Reliability analysis of the resting state sensitively and specifically identifies Parkinson disease

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Introduction: Resting brain activity has been shown with a variety of techniques to have consistent, reliable patterns among and across healthy subjects. Parkinson disease (PD) is characterized by a number of motor and behavioral abnormalities that could be considered deficits of a "no task" or "resting" state, including resting tremor, altered resting tone, as well as motor and behavioral defects when attempting to emerge from a "no-task" state (e.g., motor freezing or apathy). We sought to evaluate if we could "predict" PD using a resting state analysis.

Methods: We enrolled 15 healthy controls, 14 subjects with PD, and 1 subject who presented as a control but later developed PD. We use the amplitude of the low frequency fluctuation (ALFF) as an index of brain activity level in the resting state. Standard voxel-wise statistical techniques were used to compare resting state in PD and controls; we also developed a cross-validation technique, modifying standard statistical cross-validation approaches to be applicable to fMRI datasets. We use "validation maps" to determine which regions reliably separate PD and controls in the sample.

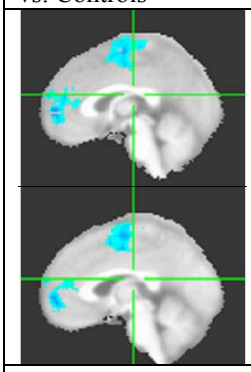
Results: We show that individuals with PD have significant alterations in brain resting activity. We show decreased activity in a number of regions (Table 1, Figure 1).

Regions of Significant Difference between PD and Controls

Region	Side	Volume (mm^3)	X	Y	Z	*t*-stat	*p*	*Sens*	*Spec*
MesFG	R	7120	-5	-52	9	-2.9	< 0.001	0.92	0.67
SMC	L	6971	-2	5	56	-2.7	< 0.001	0.85	0.73
IOG	R	2236	-38	70	-13	-2.6	< 0.001	NR*	NR*
PG	R	1646	42	18	55	-2.6	0.01	NR*	NR*
MFG	L	1430	41	-30	30	-2.7	0.01	0.92	0.60
							Combined Sensitivity and Specificity	***0.92***	***0.86***

Legend: NR* = Not Reliable on repeated one-out analysis. Sens = Sensitivity. Spec = Specificity. MesFG = Mesial Frontal Gyrus. SMC = Supplementary Motor Cortex. IOG = Inferior Occipital Gyrus. PG = Precentral Gyrus. MFG = Middle Frontal Gyrus.

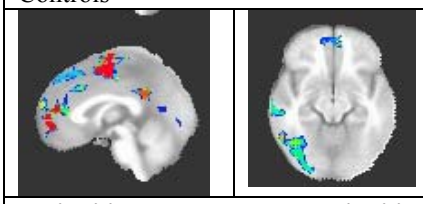
Figure 1: Voxel-wise significance map, PD vs. Controls



Blue regions illustrate alterations in Supplementary Motor Area and Mesial Frontal Gyrus ALFF signal in PD group.

Our reliability maps (Figure 2) show that certain regions (e.g. see image left, Fig 2, supplementary motor area and mesial frontal gyrus) reliably separate the sample, while other regions (note image right, Fig 2, right inferior occipital gyrus) despite significance using standard voxel-wise techniques in separating the samples are not reliable in repeated analysis. Focusing on reliable regions, we were able to distinguished participants with PD from controls with 92 % sensitivity and 86 % specificity. We were able to "predict" the onset of PD our subject who presented initially as a control but developed initial symptoms 6 months after our resting state scan.

Figure 2: Reliability map, PD vs. Controls



Reliability map measures reliability of differences in cross-validation. Color Key: Red spectrum = reliably significant in cross-validation. Blue-Green spectrum = more limited reliability in cross-validation.

Discussion: Our cross validation approach shows that significance and reliability are distinct properties of functional images. Our results suggest that, using techniques focused on discerning reliable differences between samples, resting fMRI may be considered for development as a biomarker for PD.