Investigating Brain Connectomic Alterations in Autism using Reproducibility of Independent Components derived from Resting State fMRI

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Introduction: Autism is considered a developmental disability that can lead to significant social, communication, and behavioral challenges. A 2008 estimate from 14 sites revealed that 11.3 per 1000 or 1 in 88 children were affected by this disorder [1]. Considering the societal implications of autism, it is imperative that this disorder be diagnosed early and definitively. Autism is currently diagnosed using behavioral tests that can be subjective, but objective non-invasive biomarkers of autism are being actively researched. Previous and current research studies have been focusing on combining functional magnetic resonance imaging (fMRI) with machine learning and data mining techniques for classification of individuals with autism from typically developing peers. The common theme emerging is that autism is characterized by functional alterations in certain brain networks and that appropriately using MRI-based methods to characterize these alterations may provide a biomarker for classification and objective diagnosis. However, identification of individuals with autism solely based on these measures has not been reliable especially when larger sample sizes are taken into consideration. We surmise that one of the contributing factors may be that autism is a highly heterogeneous spectrum disorder, hence metrics derived from the autism group may not be highly reproducible within that group, leading to poor generalizability which in turn leads to lower classification accuracies. We hypothesize that functional brain networks that are most reproducible within autism and healthy control groups separately, but not when the two groups are merged, may possess the ability to distinguish effectively between the groups. In this study, we propose a methodology based upon the assessment of reproducibility of independent components derived from resting state fMRI followed by a clustering analysis of these components to evaluate their ability to discriminate between groups in an unsupervised way.

Methods: Resting state fMRI data of 799 subjects from 13 institutes provided by the Autism Brain Imaging data Exchange (ABIDE) [2] were used in our study. This data set included a total of 700 males and 99 females in the age range 6.5 – 64 years. In addition, it included 392 subjects with autism and 407 subjects in the healthy control group. Our pre-processing steps included realignment, normalization, spatial smoothing, de-trending and temporal band-pass filtering using DPARSF toolbox with SPM [5], followed by the application of the MELODIC algorithm [6] in FSL [7] to obtain independent components (ICs) at both the individual subject and group levels. These were input into the 'generalized Ranking and Averaging Independent Component Analysis by Reproducibility' (gRAICAR) algorithm [8] in order to retrieve the most reproducible group-level components from the autism group, the healthy control group and from the combined (autism + control) group. Most reproducible components that were found both in the separate and combined groups were rejected because they do not contain any discriminative information. Components now left within autism (11 ICs) and healthy control (3 ICs) groups were examined further in post-gRAICAR processing. We obtained individual subject spatial maps of each group-level component from autism and control groups and stacked it into matrices A and C, respectively. We then ran k-means clustering algorithm after pairing A and C for all group-level component permutations ($11 \times 3 = 33$) in order to examine whether individual subject ICs cluster (unsupervised) into autism and control clusters. Components from autism (A^x) and control (C^x) groups that form the purest clusters (with highest accuracy for discrimination) when combined were then further analyzed. We identified a component called C_a^x in the control group which had the highest spatial correlation with A^x and another component A_c^x in the autism group which had the highest spatial correlation with C^x. We ran k-means clustering analysis again, once on A_x paired with C_a^x and then on C^x paired with A_c^x. The second round of clustering analysis was carried out to ascertain whether the reproducible components in each group, when paired with the corresponding component with similar spatial distribution in the other group, can effectively discriminate between the groups.

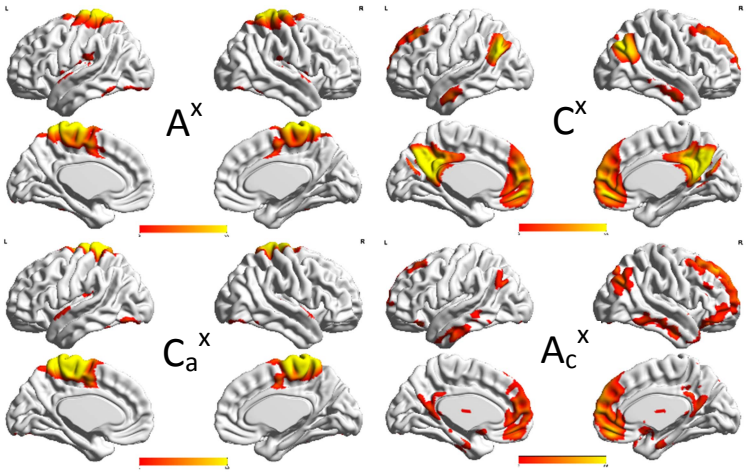

Fig.1 *Spatial maps of the most reproducible ICs in Autism (A^x) and Control (C^x) groups giving highest classification accuracy after k-means clustering when paired. Spatial maps of the IC in control group most correlated with A^x (denoted C_a^x) and the IC in Autism group most correlated with C^x (denoted A_c^x) are also shown*

Results and Discussion: The classification accuracy obtained by pairing the most reproducible components in Autism and Control groups ranged from 69.5% to 97.12%, with the highest accuracy of 97.12% (Sensitivity = 98.7%, Specificity = 95.6%) being attributed to IC A^x in autism group paired with C^x in control group (spatial maps in Fig.1). A^x paired with C_a^x produced a classification accuracy of 60.7% (Sensitivity = 43%, Specificity = 77%) whereas C^x paired with A_c^x produced an accuracy of 89.48% (Sensitivity = 89.28%, Specificity = 89.68%). Note that C^x and A_c^x represent the default mode network (DMN) in control and autism groups, respectively and the DMN in autism appears less prominent and cohesive. This agrees with previous studies showing DMN alterations in autism [9, 10]. Our results demonstrate that functional brain networks that are most reproducible within autism and healthy control groups separately, but not when the two groups are merged, possess the ability to distinguish effectively between autism and healthy control groups

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References: 1) Wingate et al., *Morbidity and Mortality Weekly Report*, 61(1):1-19, 2012 **2)** http://fcon_1000.projects.nitrc.org/indi/abide **3)** http://nifti.nimh.nih.gov/nifti-1 **4)** http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html **5)** www.restfmri.net/forum/DPARSF **6)** http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC **7)** Jenkinson et al., *Neuroimage*, 62(2):780-90, 2012. **8)** Yang et al., *Neuroimage*, 63(1):403-414, 2012 **9)** Assaf et al., *Neuroimage*, 53(1):247-256, 2010 **10)** Kennedy and Courchesne, *Social Cognitive and Affective Neuroscience,* 3(2):177-190, 2008