Cerebral Blood Flow Changes Induced by Pedunculopontine Nucleus Stimulation in Patients With Advanced Parkinson's Disease: A [^{15}O] H_2O PET Study

Benedicte Ballanger,^{1,2} Andres M. Lozano,^{1,3} Elena Moro,⁴
Thilo van Eimeren,^{1,2} Clement Hamani,^{1,3} Robert Chen,^{1,4} Roberto Cilia,^{1,2}
Sylvain Houle,² Yu Yan Poon,⁴ Anthony E. Lang,^{1,4}
and Antonio P. Strafella^{1,2,4*}

¹Toronto Western Research Institute (Division of Brain, Imaging and Behaviour - Systems Neuroscience, BIB-SN), UHN, University of Toronto, Toronto, Ontario, Canada

²PET Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, Toronto, Ontario, Canada

³Department of Neurosurgery, Toronto Western Hospital, UHN, University of Toronto, Toronto, Ontario, Canada

⁴Movement Disorders Center, Toronto Western Hospital, UHN, University of Toronto, Toronto, Ontario, Canada

Abstract: Patients with advanced Parkinson's disease (PD) develop disabling axial symptoms, including gait disturbances, freezing and postural instability poorly responsive to levodopa replacement therapy. The pedunculopontine nucleus (PPN) is involved in locomotion, control of posture, and behavioral states [i.e. wakefulness, rapid eye movement sleep]. Recent reports suggested that PPN modulation with deep brain stimulation (DBS) may be beneficial in the treatment of axial symptoms. However, the mechanisms underlying these effects are still unknown. We used [^{15}O] H_2O PET to investigate regional cerebral blood flow in three patients with advanced PD who underwent a new experimental surgical procedure with implantation of unilateral PPN-DBS. Patients were studied Off-medication with stimulator Off and On, both at rest and during a self-paced alternating motor task of the lower limbs. We used SPM2 for imaging data analysis, threshold $P < 0.05$ corrected at the cluster level. Stimulation induced significant regional cerebral blood flow increment in subcortical regions such as the thalamus ($P < 0.006$), cerebellum ($P < 0.001$), and midbrain region ($P < 0.001$) as well as different cortical areas involving medial sensorimotor cortex extending into caudal supplementary motor area (BA 4/6; $P < 0.001$). PPN-DBS in advanced PD resulted in blood flow and presumably neuronal activity changes in subcortical and cortical areas involved in balance and motor control, including the mesencephalic locomotor region (e.g. PPN) and closely interconnected structures within the cerebello-(rubro)-thalamo-cortical circuit. Whether these findings are associated with the DBS-PPN clinical effect remains to be proven. However, they suggest that PPN modulation may induce functional changes in neural networks associated with the control of lower limb movements. *Hum Brain Mapp* 30:3901–3909, 2009. © 2009 Wiley-Liss, Inc.

*Correspondence to: Antonio P. Strafella, Toronto Western Hospital and Institute, UHN, CAMH-PET Imaging Centre, University of Toronto, Toronto, ON, Canada. E-mail: antonio.strafella@uhnres.utoronto.ca or antonio.strafella@camhpet.ca

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INTRODUCTION

Axial symptoms such as gait disturbances and postural instability are disabling symptoms in patients with advanced Parkinson's disease (PD) [Muslimovic et al., 2008]. These symptoms are generally associated with involvement of nondopaminergic structures by the disease [Kempster et al., 2007], which may explain the poor response to levodopa replacement therapy. So far, there is no effective treatment for these symptoms. Recent research reports have suggested that modulation of the activity of the pedunculopontine nucleus (PPN) may be beneficial in the treatment of gait and akinesia [Mena-Segovia et al., 2004; Pahapill and Lozano, 2000].

The PPN is a neurochemically and morphologically heterogeneous cluster of neurons in the caudal mesopontine tegmentum. It has been implicated in the initiation and maintenance of walking, in the production of cortical rhythms during wakefulness [Datta et al., 2001; Steriade, 2006; Takakusaki et al., 2004a], and in the generation and maintenance of the phasic events that characterize rapid eye movement (REM) sleep [Datta et al., 2002; Lim et al., 2007; Takakusaki et al., 2004b]. In PD, the increased inhibitory GABA-ergic activity from the globus pallidus internus is believed to inhibit the PPN [Pahapill and Lozano, 2000]. This has also been confirmed by electrophysiological studies in rats revealing a decreased firing rate of PPN neurons in the Parkinsonian state [Ogura et al., 1997]. In MPTP monkeys, while lesions of the PPN cause akinesia [Matsushima and Kojima, 2001; Munro-Davies et al., 1999], either stimulation [Jenkinson et al., 2004] or disinhibition with the GABA antagonist bicuculline [Nandi et al., 2002] can alleviate akinesia. In keeping with these observations, recent studies have provided evidence that the PPN could be a potential target for deep brain stimulation (DBS) to improve gait and other axial symptoms [Mazzone et al.,

2005; Plaha and Gill, 2005; Stefani et al., 2007], and its modulation may be able to induce corresponding regional cerebral blood flow (rCBF) changes [Strafella et al., 2008].

Using [^{15}O] H_2O positron emission tomography (PET), the aim of the present study was to assess cortical and subcortical changes in rCBF induced by PPN-DBS both at rest and during a motor task involving the lower limbs.

METHODS

Experimental Procedure and Participants

PPN-DBS is a novel experimental surgical procedure, and only a limited sample of patients have been selected and allowed to enter the study so far. The PET experiments were approved by our Local Research Ethics Committees and subjects gave informed written consent after the aims of the study and the nature of the procedures were fully explained.

Three patients with advanced PD and history of freezing of gait and postural instability treated with unilateral PPN stimulation for at least 3 months were investigated. To note, these patients did not receive previous surgery in the subthalamic nucleus or globus pallidus. Axial symptom scores (Item 28 posture; Item 29 gait; Item 30 postural instability) included in the Unified Parkinson's Disease Rating Scale motor examination (UPDRS part III) after overnight medications withdrawal were assessed. The main demographic and clinical features of the patients and stimulation parameters are presented in Table I.

The implantation of the electrodes (Model 3387; Medtronic, Minneapolis, MN) was performed under local anesthesia, guided by stereotactic magnetic resonance imaging (MRI) and microelectrode recordings. Postoperative MRI images were reconstructed on a surgical navigation

TABLE I. Clinical features of the patients with Parkinson's disease

Patient	Sex	Age	Disease duration (years)	LEDD (mg/day)	Time since surgery (months)	Side stimulation	Stimulation parameters	UPDRS III (OFF/ON)			
								UPDRS III (OFF/ON)	Item 28 Posture	Item 29 Gait	Item 30 Postural instability
1	M	70	17	700	22	L	2+3- /70 Hz/120 μs /1.4 V	33.5/36	2/1	2.5/2	1.5/2
2	M	65	25	1,550	4	R	1-/case+/50 Hz/60 μs /1.4 V	28/32	1/1	2/2	2/2
3	M	67	23	1,250	20	L	1+2-/90 Hz/70 μs /2.6 V	38/25	2.5/2	2/1	2/0
Mean (SD)		67 (3)	22 (4)								

LEDD, levodopa equivalent daily dose calculation based on theoretical equivalence of anti-Parkinsonian therapy to levodopa [Katzenschlager et al., 2005].

workstation (Stealth Station; Medtronic, Minneapolis, MN). The accurate placement of the electrodes was confirmed on postoperative MRI. The technique used to localize the electrode contacts used for stimulation on postoperative images has been previously described in detail [Hamani et al., 2008; Lim et al., in press]. Electrode contact locations were plotted onto a standard brainstem atlas [Paxinos and Huang, 1995] (see Fig. 1). The electrodes were connected to a pulse generator (Kinetra or Soletta, Medtronic). The electrodes were in the left PPN for two patients and in the right PPN in the third one. Imaging data in this latter subject was flipped along the transverse axis to allow for group analysis.

Motor Task and EMG Recordings

We evaluated alternating feet movements as a potential marker for gains in motor control of the lower extremity during PPN-DBS. The knees were flexed and the thighs supported to ensure that the spine was relaxed and that a minimum amount of movement was transferred to the head during the task. A pillow was placed under the calves and patients were asked to alternatively dorsiflex and plantarflex their feet. To monitor these movements during PET, surface electromyography (EMG) was recorded from the left and right tibialis anterior (TA) muscles with surface electrodes (nonpolarizable Ag-AgCl). EMG was recorded using a Brain Vision Recorder (Brain Products, Munich, Germany). The EMG electrodes were connected to the amplifier via an electrode input box. Data were sampled at 5,000 Hz and processed using Spike 2 software. A high-pass filter with a 10 Hz cut-off was applied to remove movement artifacts in the EMG signals. The frequency of the movements and the average area under the curve (AUC) of the rectified EMG signal, reflecting the level of contraction from the TA muscles, were calculated for each scan.

PET Scanning Procedure

Patients were imaged after overnight withdrawal of their anti-Parkinsonian medications. Subjects were positioned supine on the PET scanner bed. Head was maintained in a fixed position using a thermoformed mask. PET measurements were obtained using a whole body PET camera system, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN) operating in 3D mode with an in-plane resolution of ~ 4.6 mm full width at half-maximum (FWHM). To measure rCBF, 10 mCi $H_2^{15}O$ were administered intravenously over 50 s with a semibolus injection using an infusion pump. Scanning of emission data was started 10 s after the injection and lasted for 90 s. The motor task was started parallel to the acquisition of the frame. The interval between successive $H_2^{15}O$ administrations was 11 min for adequate decay of radioactivity. Before the first emission scan, a scout view

Figure 1.

Schematic representation of the location of the electrode contact used for stimulation for one patient. PPTgD = PPN pars dissipata; PPTgC = PPN pars compacta; scp = superior cerebellar peduncle (Modified and reprinted with permission from Paxinos G and Huang XF, Atlas of the Human Brainstem, 1995, ©Academic Press).

was obtained to determine accurate positioning of the subject, and a low dose (0.2 mSv) CT scan was acquired to correct for attenuation. Images were reconstructed by two-

dimensional filtered back-projection, resulting in 81 slices with a 256×256 pixel-matrix (pixel size, 2 mm).

Twelve emission scans were obtained with both stimulators OFF and ON (six scans each) in a block design randomized among patients. After the first block, patients were removed from the PET scanner and stimulator settings were then changed. Patients were replaced in the scanner after 30 min using the original thermoformed mask and identical laser landmarks to minimize changes in head position between the two sessions. The interval of 30 min in-between blocks was chosen to maximize differences between stimulation conditions. A second CT scan and a second set of emission scans were then performed. The following conditions were studied: (1) Rest-ON and Task-ON (with unilateral PPN-DBS ON); (2) Rest-OFF and Task-OFF (with unilateral PPN-DBS OFF). In each block, each condition was performed up to three times in randomized order.

PET Images Transformation and Statistical Analysis

Image and statistical analysis were performed in MATLAB version 7.4 (Mathworks, Natick, MA) using statistical parametric mapping software (SPM2; Wellcome Department of Imaging Neuroscience, London, UK) [Friston et al., 1994] to implement the following steps: (1) a mean image was generated; (2) all images were then realigned to the image to correct for interscan head movement; (3) the mean image was normalized to the standard SPM2 PET Montreal Neurological Institute (MNI) space template; (4) the resulting normalization parameter set was used to spatially normalize the individual images; (5) normalized images were thereafter smoothed using an isotropic, Gaussian kernel of 12 mm to reduce the variance due to individual anatomical variability and to improve the signal/noise ratio. Variations in global flow across subjects and scans were removed by proportionally scaling each image to have an arbitrary level of 50 mL/100 mL/min. To identify voxels associated with the effect of PPN DBS at rest and during the motor task, a multisubjects $\times$ conditions and covariates model was used. The following analyses were performed.

Main effect of PPN stimulation

The contrast (Task-On + Rest-On) – (Task-Off + Rest-Off) assessed the increase of rCBF related to the stimulation-On compared with the stimulation-Off state, independent of the task.

rCBF changes induced by the motor task

Inclusive mask analysis. To show areas commonly activated by the task in *both* PPN stimulation conditions, we used an “inclusive mask.” The contrast (Task-Off) – (Rest-Off) [masked (inclusively) by the contrast (Task-On) –

(Rest-On) (mask P -value < 0.05)] assessed the common increases in rCBF during the motor task compared to the resting state irrespective of PPN stimulation conditions.

Exclusive mask analysis. To extract regions specifically activated by the motor task in the ON-stimulation condition, we used an “exclusive mask.” The contrast (Task-On) – (Rest-On) [masked (exclusively) by the contrast (Task-Off) – (Rest-Off) (mask P -value < 0.05)] assessed the increases in rCBF during the motor task compared to the resting state specifically associated with the PPN stimulation, by “excluding” the areas activated by the task while the stimulator was OFF.

Correlation analysis

To identify brain regions where rCBF correlated with lower limb movements while ON stimulation, the average movement frequency and AUC of the EMG response for each scan and each subject were used as a covariate in a covariate model.

In all analyses, statistical maps were thresholded at a level of $P < 0.001$ uncorrected with an extent threshold of at least 80 contiguous voxels. Regions were considered significant at the strict threshold of P -value < 0.05 corrected at the cluster level. All P -values quoted in the text are at the corrected cluster level. All coordinates reported are based on the Talairach atlas and were derived from procedures developed by M. Brett (<http://www.mrc-bu.cam.ac.uk/Imaging/>).

RESULTS

Main Effect of PPN Stimulation

The main effect of stimulation revealed at subcortical level a significant increase in rCBF bilaterally in the thalamus ($P < 0.006$) and cerebellum ($P < 0.001$) and in the ipsilateral ventral midbrain entailing the PPN region ($P < 0.001$). At the cortical level, significant clusters were found in the contralateral dorsolateral prefrontal cortex (BA 8/9 and 10; $P < 0.001$ and $P < 0.02$), caudal anterior cingulate cortex (ACC) extending to the posterior cingulate cortex (PCC) (BA 24 and BA 23/30; $P < 0.001$), the orbitofrontal cortex (BA 11; $P < 0.02$), the superior and middle temporal gyrus (BA 38 and 21; $P < 0.001$ and $P < 0.008$), and ipsilateral occipital cortex (BA 19; $P < 0.01$) (Table II, Fig. 2).

Effect of Motor Task

The comparison motor task to resting condition with inclusive mask analysis revealed a significant increase in rCBF in the bilateral medial sensorimotor cortex marginally extending into the caudal supplementary motor area (SMC/SMA, BA 4/6; $P < 0.001$). The exclusive mask analysis showed a stronger and larger cluster of activation of the caudal SMA related to PPN-DBS (Table III, Fig. 3). The

TABLE II. Main effect of PPN stimulation (ON vs. OFF)

Areas	Left/right	BA	Stereotactic coordinates (regional maximal)			Z-score
			X	y	z	
Subcortical structures						
Cerebellum	L		−15	−67	−42	6.38
Cerebellum	R		29	−38	−32	4.98
Thalamus	R		19	−21	9	5.82
Thalamus	L		−6	−21	4	4.84
Midbrain (red nucleus)	L		−3	−17	−5	5.14
PPN region	L		−4	−38	−16	5.10
Cortical structures						
Superior temporal gyrus	R	38	41	20	−20	6.14
Middle temporal gyrus	R	21	64	−36	1	5.14
Orbitofrontal gyrus	R	11	10	59	−15	5.88
Middle frontal gyrus	R	8/9	45	20	38	5.72
Superior frontal gyrus	R	10	26	55	15	4.46
Caudal ACC	R	24	13	−21	34	5.05
PCC	R	23/30	8	−42	22	4.58
Middle occipital gyrus	L	19	−36	−60	−3	4.26

correlation analysis between EMG changes (Frequency: OFF 1.6 ± 0.4 Hz; ON 1.2 ± 0.3 Hz; AUC: OFF 0.34 ± 0.18 V s; ON 0.5 ± 0.39 V s) during lower limb movement and cerebral activation revealed that, while movement frequency negatively correlated with rCBF in the medial sensorimotor cortex (SMC/SMA, BA 4/6; $P < 0.001$), the EMG area showed a significant positive covariation with rCBF in the left middle frontal gyrus (BA 10; $P < 0.01$) and in the medial sensorimotor cortex (SMC/SMA, BA 4/6; $P < 0.001$) (Table IV, Fig. 4A,B). These findings imply that PPN-DBS-related changes in motor performance (i.e. lower frequency and high amplitude of movement) were associated with higher blood flow measurements.

DISCUSSION

One of the main findings of this study was that unilateral PPN-DBS increased rCBF in different subcortical areas interconnected with the PPN [Aravamuthan et al., 2007; Muthusamy et al., 2007], most notably the cerebellum and the thalamus bilaterally, including medial nuclei, and the brainstem region itself [mesencephalic locomotor region (MLR)]. These findings confirm and further extend those observations reported in our previous studies [Strafella et al., 2008] and are consistent with previous anatomical reports demonstrating direct bilateral descending PPN projections to the cerebellum [Pahapill and Lozano, 2000] as well as ascending fibers projecting through the dorsal tegmental pathway to thalamic nuclei, including those located in the midline [Garcia-Rill, 1991; Pahapill and Lozano, 2000].

Figure 2.

Statistical parametric maps of brain regions showing the main effect of the PPN stimulation at a statistical threshold of $P < 0.001$ (uncorrected) at the single voxel level and $P < 0.05$ (corrected) at the cluster level. Areas of increased rCBF involve mainly the subcortical structures. These areas are superimposed on sagittal, coronal, and transverse sections of a single subject brain MRI from SPM2. rCBF = regional cerebral blood flow; PPN = pedunculopontine nucleus; R = right; L = left.

TABLE III. Effects of the task

Areas	Left/right	BA	Stereotactic coordinates (regional maximal)			Z-score	Cluster size
			<i>x</i>	<i>y</i>	<i>z</i>		
Increased activation induced by the motor task while OFF PPN-DBS (Task-Off vs. Rest-Off) also present during ON PPN-DBS (Task-On vs. Rest-On) (Inclusive mask)							
SMC	R	4	3	−30	60	4.41	1,120
SMA	R	6	12	−13	59	4.10	
SMC/SMA	L	4/6	−10	−19	62	3.81	
Increased activation induced by the motor task while ON PPN-DBS (Task-On vs. Rest-On) not present without PPN-DBS (Task-Off vs. Rest-Off) (Exclusive mask)							
SMA	R	6	1	−5	51	4.41	590
SMA	L		−10	−7	50	4.35	

The increase in rCBF seen in those different subcortical structures is believed to be the result of the DBS-induced stimulation and/or disinhibition effect of the PPN obtained with relatively low stimulation frequencies [Jenkinson et al., 2004] as used in the patients (50, 70, and 90 Hz). This interpretation is in line with the original hypoth-

Figure 3.

Areas of rCBF changes with the task compared to the resting condition at a statistical threshold of $P < 0.001$ (uncorrected) at the single voxel level and $P < 0.05$ (corrected) at the cluster level. These areas involve the medial sensorimotor cortex and supplementary motor area. In red: areas commonly activated by the task in *both* PPN stimulation conditions (inclusive masking analysis). In green: areas specifically activated by the task while ON PPN-DBS (exclusive masking analysis). rCBF = regional cerebral blood flow; PPN = pedunclopontine nucleus.

esis proposing that, in PD, the PPN is overinhibited by the increased inhibitory GABA-ergic activity from the globus pallidus internus and that direct stimulation of this nucleus may remove this disruptive influence facilitating a return toward normal activation of the related anatomical network [Aravamuthan et al., 2007; Pahapill and Lozano, 2000]. However, a potential contribution could also be played by activation of neural pathways passing nearby the electrode, with remote antidromic and/or orthodromic effects [Wu et al., 2001]. Indeed, the spreading of the current from the electrode located in the PPN region may involve the adjacent superior cerebellar peduncle and/or the central tegmental tract [Zrinzo et al., 2008] and thus possibly play a supplementary role in the rCBF changes we detected in the cerebellum and/or thalamus.

Another important observation was the impact of PPN stimulation on the self-paced alternating lower limb movements, which correlated with rCBF changes in the medial sensorimotor areas (including caudal SMA). Indeed, greater activations of these regions were associated with

TABLE IV. Correlation analyses

Areas	Left/ right	BA	Stereotactic coordinates (regional maximal)			Z-score	Cluster size
			<i>x</i>	<i>y</i>	<i>z</i>		
Negative covariation of rCBF with movement frequency							
SMC	R	4	1	−25	55	4.13	573
SMA	L	6	−6	−15	59	4.01	
Positive covariation of rCBF with AUC							
Middle frontal gyrus	L	10	−25	41	25	5.40	169
SMA	L	6	−1	−15	57	4.22	341
SMC	R	4	1	−29	62	3.35

Figure 4.

Areas showing an increase of rCBF correlating with the decrease in movement frequency (**A**) and with the increase in the area under the curve (AUC) of the rectified EMG signal (**B**). At a statistical threshold of $P < 0.001$ (uncorrected) at the single voxel level and $P < 0.05$ (corrected) at the cluster level, these areas involve for both correlation analyses the medial sensorimotor cortex and supplementary motor area (SMC/SMA). rCBF = regional cerebral blood flow.

changes in the lower limb movement pattern represented by lower frequency and increase in amplitude. This is not surprising if we consider in light of previous studies that alternate foot movements in patients with PD are able to modulate neuronal tonic firing in PPN/sub-cuneiform neurons [Piallat et al., 2008] and that SMA is clearly involved in internally generated motor actions [Debaere et al., 2003; Deiber et al., 1991; Jenkins et al., 2000; Ogawa et al., 2006; Rao et al., 1997]. SMA underactivity has been proposed to play an important role in the pathophysiology of PD motor symptoms [DeLong, 1990; Georgiou et al., 1993; Playford et al., 1992; Sabatini et al., 2000; Samuel et al., 1997]. Several imaging studies have shown how increased activation of SMA is often associated with motor improvement induced by effective treatments, such as GPi and STN surgery [Brooks and Samuel, 2000] as well as dopaminergic medications [Haslinger et al., 2001; Jenkins

et al., 1992]. Although our findings are obtained from a limited number of patients, they are in line with those reports and suggest that changes in the activity of SMA induced by PPN stimulation may have some relation with the pattern of locomotion. These observations are consistent with a number of animal and human studies. In fact, while the animal literature has shown that lesions of the PPN decreases locomotor activity in Parkinsonian animals [Munro-Davies et al., 1999], either stimulation [Jenkinson et al., 2004] or disinhibition with the GABA antagonist bicuculline [Nandi et al., 2002] can alleviate akinesia. Similarly, gait disturbance in patients with PD Off-medication characterized by higher cadence and shorter stride length [Hanakawa et al., 1999; Huxham et al., 2008] has been shown to be associated with underactivity of the medial frontal motor area and cerebellar hemispheres [Hanakawa et al., 1999].

While the described changes provide unique evidence of the PPN-induced modulation of rCBF in interconnected subcortical and cortical structures in the human brain linked with locomotion, we should also keep in mind the importance of the PPN to wakefulness and REM sleep behaviors [Lim et al., 2007]. Indeed, it may be argued that the stimulation-induced activation of medial thalamus may also involve the midline and intralaminar nuclei whose role in arousal is well documented [Krout et al., 2002]. Thus, a potential contribution of PPN-DBS-induced arousal changes cannot be ruled out.

CONCLUSION

While the clinical effectiveness of DBS-PPN in PD remains to be determined, in our limited PD sample, this treatment led to significant neuronal activity changes in cortical and subcortical areas involved in balance and motor control, including the PPN/MLR region and closely interconnected structures within the cerebello-(rubro)-thalamo-cortical circuit. Whether these findings account for the proposed clinical effects of DBS-PPN remains to be proven; however, they suggest that PPN-DBS may induce significant functional changes in neural networks associated with the control of voluntary movements of the lower limbs.

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