INFERENCE OF FUNCTIONAL CONNECTIVITY FROM DIRECT AND INDIRECT STRUCTURAL BRAIN CONNECTIONS

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ABSTRACT

We propose statistical inference based on the Least Absolute Shrinkage and Selective Operator (Lasso) regression as a framework to investigate the relationship between structural brain connectivity data (DTI) and functional connectivity data (fMRI). Regions of interest (ROIs) are obtained from an accurate atlas-based segmentation. We use direct structural connections to model indirect (higher-order) structural connectivity. Subsequently, we use Lasso to associate each functional connection with a subset of structural connections. Lasso offers the advantage of simultaneous dimensionality reduction and variable selection. We use a cohort of 22 subjects with both resting-state fMRI and DTI and we provide both qualitative and quantitative results based on leave-one-out cross validation. The results demonstrate that the performance of prediction is enhanced through the incorporation of indirect connections. In fact, the mean explained variance was improved from 54%±6.53 to 58%±4.31 when indirect connections of up to second order are added and the improvement in performance was statistically significant ($p < 0.05$).

Index Terms— Brain connectivity, rs-fMRI, whole-brain connectivity matrices, functional connectivity, structural connectivity, indirect structural connections

1. INTRODUCTION

Typically, in task-related activation the fMRI BOLD signal is compared to the BOLD signal during a control task, which reflects the baseline brain activity. This methodology has considerably advanced our knowledge on functional specialization, which investigates how different brain areas are consistently engaged in some aspects of cognitive or motor processing. These results are interpreted under the implicit assumption that the brain during rest is in a relatively constant state. On going research is focused in investigating resting-state (rs)-fMRI based on functional integration/connectivity as it is measured by temporal correlation between spatially remote neurophysiological events [1]. Recent results suggest that networks, which are neurophysiologically relevant, are consistently active during resting-state. However, their reliability is limited due to physiological noise and lack of structural evidence to confirm their presence [2].

Therefore, investigating the relationship between functional and structural brain connectivity is vital in understanding and interpreting neurophysiological findings. A number of statistical tools have been used to quantitatively measure this relationship [3, 4, 5]. These methodologies showed that there is a high correlation between rs-fMRI and DTI data. In Deligianni et al. inference of functional connectivity from structural brain connectivity was implemented with a combination of Principal Component Analysis (PCA) and Canonical Correlation Analysis (CCA) [5]. Prediction is a common tool in statistics. In this work, the ultimate goal was not the prediction itself but the discovery of the relationship among the variables, which assists in gaining a deeper understanding of the underlying mechanisms. However, this approach was limited in two major ways: Firstly, indirect connections are not modeled and, secondly, PCA is not designed to select relevant variables.

Strong functional connectivity is also observed between unconnected areas suggesting that indirect structural connections also influence functional connectivity. Here we demonstrate that the prediction's performance of structural brain connectivity from functional connectivity is improved when indirect connections are incorporated. We estimate functional and structural networks based on ROIs derived from a combined atlas-tissue segmentation approach. Subsequently, we model indirect connectivity and we use Least Absolute Shrinkage and Selection Operator (Lasso) regression [6] to infer functional from both direct and indirect connections. This allows us to formulate a generic framework that offers simultaneous statistical prediction and selection of a subset of structural connections that predict each functional connection. We show both qualitative and quantitative results based on leave-one-out cross validation that demonstrate that the incorporation of indirect connections improve the prediction's performance consistently across subjects.

2. METHODS

In this section, we present a detailed description of our methodology. We start with how to obtain an intuitive network description of brain connectivity across imaging modalities. Subsequently, we describe how to model indirect connections from direct structural connections. Finally, we use statistical inference based on Lasso to explore the relationship between structural and functional connectivity.

2.1. Brain Network Construction

BOLD fluctuations are stronger in gray matter, while DTI is reliable in delineating white matter fibers. This is the reason, we are interested in defining cortical ROIs that are located in gray matter and they are anatomically consistent with a widely used brain atlas [7]. This methodology has been previously described in details [5, 8]. Briefly, this is based on the fusion of atlas-based [7] and tissue based segmentation [9].

Whole-brain structural connectivity matrices are obtained based on a probabilistic framework described previously in Robinson et al. [8, 5]. In this framework, the weights of the connections between each pair of ROIs are estimated based on the local diffusion anisotropy. This reflects differences in myelination, fiber density and packing and, thus, it allows comparisons across subjects. To construct corresponding functional networks the fMRI signal was averaged across voxels within each ROI. Partial correlation was used to compute functional connectivity accounting for the whole brain mean signal. Fishers transform was used to obtain the corresponding z-scores. This produces normal random variables with variance one and allows inter-subjects comparisons.

2.2. Modeling of Indirect Brain Connections

Each connection between brain regions is treated as variable with a number of observations equal to the number of subjects for both functional and structural data. The weights of indirect connections of 1^{st} order are estimated with the following algorithm:

1. Find pair of regions (A,B) with no direct structural link.
2. Find all possible paths that connect area A to B via one other area.
3. Find the minimum weight of connections between A to B for each of the paths, assuming that indirect connectivity is constrained by the weakest connection.
4. Indirect connectivity strength between A and B is the maximum value over all paths.

This procedure can be repeated up to k^{th} order by finding paths via k areas. In Fig. 1 (a-c) you see an example of augmented connectivity matrices with up to 2^{nd} order connections.

2.3. Statistical Prediction

The Least Absolute Shrinkage and Selective Operator (Lasso) utilises a multiple linear regression model to perform both variable selection and prediction [6]. For each functional connection Y_k a linear regression model is formulated as:

$$Y_k = b_0 + \sum_{j=1}^{N} b_j X_j \tag{1}$$

Here b_0 is the intercept, $X^T = (X_1, X_2, ..., X_N)$ is the input variables (structural connections), b_j are the regression coefficients and Y_k is the k^{th} functional connection (response). Over classical least square regression Lasso offers two major advantages that are very useful in modeling brain connectivity: Firstly, it improves prediction by setting some coefficients to zero. This results in removing noisy and irrelevant variables and thus reducing the total variance. Secondly, it allows the selection of the most relevant variables and thus it links each functional connection with a subset of structural connection in a data driven way. In other words, it highlights structural connections that are highly likely to affect functional connectivity between a pair of regions. It has been also shown that it identifies the correct predictors with high probability when the number of variables is higher than the number of observation under the assumption that the true model is sparse [10]. The Lasso estimate is defined as:

$$b_L = \arg\min_b \sum_{i=1}^{M} \left(y_i^k - b_0 - \sum_{j}^{N} b_j x_{i,j} \right)^2 \tag{2}$$

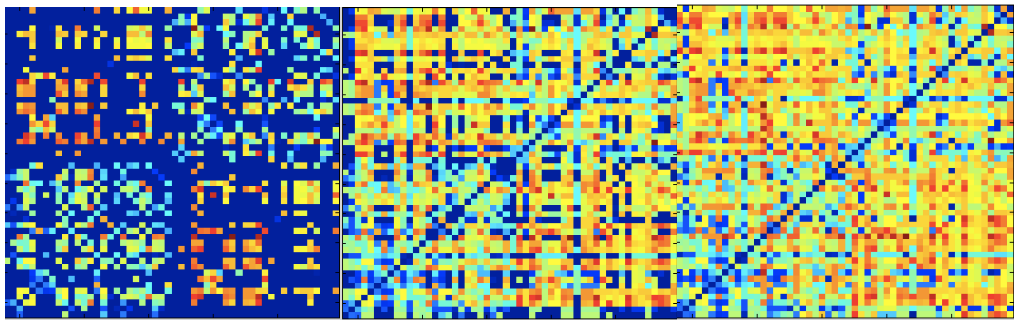
Where M is the number of observations/subjects and the minimization is subject to the $L1$ lasso penalty:

$$\sum_{j=1}^{N} |b_j| \le t \tag{3}$$

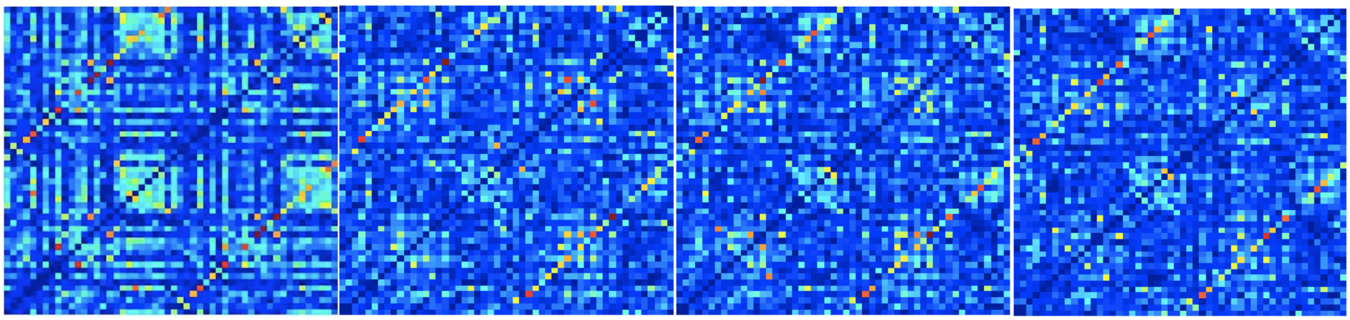
Note that t controls the number of coefficients that shrunk toward zero. Subsequently, the above equation can take the equivalent Lagrangian form:

$$b_L = \arg\min_b \left\{ \sum_{i=i}^{M} (y_i^k - b_0 - \sum_{j}^{N} b_j x_{i,j})^2 + \lambda \sum_{j=1}^{N} |b_j| \right\} \tag{4}$$

Where λ is the parameter that controls the shrinkage of the coefficients b_j. Because of the $L1$ lasso penalty, making λ sufficiently small results in some of the coefficients to be zero. This is called soft thresholding and it allows Lasso to perform continuous coefficient selection, which is a clear advantage over other approaches, such as forward-stagewise regression. We used the LARS implementation of the Lasso, available in R statistics, which computes the complete Lasso solution simultaneously for all values of the shrinkage parameter λ [11].



(a) Direct Structural Connections (b) Direct plus indirect 1^{st} order (c) Direct plus indirect 1^{st}&2^{nd} order



(d) Original fMRI (e) EV=51.35% (f) EV=56.89% (g) EV=61.16%

Fig. 1: Top row shows: a) Direct structural connections, b) Direct plus indirect connections of 1^{st} order and c) Direct plus indirect connections of 1^{st} and 2^{nd} order, respectively. Bottom row shows a qualitative view of the results for one subject: d) the original functional connectivity data, e-g) The results of the prediction algorithm based on Lasso for each of the inputs in top row. The explained variance (EV) increases from 51.35% up to 61.16% with the incorporation of indirect connectivity.

3. RESULTS

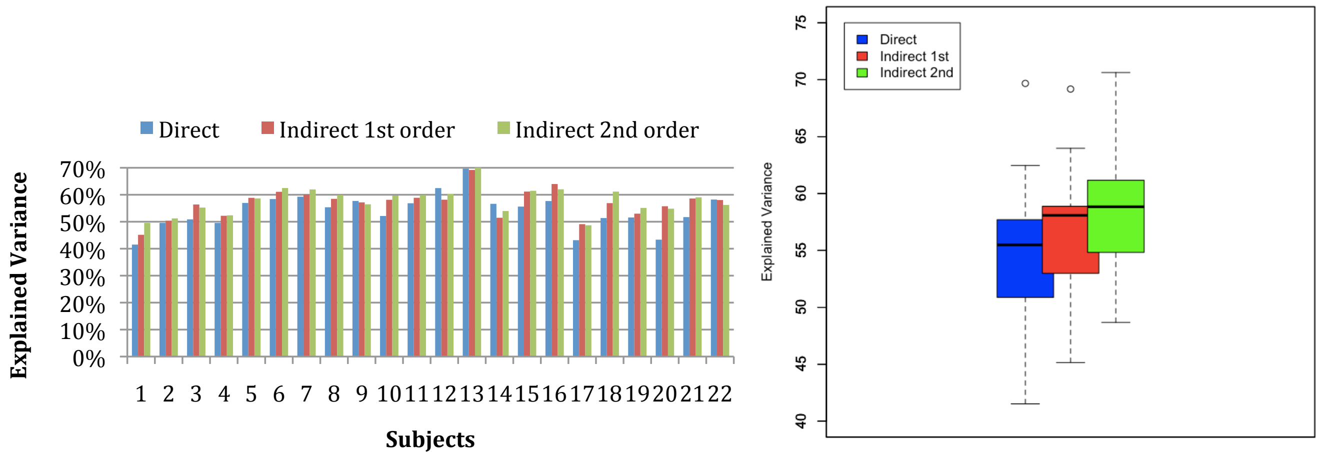
Brain connectivity analysis was performed in 22 normal adults. rs-fMRI: T2*-weighted gradient EPI sequence, TR/TE=2000/30, 31 ascending slices with thickness 3.25mm, gap 0.75mm, voxel size 2.5x2.5x4 mm, flip angle 90, FOV 280x220x123mm, matrix 112x87. DWI: 64 non-collinear directions, in 72 slices, slice thickness 2mm, FOV 224mm, matrix 128x128, voxel size 1.75x1.75x2mm^3, b value 1000 s/mm^2.

A leave-one-out cross-validation approach was adapted to test the robustness of the suggested methodology. Fig. 1 shows the results for one left-out subject. Fig.1a shows direct structural connections, then in Fig. 1b for each absent connection indirect connection of 1^{st} order are added and finally in Fig. 1c indirect connections of 2^{nd} order are added. 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. 1d depicts the actual functional connectivity data. Fig. 1(e-g) shows the prediction results for each of the structural connectivity matrices in Fig. 1 (a-c). Indirect connectivity improves subtle details of functional connectivity in a progressive manner. In fact, the explained variance (EV) increases from 51.35% up to 61.16% with the incorporation of indirect connectivity. EV is measured as the correlation coefficient between the prediction and the original fMRI connectivity matrix.

Fig 2 shows quantitative results over all subjects. Fig. 2a shows the EV for each subjects functional connectivity matrix when their structural connectivity matrix is used as a predictor. The mean EV is improved from 54%$\pm$6.38 to 57%$\pm$5.11 for 1st order and finally to 58%$\pm$4.92 when 2^{nd} order indirect connections are added. Fig. 2b shows a summary of the results over all subjects for all three scenarios. The Lasso shows consistent improvement when indirect connections are taken into consideration. The enhanced performance is statistically significant $p < 0.05$.

4. DISCUSSION AND CONCLUSIONS

So far, there has been a lot of speculation in the literature that indirect structural connectivity affects functional connectivity [4, 2]. Here we developed an intuitive framework that quantifies this relationship. We used a cohort of 22 subjects and qualitative as well as detailed quantitative evaluation based on leave-one-out cross validation. Statistical inference based on Lasso regression showed that indirect connections add sub-



(a)

(b)

Fig. 2: Prediction performance of Lasso regression with leave-one-out cross validation. a) The explained variance for each subjects functional connectivity matrix is shown when their structural connectivity matrix is used as a predictor. b) Box-and-Whisker diagram over all subjects of Fig. 2a). The mean EV is improved from $54\% \pm 6.38$ to $57\% \pm 5.11$ for 1^{st} order and finally to $58\% \pm 4.92$ when 2^{nd} order indirect connections are added. The enhanced performance is statistically significant $(p < 0.05)$.

tle information that improves predictions performance consistently across subjects. There are several advantages we could explore with the suggested methodology. Variable selection allows the association of a subset of structural connections with each functional connection. Detecting changes in the relationship between functional connections and structural connections in disease is a promising approach in highlighting affected areas and understanding how disease alters the relationship between fMRI and DTI data.

5. REFERENCES

[1] C Beckmann and S Smith, "Tensorial extensions of independent component analysis for multi-subject fmri analysis," *NeuroImage*, vol. 25, no. 1, pp. 294–311, Mar 2005.

[2] J Damoiseaux and M 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, no. 6, pp. 525–533, 2009.

[3] P Hagmann, L Cammoun, X Gigandet, R Meuli, C Honey, V Wedeen, and O Sporns, "Mapping the structural core of human cerebral cortex," *PLoS Biol*, vol. 6, no. 7, pp. 1479–1493, 2008.

[4] C Honey, O Sporns, L Cammoun, X Gigandet, J Thiran, R Meuli, and P Hagmann, "Predicting human resting-state functional connectivity from structural connectivity," *P Natl Acad Sci Usa*, vol. 106, no. 6, pp. 2035–2040, 2009.

[5] F Deligianni, E Robinson, C Beckmann, D Sharp, AD Edwards, and D Rueckert, "Inference of functional connectivity from structural brain connectivity," *ISBI*, pp. 1113 –1116, 2010.

[6] R Tibshirani, "Regression shrinkage and selection via the lasso," *Journal of the Royal Statistical Society. Series B*, vol. 58, no. 1, pp. 267–288, Jan 1996.

[7] P Aljabar, R Heckemann, A Hammers, J Hajnal, and D Rueckert, "Multi-atlas based segmentation of brain images: atlas selection and its effect on accuracy," *NeuroImage*, vol. 46, no. 3, pp. 726–38, Jul 2009.

[8] E Robinson, A Hammers, A Ericsson, AD Edwards, and D Rueckert, "Identifying population differences in whole-brain structural networks: a machine learning approach," *NeuroImage*, vol. 50, no. 3, pp. 910–919, 2010.

[9] K Friston, *Statistical parametric mapping: the analysis of functional brain images*, Academic Press, 2007.

[10] D Donoho, "For most large underdetermined systems of linear equations the minimal l1-norm solution is also the sparsest solution," *Comm. Pure Appl. Math.*, vol. 59, no. 6, pp. 797–829, 2006.

[11] B Efron, T Hastie, I Johnstone, and R Tibshirani, "Least angle regression," *Annals of statistics*, vol. 32, no. 2, pp. 407–499, Jan 2004.