

Supplementary Material

Subthalamic nucleus-language network connectivity predicts dopaminergic modulation of speech function in Parkinson's disease

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Supplementary Methods

Medication ON versus OFF order

To minimize the physical discomfort experienced by PD participants when are OFF dopaminergic medications, the OFF session was scheduled at a time based on patient convenience and preference; therefore, the ON versus OFF order was not fully counterbalanced across PD participants. The mean (SD) time between ON and OFF scans was 16 (109) days with 12 PD participants who had their OFF scan first and 24 PD participants who had their ON scan first. We confirmed that unbalanced ON vs. OFF order does not significantly affect any result reported in this study.

Supplementary Results

Medication order effect on the relation between medication-induced change in MDS-UPDRS and PD-OFF MDS-UPDRS scores

We conducted multiple linear regression analysis to examine the relation between medication-induced change in MDS-UPDRS score and PD-OFF MDS-UPDRS score while controlling age, gender, education, LEDD and order effect and found that the PD-OFF MDS-UPDRS score is the significant predictor of medication-induced change in MDS-UPDRS ($p < 0.05$, **Supplementary Table 6**).

Medication order effect on the relation between medication-induced change in oSDMT and PD-OFF oSDMT scores

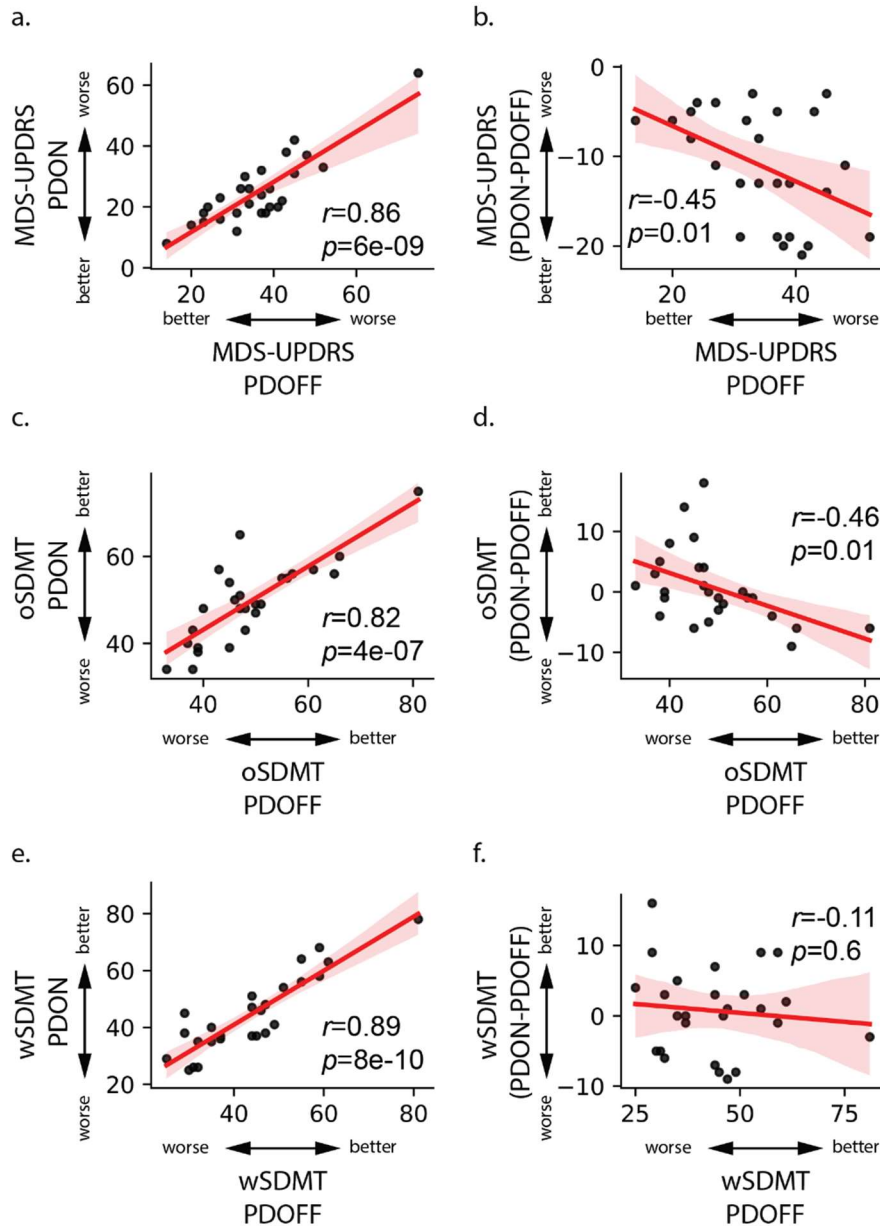
We conducted multiple linear regression analysis to examine the relation between medication-induced change in oSDMT score and PDOFF oSDMT score while controlling age, gender, education, LEDD and order effect and found that the PD-OFF oSDMT score is the significant predictor of medication-induced change in MDS-UPDRS ($p < 0.05$, **Supplementary Table 7**).

Medication ON versus OFF order effect on the relation between STN subdivision and Language regions and dopaminergic modulation of oSDMT performance

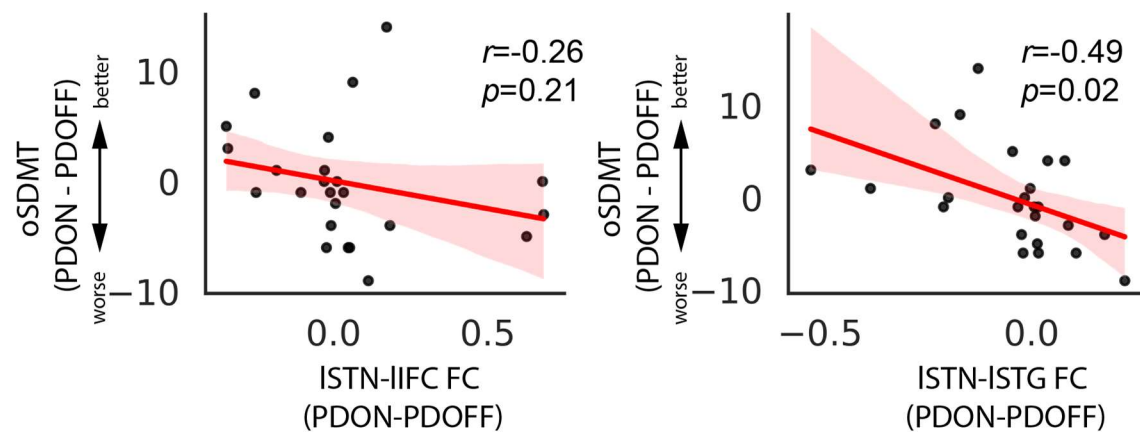
We conducted multiple linear regression analysis to examine the relation between STN subdivision and Language regions and dopaminergic modulation of oSDMT performance while controlling age, gender, education, LEDD, head motion and medication order effect. We found that the effect of medication on oSDMT performance is significantly associated with functional connectivity between rSTN_dl and ISTG ($p = 2E-05$), between ISTN_dl and ISTG ($p = 0.001$) and between ISTN_dl and IIFC ($p < 0.05$) (**Supplementary Table 8**).

Supplementary Figure 1. Medication effects on motor, speech and cognitive functions.

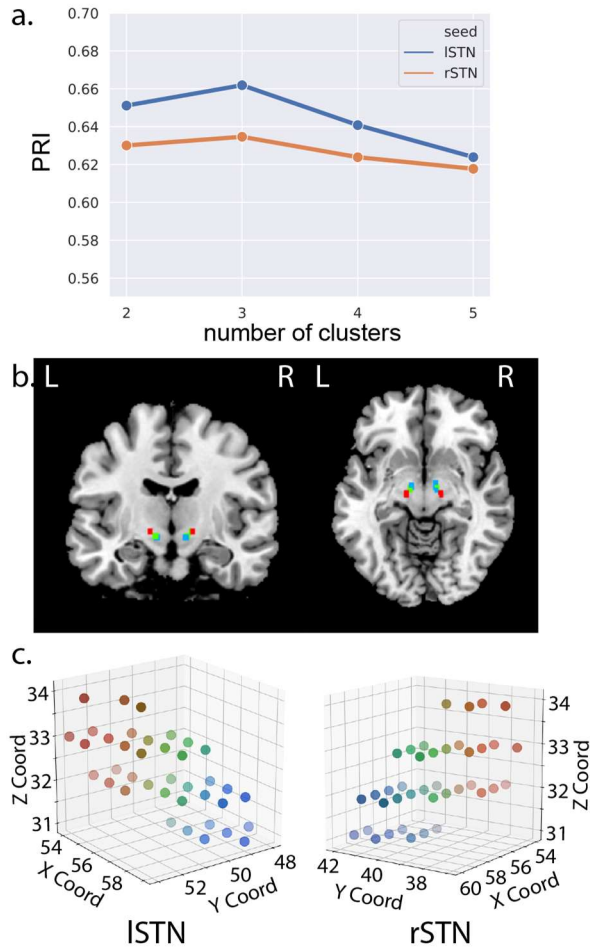
(a) PD-OFF MDS-UPDRS scores were significantly correlated with PD-ON scores ($r=0.86$, $p=6e-09$), (b) PD-OFF MDS-UPDRS scores were significantly correlated with medication-induced change in MDS-UPDRS score ($r=-0.45$, $p=0.01$), (c) PD-OFF and PD-ON showed significant correlation in the oSDMT ($r=0.82$, $p=4e-07$), (d) PD-OFF oSDMT scores were significantly correlated with medication-induced change in oSDMT score ($r=-0.46$, $p=0.01$), (e) PD-OFF and PD-ON showed significant correlation in the wSDMT ($r=0.89$, $p=8e-10$), (f) PD-OFF wSDMT scores were not significantly correlated with medication-induced change in wSDMT score ($r=-0.11$, $p=0.6$).



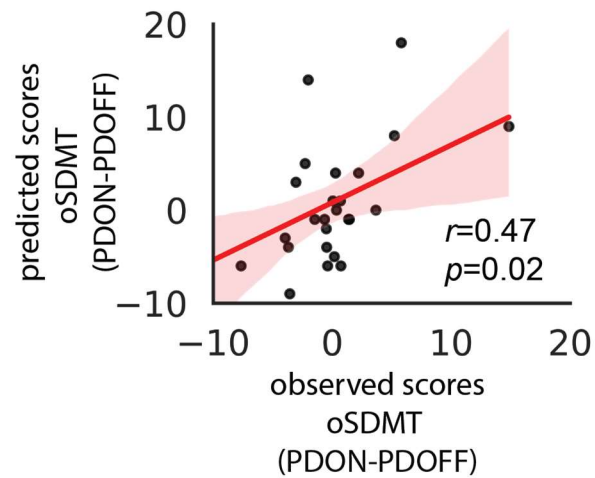
Supplementary Figure 2. Functional connectivity between ISTN and key regions in the language network in association with medication-induced changes in speech function. Medication-induced changes in oSDMT scores (PDON – PDOFF) is associated with medication-induced changes in ISTN-ISTG FC ($r=-0.49$, $p=0.02$) but not in ISTN-IIFC FC. FC: functional connectivity; STN: subthalamic nuclei; IIFC: left inferior frontal cortex; ISTG: left superior temporal gyrus; oSDMT: oral the Symbol Digit Modalities Test.



Supplementary Figure 3. Functional parcellation of STN from Human Connectome Project resting-state fMRI data (N=801). (a) Consensus clustering produced the best parcellation solution with 3 clusters for both left and right STN. (b) Both the left and right STN ROIs were composed of dorsolateral (red), central (green) and ventromedial (blue) parts. (c) Stability of each voxel being assigned to dorsolateral, central and ventromedial parts of the STN was coded by the scale of red, green and blue colors in each RGB colored dot, respectively, which presents the voxel's color in a 3D space. STN: subthalamic nucleus; PRI: probability rand index.



Supplementary Figure 4. Prediction analysis. Linear support vector regression model trained on medication-induced changes in functional connectivity between rSTN_dl and regions in Language network can predict medication-induced changes in oSDMT performance on unseen data ($r=0.47$, $p=0.02$). STN_dl: subthalamic nuclei dorsolateral part; oSDMT: oral the Symbol Digit Modalities Test.



Supplementary Table 1 Demographic information of participants.

	CTL	PD		CTL vs. PD-OFF		PD-OFF vs. PD-ON	
		PD-OFF	PD-ON	t-/chi-stats	p-value	t-/chi-stats	p-value
sample size	42	27					
age (years old)	71±6	68±6		1.92	0.06		
sex (f/m)	23/19	14/13		0	1		
education (years)	17±2	17±2		0.66	0.51		
MDS-UPDRS		36±12	25±11			9.42	7.22E-10
SDMT-W	51±11	44±13	45±13	2.36	0.02	0.6	0.55
SDMT-O	54±9	49±11	50±9	1.96	0.06	0.56	0.58
max Disp (mm)	1.39±0.6	1.41±0.71	1.52±0.71	0.27	0.79	0.72	0.47
mean FD (mm)	0.07±0.04	0.07±0.05	0.07±0.03	0.6	0.55	0.21	0.84

Supplementary Table 2 Multiple linear regression analysis revealed that baseline (PD-OFF) UPDRS predicts the effect of dopaminergic medication (PD-ON – PD-OFF) on UPDRS after controlling age, sex, education and LEDD. PD-OFF: Parkinson’s disease OFF medication; PD-ON: Parkinson’s disease ON medication; LEDD: levodopa equivalent daily dosage; UPDRS: the Movement Disorders Society-Unified Parkinson's disease Rating Scale motor assessment.

	beta	t-value	p-value
UPDRS (PD-OFF)	-0.33	-2.62	0.02
Age	-0.09	-0.49	0.63
Sex	-2.11	-0.94	0.36
Education	0.9	1.65	0.11
LEDD	-0.01	-1.84	0.08

Supplementary Table 3 Multiple linear regression analysis revealed that baseline (PD-OFF) oSDMT predicts the effect of dopaminergic medication (PD-ON – PD-OFF) on oSDMT after controlling age, sex, education and LEDD. PD-OFF: Parkinson’s disease OFF medication; PD-ON: Parkinson’s disease ON medication; LEDD: levodopa equivalent daily dosage; oSDMT: oral the Symbol Digit Modalities Test.

	beta	t-value	p-value
oSDMT (PD-OFF)	-0.35	-3.13	0.005
Age	-0.35	-1.69	0.11
Sex	-3.8	-1.68	0.11
Education	0.62	1.12	0.27
LEDD	0.0001	-0.04	0.97

Supplementary Table 4. Canonical loadings of the effect of dopaminergic medication on STN-FBN FC measures and on Motion-Cognition measures in the significant canonical correlation models, i.e. rSTN_dl and rSTN_vm. STN-FPN FC: subthalamic nuclei-functional brain network functional connectivity; SN: salience network; DMN: default mode network; LECN: left executive central network; RECN: right executive central network; Visuospatial: visuospatial network; Language: language network; Auditory: auditory network; high_Visual: high visual network; prim_Visual: prime visual network; sensorimotor: sensorimotor network; UPDRS: the Movement Disorders Society-Unified Parkinson's disease Rating Scale motor assessment; oSDMT: oral the Symbol Digit Modalities Test; wSDMT: written the Symbol Digit Modalities Test; rSTN_dl: right subthalamic nucleus dorsolateral subregion; rSTN_vm: right subthalamic nucleus ventromedial subregion.

	Subregions of STN			
	rSTN_dl		rSTN_vm	
STN-FBN FC	r	p	r	p
SN	-0.022	0.9151	-0.3589	0.0718
DMN	-0.1912	0.3495	-0.2835	0.1605
LECN	-0.072	0.7267	-0.2331	0.2517
RECN	-0.3031	0.1323	-0.177	0.387
Visuospatial	0.0601	0.7704	-0.0533	0.7959
Language	0.3672	0.065	-0.4195	0.0329
Auditory	0.1909	0.3503	-0.1581	0.4406
high_Visual	0.5567	0.0031	-0.3928	0.0471
prim_Visual	0.0634	0.7585	-0.0166	0.9359
Sensorimotor	0.1601	0.4348	0.0644	0.7545
Motor-Cognition				
UPDRS	0.0967	0.6384	-0.0225	0.9133
oSDMT	-0.9276	0	0.9107	0
wSDMT	-0.1878	0.3583	0.1527	0.4564

Supplementary Table 5. Medication-induced changes in STN-Language ROI FC (PDON-PDOFF) predicts medication-induced changes in oSDMT performance (PDON-PDOFF)

	beta	t-value	p-value
ISTN_dl-IIFG (PD-ON – PD-OFF)	-7.8021	-2.134	0.0469
age	-0.2079	-1.087	0.2916
sex	-0.3181	-0.149	0.8834
education	0.17571	0.334	0.7425
LEDD	-0.0045	-1.289	0.2138
head motion	2.76902	0.11	0.9137
	beta	t-value	p-value
ISTN_dl-ISTG (PD-ON – PD-OFF)	-26.563	-4.594	0.00026
age	-0.2379	-1.639	0.11958
sex	-2.8391	-1.645	0.11825
education	0.20595	0.515	0.61327
LEDD	-0.0049	-1.72	0.10351
head motion	-24.364	-1.179	0.25463
	beta	t-value	p-value
rSTN_dl-IIFG (PD-ON – PD-OFF)	-7.391	-1.803	0.0882
age	-0.2274	-1.159	0.2615
sex	0.24433	0.109	0.9147
education	0.29977	0.562	0.5811
LEDD	-0.0055	-1.511	0.1482
head motion	7.02382	0.274	0.7873
	beta	t-value	p-value
rSTN_dl-ISTG (PD-ON – PD-OFF)	-38.711	-5.556	3E-05
age	0.01019	0.073	0.9425
sex	3.02379	1.85	0.0818
education	0.3612	1.02	0.3219
LEDD	-0.0012	-0.444	0.6625
head motion	10.3919	0.618	0.5446

Supplementary Table 6 Multiple linear regression analysis revealed that baseline (PD-OFF) UPDRS predicts the effect of dopaminergic medication (PD-ON – PD-OFF) on UPDRS after controlling age, sex, education, LEDD and medication order. PD-OFF: Parkinson’s disease OFF medication; PD-ON: Parkinson’s disease ON medication; LEDD: levodopa equivalent daily dosage; UPDRS: the Movement Disorders Society-Unified Parkinson’s disease Rating Scale motor assessment.

	beta	t-value	p-value
UPDRS (PDOFF)	-0.33	-2.7	0.01
Age	-0.13	-0.65	0.52
Sex	-2.15	-0.98	0.34
Education	0.77	1.42	0.17
LEDD	-0.01	-2.21	0.04
Order	-3.51	-1.43	0.17

Supplementary Table 7 Multiple linear regression analysis revealed that baseline (PD-OFF) oSDMT predicts the effect of dopaminergic medication (PD-ON – PD-OFF) on oSDMT after controlling age, sex, education, LEDD and medication order. PD-OFF: Parkinson’s disease OFF medication; PD-ON: Parkinson’s disease ON medication; LEDD: levodopa equivalent daily dosage; oSDMT: oral the Symbol Digit Modalities Test.

	beta	t-value	p-value
oSDMT (PDOFF)	-0.32	-2.87	0.01
Age	-0.31	-1.47	0.16
Sex	-3.28	-1.45	0.16
Education	0.85	1.48	0.15
LEDD	0.001	0.18	0.85
Order	3.49	1.26	0.22

Supplementary Table 8. Medication-induced changes in STN-Language ROI FC (PDON-PDOFF) predicts medication-induced changes in oSDMT performance (PDON-PDOFF) (controlling age, sex, education, LEDD, head motion and medication order).

	beta	t-value	p-value
ISTN_di-IIFG (PDON - PDOFF)	-7.860	-2.136	0.048
age	-0.177	-0.906	0.378
sex	-0.161	-0.075	0.942
education	0.347	0.615	0.547
LEDD	-0.004	-0.991	0.336
head motion	3.120	0.123	0.904
order	2.398	0.884	0.389
	beta	t-value	p-value
ISTN_di-ISTG (PDON - PDOFF)	-26.361	-4.321	0.001
age	-0.234	-1.540	0.143
sex	-2.806	-1.567	0.137
education	0.233	0.520	0.610
LEDD	-0.005	-1.584	0.133
head motion	-24.019	-1.122	0.278
order	0.334	0.153	0.881
	beta	t-value	p-value
rSTN_di-IIFG (PDON - PDOFF)	-7.363	-1.778	0.093
age	-0.199	-0.991	0.336
sex	0.387	0.170	0.867
education	0.463	0.804	0.433
LEDD	-0.005	-1.221	0.239
head motion	7.472	0.288	0.777
order	2.254	0.803	0.433
	beta	t-value	p-value
rSTN_di-ISTG (PDON - PDOFF)	-39.350	-5.940	2E-05
age	0.054	0.401	0.694
sex	3.243	2.083	0.054
education	0.580	1.612	0.127
LEDD	0.000	-0.039	0.969
head motion	10.740	0.673	0.510
order	2.981	1.693	0.110