Parkinson's disease related pattern from resting state fMRI

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Target Audience Neuroscientist, Parkinson's disease researcher, resting state fMRI analyst, neuro-imaging scientist

Purpose Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder associated with a chatacteristic pattern of regional metabolic covariation[1]. Abnormal PD-related functional topographies have been consistently reported in the resting state using metabolic imaging with PET[1,2] as well as cerebral perfusion techniques[3]. Quantitative measurements of PD-related network activity have proven useful for differential diagnosis, and for the objective assessment of disease progression and treatment effects. To date, the identification of stable disease-related covariance patterns using resting state fMRI (rsfMRI) has been limited by temporal variation in the imaging signal. Here, we report a method to identify and validate reliable disease-related network topographies in rsfMRI data.

Methods We studied 30 PD subjects and 30 healthy controls. 16 PD (12M/4F; 60.5±8.3 years) and 16 controls (8M/8F; 55.1±8.2 years) were scanned at North Shore University Hospital (NS) using a GE 3T clinical scanner. 14 PD (12M/2F; 63.6 ± 11.2 years) and 14 controls (10M/4F: 63.8±6.7 years) scanned at the University of Florida (UF) at Gainsville using a Siemens clinical scanner and were used as an independent testing dataset. All PD subjects were scanned off medication. 6 patients in NS group were additionally scanned while on medication. The resting state fMRI protocol included: 8 mins image acquisition, 240 volumes, FOV=24 cm, TE=28 ms, TR=2 sec, 77° flip angle, 40 slices of 3 mm. In addition, a T1-weighted structural image volume was acquired for each subject. The 8 minute rsfMRI acquisitions were divided into two 4 min blocks which were used for either pattern derivation (training) or prospective subject score computation (testing). To obtain the same duration as the NS dataset, we used the first 4 mins of rsfMRI acquired in the UF data. The rsfMRI preprocessing included motion correction, brain extraction, spatial smoothing with FWHM kernel of 10 mm, and temporal high-pass filtering using FMRIB software library (www.fmrib.ox.ac.uk/fsl). The fMRI volumes were registered to the individual subject's structural T1 and then to the standard Montreal Neurological Institute template. The rsfMRI data from all NS subjects were then analyzed using spatial group independent component analysis[4] (ICA) using GIFT software[4]. 44 independent components (ICs) were determined. Subject spatial maps and temporal dynamics were estimated using dual regression. Subject scores, reflecting the individual expression of each IC, were computed by taking the dot product of the mean group map with the subject's spatial map using a previously described voxel-based computational algorithm[2,3]. Multivariate linear regression (JMP software, SAS Institute Inc., Cary, NC) was then utilized to identify a subset of ICs that yielded a maximum separation of PD and control subject scores in the training dataset. A specific PD-related regional covariance pattern (PDRP) was identified by linear combination of the group ICs in this subset according to the parameters estimated through regression analysis. PDRP expression (subject scores) in testing scan data (NS and UF) were computed as in the training dataset[3].

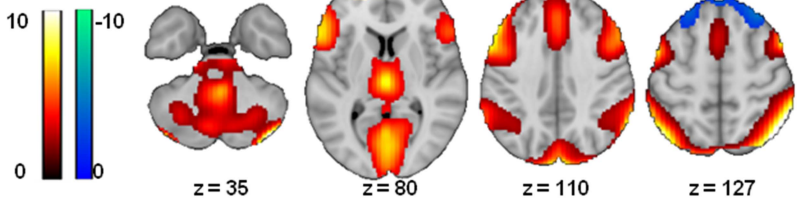

Figure 1. The Parkinson's disease-related pattern obtained from resting state fMRI.

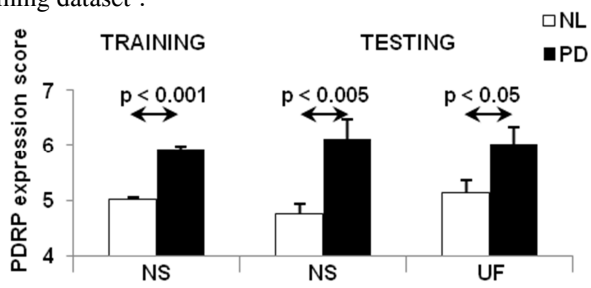

Figure 2. Parkinson's disease-related pattern expression scores.

Results Thirteen components representing independent contributions from the cerebellum, thalamus, SMA, and from premotor/ prefrontal and parietal cortex achieved maximum separation between patients and controls in training set ($F = 14.91$; $df = 13$, $p < 0.0001$). An abnormal PDRP topography (Fig. 1) was idebtified by linear combination of these 13 components. The estimated parameters of linear regression model was then applied to the testing data to compute expression values (subject scores) for each case. We found that PDRP expression (Fig. 2) in the off-state PD rsfMRI scans of the training set were elevated ($p<0.001$, Student *t*-test) relative to analogous control values (NL). PDRP scores computed in off-state PD scans from the NS testing cohort (Fig. 2, left) were elevated relative to control values ($p<0.005$). A significant correlation ($r=0.66$, $p<0.05$) was observed in this group between levodopa-mediated changes in PDRP expression and baseline network activity values. Similar findings were observed the UF validation sample. In this group, prospectively computed PDRP values (Fig. 2, right) were also elevated in PD relative to control subjects ($p<0.05$). Pattern expression did not differ across sites for PD or control values ($p>0.9$ for NS *vs.* UF).

Discussion/Conclusions The abnormal PDRP network identified with rsfMRI resembled the previously described PET-based metabolic topography. Despite some regional differences, both patterns were abnormally elevated in off-state PD patients. As with PET-based topography, the expression of the rsfMRI-based PDRP declined toward normal with dopaminergic treatment.

References 1. Eidelberg D. Trends in Neurosciences 2009; 32(10): 548-557. 2. Spetsieris P et al. *Neuroimage* 2011; 54(4):2899-914. 3. Spetsieris P et al. *J Vis Exp*. 2013; (76): 50319. 4. Calhoun VD et al. *Hum Brain Mapp* 2001; 14:140–151.

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