The abnormality of functional connectivity in Parkinson's in dopaminergic regions

Yue Xing[1], Stefan Schwarz[1], Nin Bajaj[2], Penny Gowland[3], and Dorothee Auer[1]

[1]Sir Peter Mansfield Imaging Centre, School of Medicine, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom, [2]Division of Neurology, Nottingham University Hospitals NHS Trust, Nottingham, Nottinghamshire, United Kingdom, [3]Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom

Target: People interested in functional connectivity of Parkinson's disease

Introduction: Motor-task fMRI have consistently identified a differential neural motor activation pattern on people with Parkinson's (PwP) and healthy volunteers (HV). This has been aggregated in our on-going meta-analysis based on seventeen articles, which demonstrates consistently reduced activity in striatal- and nigral-related regions in motor tasks performed by PwP, Fig 1. In parallel, resting-state (RS) functional connectivity (FC) [1] has provided an ideal complement to investigate dysfunctional circuits in the brain of PwP. Most previous studies focused on ICA defined resting state networks or seed-based analysis of the basal ganglia [2-4]. In this study, we used seed-based analysis of the substantia nigra (SN) and the putamen to compare the connectivity pattern of these dopaminergic midbrain regions and their main striatal projections in PwP and age- and sex-matched healthy volunteers. Further, we assessed the regional-specificity of seed-based FC by dividing the SN seed points into anterior and posterior segments.

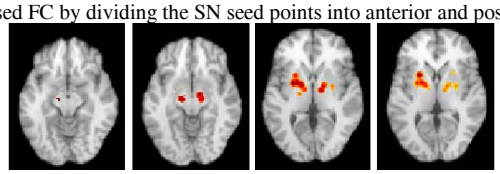

Fig1: Regions that showed significantly stronger activity in HC than PD when executing upper-limb motor tasks in our meta-analysis. Color scale: FDR corrected Z-score: yellow indicates bigger values.

Methods: 17 PwP (9 males, mean age: 62.71) and 17 HV (6 males, mean age: 65.98) were scanned using two 3T scanners locally. T1-weighted anatomical images and RS T2*WI (see table below for protocol details) were collected while subjects lay still with eyes closed. ***FC analysis***: The motion of all the included RS data were less than 3mm. Following processing steps of RS fMRI were performed using the FSL 5.0 (www.fmrib.ox.ac.uk/fsl): 1) skull extraction, affine motion correction; 2) Spatial smoothing using a Gaussian kernel of full-width at half-maximum 5 mm, and high-pass temporal filtering (100s); 3) Independent component analysis to visually filtered out the noise components, including cardiac pulse and breathin [5]; 4) Registration to individual structural image and normalization to MNI space, including reslicing to 2*2*2 mm voxels. 5) Given the small volume of SN and the possible volume loss in PwP, three 2mm radius spheres in both anterior and posterior parts of SN (ASN and PSN) were created at 3 consecutive slices on individual space separately and were combined. 6) Extraction time course of ASN, PSN and putamen in each participant. 7) Calculate temporal correlation of these regions of interest, respectively, to the rest of the brain after regressing out six motion vectors (3 translations and 3 rotations), mean intensity of white matter, cerebrospinal fluid. To control the variance due the inter-scanner differences or unwanted inter-subject differences, the average time series of central occipital lobe were also regressed out. 8) Second-level analysis: FC comparison between PwP vs. HC using ASN, PSN and putamen individually. Statistical analyses were conducted with clusters thresholding (P=0.05) and Z threshold=2.3.

EPI sequence	**GE (3T)**	**Philips (3T)**
TR (s)/ TE (ms)/ Flip angle	2/77/35	2.2/90/35
Bandwidth	7812.5	2875.2
Receiving coil	32 channel	8 channel
Matrix/ FOV	64 * 64/240	64 * 64/100
voxel size	3.75*3.75*3.6	3.25*3.25*3
Number of subjects	HC/PD: 11/10	HC/PD: 7/8
Total stabilised volumes/ Scanning duration (s)	160/320	145/319

Results: Both ASN and PSN showed significant higher FC in HV compared to PwP (Fig 2 upper row Left and Right, respectively), but we failed to find significant striatal FC increase in PwP. Significantly decoupling of the SN in PwP was found with regions included in default mode network, basal ganglia network, and motor network, such as left putamen, left caudate, right thalamus, pallidum, precentral gyrus, postcentral gyrus, and precuneus cortex and cingulate gyri in both hemispheres. Findings of ASN and PSN differential disconnection in PwP show largely similar patterns with more SMA decoupling only seen from ASN not from PSN. FC of putamen (Fig 2, lower row left) provides supportive evidence of SN decoupling by showing a consistently reduced connectivity pattern between the putamen and the SN and locus coeruleus.

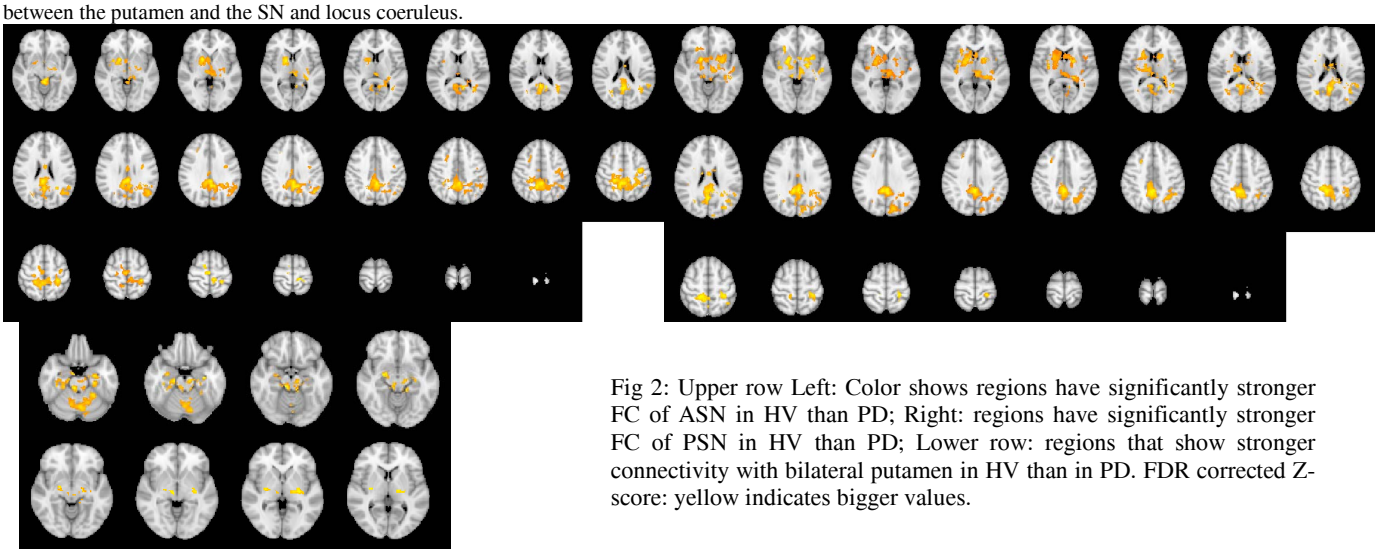

Fig 2: Upper row Left: Color shows regions have significantly stronger FC of ASN in HV than PD; Right: regions have significantly stronger FC of PSN in HV than PD; Lower row: regions that show stronger connectivity with bilateral putamen in HV than in PD. FDR corrected Z-score: yellow indicates bigger values.

Discussion: We investigated differential FC patterns of ASN and PSN in Parkinson's compared to age- and sex-matched HV with seed-based analysis on cross-scanner RS data. Most previous studies focused on using regions in basal ganglia network as the seeds to identify the abnormal striatal connectivity in Parkinson's [2-4] (or in addition to interventional approach [7-8]). One recent investigation used the whole SN and ventral tegmental area and broadly similar connectivity maps were found, including supplementary motor area [9]. It is also noticeable that connectivity of default-mode network has been reported to be weaker in PwP than in HV [10-11], which may suggest its abnormality is related to the reduced input from dopaminergic midbrain areas.

Conclusion: This study reveals a similar pattern of abnormal functional connectivity reduction of the anterior and posterior SN in Parkinson's, suggesting a link between posterior default-mode network impairment and dopaminergic deficit. Moreover, the feasibility of pooling cross-scanner result proves the feasibility of the on-going multi-centre creation of a large MRI data repository in PwP.

References: 1.Biswal et al., 1995; 2. Szewczyk-Krolikowski et al. 2014; 3. Martino et al., 2008; 4. Dragnaski et al., 2008; 5. McKeown et al., 2003; 6. Luo, et al, 2014; 7. Kahan et a., 2014; 8. Fox et al., 2014; 9. Murty et al, 2014. 10. Eimeren et al., 2009; 11. Tessitore et a., 2012

Acknowledgement: Yue Xing funded by Parkinson's UK; MRC CiC grant.