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Effect of STN DBS on vesicular monoamine transporter 2 and glucose metabolism in Parkinson's disease

Gwenn S. Smith[a,g,*,1], Kelly A. Mills[b,1], Greg M. Pontone[a,b], W. Stanley Anderson[c,d], Kate M. Perepezko[a], James Brasic[e], Yun Zhou[e], Jason Brandt[a,b], Christopher R. Butson[f], Daniel P. Holt[g], William B. Mathews[g], Robert F. Dannals[g], Dean F. Wong[a,b,e,h], Zoltan Mari[b,i]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[d] Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[e] Section of High Resolution Brain PET, Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[f] Scientific Computing & Imaging (SCI) Institute, Departments of Biomedical Engineering, Neurology, Neurosurgery & Psychiatry, University of Utah, USA
[g] Division of Nuclear Medicine and Molecular Imaging, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[h] Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[i] Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA

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ABSTRACT

Introduction: Deep brain stimulation (DBS) is an established treatment Parkinson's Disease (PD). Despite the improvement of motor symptoms in most patients by sub-thalamic nucleus (STN) DBS and its widespread use, the neurobiological mechanisms are not completely understood. The objective of the present study was to elucidate the effects of STN DBS in PD on the dopamine system and neural circuitry employing high-resolution positron emission tomography (PET) imaging. The hypotheses tested were that STN DBS would decrease striatal VMAT2, secondary to an increase in dopamine concentrations, and would decrease striatal cerebral metabolism and increase cortical metabolism.

Methods: PET imaging of the vesicular monoamine transporter (VMAT2) and cerebral glucose metabolism was performed prior to DBS surgery and after 4–6 months of STN stimulation in seven PD patients (mean age 67 ± 7).

Results: The patients demonstrated significant improvement in motor and neuropsychiatric symptoms after STN DBS. Decreased VMAT2 was observed in the caudate, putamen and associative striatum and in extra-striatal, cortical and limbic regions. Cerebral glucose metabolism was decreased in striatal sub-regions and increased in temporal and parietal cortices and the cerebellum. Decreased striatal VMAT2 was correlated with decreased striatal and increased cortical and limbic metabolism. Improvement of depressive symptoms was correlated with decreased VMAT2 in striatal and extra-striatal regions and with striatal decreases and cortical increases in metabolism.

Conclusions: The present results support further investigation of the role of VMAT2, and associated changes in neural circuitry in the improvement of motor and non-motor symptoms with STN DBS in PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of adults over age 60, and is associated with significant morbidity and early mortality [1]. The primary pharmacotherapy for motor symptoms, including rigidity, bradykinesia, and resting tremor, is dopamine replacement with levodopa [2]. With disease progression, the duration of therapeutic benefit from levodopa

* Corresponding author. Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Drive, 4th floor, Baltimore, MD, 21224, USA.
E-mail address: gsmith95@jhmi.edu (G.S. Smith).
[1] Authors contributed equally to the manuscript.

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shortens and susceptibility to levodopa-induced dyskinesias increases [3]. PD patients with fluctuations in motor symptom control from levodopa, levodopa-induced dyskinesia, or medication-refractory tremor often benefit from deep brain stimulation (DBS). The sub-thalamic nucleus (STN) is the most common DBS target in PD. STN stimulation is associated with improvement in motor symptoms and reduction of levodopa dose, but also variable non-motor (cognitive and mood) effects [4]. Despite the improvement of motor symptoms in most patients after STN DBS and its widespread use and cost-effectiveness, its neurobiological mechanisms are not completely understood.

Positron emission tomography (PET) imaging has advanced the understanding of the neural circuitry and neurochemical mechanisms underlying motor and non-motor symptoms in PD, as well as the effects of pharmacologic and surgical interventions (including STN DBS). PET studies have shown that STN DBS decreased glucose metabolism in frontal, thalamic and striatal regions and increased metabolism in motor cortex, temporal and parietal cortical regions and the cerebellum [5,6]. Studies of the dopamine system have employed a well-established paradigm to image endogenous dopamine concentrations with the striatal $D_{2/3}$ radiotracer [^{11}C]-raclopride or the dopamine metabolism radiotracer [^{18}F]-fluorodopa [7–9]. As motor and non-motor symptoms in PD improve with higher brain dopamine concentrations, increased dopamine concentrations could explain symptomatic improvement following STN DBS. Despite improvement in motor symptoms, the majority of studies showed no decreases in striatal $D_{2/3}$ receptor availability and no increases in dopamine metabolism comparing on to pre surgery or to off STN DBS (ranging 1–12 h OFF DBS) [7,8]. One study showed a variable, non-significant decrease in putaminal [^{11}C]-raclopride binding comparing DBS on versus off STN DBS [10].

Given the relative lack of sensitivity of radiotracers for the $D_{2/3}$ receptors or dopamine metabolism to DBS-induced changes, the present study focused on the vesicular monoamine transporter (VMAT2) to measure the effects of STN DBS on the dopamine system. (+)-[11C] Dihydrotetrabenazine ((+)-[11C]DTBZ) is a well-characterized radiotracer that binds to the intra-vesicular site of VMAT2 and is sensitive to decreases associated with aging and PD, consistent with neuropathological data [11]. Initial studies in rats showed that [^{11}C]DTBZ was not affected by increases in dopamine (possibly due to the relatively low drug doses administered). Subsequent studies in rats and humans have shown that decreases in dopamine are associated with increases in VMAT2 and increases in dopamine are associated with decreases in VMAT2 [12]. Importantly, dose and time dependent decreases in VMAT2 were observed after levodopa administration in patients with PD [13,14].

Motor and non-motor-symptoms, VMAT2 and cerebral glucose metabolism were measured pre-operatively and on STN DBS in patients with PD. The primary hypotheses tested were that after 4–6 months of continuous, stable STN DBS at optimal stimulation levels 1) decreased VMAT2, secondary to an increase in dopamine concentrations, will be observed in striatal and cortical regions and 2) cerebral glucose metabolism will be decreased in the striatum and increased in cortical regions. The exploratory hypotheses were tested that decreased striatal VMAT2 will be correlated with decreased striatal and increased cortical metabolism and with improvements in motor and non-motor symptoms.

2. Methods

2.1. Participant screening and selection

Seven patients who were evaluated in the Johns Hopkins Neuromodulation and Advanced Treatments Clinic in the Division of Movement Disorders, Department of Neurology, and were diagnosed with idiopathic PD, based on the UK Brain Bank Criteria were enrolled [15]. All PD patients were reviewed at a multi-disciplinary DBS case conference to determine DBS candidacy, procedure type, brain target and laterality (unilateral vs. bilateral). Patients with PD for whom the consensus decision was bilateral STN DBS surgery and who were scheduled for surgery were asked about their interest in participating in the PET study.

All PD patients met standard DBS criteria (Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD) and NICE criteria ([16], https://www.nice.org.uk/guidance/ipg19). DBS candidates had complications of medical therapy ('wearing-off', levodopa-induced-dyskinesias, other medication side effects) or limited benefit from using adequate medication dosages [17]. Exclusionary criteria for the PET study included diabetes (not controlled by diet), another neurological diagnosis (e.g. stroke) and severe tremor/dystonia of the upper body/head. The study protocol and consent forms were approved by the Institutional Review Board and the Radiation Research Committee of the Johns Hopkins University School of Medicine.

2.2. Surgical placement of DBS, lead localization and dosing

STN DBS surgery was performed using the traditional stereotactic frame-based procedure with intraoperative microelectrode recordings, microstimulation, and test macrostimulation [18]. A monopolar review was performed upon device activation 4 weeks later. If symptoms were inadequately controlled after the initial programming, slight adjustments were made until the DBS was optimized, according to criteria consistent with other studies: a) lack of DBS-induced side effects such as slurred speech or tonic muscle contraction and b) subjective improvement in 'off' time symptoms between medication doses, reduction of medication-refractory tremor, and/or reduction of dyskinesia. The post-operative PET scans were scheduled about 4–6 months after optimal stimulation was achieved. All subjects underwent PET scans before DBS surgery and then after DBS surgery with stimulation on. The last three subjects had additional scans after DBS surgery, but with STN DBS off (2 h off in two subjects, and 12 h off in one subject). Following STN DBS withdrawal, the effects on the majority of motor symptoms wash-out by approximately 5 min and then reach a plateau by 30 min [19]. Twelve hours off STN DBS was the longest interval feasible off-stimulation that could be tolerated for most advanced patients who require DBS. Glucose metabolism has been shown to return to pre-operative levels by this time [5]. Lead localization was performed using post-operative CT scans merged with pre-operative MRI's [20].

2.3. Clinical and cognitive assessments

After each PET scan session, PD patients underwent the following tests: Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale (MDS-UPDRS), Neuropsychiatric Inventory (NPI) and the Hamilton Depression Rating scale (HDRS) [21–23]). Cognitive assessments included Delis-Kaplan Executive Function System letter and category fluency, verbal and visual-spatial memory (California Verbal Learning Test; CVLT-First Edition and the Brief Visual Memory Test; BVMT-R) [24–26]. Alternate forms were administered. A neurologist with considerable expertise in the assessment of PD patients (who completed the MDS-UPDRS training program) administered the MDS-UPDRS and clinical measures. The cognitive assessments were administered by trained psychometricians. The raters were not blind to DBS status. Paired-T-tests were used to determine whether the difference in the clinical and cognitive measures before STN DBS compared to after STN DBS on stimulation was significantly different. Age and disease progression were not included in the statistical models because the scans were performed within a relatively short timeframe (4–6 months).

2.4. MR imaging procedures

MR scans were acquired using a Siemens 3.0T TrioTrim MRI

(Siemens Healthcare, Tübingen, Germany). The magnetization-prepared rapid acquisition with gradient echo (MPRAGE) pulse sequence before DBS surgery was used for MR to PET co-registration and volume of interest (VOI) analysis.

2.5. PET imaging procedures and image analysis

PET scans were acquired with a second-generation High Resolution Research Tomograph scanner (HRRT, Siemens Healthcare, Knoxville, TN), a dedicated brain PET scanner. The patients took their last dose of levodopa and dopamine agonist 12 h before the PET scans as is typically done in PET studies [6].

[^{11}C] dihydrotetrabenazine ([^{11}C]DTBZ) was used to measure VMAT2 (injected dose 15 mCi ± 10%). The outcome measure was the distribution volume ratio (DVR) that was calculated from the 60-min dynamic acquisition using the occipital cortex as the input function. [^{18}F]-2-deoxy-2-fluoro-D-glucose ([^{18}F]FDG) was used to measure cerebral glucose metabolism (injected dose 5 mCi ± 10%). The outcome measure was the standardized uptake value (SUV) that was calculated from a 10-min frame acquired 40–50 min post injection.

Pre-processing and voxel-wise statistical analyses of the images were performed with statistical parametric mapping, version 8 (SPM8, Institute of Neurology, London). Details regarding these methods are provided in the Supplementary Materials Section. For all voxel-wise analyses, the results reported are significant at a cluster-level $p \leq 0.001$ (FDR corrected) and peak voxel-value of $p \leq 0.001$ (uncorrected) and extent threshold (k) = 50 voxels. For the primary analyses, a within-subjects comparison of the VMAT2 and glucose metabolism images was performed using the paired *t*-test option in SPM8 to evaluate the differences between the baseline (pre-operative) scans and on STN DBS. For the exploratory analyses, covariate analyses were perform to evaluate 1) whether the covariate of the change in striatal VMAT2 contributed significant variance to the change in glucose metabolism and 2) whether the covariate of the change in the motor and cognitive and neuropsychiatric measures contributed significant variance to the change in striatal VMAT2 and change in glucose metabolism.

3. Results

3.1. Sample characteristics

Seven patients with PD were enrolled and completed all assessments, except one of the VMAT2 scans that was not completed pre-operatively in one patient who completed the rest of the PET scans (3 females/4 males, age 66 ± 7, age at onset 51 ± 10, duration 10 ± 6, Hoehn-Yahr Stage 2.5 ± 0.6). The interval between PET scan sessions was 141 ± 22 days (range 111–173). The stimulation settings and the reconstruction of the lead localization (Supplemental Table 1; Fig. 1) indicate that many of the active contacts were dorsal to the STN, which is a common target area used for maximal tremor benefit. Levodopa concentrations measured before and after the PET scans were low and could not be detected.

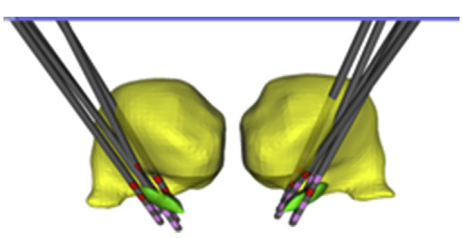

Fig. 1. Lead locations for STN DBS (bilateral stimulation) for 5 patients is shown. Sub-thalamic Nucleus (STN; green), Thalamus (yellow) and Active Cathodes on the DBS lead (red).

3.2. Motor, neuropsychiatric and neuropsychological measures

After 4–6 months on DBS compared to pre-operative assessments, the MDS-UPDRS motor score was significantly improved ($t(6) = 3.89$; $p < 0.005$; Table 1). All of the motor sub-scores showed a non-significant improvement, tremor to the greatest extent ($p > 0.05$). The NPI ($t(6) = 2.56$; $p < 0.05$) and HDRS ($t(6) = 3.99$; $p < 0.005$) showed significant improvement. All neuropsychological measures showed a non-significant worsening, after STN DBS, verbal fluency to a greater extent than memory ($p > 0.05$).

3.3. Striatal and extra-striatal VMAT2

After 4–6 months of STN DBS, VOI analyses demonstrated decreased VMAT2 distribution volume ratios (DVR's) in the striatal sub-regions (Table 2a). The decreases were statistically significant in the dorsal caudate ($t(5) = 2.94$; $p < 0.05$) and posterior caudate ($t(5) = 4.53$; $p < 0.01$), posterior putamen ($t(5) = 3.68$; $p < 0.05$) and associative striatum ($t(5) = 3.63$; $p < 0.05$), not the anterior putamen ($t(5) = 1.89$; $p > 0.05$) or ventral striatum ($t(5) = 2.27$; $p > 0.05$). Correlations were performed between the change in striatal VMAT2 sub-regions with change in the motor and non-motor measures. Improved tremor was correlated with decreased VMAT2 in motor sub-regions (striatum, putamen sub-regions; $r = 0.51$ to 0.81; $p < 0.05$). Less decline in letter fluency was correlated with greater decreases in VMAT2 in cognitive sub-regions (associative striatum and caudate sub-regions; $r = 0.43$ and 0.60, respectively; $p < 0.05$). Improved depression (HDRS) was correlated with greater decreases in VMAT2 in limbic and cognitive sub-regions (ventral striatum, caudate sub-regions; $r = 0.51$ to.081; $p < 0.05$).

Changes in striatal VMAT2 sub-regions are shown (Table 2b) for two patients who were scanned one hour off DBS and one patient who was scanned twelve hours off DBS, in addition to all three subjects also being scanned on DBS. The MDS-UPDRS Motor scores improved from pre-operatively to on DBS and worsened off DBS in all three patients (Patient 1: 32,17,42; Patient 2: 81,71,89; and Patient 3: 53, 11, 33). Comparable decreases in striatal VMAT2 were observed on and one hour off DBS relative to pre-operative levels. The decrease in striatal VMAT2 from pre-operative levels was greater on DBS versus twelve hours off DBS. Thus, the longer duration off DBS, striatal VMAT2 was closer to pre-operative levels, suggesting that comparison between pre-operative levels and on DBS 4–6 months after DBS initiation is likely measuring the effect of STN stimulation rather than that of surgery.

Decreased VMAT2 in the caudate and putamen, bilaterally, was also demonstrated by voxel-wise analyses (Table 3; Fig. 2). Decreased VMAT2 in extra-striatal regions, included the pre-central gyrus (BA 44/4), left insula (BA 13), left superior temporal gyrus (BA 22, 38), left amygdala, left precuneus (BA 7), left inferior parietal lobule (BA 40), left caudate (body), bilateral putamen and left lateral globus pallidus (values for the extra-striatal regions are shown in Supplemental Table 2). Changes in the right hemisphere were observed in these regions, but were not statistically significant at the threshold used. The magnitude decrease in representative extra-striatal regions ranged from −6 to −3% for inferior parietal lobule, insula, pre-central gyrus, amygdala, thalamus (pulvinar) and middle temporal gyrus, in order of magnitude decrease. Significant increases in VMAT2 were not observed. Exploratory, voxel-wise correlations between change in VMAT2 and change in tremor, letter fluency and depression were performed, but were significant only for depression. Significant correlations were observed between decreased VMAT2 and decreased HDRS in the superior frontal (BA 6/BA10), middle frontal (BA6/BA9) and middle temporal gyri (BA 39; all effects bilateral; data not shown).

3.4. Cerebral glucose metabolism

Decreases in cerebral metabolism were observed in the caudate (left

Table 1
Changes in Motor and Neuropsychiatric Symptoms and Cognition after 4–6 months of STN DBS in Parkinson's Disease Patients (Mean ± Standard deviations).

Name of Test	Pre-Operative	On STN DBS	% Change
MDS-UPDRS Motor Score (Part III)	57.3 ± 15.3	37.6 ± 20.0**	−25%
MDS-UPDRS Tremor Score	15.9 ± 9.3	10.4 ± 10.3	−44%
MDS-UPDRS Bradykinesia Score	17.4 ± 6.9	10.3 ± 4.5*	−34%
MDS-UPDRS Rigidity Score	13.6 ± 3.2	9.7 ± 6.0	−29%
MDS-UPDRS Axial Score	10.4 ± 3.3	8.4 ± 3.8	−17%
Neuropsychiatric Inventory (total score)	22.0 ± 24.6	12.1 ± 16.9*	−34%
Hamilton Depression Rating Scale	12.9 ± 4.1	7.4 ± 2.0**	−40%
Mini Mental State Examination	29 ± 0.8	28 ± 1.6	−3%
Total California Verbal Learning Test (CVLT) Score (Sum of Trials 1–5)	58.0 ± 9.2	51.8 ± 15.5	−11%
Brief Visuospatial Memory Test, Revised (Sum of Trials 1–3)	20.3 ± 9.3	20.3 ± 8.7	−7%
DKEFS Letter Fluency	45.6 ± 12.9	36.6 ± 13.9	−20%
DKEFS Category Fluency	42.0 ± 6.3	35.9 ± 9.6	−15%

D-KEFS™ = Delis-Kaplan Executive Function System™.
MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.
All assessments were performed off PD medications.
* Significant within group difference ($p < 0.05$).
** Significant within group difference ($p < 0.01$).

Table 2a
Changes in Striatal VMAT2 Availability after 4–6 months of STN DBS in Parkinson's Disease (Distribution Volume Ratios [DVR's] Mean ± Standard deviations).

Region	Pre-Oerative	On STN DBS	%Change
Dorsal Caudate	1.07 ± 0.44	0.86 ± .35*	−17 ± 15
Posterior Caudate	0.77 ± 0.37	0.40 ± 0.25**	−49 ± 22
Anterior Putamen	0.77 ± 0.13	0.71 ± 0.13	−7 ± 9
Posterior Putamen	0.54 ± 0.11	0.46 ± 0.08**	−15 ± 7
Associative Striatum	0.90 ± 0.33	0.69 ± 0.24*	−22 ± 11
Ventral Striatum	1.20 ± 0.31	1.08 ± 0.21	−9 ± 8

* Significant within group difference ($p < 0.05$).
** Significant within group difference ($p < 0.01$).

head, body), thalamus (right ventral anterior nucleus), sub-thalamic nucleus, left lateral globus pallidus and right putamen (results bilateral unless otherwise indicated; (Table 4; Fig. 2). Increases in cerebral metabolism were observed in the left insula (BA 13), superior temporal gyri (BA 22/38), right parahippocampal gyrus (BA 36), precuneus (BA 7/31), left inferior parietal lobule (BA 40), fusiform (BA 37), cerebellum (culmen and declive). Exploratory, voxel-wise correlations showed that improvement of depression was associated with decreased metabolism in the right thalamus (ventral lateral nucleus), left caudate (body) and right lateral globus pallidus and increased metabolism in the left pre-central (BA 4), left insula (BA 13), left superior temporal (BA 22), left middle temporal (BA 21), right precuneus (BA 7) right superior and inferior parietal lobule (BA 7, 40; data not shown).

3.5. Correlations between changes in striatal VMAT2 and changes in cerebral glucose metabolism

Decreased striatal VMAT2 was correlated with increased cerebral metabolism in the right insula (BA 13), superior temporal (BA 38/BA 39), middle temporal (BA 38/BA 22), right inferior temporal gyri (BA 20/BA 37), precuneus (BA 7), posterior cingulate (BA 31), inferior parietal lobule (BA 40), right fusiform (BA 37), right angular gyrus (BA 39), cerebellum (decline; results bilateral unless otherwise indicated; Supplementary Table 3). Correlations between decreased striatal VMAT2 and decreased cerebral metabolism were observed in the caudate (left body). A similar pattern of correlation was observed between VMAT2 in the associative striatum and increases and decreases in cortical metabolism (data not shown).

4. Discussion

A significant improvement in motor and non-motor symptoms (neuropsychiatric symptoms and depression) was observed after 3–4 months of continuous stable STN DBS, which was accompanied by a decrease in striatal and extra-striatal VMAT2 that was correlated with improved tremor and depression. The concentration of VMAT2 in the cortical and limbic extra-striatal regions is relatively low compared to the striatum. The ability to detect decreases in VMAT2 may be enhanced by the use of the high resolution PET scanner in the present study. Preliminary data showed that in a sub-sample of PD patients, striatal VMAT2 increased closer to pre-operative levels the longer the duration of STN DBS washout (12 versus 1 h). After STN DBS, decreases in striatal and thalamic glucose metabolism and increases in cortical and limbic glucose metabolism were correlated with decreased striatal VMAT2. The limitations of the study included the relatively small

Table 2b
Comparisons between Pre-Operative to Off and On STN DBS in Parkinson's Disease: Mean Percent differences in VMAT2 Distribution Volume Ratios (DVR) in striatal-sub-regions.

Comparison		CAD	DCA	PCA	PUT	ANP	POP	AST	VST	STR
1 Hr OFF (n = 2)	OFF versus Pre-Op	−46	−35	−78	−19	−15	−21	−39	−8	−30
	ON versus Pre-Op	−42	−32	−70	−15	−9	−19	−34	−13	−26
	ON versus OFF	**9**	**6**	**35**	**4**	**6**	**2**	**8**	**−1**	**5**
12 Hr OFF (n = 1)	OFF versus Pre-Op	−17	−7	−37	−5	0	−9	−14	−10	−13
	ON versus Pre-Op	−23	−15	−39	−11	−6	−17	−21	−11	−19
	ON versus OFF	**−7**	**−9**	**−4**	**−7**	**−6**	**−8**	**−7**	**−2**	**−7**

CAD = Caudate DCA = Dorsal CAD; PCA = Posterior CAD; PUT = Putamen; ANP = Anterior PUT; POP = Posterior PUT; AST = Associative STR; VST = Ventral STR; STR = Striatum.

Table 3
Decrease in VMAT2 availability after 4–6 Months of STN DBS in Parkinson's Disease: Voxel-wise Comparison of Pre-Operative to On STN DBS.

Left Hemisphere				Structure	Right Hemisphere			
X (mm)	Y (mm)	Z (mm)	Z-Score		X (mm)	Y (mm)	Z (mm)	Z-Score
−42	13	8	3.20	Pre-Central Gyrus (BA 44/4)	−53	−14	40	3.38
−44	−3	1	3.37	Insula (BA 13)				
−51	−11	8	3.26	Superior Temporal Gyrus (BA 22)				
−45	11	−6	3.04	Superior Temporal Gyrus (BA 38)				
−25	−6	−9	3.11	Amygdala				
−28	−63	36	3.71	Precuneus (BA 7)				
−39	−55	45	3.61	Inferior Parietal Lobule (BA 40)				
−14	−7	21	3.32	Caudate (Body)				
−29	−12	−3	2.92	Putamen	29	−11	−3	3.11
−21	−2	−7	3.67	Lateral Globus Pallidus				

Within-subject comparisons are reported that are significant at a cluster-level $p \leq 0.001$ (FDR corrected) and peak voxel-value of $p \leq 0.001$ (uncorrected).

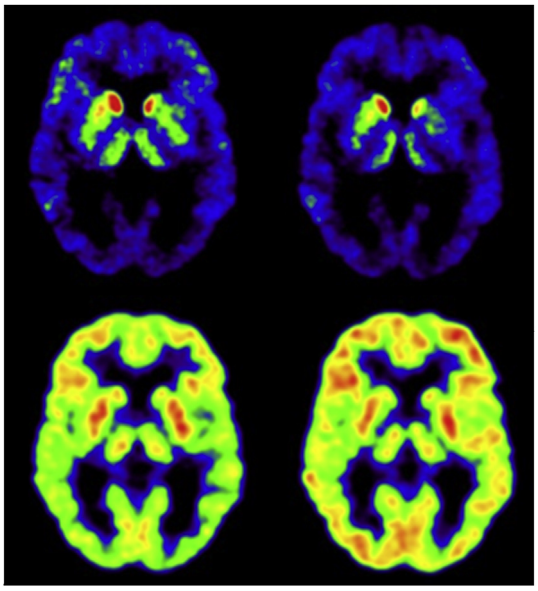

Fig. 2. PET VMAT2 and cerebral glucose metabolism scans from a PD patient (male, age 59) are shown (Pre-Operative and DBS ON scans) indicating decreased striatal VMAT2 (left panels) and cerebral glucose metabolism and increased iemporal and iarietal cerebral glucose metabolism ON STN DBS (right panels; Pre-Operative and DBS ON scans).

sample size and the limited data acquired with STN DBS off.

The observed motor, mood and cognitive effects of 4–6 months of continuous STN DBS are consistent with the previous reports of improvement in motor symptoms (rigidity, bradykinesia and resting tremor) and mood and slight worsening of specific cognitive functions (especially verbal fluency) [27]. Tremor, the focus of DBS programming in these patients, showed greater improvement than rigidity and bradykinesia. These patients had tremor as a significant portion of their preoperative motor disability, as opposed to other patients who would be referred for globus pallidus DBS.

The observed changes in glucose metabolism are consistent with most prior studies of STN DBS on cerebral blood flow and metabolism [5,6]. Increased metabolism in frontal cortical regions and decreased metabolism in striatal regions was correlated with improved depression. Decreased VMAT2 in total striatum and associative striatum were correlated with the increases and decreases in cerebral glucose metabolism in similar temporal, parietal, cerebellar and striatal regions, suggesting that modulation of dopamine by STN DBS has an effect on cortico-striatal circuits. Further, the regional difference in metabolism associated with STN DBS could be related to the broader pattern of compensatory hyperactivation in Parkinson disease. According to this hypothesis, prefrontal areas (with connectivity to the anterior putamen) are metabolically more active to compensate for deficits related to disease in other brain regions. Dopamine replacement, or in this case, STN DBS, decreases this compensatory hyperactivity in the putamen and frontal regions such as the DLPFC while increasing metabolic activity in regions that were previously deficient due to their heavier reliance on dopamine signaling [28].

Decreased VMAT2 was observed to a greater extent in caudate (dorsal and posterior), putamen (posterior) and associative striatum than other striatal sub-regions. A decrease in VMAT2 (and glucose metabolism) was observed in the lateral globus pallidus after STN DBS. Decreased pallidal VMAT2 in PD was shown in a recent study, which may explain why this region is affected by STN DBS [29]. The ventral striatum shows less of a change than the other striatal sub-regions, but does show a 9% decrease. The ventral striatum may show less change because it has less dopaminergic denervation in PD than the other striatal sub-regions, except in patients with impulse control disorders who show dopaminergic deficits in the ventral striatum [30]. The patients in the study did not have symptoms of impulse control disorders before or after the STN DBS. Voxel-wise analyses replicated the VOI results and also revealed decreased VMAT2 in cortical (frontal, temporal and parietal) and limbic (insula, amygdala) regions implicated in neuropsychiatric symptoms and neuropsychological deficits in PD [31]. Correlations were observed between decreased VMAT2 and tremor, but not with rigidity and bradykinesia. This may be due to the greater magnitude and variability of improvement in tremor compared to rigidity and bradykinesia. Improvement in depressive symptoms was correlated with decreased VMAT2 in frontal and temporal cortical regions and with decreased metabolism in striatum and thalamus and increased metabolism in frontal, temporal and parietal cortical regions.

In contrast to the lack of effect of STN DBS on striatal D2/3 availability or dopamine metabolism in previous studies, decreased striatal and extra-striatal VMAT2 was observed in the present study. The maximal decrease in VMAT2 was observed in comparing STN DBS on to pre-operative levels, not STN DBS off. While the comparison of STN DBS on to pre-operative levels may be more clinically meaningful, the comparison to the off state might take into account potential effects of surgery (implantation-related microlesion effects and focal edema), which should have been minimized by re-scanning patients 4–6 months after surgery, as was done in the present study. Age and disease progression should not have contributed to the VMAT2 results as the annual rate of change associated with each variable (−0.77% and −3%, respectively), is much less in magnitude than the decreases observed in the present study [32,33].

Time-dependent effects of STN DBS and levodopa on striatal VMAT2 have been observed [12–14], in contrast to the lack of effect on striatal $D_{2/3}$ receptor availability or dopamine metabolism [8–10]. The duration off DBS that is feasible to study in PD patients after months of chronic stimulation may not be sufficient for dopamine to return to baseline levels, even after 12 h when glucose metabolism has returned

Table 4
Changes in cerebral glucose metabolism after 4–6 months of STN DBS in Parkinson's Disease: Voxel-wise Comparison of Pre-Operative.to On STN DBS.

Left Hemisphere				Decreases in Metabolism	Right Hemisphere			
X (mm)	Y (mm)	Z (mm)	Z-Score	Structure	X (mm)	Y (mm)	Z (mm)	Z-Score
−3	2	1	3.19	Caudate (Head)				
−9	−1	15	3.32	Caudate (Body)	12	−1	19	4.86
				Thalamus (Ventral Anterior Nucleus)	16	−4	10	3.32
−12	−11	−2	4.19	Subthalamic Nucleus	16	−12	−6	3.06
−25	−20	−5	3.11	Lateral Globus Pallidus				
				Putamen	23	2	19	3.37
Left Hemisphere				**Increase in Metabolism**	**Right Hemisphere**			
X (mm)	Y (mm)	Z (mm)	Z-Score	Structure	X (mm)	Y (mm)	Z (mm)	Z-Score
−42	−29	19	2.93	Insula (BA 13)				
−59	−46	17	4.42	Superior Temporal Gyrus (BA 22/38)	33	15	−33	3.05
				Parahippocampal Gyrus (BA 36)	32	−32	−14	3.20
−17	−80	34	3.79	Precuneus (BA 7/31)	13	−58	22	3.56
−55	−43	24	3.73	Inferior Parietal Lobule (BA 40)				
−20	−81	−11	3.40	Fusiform Gyrus (BA 37)	28	−93	−11	3.56
−16	−59	−11	4.10	Cerebellum (Culmen)	32	−33	−20	2.89
−27	−65	−17	2.84	Cerebellum (Declive)	23	−71	−15	4.02

Within-subject comparisons are reported that are significant at a cluster-level $p \leq 0.001$ (FDR corrected) and peak voxel-value of $p \leq 0.001$ (uncorrected).

to pre-operative levels [5]. A study of nucleus accumbens DBS in obsessive-compulsive disorder showed minimal (< 10%) increase to baseline levels of striatal D2/3 receptors after 8 days off compared to on DBS [34]. In fact, persistent reductions in striatal $D_{2/3}$ availability after D-amphetamine have been observed, despite the return of dopamine to baseline levels confirmed by *in vivo* microdialysis [35].

In conclusion, decreases in striatal and extra-striatal VMAT2 with STN DBS were observed and correlated with clinical outcomes (improved tremor and depression) and changes in neural circuits known to be affected by STN DBS. Replicating the results in a larger sample would support the use of VMAT2 and glucose metabolism as neurobiological markers of motor and non-motor STN DBS effects for pre-operative patient selection and treatment response predictors. The multi-modality imaging approach could be applied to other DBS targets (globus pallidus) and network-based interventions (e.g. transcranial direct current stimulation, focused ultrasound, closed loop DBS). Elucidating the neurobiology of DBS in PD will inform development of more effective treatments, treatment response predictors and ultimately, will have implications for improving the clinical care of patients with network based disorders including PD, depression and Alzheimer's disease.

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Appendix A. Supplementary data

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References

[1] L.M. de Lau, M.M. Breteler, Epidemiology of Parkinson's disease, Lancet Neurol. 5 (6) (2006) 525–535.
[2] G.C. Cotzias, M.H. Van Woert, L.M. Schiffer, Aromatic amino acids and modification of parkinsonism, N. Engl. J. Med. 276 (7) (1967) 374–379.
[3] C.D. Marsden, J.D. Parkes, On/off effect in patients with PD on chronic levodopa therapy, Lancet 1 (1976) 292–296.
[4] A. Fasano, A. Daniele, A. Albanese, Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation, Lancet Neurol. 11 (5) (2012) 429–442.
[5] R. Hilker, J. Voges, S. Weisenbach, E. Kalbe, L. Burghaus, M. Ghaemi, R. Lehrke, A. Koulousakis, K. Herholz, V. Sturm, W.D. Heiss, Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease, J. Cereb. Blood Flow Metab. 24 (1) (2004) 7–16.
[6] K. Asanuma, C. Tang, Y. Ma, V. Dhawan, P. Mattis, C. Edwards, M.G. Kaplitt, A. Feigin, D. Eidelberg, Network modulation in the treatment of Parkinson's disease, Brain: J. Neurol. 129 (Pt 10) (2006) 2667–2678.
[7] G.S. Smith, S.L. Dewey, J.D. Brodie, et al., Serotonergic modulation of dopamine measured with [11C]raclopride and PET in normal human subjects, Am. J. Psychiatry 154 (4) (1997) 490–496.
[8] A. Abosch, S. Kapur, A.E. Lang, et al., Stimulation of the subthalamic nucleus in Parkinson's disease does not produce striatal dopamine release, Neurosurgery 53 (5) (2003) 1095–1102.
[9] N. Arai, F. Yokochi, T. Ohnishi, et al., Mechanisms of unilateral STN-DBS in patients with Parkinson's disease : a PET study, J. Neurol. 255 (8) (2008) 1236–1243.
[10] R. Hilker, J. Voges, M. Ghaemi, et al., Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans, Mov. Disord. 18 (2003) 41–48.
[11] K.A. Frey, R.A. Koeppe, M.R. Kilbourn, Imaging the vesicular monoamine transporter, Adv. Neurol. 86 (2000) 237–247.
[12] I. Boileau, S. Houle, P.M. Rusjan, et al., Influence of a low dose of amphetamine on vesicular monoamine transporter binding: a PET (+)[11C]DTBZ study in humans, Synapse (New York, NY) 64 (6) (2010) 417–420.
[13] R. de La Fuente-Fernandez, V. Sossi, S. McCormick, M. Schulzer, T.J. Ruth, A.J. Stoessl, Visualizing vesicular dopamine dynamics in Parkinson's disease, Synapse (New York, NY) 63 (8) (2009) 713–716.
[14] R. de La Fuente-Fernandez, S. Furtado, M. Guttman, et al., VMAT2 binding is elevated in dopa-responsive dystonia: visualizing empty vesicles by PET, Synapse (New York, NY) 49 (1) (2003) 20–28.
[15] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (3) (1992) 181–184.
[16] G.-L. Defer, H. Widner, R.-M. Marie, P. Rémy, M. Levivier, Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD), Mov. Disord. 14 (4) (1999) 572–584.

[17] E. Moro, N. Allert, R. Eleopra, J.L. Houeto, T.M. Phan, H. Stoevelaar, A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease, J. Neurol. 256 (1) (2009) 83–88.
[18] W.S. Anderson, F.A. Lenz, Surgery insight: deep brain stimulation for movement disorders, Nat. Clin. Pract. Neurol. 2 (6) (2006) 310–320.
[19] L. Lopiano, E. Torre, F. Benedetti, B. Bergamasco, P. Perozzo, A. Pollo, M. Rizzone, A. Tavella, M. Lanotte, Temporal changes in movement time during the switch of the stimulators in Parkinson's disease patients treated by subthalamic nucleus stimulation, Eur. Neurol. 50 (2) (2003) 94–99.
[20] C.R. Butson, S.E. Cooper, J.M. Henderson, C.C. McIntyre, Patient-specific analysis of the volume of tissue activated during deep brain stimulation, Neuroimage 34 (2) (2007) 661–670.
[21] C.G. Goetz, B.C. Tilley, S.R. Shaftman, et al., Movement disorder society UPDRS revision task force. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (15) (2008) 2129–2170.
[22] J.L. Cummings, M. Mega, K. Gray, S. Rosenberg-Thompson, D.A. Carusi, J. Gornbein, The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia, Neurology 44 (12) (1994) 2308–2314.
[23] M. Hamilton, A rating scale for depression, J. Neurol. Neurosurg. Psychiatry 23 (1960) 56–62.
[24] D.C. Delis, J.H. Kramer, E. Kaplan, J. Holdnack, Reliability and validity of the Delis-Kaplan executive function system: an update, J. Int. Neuropsychol. Soc. 10 (2004) 301–303.
[25] D.C. Delis, J. Freeland, J.H. Kramer, E. Kaplan, Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test, J. Consult. Clin. Psychol. 56 (1) (1988) 123.
[26] R.H. Benedict, Brief Visuospatial Memory Test-Rrevised: Professional Manual, PAR, 1997.
[27] T.D. Parsons, S.A. Rogers, A.J. Braaten, S.P. Woods, A.I. Troster, Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis, Lancet Neurol. 5 (7) (2006) 578–588.
[28] K.L. Poston, S. YorkWilliams, K. Zhang, W. Cai, D. Everling, F.M. Tayim, S. Llanes, V. Menon, Compensatory neural mechanisms in cognitively unimpaired Parkinson disease, Ann. Neurol. 79 (3) (2016 Mar) 448–463.
[29] S.S. Cho, L. Christopher, Y. Koshimori, C. Li, A.E. Lang, S. Houle, A.P. Strafella, Decreased pallidal vesicular monoamine transporter type 2 availability in Parkinson's disease: the contribution of the nigropallidal pathway, Neurobiol. Dis. 124 (2019 Apr) 176–182.
[30] P.A. Macdonald, O. Monchi, Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function, Parkinsons Dis 2011 (2011 Mar 6) 572743.
[31] M.J. Mentis, A.R. McIntosh, K. Perrine, et al., Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease, Am. J. Psychiatry 159 (5) (2002) 746–754.
[32] K.A. Frey, R.A. Koeppe, M.R. Kilbourn, T.M. Vander Borght, R.L. Albin, S. Gilman, D.E. Kuhl, Presynaptic monoaminergic vesicles in Parkinson's disease and normal aging, Ann. Neurol. 40 (6) (1996 Dec) 873–884.
[33] R. Nandhagopal, L. Kuramoto, M. Schulzer, et al., Longitudinal evolution of compensatory changes in striatal dopamine processing in Parkinson's disease, Brain: J. Neurol. 134 (Pt 11) (2011) 3290–3298.
[34] M. Figee, P. de Koning, S. Klaassen, et al., Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder, Biol. Psychiatry 75 (8) (2014) 647–652.
[35] M. Laruelle, R.N. Iyer, M.S. Al-Tikriti, et al., Microdialysis and SPECT measurements of amphetamine-induced dopamine release in nonhuman primates, Synapse (New York, NY) 25 (1) (1997) 1–14.