denoted as two groups of variables: $S_{n\times p}$ and $F_{n\times p}$, respectively, where n is the number of connections and p are the observations/ subjects.

To reduce dimensionality principal component analysis (PCA) is applied to each group of variables. PCA can be thought as an intuitive way to represent our data in a new coordinate system, which itself models the direction of maximum variance in the data. PCA is calculated by firstly estimating the covariance matrix C and subsequently finding its eigenvectors $P_{n\times n}$ and eigenvalues. For example, the covariance matrix of structural connections is calculated as:

$$C_S = \frac{1}{p-1} \cdot dS_{n\times p} \cdot dS_{n\times p}^T, \text{ where } dS_{n\times p} = S_{n\times p} - \overline{S_n} \qquad [1]$$

Structural connectivity can be written in the new base system as a linear combination of the data projected on m principal axes, which corresponds to the m most significant eigenvectors of the covariance matrix.

$$S_{n\times p} = \overline{S_n} + \mathcal{X}, \text{ where } \mathcal{X} = P_{n\times m}^T \cdot S_{n\times p} \qquad [2]$$

Hence, $\mathcal{X}$ is a reduced data vector, also called latent variable that aims to explain most of the variance in the data. Similarly, for functional connectivity we denote as $\mathcal{Y}$ the corresponding latent variable.

3.3. Predictive Model based on CCA

Canonical correlation analysis (CCA) is generally applied when one set of independent/predictor variables $\mathcal{X}$ is to be related to another set of dependent/predicted variables $\mathcal{Y}$ and observations are available for both groups. Note that CCA is designed to deal with situations where the underlying variables are not statistically independent and, hence, they are inherently inter-correlated. The ultimate goal of CCA is to find two basis vectors, one for each variable, so that the projections of these variables onto the basis vectors are maximally linearly correlated. In this way, hidden correlations between multidimensional variables can be obtained.

The covariance matrix $\mathcal{C}$ of $\mathcal{X}$ and $\mathcal{Y}$ is defined as:

$$\mathcal{C} = \begin{bmatrix} \mathcal{C}_{xx} & \mathcal{C}_{xy} \\ \mathcal{C}_{yx} & \mathcal{C}_{yy} \end{bmatrix} \quad [3]$$

The canonical correlation between $\mathcal{X}$ and $\mathcal{Y}$ is calculated by solving the eigenvalue equations:

$$\begin{cases} \mathcal{C}_{xx}^{-1} \cdot \mathcal{C}_{xy} \cdot \mathcal{C}_{yy}^{-1} \cdot \mathcal{C}_{yx} \cdot \boldsymbol{w_x} = \rho^2 \cdot \boldsymbol{w_x} \\ \mathcal{C}_{yy}^{-1} \cdot \mathcal{C}_{yx} \cdot \mathcal{C}_{xx}^{-1} \cdot \mathcal{C}_{xy} \cdot \boldsymbol{w_y} = \rho^2 \cdot \boldsymbol{w_y} \end{cases} \quad [4]$$

Where ρ are the canonical correlations and $\boldsymbol{w_x}$, $\boldsymbol{w_y}$ are the normalized canonical correlation basis vectors.
Prediction of a new variable $\mathcal{Y}'$ based on a predictor variable $\mathcal{X}'$ can be derived as:

$$\mathcal{Y}' = \rho \cdot (\mathcal{X}' \cdot \boldsymbol{w_x}) \cdot inv(\boldsymbol{w_y}) \quad [5]$$

Note that the predictive variable needs to be projected back to Cartesian coordinate system from the PCA-derived coordinate system.

4. 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.2 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. Fig.2a is the true functional connectivity as it has been extracted from fMRI data. Fig.2b is the structural connectivity, which is used as an input to the predictive model. Fig.2c shows the prediction derived from the combined PCA and CCA methodology. On the other hand, Fig.1d shows the estimated prediction when each of the connections treated as an independent variable. In this case, CCA was applied for each connection separately. It is apparent that correlations among the variables play an important role in the robustness of the predictive model. The results indicate that the suggested model is capable in capturing the relative pattern of the brain networks. It is particularly successful in distinguishing connections between left and right hemisphere, even when inter-hemispheric connections are underestimated with tractography techniques. This is because the model utilizes information across variables and subjects. Underestimation of inter-hemispheric connections is a common problem with current tractography techniques [1, 2].

Quantitative assessment was performed by estimating the coefficient of determination R^2, as the squared correlation coefficient, for each subject in a leave-one-out fashion (mean: 42.43%, std: 5.12%). This gives the proportion of functional connectivity's variance explained by structural connectivity for each subject. 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.

Table 1. Coefficient of determination, R^2

Sub1	Sub2	Sub3	Sub4	Sub5	Sub6	Sub7	Sub8
0.51	0.36	0.37	0.39	0.44	0.45	0.46	0.40

5. DISCUSSION AND CONCLUSIONS

This paper exploits a multivariate statistical technique to predict functional connectivity from structural connectivity. PCA is employed for dimensionality reduction and CCA for modeling hidden linear correlations. The results demonstrate that the suggested methodology is capable of capturing subtle details of brain network characteristics. Hence, there are two main outcomes of our research: (a) We have added further evidence that resting-state functional networks are of neuronal origin and (b) we have showed that statistical prediction is a potentially powerful tool in investigating the interactions between anatomical and functional connectivity. There are, indeed, factors that are not accounted in the current model and they may influence functional connectivity. The current scientific view is that indirect connections may explain why functional connectivity can be strong between areas that a direct anatomical link has not been detected [1, 2, 17]. It is yet to be determined whether such a model would be able to significantly improve the performance of statistical inference of functional data from structural data.

The investigation of this hypothesis with existing statistical techniques is extremely challenging because of the high-dimensional space of predictors and the limited availability of datasets. Here, we applied PCA in order to produce a low-dimensional embedding of brain connectivity data that best describes their variance. There are, other dimensionality reduction approaches capable of detecting non-linearities [18]. These techniques, though, would require an even larger number of samples in order to accurately model non-linear effects. Future work should 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.

Finally, it has been also argued that the relationship between resting-state fMRI and DTI data may be far more complex. For example, the influence of sub-cortical structures via both driving and modulating inputs may play an important role in describing functional from structural connectivity [17, 19]. Perhaps, investigating these relationships would also require examining causal relationships and determining the directionality of information flow from one area to another. The suggested framework is based on correlations and hence relationship between two areas does not necessarily imply causality. Other approaches such as Granger causality could be employed towards this end [20].

6. ACKNOWLEDGMENTS

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7. REFERENCES

[1] P. Hagmann, L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen, and O. Sporns, "Mapping the structural core of human cerebral cortex," *PLoS Biol,* vol. 6, pp. 1479-1493, 2008.

[2] C. J. Honey, O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, and P. Hagmann, "Predicting human resting-state functional connectivity from structural connectivity," *P Natl Acad Sci Usa,* vol. 106, pp. 2035-2040, 2009.

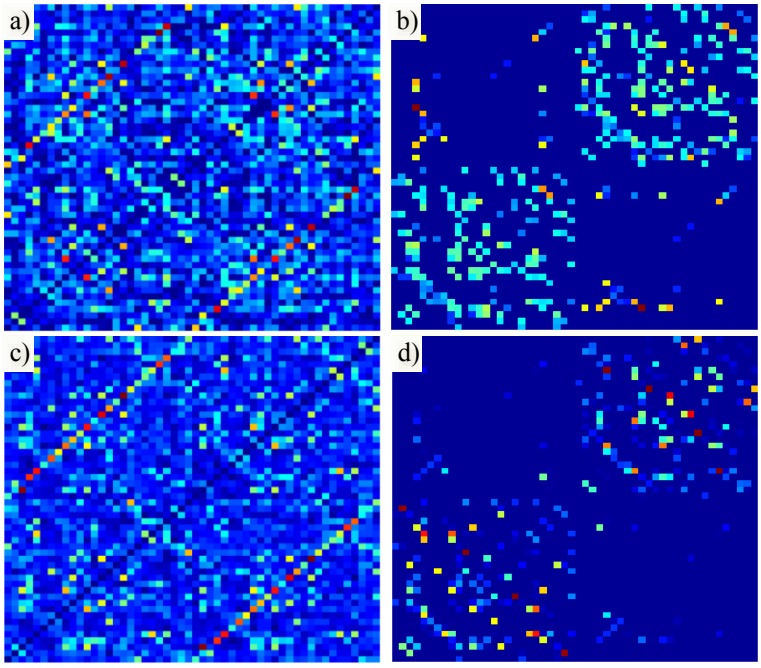

Fig. 2. Inference of functional connectivity from structural connectivity. a) The original functional connectivity matrix, b) The structural connectivity matrix, c) The predicted functional connectivity matrix in a one left-out fashion. d) The predicted functional connectivity matrix with each connection treated independently.

[3] K. Friston, "Functional and effective connectivity in neuroimaging: a synthesis," *Human Brain Mapping,* vol. 2, pp. 56-78, 1994.

[4] B. Horwitz, "The elusive concept of brain connectivity," *NeuroImage,* vol. 19, pp. 466-470, 2003.

[5] T. Behrens, M. Woolrich, M. Jenkinson, H. Johansen-Berg, R. Nunes, S. Clare, P. Matthews, J. Brady, and S. Smith, "Characterization and propagation of uncertainty in diffusion-weighted MR imaging," *Magnet Reson Med,* vol. 50, pp. 1077-1088, 2003.

[6] T. Dyrby, L. Søgaard, and G. Parker, "Validation of in vitro probabilistic tractography," *NeuroImage,* vol. 37, pp. 1267-1277, 2007.

[7] E. C. Robinson, A. Hammers, A. Ericsson, A. D. Edwards, and D. Rueckert, "Identifying population differences in whole-brain structural networks: a machine learning approach," *NeuroImage,* in press, 2010.

[8] S. Smith, M. Jenkinson, M. Woolrich, C. Beckmann, T. Behrens, H. Johansen-Berg, P. Bannister, M. De Luca, I. Drobnjak, D. Flitney, R. Niazy, J. Saunders, J. Vickers, Y. Zhang, N. De Stefano, J. Brady, and P. Matthews, "Advances in functional and structural MR image analysis and implementation as FSL," *NeuroImage,* vol. 23, pp. 208-219, 2004.

[9] R. A. Heckemann, J. V. Hajnal, P. Aljabar, D. Rueckert, and A. Hammers, "Automatic anatomical brain MRI segmentation combining label propagation and decision fusion," *NeuroImage,* vol. 33, pp. 115-126, 2006.

[10] P. Aljabar, R. Heckemann, and A. Hammers, "Classifier selection strategies for label fusion using large atlas databases," *Proc. Intl. Conf. MICCAI,* vol. 4791, pp. 523-531, 2007.

[11] M. Koch, D. Norris, and M. Hund-Georgiadis, "An investigation of functional and anatomical connectivity using magnetic resonance imaging," *NeuroImage,* vol. 16, pp. 241-250, 2002.

[12] K. J. Friston, "Statistical parametric mapping: the analysis of functional brain images," Academic Press, p. 647, 2007.

[13] D. Rueckert, L. Sonoda, C. Hayes, and D. Hill, "Nonrigid registration using free-form deformations: application to breast MR images," *IEEE Transactions on Medical Imaging,* vol. 18, pp. 712-721, 1999.

[14] E. Robinson, M. Valstar, and A. Hammers, "Multivariate statistical analysis of whole brain structural networks obtained using probabilistic tractography," *Proc. Intl. Conf. MICCAI,* vol. 5241, pp. 486-493, 2008.

[15] Y. Iturria-Medina and E. Canales-Rodriguez, "Characterizing brain anatomical connections using diffusion weighted MRI and graph theory," *NeuroImage,* vol. 36, pp. 645-660 2007.

[16] B. Mädler, S. Drabycz, and S. Kolind, "Is diffusion anisotropy an accurate monitor of myelination? Correlation of multicomponent T2 relaxation relaxation and diffusion tensor anisotropy in human brain.," *Magnetic Resonance Imaging,* vol. 26, pp. 874-888, 2008.

[17] J. S. Damoiseaux and M. D. Greicius, "Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity," *Brain Struct Funct,* vol. 213, pp. 525-533, 2009.

[18] J. B. Tenenbaum, V. de Silva, and J. C. Langford, "A global geometric framework for nonlinear dimensionality reduction," *Science,* vol. 290, pp. 2319-23, 2000.

[19] D. Zhang, A. Z. Snyder, M. D. Fox, M. W. Sansbury, J. S. Shimony, and M. E. Raichle, "Intrinsic Functional Relations Between Human Cerebral Cortex and Thalamus," *Journal of Neurophysiology,* vol. 100, pp. 1740-1748, 2008.

[20] A. Roebroeck, E. Formisano, and R. Goebel, "Mapping directed influence over the brain using Granger causality and fMRI," *NeuroImage,* vol. 25, pp. 230-42, 2005.