PMS Analysis of Resting-State OCD Data

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**Introduction**

**Overview**

The methodology of the PMS space analysis may be broken into three main segments: characterization, fitting, and simulation.

The characterization phase, as the name implies, consists of characterizing the PMS space. This phase, in turn, consists of four sub-phases: determining the number of substates in the space, extracting the spatial substates that compose the space, extracting the activation time series of each substate, and determining the activation probabilities, lifetimes, and transition probabilities of each substate. These three metrics, along with the spatial topology of the substates, fully characterize the probabilistic metastable substate space.

The fitting phase of PMS analysis consists of designing a dynamic model of the network (in our case, the human brain) and fitting this model to the activation and transition probabilities found during the characterization phase. This phase has the goal of producing a dynamic network model which is able to replicate the activation and transition probability distributions extracted from empirical data. To this end, the free parameters of the dynamic model are methodically adjusted in order to minimize the distance between the selected test statistic(s) of the model and the empirical data. Typical test statistics consist of the substate activation probabilities, the substate activation lifetimes, and the substate transition probabilities. Distance between the modeled and the empirical test statistics is measured using the Kolmogorov-Smirnov two-tailed test statistic or the Kullback-Liebler divergence.

Finally, the simulation phase of the PMS space analysis utilizes the fitted dynamic model to simulate the activation time series of extracted from the empirical data. Importantly, the effect of stimulating or dampening brain regions may be methodically tested in this model in order to determine the influence of each region on the overall dynamics of the brain. Thus far, this simulation has sought the region(s) which most efficiently force a transition from one PMS space to another, e.g. those regions which can most efficiently force a transition from the “sleeping” space to the “awake” space. It may be possible to explore alternative effects through this stimulation protocol, but thus far none have been implemented.

**I: Characterization**

The current study utilizes the LEIDA protocol (to be detailed in a separate report) to characterize the PMS space of both patient and control groups. In summary, this protocol detects the number of substates in the concatenated BOLD time series using the Marcenko-Pasteur distribution (Lopes-dos-Santos, Ribeiro, and Tort 2013). Upon finding the number of substates, the fastICA algorithm is used to extract the appropriate spatial independent components and their associated temporal activation sequences from the concatenated BOLD signal. The concatenated BOLD signal and ICA activation sequences are then segmented according to condition, and these condition-wise sequences are themselves segmented to recover the subject-wise activation sequences. This produces two *S* x *C* MATLAB cell arrays, where *S* is the number of subjects and *C* the number of conditions. In the first of these arrays, each cell containing the BOLD signal of a single subject, indexed by subject number and condition. The second array is organized in an identical fashion but contains the independent component activation sequences instead of the BOLD signals.

Upon obtaining the BOLD signals and activation sequences for each subject, the author elected to extract the following metrics from each subject’s component activation sequences:

* Component activity distributions (time series, means, and standard deviations)
* Probability of activity events (means and standard deviations)
* Probability of activation, with activation defined as activity with a magnitude more than one standard deviation from the mean.
* Activity lifetimes (histograms, means, and standard deviations)
* Matrix distance from spatial components to resting-state networks
* Inter-component switching probabilities
* Inter-component transition matrices
* Kuramoto order parameter (time series, means, and standard deviations)
  + Global, per subject
  + Per assembly
* Shannon entropy
  + Global, per subject
  + Per assembly
* Cohesion (fairly sure this is incorrectly implemented)
  + Global, per subject
  + Per assembly

These metrics were then tested for group-level differences using the Kolmogorov-Smirnov two-sample test. Since assembly-wise metrics require testing the same subject multiple times, the results of these tests underwent multiple-comparison correction with the Benjamini-Hochberg False Discovery Rate (FDR), the Bonferroni correction, and the Dunn-Sidak correction. Only those differences which passed at least one of these corrections were considered truly significant. As global statistics do not compare individuals multiple times, no multiple-comparison correction was judged necessary in these cases.

It was decided to use the activity distributions of the individual ICs as the primary metric of interest. Of the thirteen assemblies extracted from the concatenated signal, twelve displayed significantly different activity distributions. Of these twelve assemblies, all survived the Benjamini-Hochberg FDR, and eight survived both the Bonferroni and the Dunn-Sidak corrections. We thus presume that these eight assemblies display strongly significantly different activation distributions between conditions, and that the original twelve also display significant differences in their condition-wise activation distributions.

**II: Fitting**

The fitting stage of this study trains a dynamic model to replicate the activation distribution of each subject in the dataset. Specifically, the model is defined as a network of normal supercritical Hopf bifurcations (also known as a Landau-Stuart oscillator). The Hopf oscillators form the nodes of this dynamic network model, and edges are defined according to the brain structural connectivity. This results in a dynamic network model which uses Hopf oscillators, connected in the same way as real brain regions, simulate regional time series. This is a well-established model in the Computational Neuroscience Group of the Universitat Pompeu Fabra, and has been described in a number of previous papers.

In previous studies, several parameters of the Hopf dynamic network model have been tuned in order to replicate specific characteristics of brain activity. In this study, the model’s individual connection weights were tuned to best replicate the temporal activation distributions of the independent components extracted in the LEICA protocol (Section II.1). Tuning was achieved with the particle swarm algorithm of Kennedy and Eberhart (Kennedy and Eberhart 1995; Wilke 2005; Mezura and Coello 2011; Erik, Pedersen, and Pedersen 2010). The Kolmogorov-Smirnov test statistic is used as a cost function, with the goal of the optimization being to minimize this value. The result of this optimization is an estimate of the effective connectivity matrix for a single subject. This optimization is then repeated for each subject, with each effective connectivity matrix indexed according to condition and subject.

**III: Network Analysis**

Differences in the network structure were extracted using the network-based statistic (NBS). The general linear model (GLM) of the NBS was initialized with a three-column design matrix of 79 rows. The first column provides the GLM with an intercept term, while the second and third columns serve to index to which group each subject belongs. Accordingly, the contrast vector was set to [0, 1, -1], with the zero serving to remove the intercept term from analysis and the [1, -1] serving to test the size of the difference between control and patient populations.

Upon setting the contrasts for the GLM, the statistical test, effect type, and effect size had to be set. The NBS supports two statistical tests: a standard Student’s *t*-test, and a Fisher’s *F*-test. The selected test is applied to each connection in the connectivity array in order to generate connection-wise test statistics. A threshold is then applied to this test statistic matrix in order to locate subnetworks with statistically significant group-level differences. These subnetworks may then be tested for significance using two effect types: intensity or extent. Testing for extent emphasizes effects with a distributed signature in the network topology, whereas testing for intensity emphasizes effects with maximal contrast between conditions.

As the effect distribution was not known, both the *t*-test and the *F*-test were utilized in parallel. Thresholds of both statistics were varied over the range of 0.5 to 4.0 in intervals of 0.5 in order to thoroughly test for significant differences, and both the extent and intensity of cluster effects were examined. This resulted in a [2 × 2 × 8] array of results, in which each cell corresponds to a specific combination of tests. No combination displayed significant differences between conditions.

Upon confirmation of the failure of the network-based statistic to detect significant differences in the effective connectivity between groups, the node-wise in-strength and out-strength were computed for each subject. In addition, the density of each subject was computed. These distributions were then tested for significant group-level differences. No significant group-level differences were found in the in-strength, out-strength, or density distributions. However, when the in-strength and out-strength distributions of each subject were normalized by the subject-wise densities, significant group-level differences were detected. A preliminary visual examination of the normalized strength distributions suggests that patients may have higher density-corrected in-strengths and out-strengths compared to patients; however, it is the author’s opinion that this requires further quantification. The author is currently uncertain how to interpret this result.

**Methodology**

**Results**

**Current Questions**

**Discussion**

The finding of significant differences in the density-normalized in-strength and out-strength suggests that obsessive-compulsive patients may display increased per-connection strength in the effective connectivity. However, this effect is not detected with the network-based statistic, suggesting that it is either quite weak (as suggested by the group-level strength distributions) or highly distributed and possibly unconnected. As the NBS is designed to detect significant subnetworks rather than significant links, it conveys no improvement to traditional statistical testing in detecting unconnected alterations in connection strength.

**Proposed Future Steps**

The finding of significant differences in the density-normalized in-strength and out-strength suggests that additional graph analyses may prove beneficial. The author thus proposes the application of further graph analyses to the dataset, as laid out in the Utrecht Summer School exercises. This will serve to exhaustively explore the potential alterations in the effective connectivity of obsessive-compulsive patients. It will also allow the author to thoroughly explore graph analyses as applied to directed connectivity.

The author has experienced some difficulty in quantifying the inter-state switching behavior of patients and controls. This is due to the fact that the LEiDA algorithm, from which the LEICA process was developed, segments the time series with a *k*-NN algorithm, which classifies each time point into a single state. As such, LEiDA segments the time series into strictly non-overlapping states. Independent component analysis, on the other hand, assigns each spatial component an activity weight at each time point. LEICA thus allows two possibilities which are impossible under the LEiDA algorithm: that multiple components may be active simultaneously, or that there may be a time point in which no components are active.

The author proposes that the LEICA state time series should be treated, not as strictly exclusive states, but as an activation “spectrum” which varies over time. This will capture the activation behavior of each state and will allow precise quantification of the co-activation tendencies of each assembly. However, the author is uncertain how to extract meaningful summary statistics from such a spectral time series. In particular, the author remains uncertain how to quantify inter-component transition matrices, as the fundamental problem of co-active or non-active assemblies will remain.

**Proposed Future Projects**

The author suggests quantifying the number and differences between the components of each subject’s principal eigenmode. The current analysis assumes that each subject possesses comparable functional components, and thus imposed common eigenmode components across all subjects. However, it remains unclear whether each subject displays the same number of spatial components, or how similar these spatial components may be across subjects. The author proposes that the spatial components of each subjects’ principal eigenmode(s) be computed separately, and these components be compared on both the subject level and the group level. The author is particularly interested by the possibility that obsessive-compulsive patients may display a different number of spatial components compared to controls. He also wishes to more precisely quantify the similarity between individual spatial components and canonical resting-state networks.

**Known Current Problems with Ph.D. Status**