SUPPLEMENTARY MATERIAL

MRI

Controls were MRI scanned on a 3T MRI Prisma scanner (Siemens, Erlangen, Germany) using a 64-channel head coil to obtain structural T1 and T2 weighted whole brain images.

For reasons of relative MRI contraindication in individuals with implanted DBS hardware and artefacts in scans with DBS implants, we used the pre-operative T2 weighted MRI scan of the PD patients for delineation of regions of interest. These scans had all been conducted on a 1.5 T MRI system. The average time interval between the structural MRI and the PET scan was 2.6 ± 1.8 years.

To evaluate the impact on PET outcomes using either T1 or T2 weighted MR images, we processed the PET data twice, using either the T1 or T2 weighted images as available, in nine controls. Since we found no significant difference in either $BP_{ND}0$ or $BP_{ND}1$ whether T1 or T2 was applied when analyzed with paired t-test of neocortex, we used the T2 weighted images for the analyses in all participants except for one control and one PD patient where only the T1 weighted MRI were available.

PET

PET scanning was conducted using a high-resolution research tomography (HRRT) PET scanner (CTI/Siemens, Knoxville, TN, USA). The dynamic data acquisition scanning protocol for [^{11}C]AZ10419369 was started after an intravenous [^{11}C]AZ10419369 bolus, injected over 20 seconds. The scan-time in the healthy volunteers was 120 min (n=5), 110 min (n=1), 90 min (n=3) and 60 min (n=1). According to Da Cunha-Bang et al (2016) this difference in scan time does not change BP_{ND} outcome for young healthy subjects. The scan time was 120 min in all PD patients (n=13). Depending on the duration of the PET scan, [^{11}C]AZ10419369 images were reconstructed into 45 (or 39) dynamic frames (6 x 10 s, 6 x 20 s, 6 x 60 s, 8 x 120 s, 19 (or 13) x 300 s) using ordinary Poisson 3-dimensional ordered-subset expectation maximization with point spread function modeling (16 subsets, 10

iterations) (Hong et al., 2007; Sureau et al., 2008), with attenuation correction as previously detailed (Sureau et al., 2008; Keller et al., 2013).

After reconstruction, all PET images were motion corrected using the AIR (Automated Image Registration, v.5.2.5, LONI, UCLA) software(Woods et al., 1998) with alignment to frame 27 (first frame of 300 seconds). All time-activity and motion curves were visually inspected to identify possible head movements. Sudden head motion was identified in 6 of 13 PD patients; in these patients the PET scan was re-reconstructed using HRRT Users Software with alignment of transmission data to emission data before reconstruction, in accordance to method described in Keller et al (2012). Briefly, the μ-map for attenuation correction was aligned with the PET reference frame 27 using Vinci 2.55 (http://vinci.sf.mpg.de/). Secondly, the motion was recomputed and a new reconstruction from PET raw data was performed with the μ-map aligned to each frame for optimal attenuation correction.

The PET images were co-registered and aligned to the subject's T2-weighted MRI image and VOIs were automatically delineated (Svarer et al., 2005). Each co-registration was verified by visual inspection before extraction of time-radioactivity curves (TACs) from the gray matter of the regions of interest (VOIs), and adjusted if needed, using the Hammer's atlas (Hammers et al., 2002) and PVElab (Svarer et al., 2005) (https://nru.dk/pveout) software. For the caudate, putamen and thalamus VOIs both gray and white matter were included, while in the remaining VOIs, BP_{ND} was extracted from grey matter only. The cerebellum was used as an reference region, as the amount of 5-HT_{1B} receptors in the cerebellum is insignificant (Varnäs et al., 2004).

The injected dose (MBq) was 587 [513-611] in healthy controls and 597 [588-604] in PD patients, and the injected mass was 1.92 [0.41-4.98] and 2.02 [0.82-4.59] respectively. The specific molar activity at time of injection (GBq/μmol) was 224 [48-690] in healthy controls and 193 [61-340] in PD patients. There was no significant difference between groups of patients and healthy controls when analyzed with student's unpaired t-test.

Figure A illustrates the median head motion of participants during the longitudinal course of the PET scan. Not unexpectedly, patients with Parkinson's disease generally exhibited greater head motion than controls. Towards the end of the PET scan, the difference in head movement between groups is up to 1 mm. When data was truncated, with exclusion of the last 30 minutes (6 frames, 1800 seconds) and remodeled accordingly, $BP_{ND}1$ did,

however, not change. Also, in 6 of 13 patients with Parkinson's disease where we corrected for movements by applying a new μ-map for attenuation correction, the outcome of BP_{ND}'s was unaltered. Figure B illustrates an example of an ESRTM model fitted TAC.

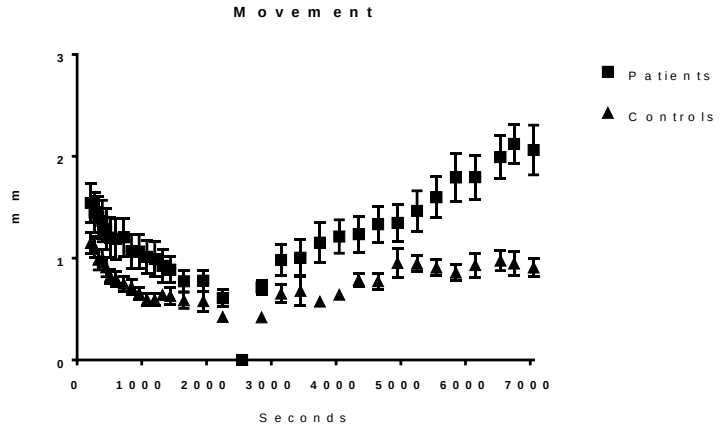

Figure A. Head movements during scan.

The mean ± SD of the participants median head movement in each frame 1-45 normalized to frame 30, where DBS was turned off in PD patients.

Quantification of [^{11}C]AZ10419369 Binding

The TACs were fitted using the Extended Simplified Reference Tissue Model (ESRTM) (Zhou et al., 2006) with the DBS intervention time at 45 minutes to estimate binding potentials BPnd's before and after intervention $BP_{ND}0$ and $BP_{ND}1$ (Figure B). For evaluation of the quality of fit the coefficient of variation for each $BP_{ND}0$ and $BP_{ND}1$ were also estimated. Parameter estimation was performed in Matlab v. 2013a (Mathworks Inc., MA, USA) and all fits were visually inspected. Frames acquired during time interval 0-44 min formed the basis for calculation of $BP_{ND}0$, and frames acquired during time interval 45-rest of scan for the calculation of $BP_{ND}1$ corresponding to the two conditions (DBS-ON and DBS-OFF). The ESRTM model parameters R1 and k2 are also estimated, but assumed to be constant during the scan time period.

Since five controls were PET-scanned for less than 120 minutes, we investigated the time stability of [^{11}C]AZ10419369 ESRTM modeling by truncating the dataset to simulate shorter scans (90 min). This did not change the $BP_{ND}1$, so the full dataset was used in all participants, regardless of scan time.

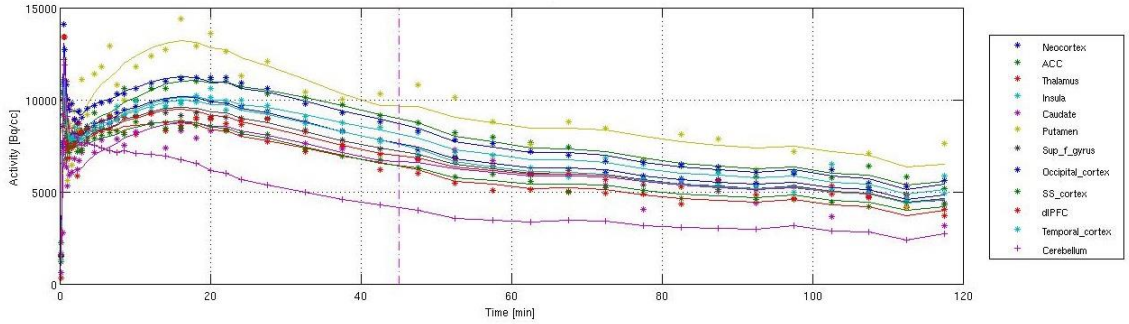

Figure B. Example of ESRTM fitted TACs in a PD patient.

The DBS was turned off at 45 minutes (dotted vertical line) and using cerebellum as the reference region for the ESRTM $BP_{ND}0$ (0-44 min) and $BP_{ND}1$ (45 – rest of scan) were estimated.

Turning the STN-DBS off

When the DBS stimulator was turned off in the patients, we observed a significant decrease in BP_{ND} in the temporal, limbic and occipital cortex (Table 2 and Figure C). The controls did not show any significant changes in $BP_{ND}0$ vs. $BP_{ND}1$.

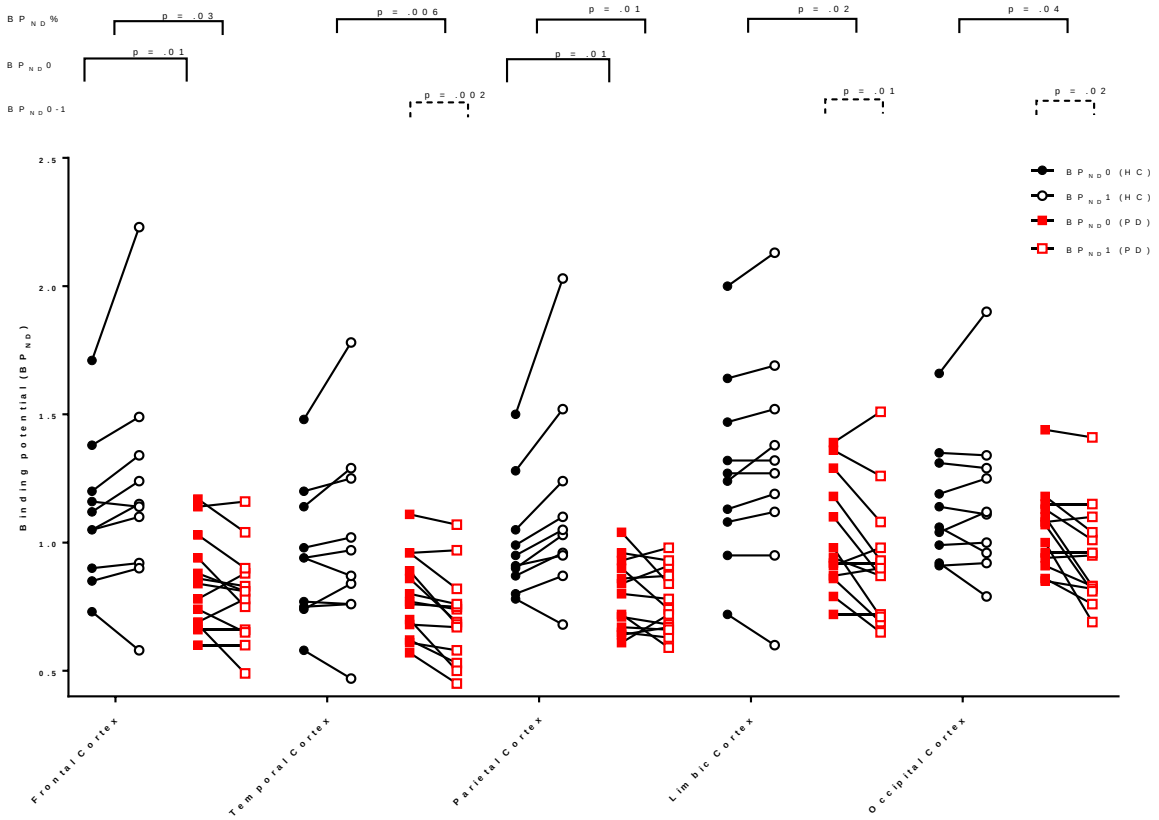

Figure C. BP_{ND} in primary regions of interests. $BP_{ND}0$ (filled circles) and $BP_{ND}1$ (empty circles) in primary VOIs in PD patients (red) and HC (black). At top, significant differences in $BP_{ND}0$ and $BP_{ND}1$ within group (dottet brackets) and in $BP_{ND}0$ and percentual change in BP_{ND} between groups (square), are shown.

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PET data (HC and DBS-STN treated PD patients) and reliability analysis of within-scan challenge with ESRTM

	Healthy controls (HC)				**Parkinson patients (PD)**				**Group-difference**	**Test-retest**		
									ΔBP_{ND} (%)	HC	HC	PD
	$BP_{ND}0$	$BP_{ND}1$	p-val	ΔBP_{ND} (%)	$BP_{ND}0$	$BP_{ND}1$	p-val	ΔBP_{ND} (%)	p-val	VAR[1]	ICC	Req (n)
FC	1.12 ± 0.27	1.21 ± 0.42	.12	6 ± 12	0.85 ± 0.17	0.80 ± 0.17	.08	-5 ± 11	.03*	0.10 ± 0.08	0.93	13
TC	0.95 ± 0.25	1.00 ± 0.35	.21	3 ± 11	0.79 ± 0.15	0.71 ± 0.17	.002 **	-11 ± 9	.006*	0.04 ± 0.04	0.96	5
PC	1.00 ± 0.21	1.13 ± 0.36	.02	12 ± 12	0.79 ± 0.13	0.77 ± 0.12	.33	-2 ± 11	.01*	0.12 ± 0.07	0.89	56
LC	1.28 ± 0.34	1.32 ± 0.40	.17	2 ± 7	1.02 ± 0.21	0.93 ± 0.23	.01 *	-9 ± 12	.02*	0.05 ± 0.05	0.99	3
OC	1.16 ± 0.22	1.17 ± 0.29	.74	0 ± 8	1.06 ± 0.16	0.95 ± 0.19	.02 *	-8 ± 9	.04*	0.06 ± 0.05	0.97	4
Neo	1.05 ± 0.24	1.13 ± 0.37	ns	6 ± 10	0.84 ± 0.14	0.78 ± 0.15	.03	-7 ± 10	.009	0.09 ± 0.07	0.94	7
SFG	1.07 ± 0.25	1.15 ± 0.39	ns	5 ± 13	0.80 ± 0.20	0.74 ± 0.14	ns	-6 ± 12	ns	0.10 ± 0.09	0.94	16
PMC	1.11 ± 0.27	1.22 ± 0.44	ns	7 ± 14	0.86 ± 0.19	0.80 ± 0.20	ns	-6 ± 16	ns	0.12 ± 0.08	0.92	13
dlPFC	1.12 ± 0.31	1.24 ± 0.47	ns	8 ± 14	0.75 ± 0.22	0.70 ± 0.17	ns	-2 ± 20	ns	0.14 ± 0.06	0.93	21
vlPFC	1.26 ± 0.32	1.40 ± 0.49	.04	9 ± 12	1.02 ± 0.19	0.99 ± 0.20	ns	-2 ± 11	.05	0.13 ± 0.07	0.93	39
MIFG	1.19 ± 0.29	1.31 ± 0.46	ns	8 ± 12	0.90 ± 0.18	0.87 ± 0.18	ns	-2 ± 12	ns	0.11 ± 0.07	0.68	144
OFG	1.00 ± 0.27	1.04 ± 0.36	ns	4 ± 19	0.86 ± 0.19	0.78 ± 0.25	.03	-11 ± 14	.05	0.14 ± 0.11	0.89	16

STG	0.97 ± 0.31	1.04 ± 0.43	ns	4 ± 12	0.79 ± 0.18	0.67 ± 0.17	.002	-15 ± 10	.002	0.10 ± 0.07	0.96	3
MITG	0.94 ± 0.22	0.97 ± 0.29	ns	2 ± 10	0.80 ± 0.14	0.75 ± 0.16	ns	-6 ± 8	.04	0.08 ± 0.07	0.89	15
SSC	1.00 ± 0.24	1.10 ± 0.38	ns	8 ± 12	0.73 ± 0.19	0.68 ± 0.18	.04	-5 ± 15	.03	0.11 ± 0.08	0.92	16
ACC	1.38 ± 0.33	1.45 ± 0.45	ns	2 ± 11	1.09 ± 0.23	1.01 ± 0.24	ns	-7 ± 10	ns	0.08 ± 0.08	0.97	5
PCC	0.89 ± 0.21	0.82 ± 0.21	ns	-5 ± 11	0.88 ± 0.19	0.75 ± 0.21	.02	-17 ± 15	ns	0.10 ± 0.09	0.83	7
Ins	1.23 ± 0.36	1.24 ± 0.37	ns	1 ± 6	0.99 ± 0.21	0.88 ± 0.24	ns	-11 ± 13	.01	0.04 ± 0.04	0.99	3
Cau	1.07 ± 0.37	1.24 ± 0.66	ns	8 ± 21	0.66 ± 0.28	0.68 ± 0.24	ns	2 ± 29	ns	0.15 ± 0.14	0.91	214
Put	1.42 ± 0.46	1.74 ± 0.68	.004	20 ± 13	1.25 ± 0.25	1.32 ± 0.36	4 ± 12	4 ± 12	.01	0.19 ± 0.09	0.89	42
Tha	0.55 ± 0.14	0.63 ± 0.40	ns	-3 ± 14	0.49 ± 0.12	0.43 ± 0.16	-16 ± 21	-16 ± 21	ns	0.13 ± 0.10	0.96	7

Abbreviations: frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), limbic cortex (LC), neocortex (Neo), superior frontal gyrus (SFG), primary motor cortex (PMC), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), medial inferior frontal gyrus (MIFG), orbitofrontal gyrus (OFG), superior temporal gyrus (STG), medial inferior temporal gyrus (MITG), somatosensory cortex (SSC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insular cortex (Ins), caudate (Cau), putamen (Put) and thalamus (Tha)

The $BP_{ND}0$ (0-44 minutes) and $BP_{ND}1$ (45 minutes – rest of scan) for healthy controls and PD, where DBS-STN was turned off in PD patients at 45 minutes. The BP_{ND} (%) was calculated as ($BP_{ND}1$-$BP_{ND}0$)/$BP_{ND}0$)*100%. Values are given as mean ± SD. Primary VOIs (n=5) that survived multiple comparisons are labelled for significance level $p < .05$ (*) and $p < .01$ (**). The test-retest analysis within-scan are shown with reliability analysis of the BP_{ND} in healthy controls, given as the intercorrelation coefficient (ICC) for average measures using two-way ANOVA absolute agreement. The a priori required sample size to demonstrate the DBS-STN induced ΔBP_{ND}(%) in PD patients are computed with power 0.8, significance level 0.05 and effect size calculated from group parameters of mean±SD

(matched pairs) and the ICC. [1]VAR statistics calculated as [(Abs($BP_{ND}0$-$BP_{ND}1$) / Average ($BP_{ND}0$-$BP_{ND}1$)], given as $VAR_{Average}$ ± SD for HC (n=10) for each region of interest.

Table B. Volumes

	Grey matter volumes			Relative volumes (%)		
	HC	PD	p-val	HC	PD	p-val
FC	127.5 ± 18.5	118.9 ±36.7	ns	8.6 ± 0.7	7.7 ± 2.2	ns
TC	67.1 ± 8.8	68.2 ± 13.8	ns	4.5 ± 0.3	4.5 ± 0.8	ns
PC	50.9 ± 10.7	43.5 ± 17.5	ns	3.4 ± 0.6	2.8 ± 1.1	ns
LC	26.4 ± 2.9	28.4 ± 4.4	ns	1.8 ± 0.1	1.9 ± 0.2	ns
OC	37.4 ± 8.4	39.3 ± 12.3	ns	2.5 ± 0.4	2.6 ± 0.7	ns
Neo	308.2 ± 49.6	295.9 ± 85.7	ns	20.7 ± 2.1	19.3 ± 5.2	ns
SFG	37.8 ± 5.6	33.5 ± 11.0	ns	2.5 ± 0.2	2.2 ± 0.7	ns
dlPFC	16.1 ± 3.0	14.3 ± 5.1	ns	1.1 ± 0.1	0.9 ± 0.3	ns
vlPFC	9.6 ± 1.3	9.6 ± 0.2.8	ns	0.6 ± 0.04	0.6 ± 0.2	ns
MIFG	48.6 ± 8.0	45.4 ± 15.2	ns	3.3 ± 0.3	3.0 ± 0.9	ns
OFG	15.3 ± 1.3	16.1 ± 2.8	ns	1.0 ± 0.1	1.0 ± 0.2	ns
STG	29.4 ± 4.8	29.3 ± 6.6	ns	2.0 ± 0.2	1.9 ± 0.4	ns
MITG	37.2 ± 4.2	38.9 ± 7.3	ns	2.5 ± 0.2	2.5 ± 0.4	ns
SSC	28.1 ± 8.2	23.8 ± 12.9	ns	1.9 ± 0.4	1.5 ± 0. 8	ns
ACC	5.9 ± 0.7	6.8 ± 1.1	.03	0.4 ± 0.02	0.4 ± .1	.03
PCC	4.3 ± 0.9	3.6 ± 1.1	ns	0.3 ± 0.04	0.2 ± 0.1	.05
Ins	11.1 ± 1.0	12.8 ± 2.0	.02	0.7 ± 0.04	0.8 ± 0.1	.03
Cau	3.5 ± 0.6	2.7 ± 1.1	.04	0.2 ± 0.04	0.2 ± 0.1	ns
Put	2.0 ± 0.7	1.7 ± 2.1	ns	0.1 ± 0.1	0.1 ± 0.1	ns
Tha	4.0 ± 1.0	3.6 ± 1.6	ns	0.3 ± 0.1	0.2 ± 0.1	ns

Abbreviations: frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), limbic cortex (LC), neocortex (Neo), superior frontal gyrus (SFG), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), medial inferior frontal gyrus

(MIFG), orbitofrontal gyrus (OFG), superior temporal gyrus (STG), medial inferior temporal gyrus (MITG), somatosensory cortex (SSC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insular cortex (Ins), caudate (Cau), putamen (Put) and thalamus (Tha)

The grey matter (GM) volumes in mL and relative volumes (% of GM, WM and CSF total brain volume) are given for each VOI, listed as Average ± SD for healthy controls (HC) and Parkinson patients (PD). The T-test was used to test for group differences in volumes between HC and PD with a significance level $p < .05$. There was no trend or significant group difference in volumes in primary VOIs, and none survived multiple comparisons in the post hoc analyses.