Visualisation of network connectomes in fMRI data for characterisation of Autism Spectrum Disorder

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Here, we present a comprehensive review of the existing literature, formally introduce the problem and give an insight into the methods we propose to follow in our study.

Literature Survey:

Part 1:

Resting state fMRI - Application to network connectomics:

In recent times, fMRI or functional magnetic resonance imaging has gained popularity owing to its growing application in the characterisation of brain activity and the localisation of critical functions by mapping them to different areas of the brain. Initially developed as an extension to the technique of spatial imaging using the MRI (magnetic resonance imaging) scanners, early fMRI research primarily involved capturing the BOLD (blood oxygen level dependent) signal based on the changing levels of oxygenated and deoxygenated blood in the vicinity of neuronal activity [1]. Typically, while the signal is being recorded, the subject is made to perform a certain task such as finger tapping or is given a visual/audio stimulus.

Owing the poor SNR along with some other major drawbacks of BOLD, (like its inability to isolate activity based signal from random fluctuations) rsfMRI or resting state fMRI proved to be more reliable for the purpose of identifying connected regions of activity in the brain. In the resting state, i.e. when the subject is lying still and isn't explicitly performing any task, it is a well established fact from neuroscience that regions of the brain that work in unison display synchronism in their patterns of fluctuation [2]. Accurate identification and localisation of these connected regions of interests is the primary objective that network analysis techniques on fMRI data being currently developed aspire to achieve.

Part 2:

Network analysis and functional connectomics:

Connectomics is the part of neuroimaging that deals with creating detailed maps of neural connections in the brain. Typically, the scale of these interconnected networks isn't fixed. On one hand, maps relating functionally similar neurons or synapses may be found, while on the other, macro scale descriptions dealing with functional and structural connectivity between subcortical structures and cortical areas in the brain may be sought out (these being both larger in size as well as more complex functionally). A variety of different techniques have already been developed in order to extract an accurate picture of these underlying networks.

Perhaps the most popular method used in order to model time courses in fMRI signals is purely statistical in its formulation and approach. As explained in [3], a GLM or generalised linear model is constructed in order to perform a wide range of hypothesis testing on the imaged data using statistical parametric maps. Another approach is to model functional connectivity in terms of correlation maps within regions of the brain. As is outlined in [4], correlation analysis has been employed on resting state EPI(Echo Planar Imaging) data in

order to draw the functional map for connected regions in the motor cortex. Conclusive proof of the existence of functional connectivity in the absence of an external motor task has been established by a careful analysis of the auditory and visual cortex responses.

There has been an increased interest in the functional parcellation of the brain because it provides an atlas that can be used to more accurately compare inter-subject fMRI time series by incorporating functional and anatomical features into inter-subject registration approaches. Grouping together functionally similar voxels can essentially be viewed as a reduction in the dimensionality of the fMRI data.

In the past, several variants of the clustering algorithm, including expectation maximization [5], hierarchical clustering [6],[7],[8], spectral clustering [9],[10], and K-means clustering [11] have been employed to study these functional parcellations.

[12] approaches this problem from the perspective of ICA or Independent Component Analysis, making use of minimal assumptions about the nature of the a priori distribution of the time courses in the fMRI data and its spatial distribution. The results illustrated show how ICA was applied in order to achieve a blind separation into the constituent components, accounting for consistently (as well as transiently) related task and non-task physiological phenomenon and separating them from motion and machine artefacts.

Part 3:

Network Analysis in relation with ASD diagnosis:

Autism spectrum disorder (ASD) is an umbrella for a group of developmental disorders, characterized by impaired social-communication and repetitive behaviors. Behaviorally, ASD includes a wide range, “a spectrum,” of symptoms, skills, and levels of disability. Typically, patients displaying signs of ASD demonstrate impaired social reciprocity, communication deficits, and stereotyped behavior. [13]

From a functional organisation perspective, the motor impairments in children and adults with Autism is associated with an abnormal functional connectivity within brain networks underlying motor control and learning.

Task based fMRI studies show inconsistent patterns of altered connectivity between the cortex and limbic structures [14],[15]. As seen in [14] though the gross organizational scheme was present in groups of children with Autism as well as in typically developing children, statistically significant group differences in the size and segregation of the primary motor cortex (a key area of the motor control network) or M1 parcellations (within regions of the motor homunculus corresponding to the upper and lower limbs) were observed. However, when the analyses are restricted to predefined neural systems, they do not characterise whole brain information.

Analysis of a multi-subject rs-fMRI imaging study has been approached from a group level perspective, typically involving the estimation group-averaged functional connectivity across subjects. However, a major limitation of group-based analysis lies in the treatment of heterogeneous patient group as a unified cohort leading to the loss of valuable information about individual variation. As a result, key differences that may be linked to the disorder are lost.

Contrary to the traditional approaches, hierarchical Bayesian framework estimates group-level network differences while simultaneously accommodating population variability. The Bayesian approaches outlined in [16],[17]. This method involves the development of a unified generative model that describes the relationship between population templates and individual subject observations. Following this, a community detection in the space of group-level functional differences, which identifies both heightened and reduced synchrony is performed. The group-level functional differences are represented by K interconnected subgraphs. Both the enhanced and impaired processes are modelled by stipulating that each community can either reflect a uniform increase or decrease in functional synchrony between regions. Assuming that the K networks are disjoint allows a disentanglement of multiple influences enabling a capture of the most salient patterns induced by the neurological disorder. A variational EM algorithm is used to model the parameters.

While the Bayesian approach provides us with an elegant formulation of the problem, it suffers from a few inherent drawbacks due to it's simplistic approach. Many of the networks in the brain may contain overlapping regions in their circuitry. As an example, the social and language circuitry of the brain have many common areas.The limitations of these methods lie in the assumption of disjoint hypo and hyper active communities. Effectively, an efficient modelling of overlapping processes isn't captured.

Part 4:

Dimensionality reduction and its application to fMRI data:

Principal Component Analysis is a statistical procedure developed with the aim of converting a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables using orthogonal transformations. When the underlying distributions in multivariate data are Gaussians, PCA works extremely well for the identification and separation of groups of components with similar variance.

Application of dimensionality reduction on fMRI data isn't a new concept. Historically, PCA has been applied in the pre-processing pipeline of fMRI in order to achieve noise suppression [18]. From the point of view of fMRI data analysis, sparse PCA and ICA have been systematically compared in [19]. This paper goes further to explain how sparse PCA has been more effective as opposed to ICA in searching for underlying representations sufficient to explain the response signal while at the same time achieving noise suppression. This is because, while ICA involves a thresholding on individual components characterising the response signal, in sparse PCA, the derived loading vectors are strictly sparse effectively doing away with the requirement of a thresholding to limit the spatial extent of the BOLD response [20]. From the point of view of disease diagnosis, kernel PCA has been developed in [21] for characterising Attention Deficit Hyperactivity Disorder (ADHD).

From a network analysis perspective, blind separation into components using ICA has been performed for the purposes of network extraction of underlying networks directly on the available fMRI data as can be seen in [12]. The limitation of this method lies in the fact that the ICA potentially splits component processes contributing to the observed fMRI signals in well-overlapping brain areas, into multiple components, while one component represents the combined effects of the two factors in the regions of overlap, others may represent the regions affected by just one of the two processes. Thus, network extraction for studying patient vs controls differences by this method isn't exactly reliable.

Experiments and proposed solutions:

Keeping in mind the salient points and limitations associated with each of the existing methods developed in order to solve the problem of network extraction from resting state fMRI data, we propose to refine the technique which attempts to capture the interconnections between these networks, while at the same time accounting for inter subject variability.

In our workflow, the preprocessing of the raw fMRI data for noise suppression and correction for patient motion is followed by a co-registration performed in order to align the image with the spatial data template, each represented in the MNI space. With an existing anatomical atlas available to us, provided in the same MNI representation, the time courses in each region are computed. Next, the functional connectivity networks need to be estimated. For this purpose, the Pearson correlation coefficients are calculated from the time courses for each subject. At this stage, a dimensionality reduction is performed on the correlation matrix.

PCA transformation results in the extraction of an uncorrelated orthogonal basis set of vectors where the first principal component has the largest possible variance (that is, accounts for as much of the variability in the data as possible), and each succeeding component in turn has the highest variance possible under the constraint that it is orthogonal to the preceding components. The underlying distribution generating the fMRI data is assumed to be Gaussian. We expect that performing a Principal Component Analysis after the conversion of the correlation matrix using Fisher's r to z transform would result in the extraction of the underlying networks characteristic of each of the correlation matrices. The behavioural symptoms associated with ASD need to be related to the networks extracted using the procedure outlined above by developing a regression model based on behavioural measures such as ADOS (Autism Diagnostic Observation Schedule), SRS (Social Responsiveness Scale), SES (Socio-Economic Scale) along with the demographic data for each of the patients that is available to us.

References

[1] Ogawa, S., et al. "Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model." Biophysical journal 64.3 (1993): 803.

[2] Lee, Megan H., Christopher D. Smyser, and Joshua S. Shimony. "Resting-state fMRI: a review of methods and clinical applications." *American Journal of Neuroradiology* 34.10 (2013): 1866-1872.

[3] Friston, Karl J., et al. "Statistical parametric maps in functional imaging: a general linear approach." Human brain mapping 2.4 (1994): 189-210.

[4] Biswal, Bharat, et al. "Functional connectivity in the motor cortex of resting human brain using echo-planar mri." Magnetic resonance in medicine 34.4 (1995): 537-541.

[5] Ryali, S., Chen, T., Supekar, K., and Menon, V. (2012). A parcellation scheme based on von MisesFisher distributions and Markov random fields for segmenting brain regions using resting-state fMRI. NeuroImage.

[6] Cordes, D., Haughton, V., Carew, J. D., Arfanakis, K., and Maravilla, K. (2002). Hierarchical clustering to measure connectivity in fMRI resting-state data. Magnetic resonance imaging, 20(4):305–317.

[7] Salvador, S., Brovelli, A., and Longo, R. (2002). A simple and fast technique for on-line fMRI data analysis. Magnetic resonance imaging, 20(2):207–213.

[8] Blumensath, T., Jbabdi, S., Glasser, M. F., Van Essen, D. C., Ugurbil, K., Behrens, T. E., and Smith, S. M. (2013). Spatially constrained hierarchical parcellation of the brain with resting-state fMRI. Neuroimage, 76:313–324.

[9] Craddock, R. C., James, G. A., Holtzheimer, P. E., Hu, X. P., and Mayberg, H. S. (2011). A whole brain fMRI atlas generated via spatially constrained spectral clustering. Human brain mapping, 33(8):1914– 1928.

[10] Nebel, M. B., Joel, S. E., Muschelli, J., Barber, A. D., Caffo, B. S., Pekar, J. J., and Mostofsky, S. H. (2014). Disruption of functional organization within the primary motor cortex in children with autism. Human Brain Mapping, 35(2).

[11] Kim, J.-H., Lee, J.-M., Jo, H. J., Kim, S. H., Lee, J. H., Kim, S. T., Seo, S. W., Cox, R. W., Na, D. L., Kim, S. I., et al. (2010). Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: functional connectivity-based parcellation method. Neuroimage, 49(3):2375.

[12] McKeown, Martin J., et al. *Analysis of fMRI data by blind separation into independent spatial components*. No. NHRC-REPT-97-42. NAVAL HEALTH RESEARCH CENTER SAN DIEGO CA, 1997.

[13] First, Michael B. "Diagnostic and statistical manual of mental disorders." DSM IV-4th edition. APA (1994): 1994.

[14] Nebel, Mary Beth, et al. "Disruption of functional organization within the primary motor cortex in children with autism." Human brain mapping 35.2 (2014): 567-580.

[15] Just, Marcel Adam, et al. "Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity." *Neuroscience & Biobehavioral Reviews* 36.4 (2012): 1292-1313.

[16] Venkataraman A, Yang D, Pelphrey K, Duncan J. Bayesian Community Detection in the Space of Group-Level Functional Differences.

[17] Venkataraman A, Duncan JS, Yang DY, Pelphrey KA. An unbiased Bayesian approach to functional connectomics implicates social-communication networks in autism. NeuroImage: Clinical. 2015 Dec 31;8:356-66.

[18] Smith SM, Hyvärinen A, Varoquaux G, Miller KL, Beckmann CF. Group-PCA for very large fMRI datasets. NeuroImage. 2014 Nov 1;101:738-49.

[19] Sjöstrand, Karl, et al. "Sparse PCA, a new method for unsupervised analyses of fMRI data." *14th Scientfic Meeting and Exhibition of International Society for Magnetic Resonance in Medicine*. 2006.

[20] Zou, Hui, Trevor Hastie, and Robert Tibshirani. "Sparse principal component analysis." *Journal of computational and graphical statistics* 15.2 (2006): 265-286.

[21] Sidhu GS, Asgarian N, Greiner R, Brown MR. Kernel Principal Component Analysis for dimensionality reduction in fMRI-based diagnosis of ADHD. Frontiers in systems neuroscience. 2012 Nov 9;6:74.