

Functional connectivity in the basal ganglia network differentiates PD patients from controls



Konrad Szewczyk-Krolikowski, MD
 Ricarda A.L. Menke, PhD
 Michal Rolinski, MD
 Eugene Duff, PhD
 Gholamreza Salimi-Khorshidi, PhD
 Nicola Filippini, PhD
 Giovanna Zamboni, PhD
 Michele T.M. Hu, MBBS, FRCP, PhD*
 Clare E. Mackay, PhD*

Correspondence to
 Dr. Mackay:
clare.mackay@psych.ox.ac.uk

ABSTRACT

Objective: To examine functional connectivity within the basal ganglia network (BGN) in a group of cognitively normal patients with early Parkinson disease (PD) on and off medication compared to age- and sex-matched healthy controls (HC), and to validate the findings in a separate cohort of participants with PD.

Methods: Participants were scanned with resting-state fMRI (RS-fMRI) at 3T field strength. Resting-state networks were isolated using independent component analysis. A BGN template was derived from 80 elderly HC participants. BGN maps were compared between 19 patients with PD on and off medication in the discovery group and 19 age- and sex-matched controls to identify a threshold for optimal group separation. The threshold was applied to 13 patients with PD (including 5 drug-naïve) in the validation group to establish reproducibility of findings.

Results: Participants with PD showed reduced functional connectivity with the BGN in a wide range of areas. Administration of medication significantly improved connectivity. Average BGN connectivity differentiated participants with PD from controls with 100% sensitivity and 89.5% specificity. The connectivity threshold was tested on the validation cohort and achieved 85% accuracy.

Conclusions: We demonstrate that resting functional connectivity, measured with MRI using an observer-independent method, is reproducibly reduced in the BGN in cognitively intact patients with PD, and increases upon administration of dopaminergic medication. Our results hold promise for RS-fMRI connectivity as a biomarker in early PD.

Classification of evidence: This study provides Class III evidence that average connectivity in the BGN as measured by RS-fMRI distinguishes patients with PD from age- and sex-matched controls. *Neurology*® 2014;83:208-214

GLOSSARY

BG = basal ganglia; **BGN** = basal ganglia network; **CI** = confidence interval; **HC** = healthy controls; **ICA** = independent component analysis; **MMSE** = Mini-Mental State Examination; **OPDC** = Oxford Parkinson's Disease Centre; **PD** = Parkinson disease; **PE** = parameter estimates; **ROC** = receiver operating characteristic; **TE** = echo time; **TFCE** = threshold-free cluster enhancement; **TR** = repetition time; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Functional changes in the basal ganglia (BG) lie at the heart of Parkinson disease (PD). fMRI employing motor tasks has identified abnormalities in BG and supplementary motor area.^{1,2} However, interpretation of those changes may be confounded by the fact that patients with PD have difficulty with performing motor tasks. Resting-state fMRI can overcome this problem by providing an index of activity across the whole brain while the participant is at rest. Independent component analysis (ICA) enables isolation of resting-state brain networks, where individual areas in a given network show tight functional connectivity.³ Recent studies demonstrated effectiveness of this technique in identifying changes in the default mode network^{4,5} and sensorimotor network⁶ in PD. Although ICA-derived BG network (BGN) has been reliably identified in other disease states,⁷⁻⁹ to our knowledge, no study so far has investigated it in PD.

*Dr. Hu and Dr. Mackay are joint senior authors.

From the Nuffield Department of Clinical Neurosciences (K.S.-K., M.R., M.H.), Oxford Parkinson's Disease Centre (OPDC) (K.S.-K., R.A.L.M., M.R., M.T.M.H., C.E.M.), Department of Psychiatry (C.E.M.), and FMRIB Centre (R.A.L.M., E.D., G.S.-K., N.F., G.Z., C.E.M.), University of Oxford, UK.

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Supplemental data
 at Neurology.org

Table 1 Demographic and clinical data of study participants

	Group			Group differences		
	Discovery	Validation	Healthy controls	Discovery vs healthy controls (p value)	Discovery vs validation (p value)	Validation vs healthy controls (p value)
Number	19	13	19	—	—	—
Sex	10:9	5:8	8:11	0.52 ^a	0.43 ^a	0.84 ^a
Age, y (SD)	58.9 (10.8)	66.8 (11.4)	60.6 (7.7)	0.59 ^b	0.07 ^b	0.11 ^b
MMSE, total score (SD)	29.0 (0.9)	27.8 (1.9)	29.4 (1.4)	0.36 ^b	0.05 ^b	0.02 ^b
Duration of diagnosis, mo (SD)	30.7 (11.8)	21.3 (15.1)	—	—	0.23 ^b	—
UPDRS-III, motor score (SD)	23.9 (9.6)	29.7 (14.7)	—	—	0.25 ^b	—
Hoehn & Yahr score (SD)	1.8 (0.4)	2.1 (0.5)	—	—	0.10 ^b	—
LEDD, ¹¹ mg (SD)	382 (205)	402 (167) ^c	—	—	0.80 ^b	—

Abbreviations: LEDD = levodopa equivalent daily dose; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Chi-square test.

^b t test.

^c Calculation excludes drug-naive patients.

In this case-control study, we aimed to investigate changes in the BGN in PD and test whether they can distinguish patients with PD from healthy controls. To that effect, we first developed a resting-state template using a large group of elderly controls, containing a BGN. Secondly, a discovery cohort was used to identify changes in the BGN and the effect of dopaminergic medication on its connectivity. In the last step, we employed a validation cohort to test reproducibility of the findings in a separate group of patients.

METHODS Participants. A breakdown of participant numbers at each stage of recruitment is presented in figure e-1 on the *Neurology*[®] Web site at Neurology.org. Thirty-two right-handed patients with early PD were recruited from the Oxford Parkinson's Disease Centre (OPDC) cohort. The OPDC recruits patients from the Thames Valley area with a diagnosis of idiopathic PD within the last 3 years according to UK PD Society Brain Bank criteria. Participants undergo assessment in designated research clinics covering medical interview, characterization of the motor and nonmotor features of PD (including the new Movement Disorder Society–Unified Parkinson's Disease Rating Scale [UPDRS]¹⁰), and cognitive assessment. Participants with PD in our study were divided into a discovery cohort and a validation cohort. The discovery cohort consisted of 19 medicated patients taking dopamine agonists, levodopa, MAO-B inhibitors, or a combination of those. However, perhaps not surprisingly given the short disease duration, there was no evidence for significant motor complications of therapy seen on the UPDRS-IV. Patients were scanned both off medication (after 12–17 hours of overnight withdrawal of dopaminergic medication, including levodopa, once daily and 3 times daily dopamine agonist preparations) and 60–90 minutes after taking their own medication in their best-defined “on” state. The validation cohort comprised 13 patients: 5 drug-naive and 8 medicated, all of whom were

scanned off medication. The validation cohort tended to be older and had slightly lower Mini-Mental State Examination (MMSE) scores than the discovery cohort but these differences were not statistically significant, and there were no differences in sex composition, disease severity, disease duration, or levodopa equivalent daily dose¹¹ (table 1). Additionally, the validation cohort tended to be older and had lower MMSE scores than the healthy control group, but the changes were statistically nonsignificant or marginally significant, respectively.

Nineteen right-handed healthy controls (HC), matched for age and sex to the discovery cohort, were recruited from the OPDC control group. Specifically, controls' age was matched to the average age of the scanned patients and the sex ratio was set at 1:1 at the start of the study. The HC participants were unrelated to patients with PD and were mostly spouses or friends of the participants with PD. Scanning procedures took place between November 2010 and February 2013. The size of the study groups was chosen based on average number of participants in similar published imaging studies.

Inclusion criteria for all participants in the study were right-handedness and ability to give informed consent. Exclusion criteria were standard contraindications to MRI scanning, dementia, other neurologic or psychiatric diseases, and more than one risk factor for cerebrovascular disease (hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease). Specific exclusion criteria for the PD groups were physician-rated certainty of diagnosis <90%, more than mild tremor in “on” medication state (>2 on any tremor item of UPDRS-III), and presence of dyskinesia or dystonia to avoid motion artifacts during imaging. A specific exclusion criterion for controls was having first- or second-degree relatives with PD. Basic demographic characteristics of study participants are provided in table 1 and participant-specific details can be found in table e-1.

The “healthy” ICA template (described in detail below) was developed using 80 elderly healthy controls—19 from the OPDC cohort (described above) and 61 healthy control scans from 3 previously published studies from our institution^{12–14} that used the same scanner and acquisition protocol (see below). Inclusion criteria for those participants were right-handedness and MMSE ≥29. Exclusion criteria were significant brain atrophy and enlarged ventricles or intracranial pathology (stroke, tumor, cyst) on structural scans. Basic details of those participants can be found in table e-2.

Image acquisition. All MRI data were acquired with a 3T Siemens (Erlangen, Germany) Trio MRI scanner with a 12-channel head coil. For each participant, T1-weighted images were obtained using a 3D magnetization-prepared rapid acquisition gradient echo sequence (192 axial slices, flip angle 8°, $1 \times 1 \times 1 \text{ mm}^3$ voxel size, echo time [TE]/repetition time [TR]/inversion time = 4.7 ms/2,040 ms/900 ms).

Functional images were acquired using gradient echoplanar imaging (TR = 2,000 ms, TE = 28 ms, flip angle 89°, resolution $3 \times 3 \times 3.5 \text{ mm}$). Thirty-four axial slices were acquired per volume, covering both hemispheres with incomplete coverage of the cerebellum; 180 repetitions were acquired in 6 minutes. Participants were instructed to remain still and awake with eyes open.

Image processing. Analysis of the resting-state scans was performed using MELODIC v3.0³, part of the FSL software package.¹⁵ The images were motion-corrected and unwarped using a fieldmap.

It has recently been shown that head motion during a resting-state scan may affect functional connectivity.^{16,17} We therefore took particular care to account for any effects of motion in our analyses and used a previously described ICA-based denoising approach.¹⁸ Subsequently, standard processing steps^{19,20} were used to register individual images to the Montreal Neurological Institute space (details in supplementary material).

Connectivity analysis. In order to create an unbiased template of resting-state networks typical for healthy elderly participants, a group ICA implemented in MELODIC was performed on all 80 controls (19 from OPDC cohort and 61 from 3 previous studies). The BGN was identified as one of 50 components in the set (details in e-Methods). Differences in BG resting functional connectivity across cohorts were then analyzed using the dual-regression method²¹ (details in e-Methods).

At the discovery stage, spatial BGN connectivity maps of 19 PD-“off” participants were compared to 19 age- and sex-matched HC participants using unpaired *t* test implemented in the FSL tool, Randomise (v2.1). Randomise provides exact false-positive control using a permutation testing implemented in threshold-free cluster enhancement (TFCE),²² which enhances sensitivity to spatially limited effects. Significant clusters (at $p < 0.05$ after family-wise error correction) were then used as a mask to identify medication effects in a paired *t* test comparison of 19 PD-“off” and 19 PD-“on” participants. The significance was set at $p < 0.05$, false discovery rate corrected within the above mask. PD-“on” patients were also compared to HC participants with an unpaired *t* test, using TFCE in Randomise.

In order to characterize connectivity changes between PD-“off” and HC in more detail, a post hoc analysis was performed on parameter estimates (PE) values. Specifically, PE were averaged participant-wise within a binary mask containing only significant clusters from the PD-“off” vs HC analysis, which produced a single value for each participant representative of individual BGN connectivity. A receiver operating characteristic (ROC) curve was generated to determine an optimal threshold for separating the 2 groups based on average connectivity. Averaged PE were also investigated for correlations with disease severity (UPDRS-III, Hoehn & Yahr), disease duration, and age using Pearson *r*.

A validation stage was included in the study design to address potential bias related to small study size. Average connectivity was extracted from 13 patients with PD from the validation cohort, using a mask of significant clusters from the discovery stage. A threshold identified in the ROC analysis was applied to the validation cohort and its accuracy in this group was determined.

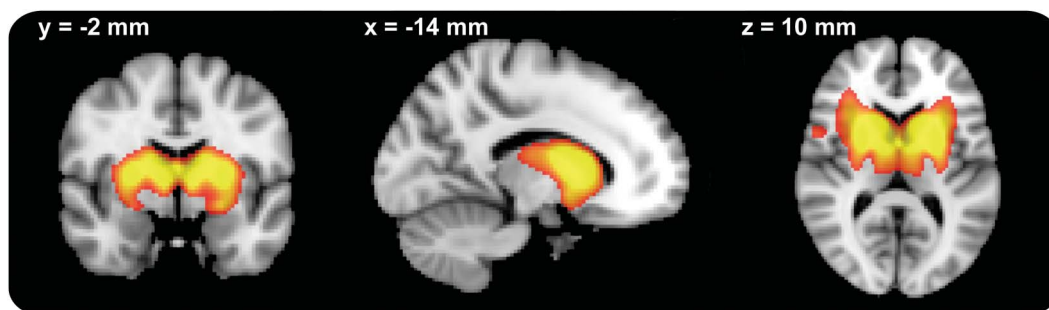
Standard protocol approvals, registrations, and patient consents. The experiments were undertaken with the understanding and written consent of each participant, with the approval from the local ethics committee, and in compliance with national legislation and the Declaration of Helsinki.

Primary research question. Can the average connectivity in the ICA-derived BGN, as measured by resting-state functional MRI, distinguish between patients with PD and matched healthy controls? This study provides Class III evidence that average resting-state functional connectivity in the BGN distinguishes patients with PD from age-matched normal controls with 100% sensitivity and 89.5% specificity (area under the curve 0.972, 95% confidence interval [CI] 0.921–1.0). Additionally, the connectivity threshold tested on the validation cohort achieved 85% accuracy.

RESULTS ICA consistently identified a BGN including the putamen and caudate bilaterally as well as anterior parts of the thalamus (figure 1). This network explained 30%–60% of the variance of voxels within the BG (figure e-2).

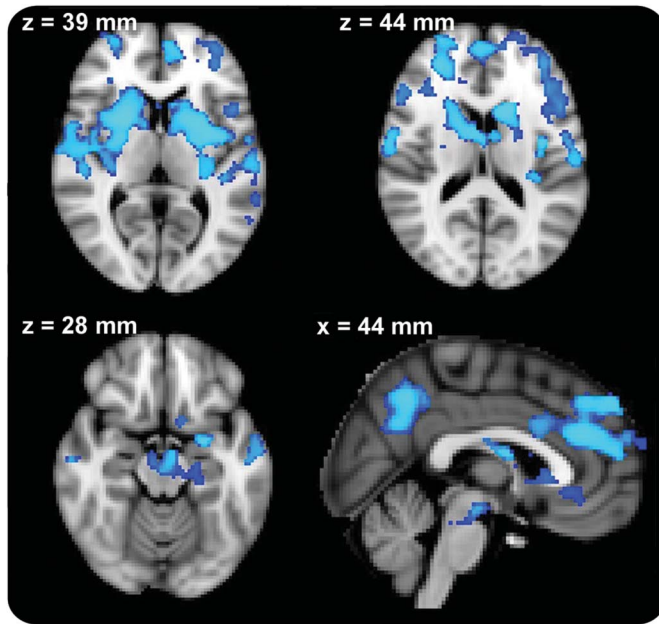
Discovery cohort. At the discovery stage, voxel-wise comparison of 19 PD-“off” patients to 19 age- and sex-matched controls demonstrated reduced BGN connectivity in the PD-“off” group in 16,273 voxels spread across 9 clusters (figure 2): putamen and caudate bilaterally, midbrain, superior temporal gyrus

Figure 1 Basal ganglia network



The image is thresholded at $z > 4$.

Figure 2 Group comparison between patients with Parkinson disease “off” medication and the healthy control group in the discovery group

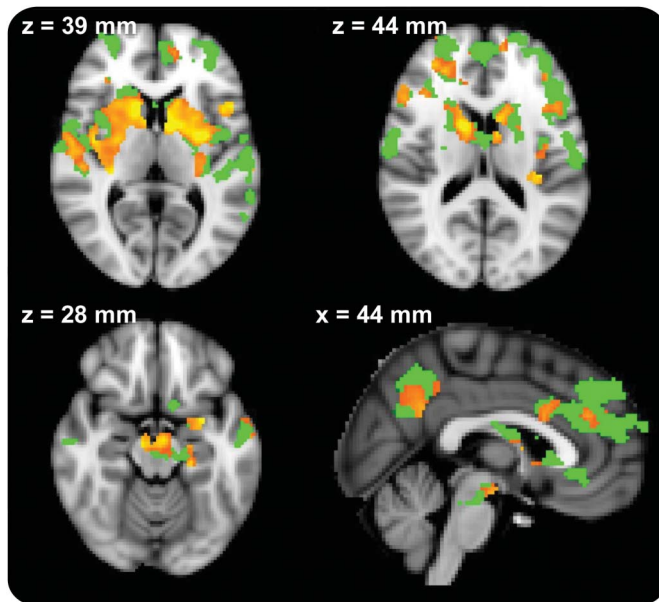


Significant clusters are located in the putamina bilaterally, medial frontal area, bilateral prefrontal areas, and precuneus. Images are displayed in radiologic convention (right is left). Slice location is displayed in Montreal Neurological Institute coordinates. Clusters are thresholded at $p < 0.05$ after correction for family-wise error.

bilaterally, dorsolateral prefrontal cortex bilaterally, medial prefrontal cortex, and precuneus.

Voxel-wise comparison of those same 19 patients with PD in “off” and “on” medication states revealed

Figure 3 Medication effect in the discovery group



Clusters with increased connectivity after medication (red–yellow) are shown on the background of the mask of significantly different clusters from the Parkinson disease–“off” vs healthy controls comparison (green). Images are displayed in radiologic convention (right is left). Slice location is displayed in Montreal Neurological Institute coordinates. Clusters are thresholded at $p < 0.05$ after false discovery rate correction.

significantly increased connectivity in the “on” state affecting mostly the BG (figure 3). PD-“on” patients did not show any significant difference in connectivity when compared to the HC group.

Average PE from the significant BGN clusters in PD-“off”/HC comparison were 1.04 (95% CI 0.42–1.65) in the discovery cohort and 7.59 (95% CI: 5.61–9.56) in the control group. In ROC analysis of averaged PE from the significant BGN clusters in PD-“off”/HC comparison, the area under the curve was 0.972 (95% CI 0.921–1.0). The cutoff value of 3.88 differentiated the PD-“off” from HC group with 100% sensitivity and 89.5% specificity (figure 4).

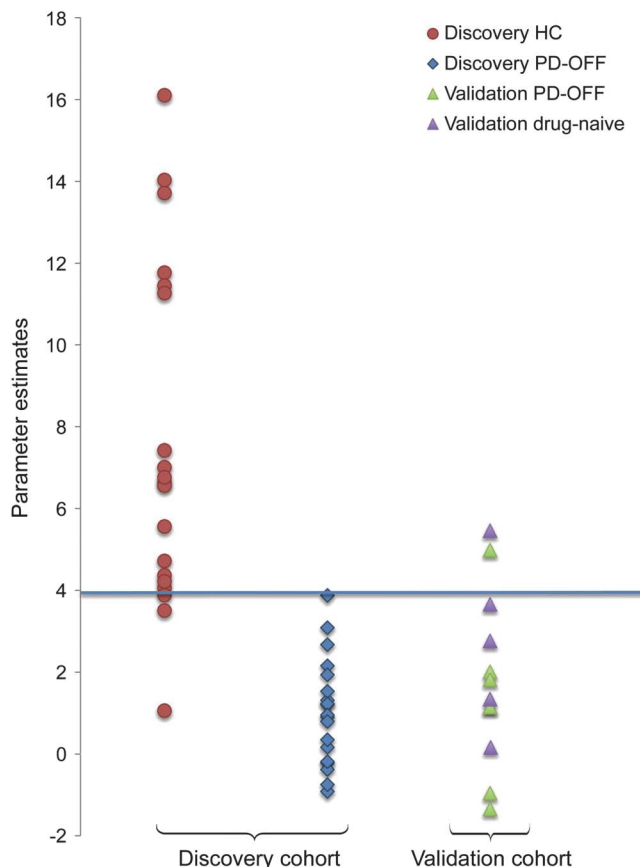
We did not find any significant correlations between averaged BGN connectivity and UPDRS-III, Hoehn & Yahr, disease duration, or age (either in the PD or the control groups).

Validation cohort. In the 13 patients with PD from the validation cohort, average parameter estimates from the significant BGN clusters were 1.72 (95% CI 0.52–2.93). Applying the threshold of average connectivity in the significant BGN clusters derived from the discovery group correctly identified participants with PD in 85% of cases (11 cases of 13) (figure 4). One drug-naïve participant and one medicated patient demonstrated average connectivity values above the threshold.

DISCUSSION This study demonstrates widely reduced functional connectivity in the BGN in cognitively intact patients with PD. The difference in connectivity robustly separates the PD group off medication from controls. Administration of dopaminergic medication improves deficient connectivity in this network. Moreover, the abnormal connectivity is validated on a separate group of drug-naïve and medicated patients.

Changes in the BGN in the PD-“off” vs HC analysis were focused in the putamen bilaterally (figure 2). Decreased functional connectivity in the putamen, understood as reduced coherence of the blood oxygenation level–dependent signal, are in line with findings of a previous study reporting reduced regional homogeneity²³ and reduced degree of seed-based connectivity²⁴ in a few voxels in the putamen. Another group examined seed-based functional connectivity of the caudate and anterior and posterior putamen with the rest of the brain.²⁵ They did not find reduced connectivity within the seeds themselves but did report a difference in the right insula, immediately next to our focus of reduced connectivity in right putamen. A recent study²⁶ using a similar technique of seed-based BG connectivity showed generally reduced connectivity with the cerebellum and particularly brainstem—a finding supported by our study. However, comparison of seed-based studies with

Figure 4 Average parameter estimates from the significantly different basal ganglia network clusters



In the discovery cohort, Parkinson disease (PD)–“off” patients are shown as blue diamonds and controls as red circles. The validation cohort consists of PD–“off” patients, as green triangles, and PD drug-naive patients, as violet triangles. The blue line indicates a threshold with 100% sensitivity and 89.5% specificity for differentiating PD–“off” from healthy controls (HC) in the discovery cohort. Fitting this threshold to the validation cohort provides 85% accuracy for classifying patients with PD.

ICA-based analyses needs to be done with caution since correlations in the former are based on a simple averaging of time series from the ROI of choice while in the latter only variance specific to the component of interest is taken into account.²⁷

The physiologic significance of reduced connectivity of the BG may be clarified by reference to the traditional task-related fMRI and PET studies. Abnormal activations have been reported in the BG in a wide range of paradigms: simple hand movements,^{2,28,29} working memory and planning,³⁰ set shifting and feedback,^{31,32} and temporal processing.^{33,34} Of note, only 3 out of the studies cited above^{28,30,33} showed increased activations in the BG in patients with PD, with the majority reporting reduced activity. It is not clear yet how the task fMRI findings relate to the resting-state changes. We hypothesize, however, that reduced functional connectivity in the BG, as shown in our resting-state experiment, may lead to reduced recruitment of this network seen in task fMRI.

Reduced connectivity was also seen in the dorso-lateral and medial prefrontal cortex as well as the precuneus. The connectivity between striatum and prefrontal areas has been linked to executive function,³⁵ which is known to be compromised early in PD.³⁶ It could then be hypothesized that connectivity deficit in this area may be linked to PD-specific executive deficit. Similarly, the precuneus as the main hub of the DMN network has been related to cognitive function and other nodes of the DMN have recently been shown to display reduced functional connectivity in relation to cognitive impairment in PD.⁴

Administration of dopaminergic medication clearly improved connectivity as shown in the PD–“off”/PD–“on” comparison, leading to disappearance of any significant differences between PD and HC. This finding suggests that reduced connectivity in the BGN is a functional rather than structural phenomenon and is related to PD-specific dopamine-dependent processes. Another possible explanation could be that reduced connectivity is somehow a reflection of tremor activity during scanning, which may be ameliorated by medication. This is, however, highly unlikely as 7 out of 19 patients did not have any resting tremor (table e-1) and yet they demonstrated the same changes as the rest of the group. Moreover, lack of significant differences in motion between the groups speaks against a strong influence of head movements on the results.

A recent study⁶ also showed increase in connectivity in patients with PD after levodopa. The authors investigated the sensorimotor network but the fact that connectivity off and on medication changed in the same direction as in our study suggests a common underlying pathologic mechanism in both networks.

BGN connectivity did not correlate with any clinical indices of severity in our study. This may indicate that BGN connectivity, similar to SN hyperechogenicity as identified by transcranial sonography,³⁷ is a trait marker of disease, reflecting a constitutional fault of the network and not the resulting clinical symptoms. Alternatively, the damage in the BGN may be profound enough to produce a floor effect where gradation of severity is lost.³⁸

Reduced connectivity in the BGN separated the PD–“off” from the HC group with high sensitivity and specificity (100% and 89.5%, respectively). A particularly strong finding from this study is a confirmation of this result in the validation cohort, 85% of which showed results below the derived threshold. The fact that 4 out of 5 drug-naive patients also showed reduced BGN connectivity increases robustness of the finding and speaks against it being a simple effect of short-term medication withdrawal.

Development of the elderly healthy control ICA template enabled us to isolate resting-state networks

that were unbiased by the pathologic changes in PD. The approach has been successfully used previously.^{39,40} Moreover, the template can be reused to test reproducibility of original findings on a separate group, as done in our study, and may serve to identify pathologic changes in at-risk groups in the future.

A major limitation of our study is small sample size of the discovery cohort. We addressed that weakness by adding a validation cohort to assess reproducibility of the results; however, testing larger independent samples with longitudinal follow-up is necessary. Moreover, we excluded participants with tremor, which limits the generalizability of our findings. However, a previous study employing seed-based connectivity in PD did not find any difference in BG connectivity between tremor-dominant and nontremor patients.²⁵

Functional connectivity at rest, analyzed with an observer-independent method, showed clear abnormalities in patients with PD in areas relevant to disease pathophysiology. This finding was successfully cross-validated on a separate group of drug-naive and medicated patients. Additionally, connectivity changes dramatically improved after dopaminergic medication. Application of this technique to a larger baseline cohort and longitudinal scanning will help critically evaluate the role of resting-state functional MRI as a potential imaging biomarker for early PD.

AUTHOR CONTRIBUTIONS

Dr. Szewczyk-Krolkowski: literature review, experimental design, data acquisition, image data analysis, result interpretation, statistical analysis, manuscript drafting and revision. Dr. Menke: experimental design, data acquisition, and manuscript revision. Dr. Rolinski: data acquisition and manuscript revision. Dr. Duff: data analysis and manuscript revision. Dr. Salimi-Khorshidi: data analysis and manuscript revision. Dr. Filippini: image data analysis and manuscript revision, provision of additional imaging datasets. Dr. Zamboni: provision of additional imaging data sets. Dr. Hu: experimental design, result interpretation, and manuscript revision. Dr. Mackay: experimental design, result interpretation, and manuscript revision.

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