Functional Network Patterns as Multivariate Predictors of Symptom Severity in Schizophrenia

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Introduction:

The relationship between aberrations in brain functional connectivity in schizophrenia and symptoms severity as independent measures is yet unknown. Some recent studies have considered univariate correlations between symptoms and neuroimaging features (Cheng, 2015, Berman, 2016, Li, 2016), reporting correlations in a range typically below 0.5. In contrast, only very few studies have attempted multivariate prediction of scales using neuroimaging features (Tognin, 2013, Koch, 2015). The objective of this study was to go beyond the univariate analysis on a single dataset, and evaluate generalization accuracy of network features when used by multivariate regression models to predict the scales of previously unseen subjects. A sparse linear regression approach with inherent feature selection, called Elastic Net (EN)(Zou, 2005) was used to generate interpretable models (models with small number of features). Stability of the EN-selected features across leave-subject-out cross-validation (CV) data subsets was also investigated to identify the 'stable' subsets of features contributing to prediction of different scales.

Methods:

fMRI data from the Auditory Oddball task in the FBIRN Phase II multi-site dataset was used. After routine, per subject, preprocessing and quality control stages, 95 subjects from 5 different sites remained in the study (46 patients diagnosed with schizophrenia and 49 controls). There were four runs per subject resulting in a total of 184 patient samples. Nine Global Rating Scales were used, from the SANS and SAPS negative and positive symptoms assessment provided for patients. The scales values ranged between 0 and 5, with the larger scores representing more severe symptoms. Whole-brain functional connectivity, i.e. pairwise Pearson correlations across (a total of 569) 'supervoxels' (cubes of size 13.75x13.75x15 mm) were extracted and used as features, referred to as 'link-weights'. EN was used in combination with link-weight features, to generate interpretable regression models for 9 Global Rating Scales. The models were evaluated using leave-subject-out CV. The EN model was evaluated for a range of sparsity level and grouping parameter. Stability of features selected by the best EN model, i.e. model that yielded the highest significant average correlation over CV folds, was determined. The 'stable' predictive feature subset, i.e. set of features that were selected in all CV folds, were visualized to provide insights on potential neuroimaging-based disease markers.

Results:

The predicted symptom severity scores were significantly correlated with actual scores (Spearman ρ between 0.2 to 0.5, $p < 0.05$, including the FDR correction for multiple comparisons), for the following five global rating scales: inattentiveness, bizarre behavior, positive formal thought disorder (FTD), avolition/apathy and alogia. The first three also survived Bonferroni correction. Figure 1a-b displays the stable subset of links contributing to prediction of scales for severity of bizarre behaviour and positive FTD. There were consistencies between areas involved in prediction of different scales: precuneus, premotor cortex, and primary sensory cortex were repeatedly involved in prediction of several scales. There were also differences in the pattern of the stable links across different scale as displayed in Figure. 1.

Conclusions:

Whole-brain functional network features have been previously successfully used in discrimination of patients diagnosed with schizophrenia from controls (Rish, 2013). Here, we were able to demonstrate the value of these connectivity features for predicting symptom severity in schizophrenia. We propose that the ability to accurately predict symptom severity based on neuroimaging features has an equal, if not greater, importance than the binary disease classification, since it can lead to a more objective, measurement-driven characterization of schizophrenia, as also emphasized in the recently proposed RDoC (Cuthbert, 2013) initiative of NIMH.

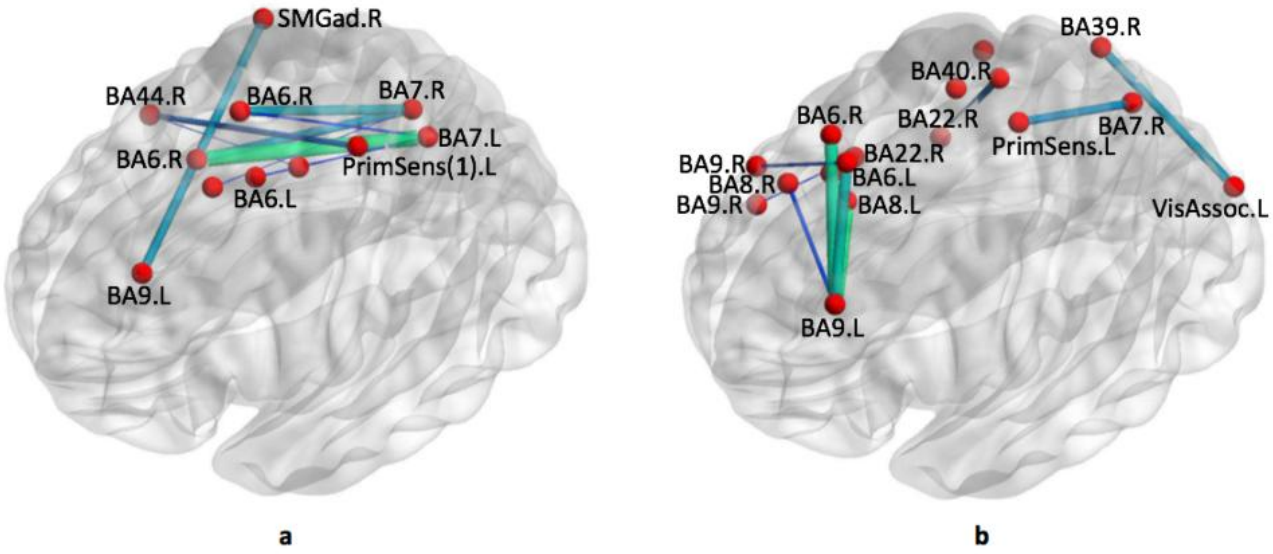

Figure 1- Stable across CV folds subset of monst-predictive links selected by Elstic Net for predicting the Global Rating of (a) Severity of Bizarre Behaviour and (b) Positive Formal Thought Disorder. Links thickness and color is scaled based on the average weight of links across CV folds in the EN model.

Disorders of the Nervous System:

Schizophrenia and Psychotic Disorders [2]

Imaging Methods:

BOLD fMRI

Modeling and Analysis Methods:

Classification and Predictive Modeling [1]

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[1|2]Indicates the priority used for review

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