Network analysis based on analytic solution to permutation tests on Support Vector Machines

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Background and Objective: Whole brain functional or structural connectivity can be modeled as a network or a graph. Population analyses of such networks is generally based on comparing the groups via computation of global and local topological features [1] or by applying a recent statistical approach known as network based statistic (NBS) [2]. Methods involving topological characterization of the network do not allow straightforward interpretation of the results, while methods like NBS use mass univariate testing at each edge and are less conservative in controlling for the multiple comparisons problem. This work harnesses the potential of a novel method which uses an analytical solution to permutation testing performed on multivariate support vector machine (SVM) classifiers. The analytical computation takes a small fraction of the time it takes to do an actual permutation test, thereby rendering it possible to quickly create statistical significance maps derived from SVMs. We apply this method to analyze the differences between the structural connectivity networks of subjects with autism spectrum disorders (ASDs) and typically developing controls (TDCs).

Dataset and Preprocessing: Our data consisted of 23 male subjects with ASD (mean age 13.1±2.92) and 23 male TDCs (mean age 13.0 ± 2.85). Both the groups were IQ matched. The ASDs were diagnosed using research gold standard procedures that include ADOS and ADI with consensus diagnosis from two clinical psychologists. Images were acquired on Siemens 3T Verio™ scanner using a 32 channel head coil. DTI was performed using a single shot spin-echo, echo-planar sequence with the following parameters: TR/TE=16900/70 ms, b-value of 1000 s/mm^2 and 30 gradient directions. Cortical parcellation and sub-cortical segmentation was obtained using Freesurfer [3] on structural T1 images and a total of 79 ROI's were extracted to represent the nodes of the structural network that include 68 cortical regions and 11 sub-cortical structures (Fig 1 (top left)). These labels were then transferred to the diffusion space via intra-subject affine transformation. Probabilistic tractography [4] was performed on all the subjects and the connectivity matrices (Fig 1(bottom-left)) were computed based on the conditional probability of the fibers reaching the target region normalized by the area of the seed region.

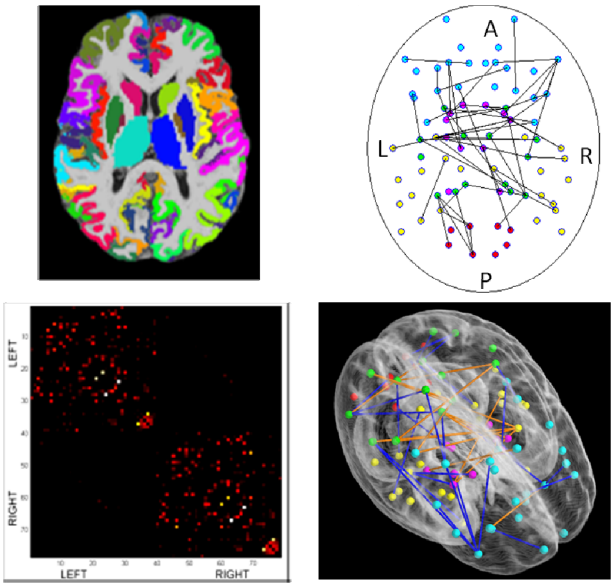

Figure 1: (top-left) Cortical parcellations (68) and the sub-cortical segmentations (10) employed as ROI's in computing the network shown below (bottom-left). (Top-right) Edges of the graph that are significantly higher in TDCs than in ASDs. (Bottom-right) 3D view of the connectivity, where orange edges are inter-hemisphere and blue are intra-hemisphere.

Method: We aim to identify statistically significant differences in connectivity between ASDs and TDCs using a multivariate analysis method. Permutation testing using support vector machines is one approach to identifying these differences. However, SVM based permutation testing is extremely time consuming and computationally costly. So we use an analytical approximation to SVM based permutation tests that was recently proposed in [5]. This results in significant savings in computational time and memory. The analytic approximation [5] associates z-tests with SVM coefficients just as linear regression associates t-tests with regression coefficients. Further, the inter dependence of the SVM coefficients implies that multiple correction testing associated with these z-tests is to the order of the number of subjects and not the number of connections(features) being tested. Thus this method offers a potential starting point to solve the multiple comparisons problem that plagues large scale connectivity analysis. Here we have used the analytical permutation testing framework of [5] to identify brain connections that differ significantly across ASDs and TDCs.

ROI to ROI connections	P-value
Left-Pallidum <---> Right-posteriorcingulate	0.0061
Left-cuneus <---> Left-fusiform	0.0064
Right-caudalanteriorcingulate <---> Right-parsorbitalis	0.0077
Left-precuneus <---> Left-inferiorparietal	0.013
Right-supramarginal <---> Right-temporalpole	0.0136
Right-fusiform <---> Left-precuneus	0.0138
Left-postcentral <---> Right-postcentral	0.015
Left-insula <---> Right-postcentral	0.0154
Right-parsorbitalis <---> Right-supramarginal	0.0156
Left-caudalmiddlefrontal <---> Left-postcentral	0.0162

Results: Fig.1 (right) shows the edges of the network that were significantly different between ASDs and TDCs (p-value<0.05) after the SVM based permutation testing. Fig 1(bottom-right) shows the 3D visualization of these edges. All these connections displayed higher weights in TDCs than in ASD dataset suggesting reduced connectivity in ASD patients. Table below displays the 10 most significant connections that weighted higher in TDCs than ASDs.

Discussion: In this work, we have used a novel method that employs an analytic solution for permutation testing on multivariate SVMs. It thus replaces the computationally intensive permutation tests when using SVMs for multivariate network analysis. We applied this method to compute edge-wise statistical maps between ASDs and TDCs from their structural connectivity networks. Results show that aside from one pathway connecting the pallidum to the cingulate, all other pathways involve cortical connections. Moreover, aside from one pathway connecting primary sensory regions, all affected pathways involve higher cortical processes including processes important to social functioning the primary deficit in ASD. Most connection pathways are in the temporal role a brain area which is over represented in prior studies of ASD differences [6].

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Acknowledgements: This work was supported by NIH grants MH060722, MH092862 and a grant from the Pennsylvania Department of Health (SAP#4100047863).