Identification of Neural Connectivity Signatures of Autism using Machine Learning

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Introduction: Interregional connectivity abnormalities have been suggested as a neural signature of the pathobiology of autism [1, 2]. There have been many reports of functional and anatomical connectivity being altered in complex cognitive and social tasks in autism. Although disrupted instantaneous correlation between cortical regions observed from functional MRI of the autistic brain is considered to be an explanatory model for autism, the causal influence of a brain area on another (effective connectivity) is a vital link which is missing in these studies. The current study focuses on addressing this in an fMRI study of Theory-of-Mind (ToM) in high-functioning adults with autism. Importantly, statistical separation of neural signatures (e.g. t-test) demonstrated in previous studies do not guarantee generalizability or predictive power of those signatures for diagnosis. Therefore, we adopt machine learning approaches for identification of effective connectivity neural signatures which can accurately classify individuals with autism from individuals with typical development.

Method: Participants viewed a series of comic strip vignettes in the MRI scanner and were asked to choose the most logical end to the story from three alternatives, separately for trials involving physical and intentional causality. For physical causality condition, participants relied on laws of physics to arrive at their judgment and in the case of intentional causality they relied on social rules or theory of mind (ToM). 15 typically developing control participants and 15 high functioning adults with autism were scanned using a standard EPI sequence on a 3T Siemens Allegra scanner. After standard pre-processing and activation analysis, mean time series were extracted from 18 activated regions of interest (ROIs) and underlying neuronal variables were extracted using Cubature Kalman filter based blind hemodynamic deconvolution [3]. The resultant neural response was input into a multivariate autoregressive model (MVAR) [4, 5] to obtain the causality matrices for each of the 30 participants. The causal connectivity weights were then input into a recursive cluster elimination based support vector machine (RCE-SVM) classifier [6] to determine the accuracy with which the classifier can predict a novel subject's group membership (autism or control) based only on causal connectivity weights.

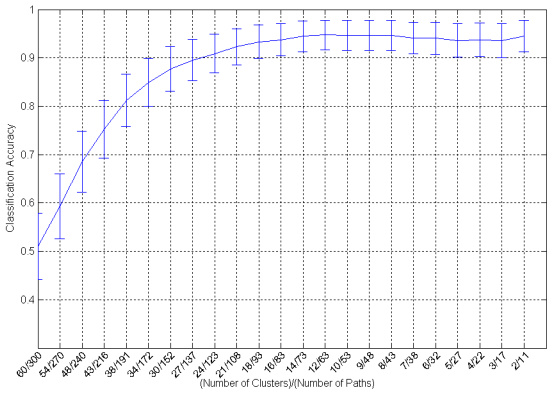

Fig.1: Plot showing increase in classification

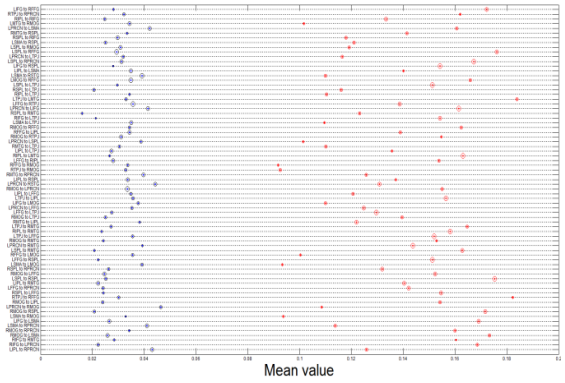

Fig.2: Plot showing separation of mean causality of paths between autism (blue) and control (red)

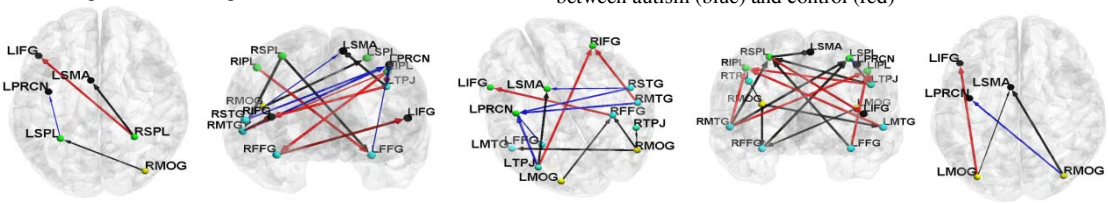

Fig.3 *Feed-forward paths: Input/output to/from TOM (blue), mirror (red), both (purple) and neither (black)*

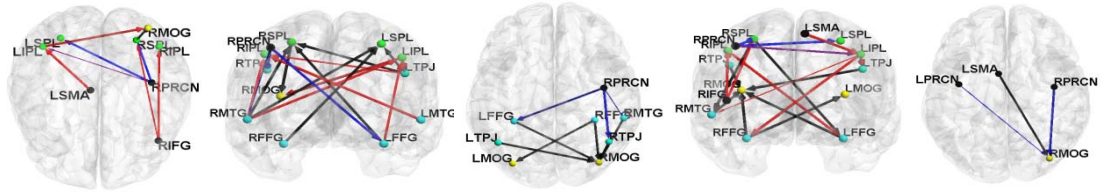

Fig.4 *Feed-back paths: Input/output to/from TOM (blue), mirror (red), both (purple) and neither (black)*

Results and Discussion: Fig.1 demonstrates the increase of classification accuracy as the number of features is decreased. With 14 feature clusters comprised of 73 paths, the classification accuracy reached a maximum and remained there even with 2 clusters and 11 paths. The causal connectivity value of 73 paths which lead to maximum accuracy of 94.3% showed clear separation between participants with autism (blue) and control participants (red) (Fig.2). This figure shows that the connectivities are significantly weaker in autism than in control participants. The 73 paths were separated into feed-forward and feed-back paths in the brain and plotted in Fig.3 & Fig.4, respectively. It shows large scale reduction of directional connectivity in the brain in individuals with autism while performing a ToM task. This could serve as a potential non-invasive neuroimaging biomarker for autism.

References: **[1]** RK Kana & MA. Just. *Handbook of Autism Spectrum Disorders*, OUP, pp. 981-989. **[2]** RK Kana et al, *Physics of Life Reviews*, In press. **[3]** M Havlicek, *et al*, *NeuroImage,* 56(4): 2109-2128, 2011. **[4]** G Deshpande, *et al*, *NeuroImage,* 49(3):1991-2000, 2010. **[5]** G Deshpande *et al*, *IEEE Transactions on Biomedical Engineering,* 57(6):1446:1456, 2010.**[6]** Deshpande**,** et al, *PLoS One*, 5(12):e14277, 2010.