SUPPLEMENTAL MATERIALS
Emergent Functional Network Effects in Parkinson Disease

Supplemental Methods

Participants: *Inclusion and Exclusion Criteria*
PD was diagnosed based on clinical diagnostic criteria from the modified United Kingdom PD Society Brain Bank, requiring clear motor response to levopdopa (Hughes et al., 1992). PD participants were excluded from the study based on: neurologic diagnosis other than PD, head injury with loss of consciousness of > 5 minutes or neurologic sequelae, presence of severe psychiatric disorders (e.g., schizophrenia), treatment with drugs that block or deplete dopaminergic signaling, or inability to complete MRI. Dementia was assessed in all participants by Clinical Dementia Rating (CDR) evaluation (Morris, 1993), with a global score of 0 indicating normal cognition, 0.5 indicating cognitive decline, and ≥1 indicating dementia. We did not include PD participants if they met criteria for dementia (CDR ≥ 1 or a Mini-Mental Status Examination score of < 24; 5 people with PD and dementia were excluded).

HC (age-matched) were recruited through the PD participants (e.g., spouses/partners), with the following additional exclusion criteria: normal neurological examination, no family history of PD, normal cognition (CDR = 0), and no evidence of pre-clinical Alzheimer's disease (Sperling et al., 2011) (based on β-amyloid PIB PET, (Mintun et al., 2006)). Five controls were excluded based on elevated cortical β-amyloid levels.

Behavioral Assessments: *Detailed Account of Tests*
Where relevant, clinical, cognitive, and motor measures were compared between groups using two-sample two-tailed t-tests or chi-squared measures (for differences in sex ratio).

Cognitive Assessment: Participants completed tests of memory (California Verbal Learning Test-II, short form (Delis et al., 2000); Logical Memory (Wechsler, 1997b)), attention (Digit Span (Wechsler, 1997a); Digit Symbol (Wechsler, 1997a)), language (Boston Naming Test (Kaplan et al., 2001)), visual-spatial (Judgment of Line Orientation (Lezak, 2004); Spatial Relations Test (Woodcock et al., 2001); Hooper Visual Organization Test (Hooper, 1983)) and executive function (Trail Making Test (Lezak, 1995); Verbal Fluency (Delis et al., 2001); Stroop (Delis et al., 2001)). Age-adjusted scaled scores, based on test manuals and published normative data (Ivnik et al., 1996), were converted to Z-scores, averaged within cognitive domains, then averaged across domains to create a global cognitive Z-score for each participant. PD participants completed the neuropsychological evaluation while OFF medication to minimize the potential confound on performance (Cools, 2006).

Motor Assessment : Movement disorder specialists rated motor severity using the Unified Parkinson Disease Rating Scale motor evaluation (UPDRS-III) (Fahn et al., 1987) after overnight withdrawal of PD medications. Motor subscores were computed as previously described (Campbell et al., 2015).

Data Preprocessing
FMRI data first underwent a standard set of preprocessing steps (Campbell et al., 2015; Fox et al., 2005; Hacker et al., 2012), which included slice-timing correction, rigid-body motion correction, mode 1000 normalization, affine alignment to the structural MRI scan, and affine alignment to an atlas template, created from equal numbers of PD and HC participants to reduce systematically biased errors in the registration procedure (Buckner et al., 2004; Campbell et al., 2015). Alignments were concatenated and applied as a single transform at the final step.

#	Reference	Aim of study	Dataset Characteristics			Motion			Scope					Results		Notes
			# subjects	on/off meds	Data per subject	GSR	Censor	anything else to address motion?	within/ between network	Cortex (#nets)	Subcor	Cereb	Region/Network definition	FC: decreases (dec.) in PD	FC: increases (inc.) in PD	
1	Baggio 2014 HBM	FC and graph theory differences in PD based on MCI status	66 PD, 36 HC (PD: MCI=23, non-MCI=43)	ON	5 min.	N	N	18 PD excluded (>0.3mm translation, 0.6 deg rotation), but motion still differs between groups, include as a covariate	both	Y (6)	Y	N	AAL	dec. widespread within & btwn systems, especially for long distance connections	inc. (few) within thalamus and within prefrontal cortex (association systems)	Supp. Fig. 1 is focus here; some differences in graph metrics and between MCI groups
2	Olde-Dubbelink 2014 Neurol	FC and cognitive decline in PD over 3 yrs	55 PD, 15 HC	ON	6 min.	N	N	4 PD excluded based on movement artifacts in registration, also looked for motion artifacts with ICA MELODIC	both - not separately reported	Y	Y	N	AAL + First (subcortical)	dec. whole-brain FC, especially in FP, SM, visual, and temporal	none reported	
3	Amboni 2015 J Neurol	FC with cognitive impairment in PD	42 PD, 20 HC (PD: MCI=21, non-MCI=21)	ON	6 min.	Y	N	report motion did not exceed voxel size, no significant differences between groups	within	Y (3)	Y	not reported	ICA with focus on DMN, FP, and visual	dec. FC within DMN and FP	none reported	impaired show dec. FC within FP
4	Baggio 2015 HBM	FC and SC in PD with MCI	65 PD, 36 HC (PD: MCI=22, non-MCI=43)	ON	5 min.	N	Y - lenient*, DVARs> 75th%ile	18 PD excluded (>0.3mm translation, 0.6 deg rotation), but motion still differs between groups, include as a covariate	both	Y (4)	N	N	ICA networks (DAN, DMN, L and R FP) + Spreng seeds	none found	none found	differences only seen when separating MCI groups; within DAN
5	Campbell 2015 Neurology	relationship of CSF protiens to FC in PD	43 PD, 22 HC	OFF	7-22 min.	Y	Y - DVARs > 0.5%	runs excluded if > 0.6mm RMS or average voxel-wise SD >0.5%; participants with > 15% volumes loss excluded (14 PD, 1 HC)	within (between shown, not analyzed)	Y (5)	BG only	N	seeds, 5 networks (SM, DAN, DMN, CO, Sal)	dec. FC within SM, also dec. magnitude FC in the caudate in seed-based analyses	inc. FC within DMN	subset of our current dataset, less stringent motion criteria
6	Canu 2015 HBM	SC and FC in PD with FOG	23 PD-FOG, 35 HC	ON	9.8 min.	N	N	no, including lack of any nuisance regression	within	Y (5)	N	N	ICA, dual-regression, 5 networks (SM, DMN, VIS, VAN, FP)	dec. FC widespread within SM, and focally within DMN and visual	none found	
7	Gorges 2015 Neurobio of Aging	FC in PD based on cognitive impairment	31 PD, 22 HC (PD: CI=17, CU=14)	ON	7.2 min.	N	N	no, including lack of any nuisance regression	within	Y (6)	Y-BG/ Thal combo	Y	seeds (DMN, L FP, R FP, VIS, DAN, VAN, BG/Thal, brainstem, cerebellum) ^	dec. DMN, SM, DAN in cognitively impaired	inc. FC within DMN, L FP, R FP, VAN, SM, brainstem, BG-Thal (PD-unimpaired)	differences also based on cognitive impairment status
8	Madhyastha 2015 Brain	Dynamics in PD; CSF correlates	24 PD, 21 HC	ON	24 min.	N	N	no filtering, don't do anything about motion (deny importance)	between (both for dynamics)	Y (23)	Y	Y	23 ICA networks (static FC analysis)	nothing survives multiple comparison correction with standard comparisons	nothing survives multiple comparison correction	differences also with dynamics analysis, here focused on stationary results
9	Onu 2015 Neuroradiology	PD vs. HC FC differences	27 PD, 16 HC	OFF 10 hrs	16 min.	N	N	remove ICs associated with motion or nuisance factors; no correlation of motion with specific ICs	both	Y (23)	Y	Y	ICA (23 networks)	dec. within DMN, btwn visual-DMN, visual-DAN	inc within DMN, FP, OFC, visual, auditory, and cerebellum; inc. between SM-FP/DAN	
10	Putcha 2015 Neuroimage Clin	PD vs. HC FC differences in cognitive networks	24 PD, 20 HC	ON	6.5 min.	N	N	2 PD, 4 HC excluded for large movements (>2mm disp.), remove ICs assoicated with motion; report motion did not differ between groups	between	Y (3)	BG only	N	ICA (DMN, Sal, FP, striatum) ^	dec. salience-R FP	inc. DMN-R FP	
11	Tan 2015 Front Hum Neurosci	pain processing in PD	14 PD, 17 HC	OFF, naïve	13.3 min.	N	N	< 1.5 mm displacement, < 1.0 deg rotation, none excluded	both	Y (4)	Y	Y	ICA (Salience, SM, DMN, FP, BG/Thal, Cerebellum)	dec. within Salience, SM, and BG, between Salience-BG/Thal	none reported	BG network overlaps insula and salience overlaps putamen; some changes were state dependent
12	Vervoort 2016 Parkinsonism & Related Disorders	FC and motor deterioration in PD subtypes	49 PD, 18 HC (PD: 33 PIGD, 16 TD)	OFF	7.25 min.	N	Y - lenient*; FD>.5mm	report FD>0.5mm or 5% signal change (unclear if DVARs or FD); excluded subjects with >50% scrubbing (N not reported); groups not significantly different on "FD"	both	Y	Y	N	Craddock for whole brain (focus here, also look in detail at BG, motor, FP)	dec. in brain-wide FC, especially (PIGD) within BG, BG-SM, within Thal, and (TD) thal-SM	few inc., especially (both) brainstem-SM, and (TD) DAN-SM	Also do a specific analysis on FP/SM/BG FC (not examined here); Some differences between subgroups
13	Guimaraes 2017 Front Neurol	SC and FC differences in PD	48 PD, 33 HC	ON	6 min.	N	Y - FD > 0.2mm	excluded subjects with excessive motion (not defined, N not reported)	within	Y (70)	Y	Y	BASC clusters^	dec. FC within visual, SM, DMN, cerebellum	none reported	
14	Imperiale 2017 Mol Psychiatry	SC and FC with impulsive-compulsive symptoms	85 PD; 50 HC (PD: ICB=35, nICB=50)	ON	12 min.	N	N	motion-contaminated ICA component removal using ICA-AROMA	both	Y (5)	N	N	ICA (focus on DMN, Vis, SM, L FP, R FP) ^	none reported	inc. within visual (and within SM in no-ICB)	no significant between network effects
15	Ma 2017 Brain Imaging Behav	determine modular differences in PD	32 PD, 31 HC	OFF - 24hrs	6.2 min.	N	N	excluded 3 PD due to very large motion (>2mm translation; 2 degree rotation); included max motion, RMS, and mean FD as covariates	between (and graph measures)	Y	Y	Y	randomly divide brain into 1,024 equal nodes	dec. SM-DMN, Salience-DMN, Visual-DMN	none reported	Primarily focus on graph theory measures, not discussed here
16	Ma 2017 Eur Neurol	FC topography based on motor subtypes	31 PD, 22 HC (PD: 12 TD, 19 PIGD)	OFF - 12hrs	8 min.	Y	N	exclude subjects with large movements (> 3mm or 3 deg; N not reported)	both - not separately reported	Y	Y	Y	whole-brain, voxel wise	dec. widespread, especially in SM, visual, CO, BG, cerebellar, and DAN (PIGD only)	none reported	
17	Peraza 2017 HBM	inter- and intra- FC changes in PD with cognitive impairment	99 PD, 30 HC (PD: 37 MCI, 62 NI)	ON	6.4 min.	N	N	removed subjects with large (2mm, 1 degree) movements, report significant differences in movement	both	Y (26)	Y	Y	26 nets from ICA	dec. within systems generally, especially small sites in (both groups) DAN and (nMCI) FP and SM, (MCI) Visual, Temporal	few inc. within, mainly in subcallosal FP; significant inc. between BG-SM (nMCI, same direction for MCI)	some decreases were inc. in anticorrelations (some in FP, DAN, Vis); some changes related to clinical variables
18	Wei 2017 Sci Rep	intra/inter network differences in PD depression	55 PD, 34 HC (PD: 20 dep, 35 non-dep)	ON	4.67 min.	N	N	exclude subjects with large movements >2.5mm trans. or 2.5 deg rot. (N=6) and micro-movements (mean FD>0.3mm, N=20)	both	Y (5)	Y-BG/ Thal combo	N	ICA, selected BG/Thal, DMN, L FP, R FP, Salience	dec. within BG/Thal	inc. FC between DMN-LFP (both), DMN-RFP (non-dep), DMN-BG-thal (non-dep)	also some differences between depressed and non-depressed groups
**	**Gratton et al - CURRENT SUBMISSION**	**Connectome-wide differences between PD and HC**	**107 PD, 46 HC**	**OFF**	**7-22 min.**	**Y**	**Y - DVARs > 0.3%**	**runs excluded if <50 low motion frames remained or had >1 mm. RMS motion; subjects excluded if <150 (5.5 min.) low motion frames or mean FD>0.5mm. (19 PD, 5 HC); examine FD-FC relationship post clean up (Ciric et al., 2017)**	**both**	**Y (12)**	**Y (4)**	**Y**	**285 regions, 17 nets: Gordon [Cortex], Freesurfer [BG&MTL], SUIT [Cereb], and RSFC [Thal], all masked by Freesurfer gray-matter ^**	**dec. FC within and between sensorimotor (SM, auditory, visual); dec. FC within and between thalamus, and cerbellum; some dec. between SM-Association**	**inc. FC between SM-thalamus, SM-cerebellum, and SM-association (pattern extends to a lesser degree to visual and auditory)**	**most FC differences represent decreases in magnitude (toward 0). FC differences replicate in split-half samples**

Supplemental Table 1 (*continued from previous page*):

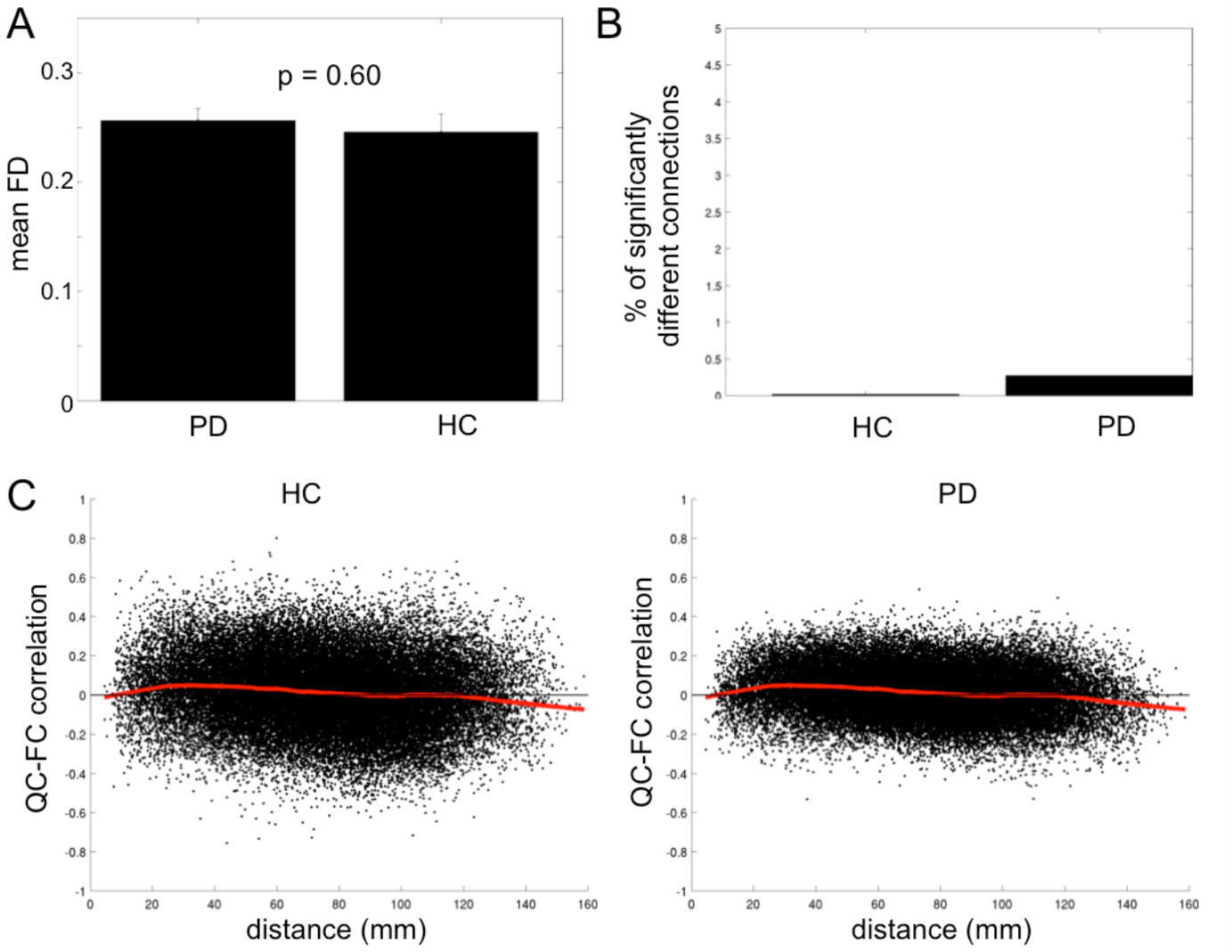
This table reviews previous results on functional connectivity differences in Parkinson's disease. To be most comparable to our manuscript, references were included in this review if they (1) included a comparison of PD vs. HC static functional connectivity, (2) had a multi-network scope (i.e., > 4 networks), (3) included PD cases without dementia (given our focus on non-demented PD), (4) reported on functional connectivity results, not focusing exclusively on graph metrics or feature weights from classifications. References were found based on literature searches, including a formal PubMed search with terms: Parkinson AND "functional connectivity" AND fMRI AND ("resting-state" OR "resting state") AND ("networks" OR "systems"). Gray rows represent papers that focused on the differences between PD and HC such as ours, rather than on differences between subtypes of PD. Additional notes: * *motion censoring criteria are lenient as defined by* (Power et al., 2014); ^ *these references include some report or account of atrophy effects in PD.*

Table References:
(Amboni et al., 2015; Baggio et al., 2014; Baggio et al., 2015; Campbell et al., 2015; Canu et al., 2015; Gorges et al., 2015; Guimaraes et al., 2016; Imperiale et al., 2017; Ma et al., 2017a; Ma et al., 2017b; Madhyastha et al., 2015; Olde Dubbelink et al., 2014; Onu et al., 2015; Peraza et al., 2017; Putcha et al., 2015; Tan et al., 2015; Vervoort et al., 2016; Wei et al., 2017)

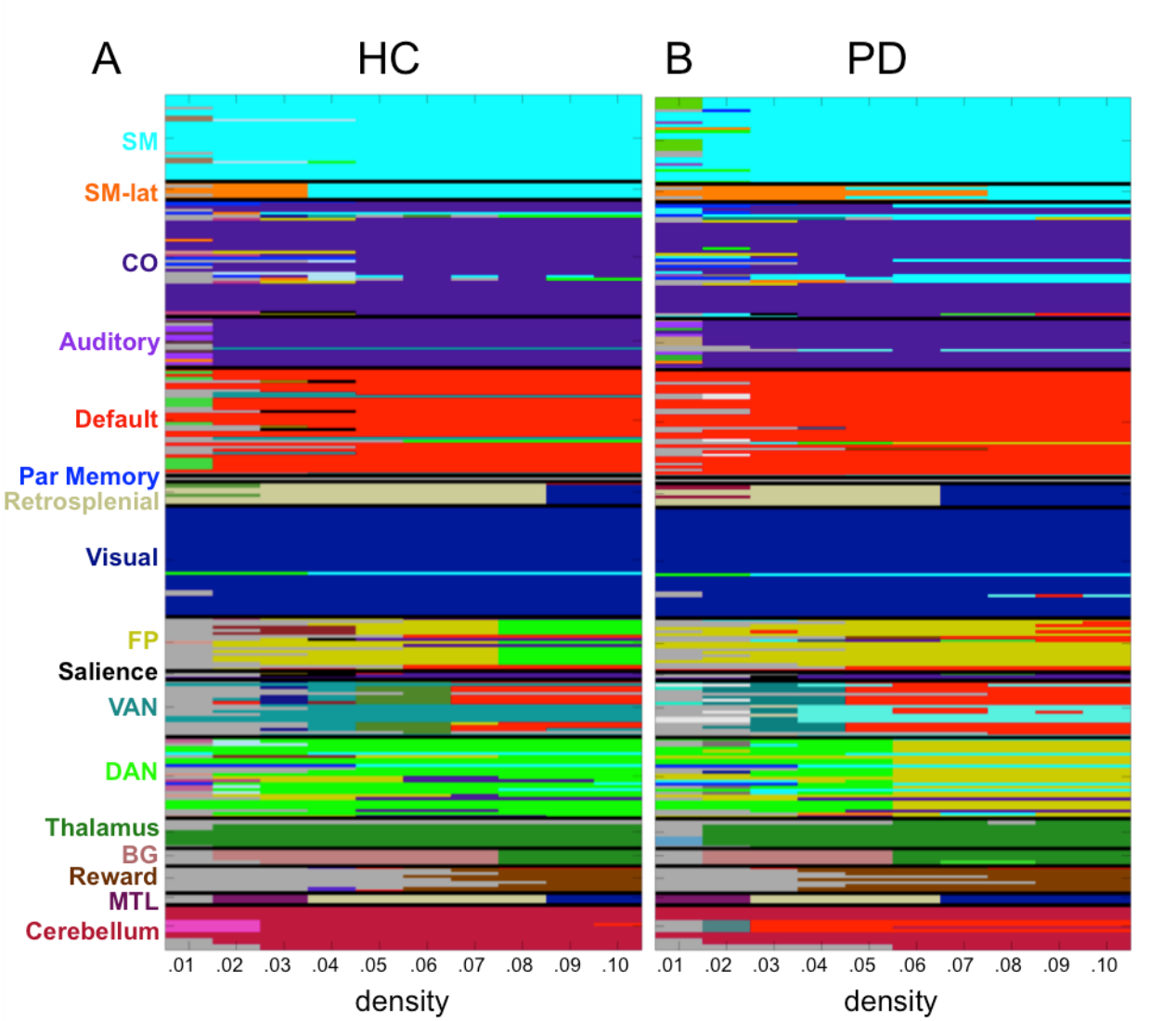
Behavioral Measures	PD Mean (SD)	HC Mean (SD)	PD vs. HC p-value
Attention	0.30 (0.84)	0.65 (0.65)	***0.01***
Memory	0.41 (0.74)	0.83 (0.59)	***0.02***
Language	0.82 (0.96)	1.09 (0.86)	0.1
Visuospatial	0.60 (0.66)	0.79 (0.62)	0.1
Executive Function	0.24 (0.88)	0.59 (0.68)	***0.02***
Global Cognition	0.47 (0.59)	0.78 (0.44)	***0.002***

Supplemental Table 2: Cognitive Assessment. PD and HC z-scores on cognitive measures related to attention, memory, language, visuospatial, and executive function, along with a summary measure of cognitive performance ("global cognition"). Sample means and standard deviations (SD) are reported, as well as the p-value of the comparison between groups. The attention, memory, and executive function z-scores were missing data from one participant, and the language function z-score was missing for two participants.

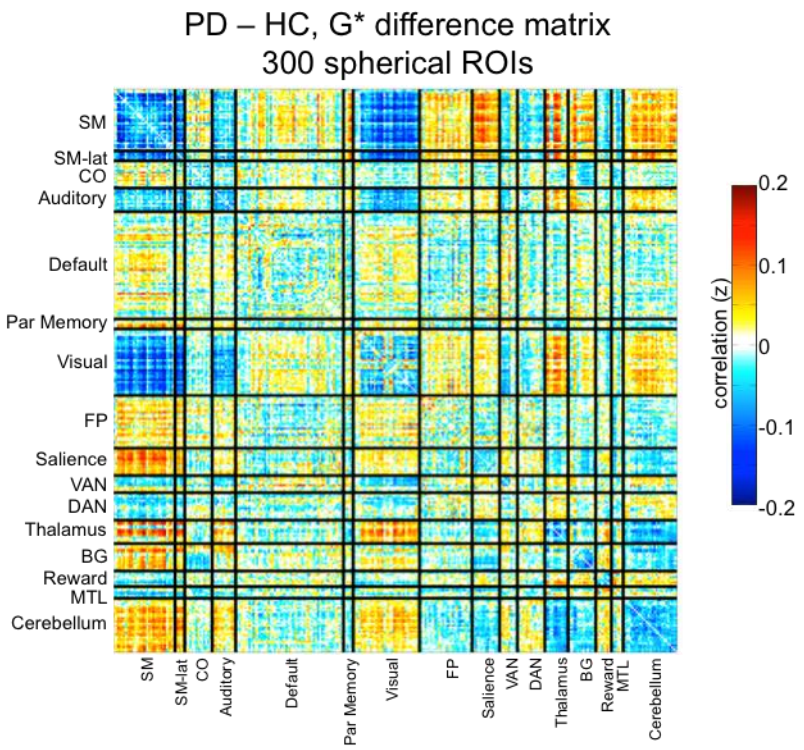
Supplemental Figures



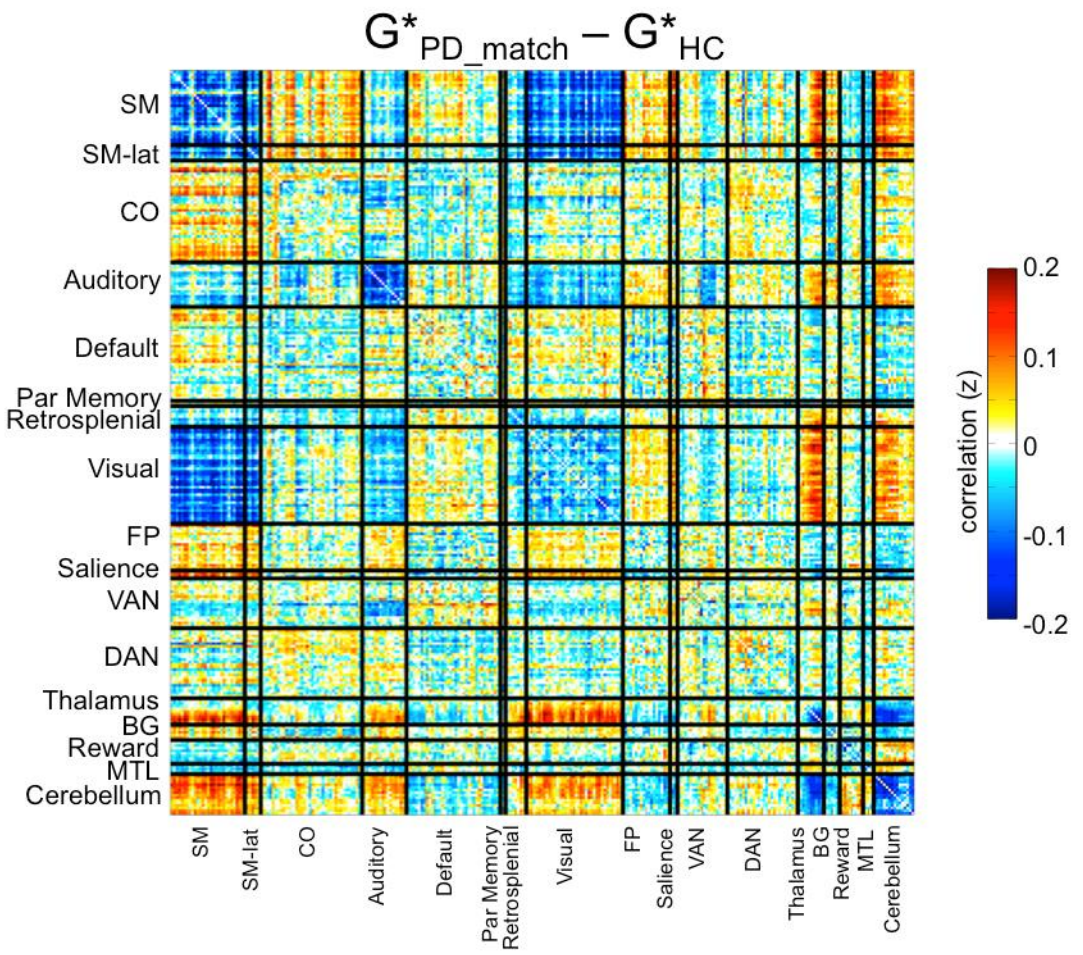
Supplemental Figure 1. Motion effects in PD and HC groups. (A) Mean Framewise Displacement (FD; see Supplemental Methods for calculation) in each group did not differ significantly (p=0.63). (B) Percent of connections significantly related to FD in PD and HCs. Both had less the 0.5% of connections related to motion. (C) Relationship between distance and FD-FC correlation – note the fairly flat line, with similar pattern across the two groups.



Supplemental Figure 2: Infomap in PD and HC participants. (A) Data-driven clustering solutions (using Infomap (Rosvall and Bergstrom, 2008)) for large-scale networks in this group of HC participants. Different colors represent different networks, shown for 0.01 – 0.1 density thresholds. Gray colors represent a lack of assignment. (B) The same plot, but for PD participants. Note substantial similarity between PD and HC participants.

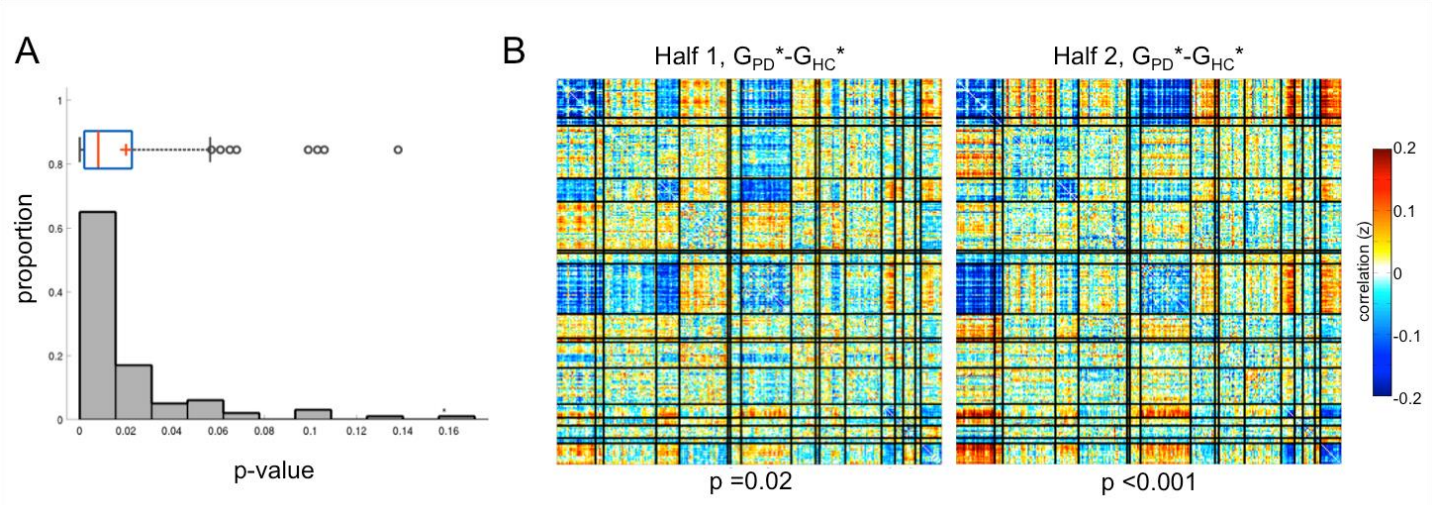


Supplemental Figure 3: PD – HC FC difference matrix for 300 spherical ROIs from (Power et al., 2011; Seitzman et al., 2017 *SFN abstract*). PD and HC exhibited significantly different matrices with this parcellation as well ($p<0.001$). Note the similarity of these results to the results reported in **Figure 2D** in the manuscript, with prominent differences within and between sensorimotor, thalamic, and cerebellar systems.

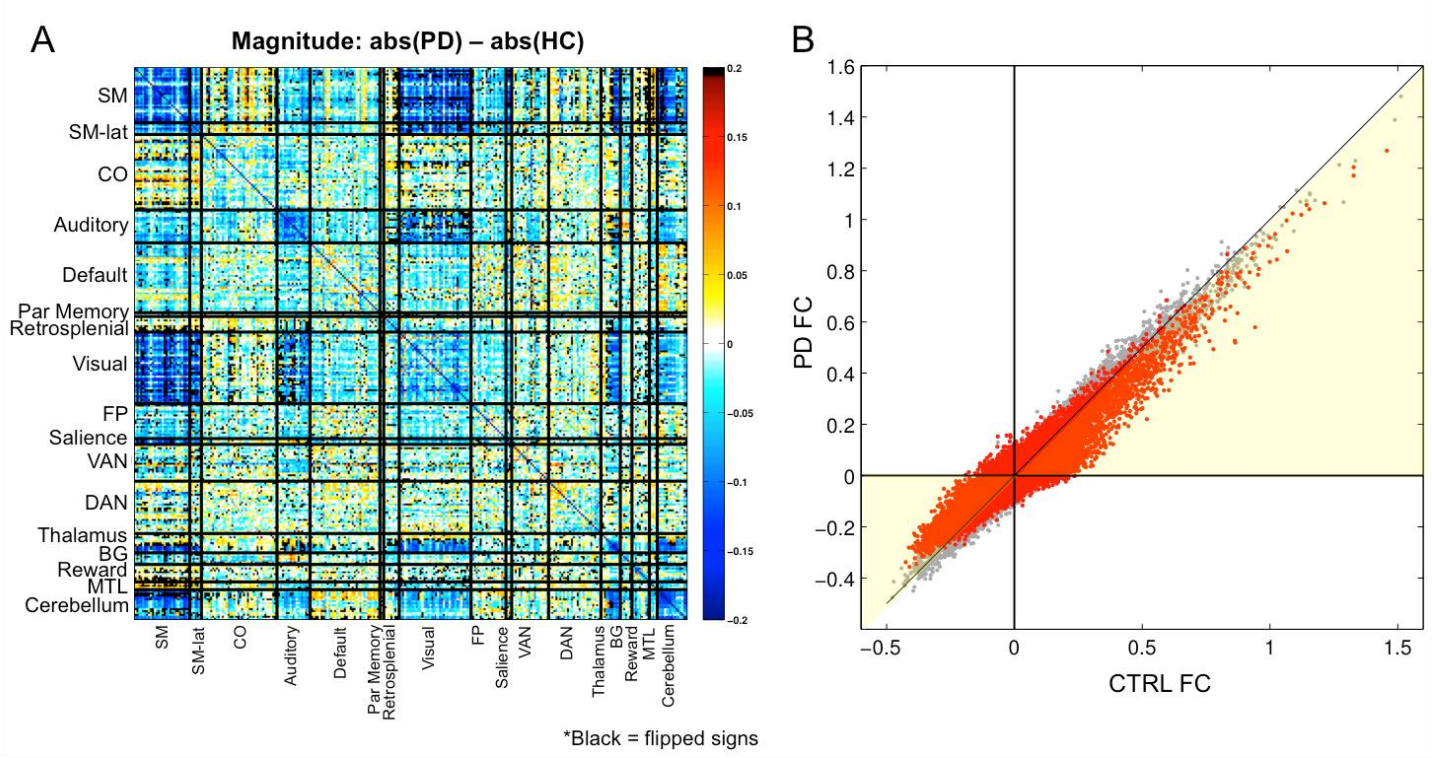


Clinical Characteristics	PD_match Mean (SD)	HC Mean (SD)	PD_match vs. HC p-value
N	47	46	-
Sex (% male)	27.7	30.4	0.77
Age	65.3 (7.7)	63.8 (11.0)	0.45
Years of Education	14.9 (2.0)	14.8 (2.7)	0.82

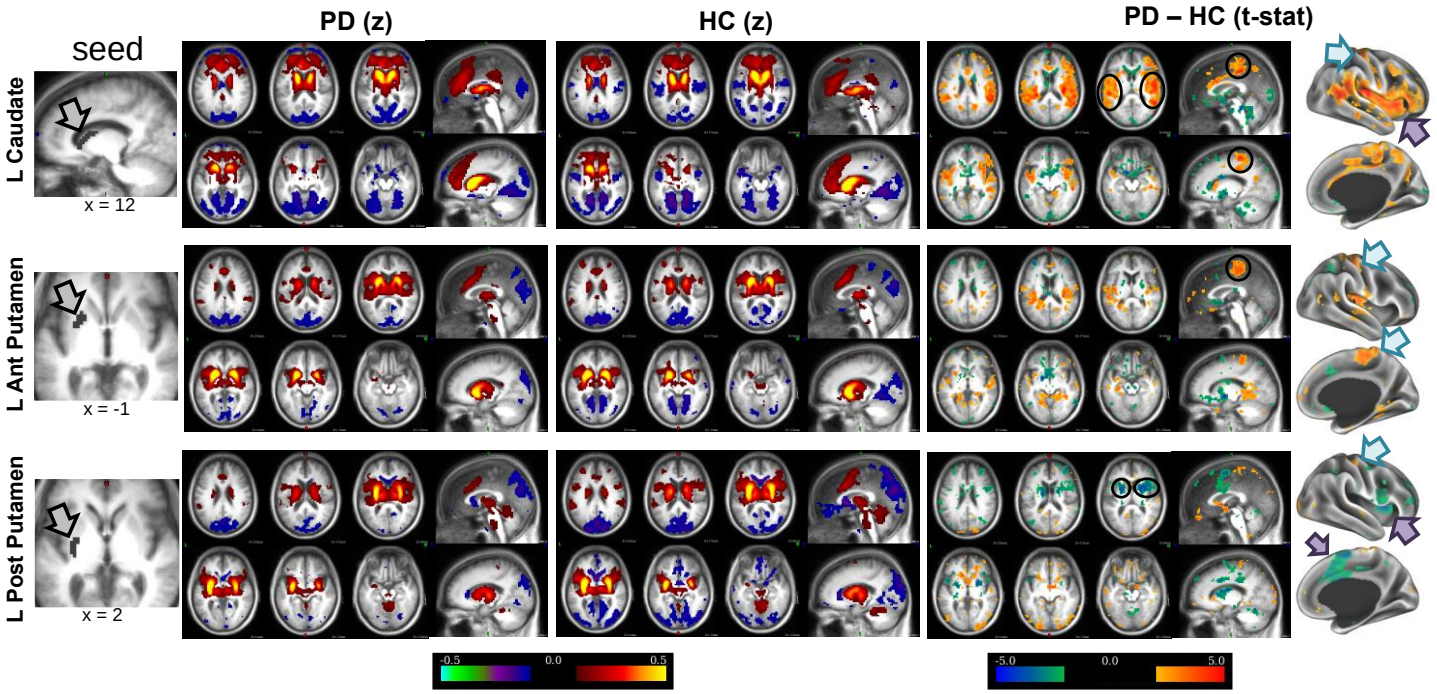
Supplemental Figure 4: PD and HC matched groups for subject number, sex, age, and years of education. The PD group was subsampled to approximately match the HC group for sex, years of education, and participant numbers (note that age was already approximately matched; see table above). The figure shows the G* difference map between groups ($G^*_{PD\_match}$-G^*_{HC}; $p<0.001$). Notably, the differences between the two groups were quite similar to those reported for the full sample of PD.



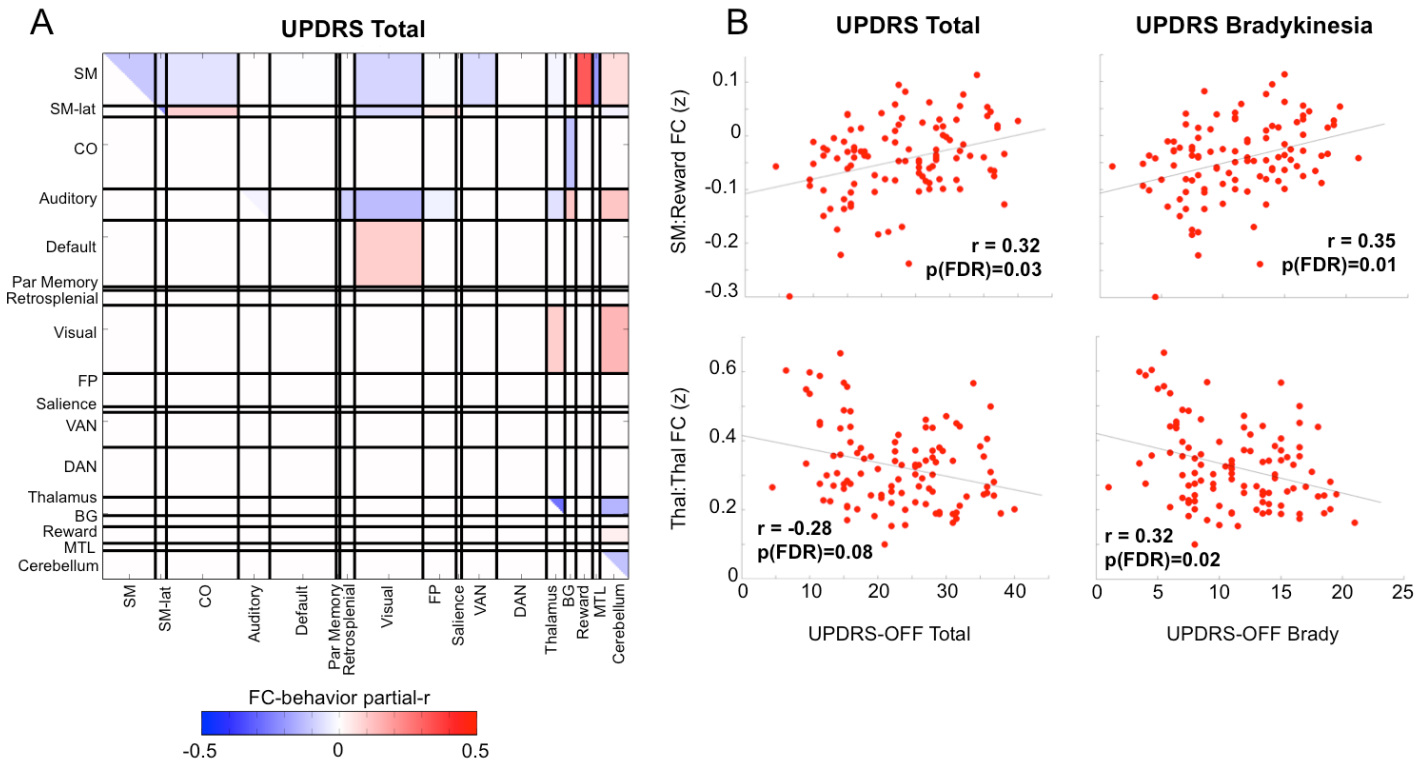
Supplemental Figure 5: Consistency of findings across split-half samples of data. (A) Distribution of p-values from OODA run on 50 split-half samples of PD and HC data (mean+/-SD: p=0.02 +/- 0.03; median: p=0.008). (B) G* difference matrices from the two halves of a split-half sampling are plotted (this iteration was selected as it had the median p-value outcome of split-half samples). G* difference matrices were largely similar between the two halves, and were both significant (p<0.05).



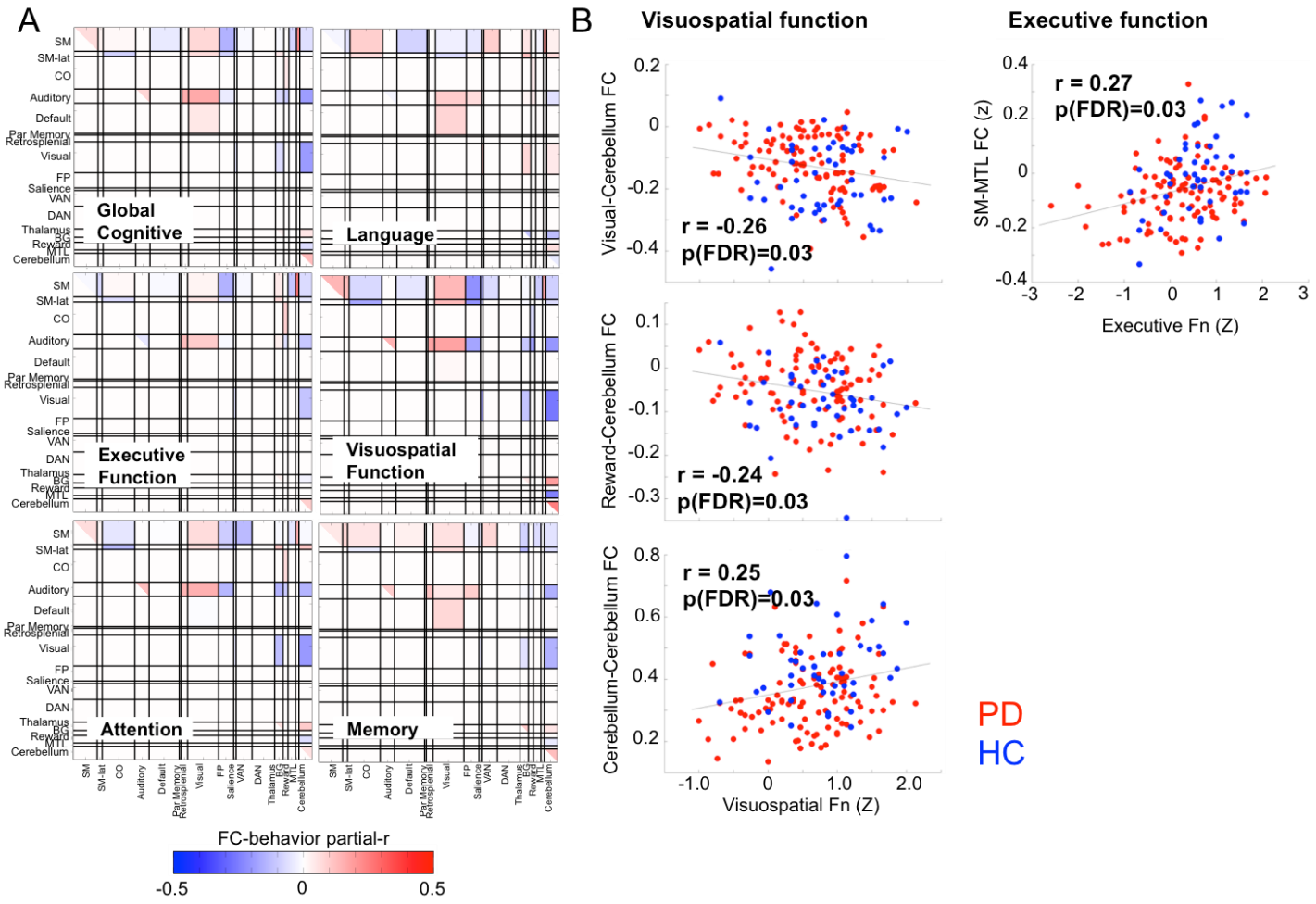
Supplemental Figure 6: Analysis of FC differences between PD and HC. (A) The absolute magnitude of differences between PD and controls; decreases in magnitude are shown in blue colors, increases in magnitude are shown in red colors, and changes in direction are shown in black. (B) FC for each connection in the correlation matrix for HC and PD participants, plotted against the unity line. Note that PD is associated with a flattening of FC, with negative values being elevated toward 0 and positive values being diminished toward 0, and thus tending to appear more in the yellow triangles. This was especially true of edges within the significant blocks (red) relative to other edges (gray) which stayed closer to the unity line.



Supplemental Figure 7: Striatal seed. FC correlation maps for the left caudate (top panel), left anterior putamen (middle panel), and left posterior putamen (bottom panel) seeds (seeds shown on the far left, indicated with gray arrows), depicted for PD participants (left column), HC participants (middle column), and the difference between the two (right column, depicted in a t-statistic map in the volume and on the surface). Note the similarity between these results and other previous investigations of altered striatal connectivity in PD (Campbell et al., 2015; Hacker et al., 2012). Black circles in the t-statistic map indicate significant clusters ($p<0.05$, permutation based FWE correction, $t>3.0$). Cyan arrows highlight motor increases with PD for each seed; purple arrows highlight prominent insular and dorsal anterior cingulate (CO/Salience) differences; additional differences were present in cerebellar and visual regions that did not pass cluster correction at this threshold. FC patterns were analogous for right hemisphere seeds.



Supplemental Figure 8: Relationship between block-FC and motor performance. (A) Full set of relationships between UPDRS-III total (off medication) scores and FC within each permutation-selected block, with covariates for age, sex, and years of education. Note that most cortical and subcortical motor regions show a negative relationship between UPDRS-III score and FC, with the exceptions of SM-Reward and SM-cerebellar FC. Some weak positive relationships between UPDRS-III and FC were also seen for relationships with sensory systems. (B) Scatter plots showing significant correlations (FDR-corrected across blocks, p<0.05) for UPDRS-III total, and related significant correlations for the bradykinesia subscale (note that the within-thalamus effect was marginally significant for UPDRS-III total, at p(FDR)=0.08).



Supplemental Figure 9: Relationship between block-FC and cognitive performance. (A) Full set of relationships between cognitive scores and FC within each permutation-selected block, with covariates for age, sex, and years of education. Note that relationships showed heterogeneous patterns, differing by cognitive test and block. (B) Scatter plots showing significant correlations (FDR-corrected across blocks, p<0.05). PD participants shown in red; HC participants shown in blue.

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