Group Comparison of Spatiotemporal Dynamics of Intrinsic Networks In Parkinson Disease

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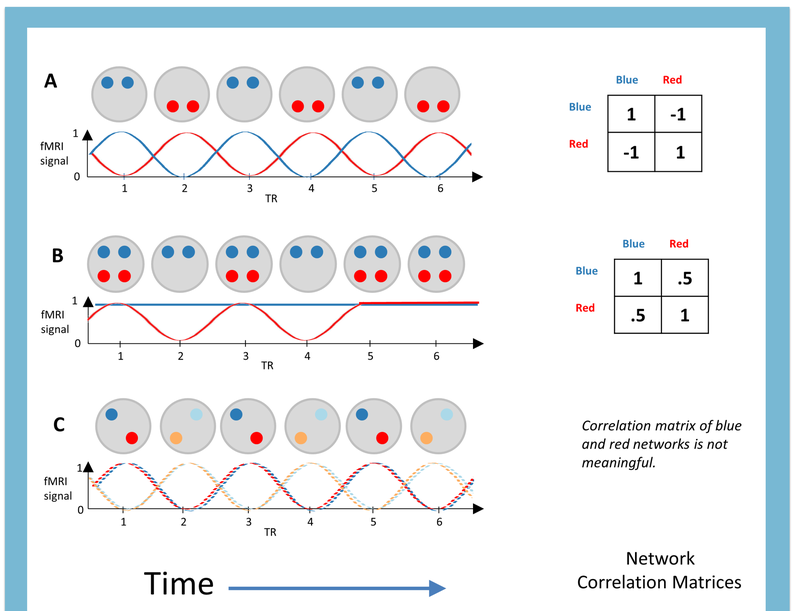
Introduction

Recent advances with functional connectivity MRI have demonstrated that at rest the brain exhibits coherent activity within a number of spatially independent maps, normally called "intrinsic" or "resting state" networks. These networks support cognition and behavior, and are altered in neurodegenerative disease. Multiple pathologic processes affect networks that support cognition in PD. Lewy body and AD pathology cause cortical dysfunction and impair multiple ascending control systems. Here, we introduce a novel modeling approach called *network kernel analysis* to compare fine-grained network ensembles that include overlapping cortical elements in PD and controls.



Intuition

We can test to see if network structure is the same across groups, and if it is, accurately measure differences in correlations between networks.

Methods

We examine resting state fMRI data obtained from 24 medicated subjects with PD (age 66, 45-86; mean H&Y stage 2.05) and 21 subjects without PD (age 62, 41-76). Subjects were scanned twice, 2-3 weeks apart. Magnetic resonance imaging was performed on Philips 3.0T Achieva scanner with a 32 channel head coil. Concentration of CSF biomarkers was available for 14 of the PD participants (α-syn, Aβ42).

After fMRI preprocessing, we extracted timecourses from 10mm diameter spheres centered at MNI coordinates identified from the literature in the default mode network (DMN), dorsal attention network (DAN), fronto-parietal task control network, and salience (SAL) network. We also obtained masks for caudate, putamen, and nucleus accumbens from FreeSurfer subcortical parcellation. Scaled timecourses from these regions of interest (ROIs) were subjected to exploratory factor analysis in a structural equation modeling framework[4] across all sessions and task runs (Figure 1).

Network kernels describe "weights" of ROIs whose activity covaries. Each network kernel is described at each TR by a score. These scores are used as regressors in a General Linear Model (GLM) to identify cortical regions more or less correlated with each network kernel. See Madhyastha et al[2] for details.

Hypothesis

- A method to probe the fine-grained spatiotemporal structure of intrinsic networks may be more sensitive to subtle network changes that occur in PD
- Alterations to the structure of intrinsic networks may reveal the impact of underlying pathophysiologic processes

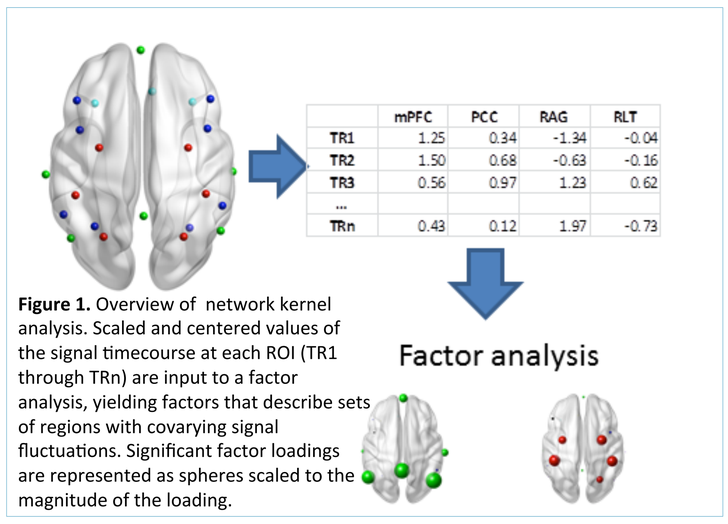


Figure 1. Overview of network kernel analysis. Scaled and centered values of the signal timecourse at each ROI (TR1 through TRn) are input to a factor analysis, yielding factors that describe sets of regions with covarying signal fluctuations. Significant factor loadings are represented as spheres scaled to the magnitude of the loading.

Results

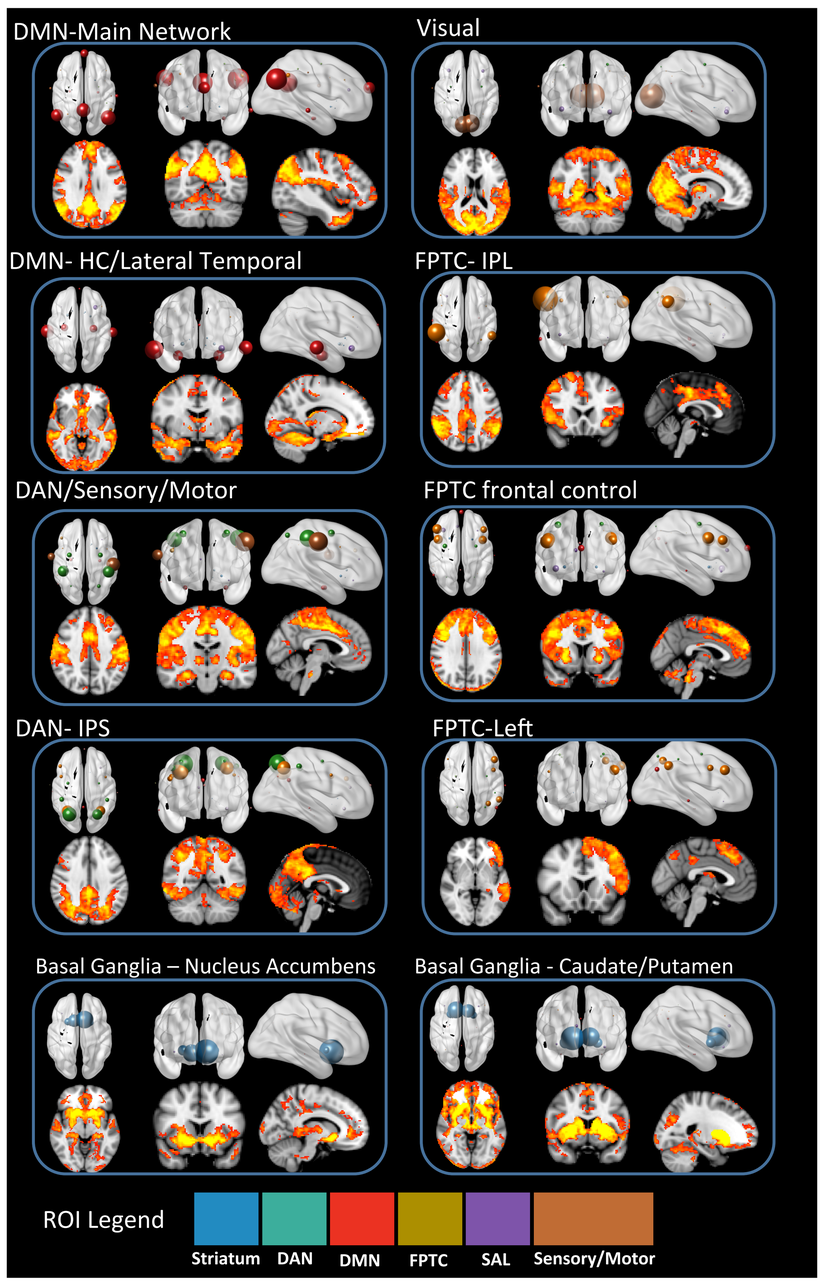


Figure 2. Network kernels identified in 24 subjects with PD and 21 controls. All images follow radiologic convention (Left is on the right).

References

1. Asparouhov, T. & Muthén, B. Exploratory Structural Equation Modeling. Structural Equation Modeling: A Multidisciplinary Journal 16, 397–438 (2009).
2. Madhyastha, et al. "Group Comparison of Spatiotemporal Dynamics of Intrinsic Networks In Parkinson Disease", Brain, in press.

Correlations between network kernels distinguish PD from controls. We used a linear support vector machine with 10-fold cross-validation to classify each of our subjects as PD or control, using resting state data alone.

Input	Sensitivity	Specificity
Correlations Between ROIs	0.82 (0.29)	0.11 (0.22)
Partial Correlations Between Cognition-Related ICA Components	0.65 (0.30)	0.29 (0.19)
Partial Correlations Between Network Kernels	0.99 (0.03)	0.99 (0.05)
Transition Probabilities Between Maximally Expressed Kernels (Fully Dynamic)	0.94 (0.16)	0.95 (0.15)

Table 1. Sensitivity and specificity of classification by diagnostic group using partial correlations between network kernels is higher than partial correlations of ICA-derived cognitive components, or stationary correlations between ROIs.

System disruption is related to concentrations of CSF biomarkers. The Euclidian distance between the adjacency matrix of network kernels for controls and each subject with PD is a measure of "system disruption".

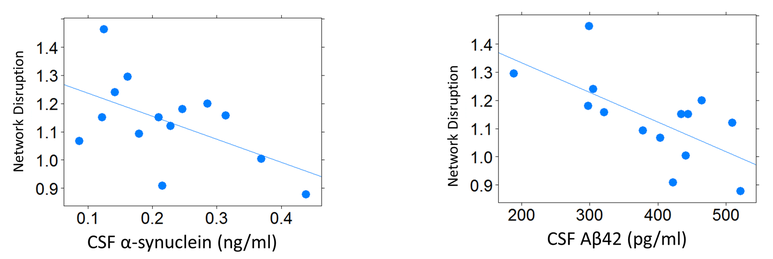


Figure 3. Controlling for time between scan and CSF acquisition, the correlation between CSF Aβ42 concentration and network disruption was r(11)=-.75, p< .001 [p_{corr}=.005], and the correlation between CSF α-syn concentration and network disruption was r(11) = -.55, p=.025 [p_{corr}=.05].

Right anterior insula is more highly correlated with DMN and FPTC activity in PD.

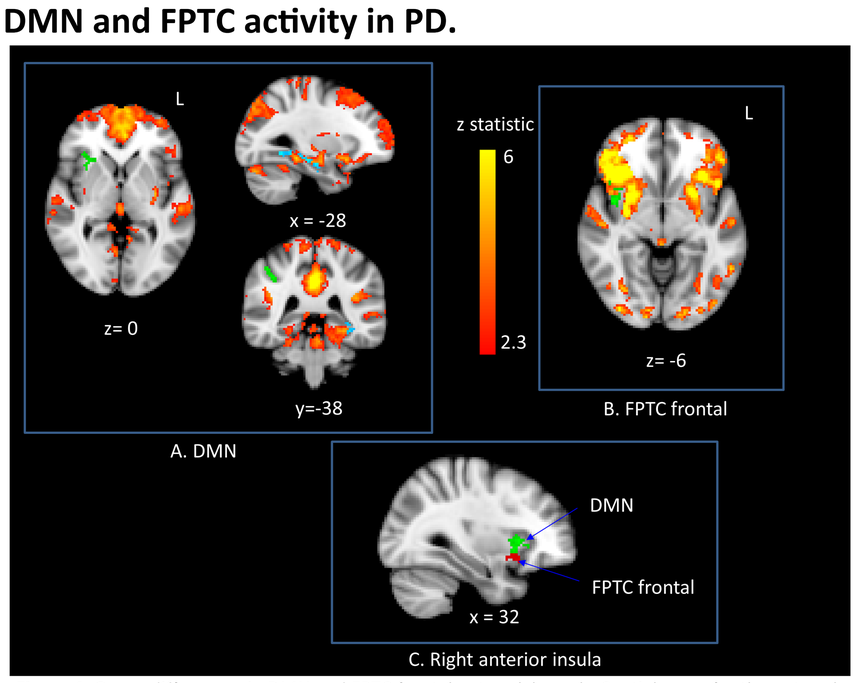


Figure 4. Group differences in DMN and FPTC frontal network kernels. Spatial maps for the network kernel in controls are shown in red/yellow. **A.** DMN **B.** FPTC frontal. Green regions are more highly correlated with the network kernel in PD (anterior insula in DMN and FPTC frontal, supramarginal gyrus in DMN) , and blue regions are less highly correlated with the network kernel in PD (hippocampus, fusiform cortex in DMN). **C.** Right anterior insula cluster in both DMN (green) and FPTC frontal (red). All images follow radiologic convention (Left is on the right).

Conclusions

- Network kernel correlations distinguish PD from controls, reflecting disruption to large-scale systems
- Greater network disruption was associated with greater extent of one facet of AD and with the "synucleinopathy" of PD.
- GLM analysis identifies the right anterior insula as more highly correlated with DMN and FPTC networks
- Network kernel analysis may be an inherently sensitive indicator of subtle physiologic change.

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