Predicting treatment in patients with major depression using Granger-based connectivity and support vector machines

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Introduction

Previous imaging studies have implicated abnormal functioning of a limbic-cortical network in patients with major depressive disorder (MDD) [1,2,3]. Furthermore, variations in effective connectivity within this network (as modeled with SEM from PET neuroimaging data) have been identified in different MDD subgroups associated with differential response to specific antidepressant treatments [1,2]. In this study, MDD patients were randomly assigned to one of two possible treatments – cognitive behavioral therapy or a drug and treated for 12 weeks. Taking advantage of fMRI's superior spatio-temporal resolution over PET, we used a more exhaustive network of ROIs and a Granger-based method [4] for obtaining effective connectivity and recursive cluster elimination (RCE) with support vector machines (SVM) [5] to predict which treatment patients were receiving. Our results show 100% accuracy in predicting treatment.

Methods

Forty treatment naïve subjects currently diagnosed with MDD with no significant psychological comorbidities or neurological disorders were recruited. The subjects were randomized to one of the two treatments – cognitive behavioral therapy (CBT) for 14 subjects or a drug (either escitalopram or duloxetine) for 26 subjects. We are blind to the information regarding which of the two drugs any subject received. Resting state EPI data were obtained using a ZSAGA sequence [6] before treatment and 2-3 weeks into treatment, (prior to significant clinical behavioral changes), with the following scan parameters: TR=2.92 ms, TE=30 ms, FA: 90º, FOV=220 mm, 30 slices with resolution 3.44×3.44×4 mm^3. The functional data was motion corrected, slice scan time corrected, written into MNI space, spatially smoothed with a 6 mm FWHM Guassian filter and time series band pass filtered (0.008 to 0.08 Hz). Mean time series from 14 ROIs which have been previously implicated in MDD [1,7], were extracted and input into the multivariate Granger model [4] to obtain effective connectivity networks pre-treatment and during treatment. For each subject, the pre-treatment network were subtracted from the network during treatment to obtain a difference network for each of the two treatments and entered as features into the RCE-based SVM [5]. We employed 10-fold cross-validation with 90% of the data considered for training and the rest for testing. During training, the features were clustered using k-means and uninformative clusters iteratively dropped to improve classification accuracy. The features were ranked based on their weights and hence their importance to classification accuracy.

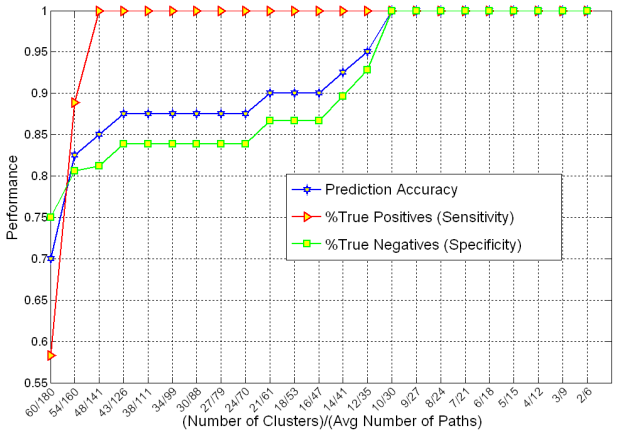

Fig.1 Progressive performance of RCE-SVM classifier as clusters of uninformative paths are eliminated

Results and Discussion

Fig.1 illustrates the performance of the RCE-SVM classifier. It can be seen that with 10 clusters and 30 paths, we are able to obtain 100% accuracy in prediction. However, not all the 30 paths are necessary for prediction and the number of paths could be reduced to 6 paths and 2 clusters for 100% accuracy, i.e. those 6 paths are necessary and sufficient for prediction. Fig.2 shows the network diagram of the 30 paths, ranked according to their weights, whose change with treatment predicts whether a given subject is receiving CBT or drug. The dotted arrows represent the top six ranked paths which are necessary and sufficient to predict treatment group membership. Five of the 7 ROIs previously implicated by PET SEM are among this minimally sufficient network for predicting treatment. In particular, the fronto-hippocampal network (RLPF9, OF11, MF10, and hippocampus) constituting the largest cluster was also previously shown to separate eventual drug and CBT responders at baseline, further validating the selection of regions modeled in previous work [1]. Granger-based effective connectivity poses a valuable, complementary approach to SEM-based instantaneous effective connectivity and correlation-based functional connectivity. All of these approaches stand to offer valuable insights into the neural mechanisms underlying MDD and its treatment. With the eventual inclusion of response outcomes, these methods may provide a new strategy for identifying baseline patterns that predict individual responses to specific treatments.

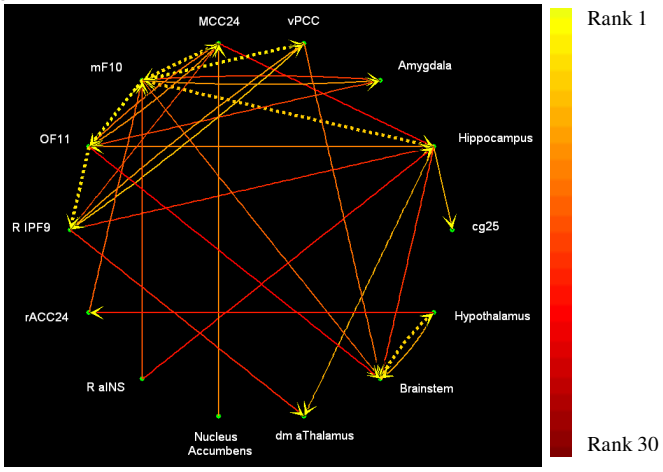

Fig.2 Difference network predicting treatment group. The dotted arrows represent the top six ranked paths which are necessary and sufficient. r = right; a = anterior; INS = insula; rACC24 – rostral anterior cingulate (BA24), lPF9 – lateral prefrontal cortex (BA 9), OF11 – orbitofrontal (BA11), mF10 – medial frontal (BA10), MCC24= midanterior cingulate (BA24), vPCC – ventral posterior cingulate (BA23), cg25 – subcallosal cingulate (BA25)

Conclusions

We have demonstrated with the RCE-SVM approach that Granger-based effective connectivity is successful in predicting treatment assignment for patients with MDD.

References

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