Combined pedunculopontine-subthalamic stimulation in Parkinson disease

S. Khan, MBChB,
MRCS
S.S. Gill, MS
L. Mooney, BSc
P. White, PhD
A. Whone, PhD
D.J. Brooks, MD, DSc
N. Pavese, MD, PhD

Correspondence & reprint
requests to Dr. Pavese:
nicola.pavese@imperial.ac.uk

ABSTRACT

Objective: To assess the effect of deep brain stimulation (DBS) in the pedunculopontine nucleus (PPN) and caudal zona incerta (cZi)—both separately and in combination—on motor symptoms and regional cerebral blood flow (rCBF) in patients with Parkinson disease (PD).

Methods: Four patients with bilateral cZi and PPN DBS electrodes were rated with the Unified Parkinson's Disease Rating Scale motor subscale (UPDRS-III) when taking and withdrawn from medication. A block of 16 [^{15}O]-H $_2$ O PET resting measurements of rCBF were performed in 4 different states with patients withdrawn from medication: 1) no stimulation, 2) cZi stimulation alone, 3) PPN stimulation alone, 4) combined PPN/cZi stimulation.

Results: When patients were medicated, combined PPN/cZi stimulation produced a statistically significant improvement in UPDRS-III score compared to cZi stimulation alone. In the “off” medication state, the clinical effect of combined stimulation was not significantly different from that induced by cZi stimulation alone. Concomitant PPN/cZi stimulation had a cumulative effect on levels of rCBF, effectively combining subcortical and cortical changes induced by stimulation of either target in isolation.

Conclusions: These findings suggest that concomitant low frequency stimulation of PPN and cZi regions induces additive brain activation changes and provides improved control of PD symptoms when medicated.

Classification of evidence: This study provides Class IV evidence that concomitant low frequency stimulation of PPN and cZi improves motor symptoms in patients with PD on dopamine replacement. It provides Class III evidence that concomitant low frequency stimulation of PPN and cZi induces additive rCBF changes in motor areas of brain. *Neurology*® 2012;78:1090-1095

GLOSSARY

BA = Brodmann area; **cZi** = caudal zona incerta; **PD** = Parkinson disease; **PPN** = pedunculopontine nucleus; **rCBF** = regional cerebral blood flow; **UPDRS-III** = Unified Parkinson's Disease Rating Scale motor subscale.

Postural instability and gait impairment are disabling symptoms in advanced Parkinson disease (PD). Subthalamic electrical deep brain stimulation (DBS) can improve gait in patients with PD in the “off” state. However, this improvement seems to be limited to those patients whose axial symptoms remain levodopa-responsive, even in late stages of the disease.^{1,2} Conversely, patients who have non-levodopa-responsive axial symptoms show minimal response of gait and posture to DBS and have an adverse outcome.^{1,3,4}

DBS of the pedunculopontine nucleus (PPN) is emerging as a treatment for non-levodopa-responsive postural and gait disorders in PD. A few pilot studies of PPN DBS in patients with PD have been published, with promising outcomes.^{5–10} However, the combined clinical efficacy of PPN and subthalamic DBS has not been extensively investigated. Functional imaging of regional cerebral blood flow (rCBF) in patients with PD has shown that subthalamic DBS helps normalize striatofrontal activation.¹¹ We investigated the relationship between clinical

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Supplemental Data

From the Departments of Neurosurgery (S.K., S.S.G., L.M.) and Neurology (A.W.), Institute of Neurosciences, Frenchay Hospital, Bristol; Department of Mathematics and Statistics (P.W.), University of the West of England, Bristol; and Centre for Neuroscience (D.J.B., N.P.), Department of Medicine, Imperial College London, UK.

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Table 1 Patient characteristics

Patient no.	Age at diagnosis of PD, y	Disease duration, y	Age at time of surgery, y	Time since implantation, mo	LEU at time of PET scan, mg	UPDRS-III score at time of PET scan (in the "off" medication/"off" stimulation state)	
						Total score	Axial subscore (items 27, 28, 29, and 30)
1	47	18	65	42	917.58	25	7
2	52	12	64	44	850	49	8
3	52	9	61	3	1,315.6	58	14
4	44	19	63	6	1,200	66	10
Mean $\pm$ SD	48.8 $\pm$ 3.9	14.5 $\pm$ 4	63.3 $\pm$ 1.7	23.8 $\pm$ 22.3	1,070.8 $\pm$ 222.7	49.5 $\pm$ 17.7	9.8 $\pm$ 3.1

Abbreviations: LEU = levodopa equivalent units; PD = Parkinson disease; UPDRS-III = Unified Parkinson's Disease Rating Scale motor subscale.

improvement and rCBF changes associated with PPN stimulation in isolation and in combination with stimulation of the subthalamic region/caudal zona incerta (cZi).

METHODS Primary objective. The aim of this study was to assess changes in Unified Parkinson's Disease Rating Scale motor score (UPDRS-III) and its axial subscore and rCBF in motor areas of brain following concomitant stimulation of PPN and cZi in patients with PD. This study provides Class IV evidence regarding the changes in the UPDRS-III and Class III evidence regarding the changes in rCBF.

Patients. We studied 4 male patients with idiopathic PD who had bilateral cZi and PPN DBS electrodes implanted. Patient details before surgery are described elsewhere.¹⁰ Briefly, all patients had significant histories of falling, freezing, or postural instability in both "on" and "off" states.

The interval between DBS surgery and PET was 23.8 $\pm$ 22.3 months (range 3–44 months). Table 1 summarizes clinical characteristics at the time of PET.

Surgical procedure, target sites, and stimulation parameters. All patients had simultaneous bilateral implantation of DBS leads (Medtronic DBS leads model 3389) into the cZi and PPN. There were no intraoperative complications. The technique used for targeting the PPN and the cZi has been described.^{5,10,12,13} A brief summary of the technique that we used to target the PPN is provided in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org. The correct positioning of the electrodes was determined with an intraoperative MRI. All patients were stimulated at both targets with 60 mcs pulse width at 60 Hz with similar contacts (cZi: left 2+1–/right 6+5–; PPN: left 3+2–1; right 7+6–5– with 1 exception where PPN was stimulated at 25 Hz with C+3–2–1– left and C+7–6–5– right) (details in table e-1). At the time of PET, all patients were stable on their optimized DBS settings for at least 1 month. These same stimulation settings were used during all the assessments performed in this study.

Clinical evaluations. Clinical examination was performed a few days before PET. The UPDRS-III score was rated in both "off" and "on" medication states with no stimulation, cZi stimulation alone, PPN stimulation alone, and combined PPN/cZi stimulation. The order of stimulation patterns was randomized,

allowing sufficient time (around 20 minutes) for the patients to have no residual effects from the previous setting.

For the "off" state clinical assessments (and PET), patients had their medications and DBS stopped overnight. The "on" state assessment was performed 1 hour after administration of 120% of the patient's morning levodopa dose.

The clinical outcome measures were the UPDRS-III scores. Changes in the axial subscores derived from items 27 to 30 (arising from chair, posture, gait, and postural stability) were also analyzed. Changes in motor function were analyzed using analysis of variance with a 2 $\times$ 4 fully repeated measures design and a post hoc paired samples *t* test. The level of significance was set at *p* < 0.05.

PET. The rCBF changes associated with DBS were detected with [¹⁵O]-H₂O PET. We used a CTI/Siemens 962 camera operated in 3D acquisition mode.¹⁴ A total of 235 MBq of [¹⁵O]-H₂O in 3 mL saline was administered IV over 20 seconds using an automatic pump. Emission data were acquired for 90 seconds with 7-minute intervals between successive [¹⁵O]-H₂O administrations.

The following sets of 4 rCBF measurements "off" medication were performed: 1) "off" state (all stimulators switched off); 2) cZi stimulation alone; 3) PPN stimulation alone; 4) combined PPN/cZi stimulation. The sequence of assessments from the "off" stimulation state to the combined PPN/cZi stimulation was chosen to make the last part of the long scanning session more tolerable for the patients who were blind to the stimulation pattern.

There was a 20-minute rest between second and third session to allow transition between cZi stimulation alone and PPN stimulation alone. During this time the patient was asked to remain in the scanner. One patient asked to stop the scan during the fourth condition; however, 2 rCBF measurements of combined PPN/cZi stimulation were completed.

A 10-minute transmission scan was acquired before the first and the third set of rCBF studies for attenuation corrections.

PET data analysis. Statistical parametric mapping software (SPM5; www.fil.ion.ucl.ac.uk/spm) was used to coalign the individual PET images and to create an image of mean rCBF. These were spatially normalized into standard Montreal Neurological Institute stereotaxic space and smoothed using an isotropic 10-mm, full-width half-maximum Gaussian kernel.

Table 2 Changes in UPDRS-III score following deep brain stimulation

	UPDRS-III scores			
	"Off" medication		"On" medication	
	Mean $\pm$ SD	% Change from baseline (p value)	Mean $\pm$ SD	% Change from baseline (p value)
Baseline ("off" stimulation)	49.5 $\pm$ 17.7	—	27.8 $\pm$ 9.7	—
PPN stimulation	40.3 $\pm$ 17.5	18.7 (0.109)	21.8 $\pm$ 12.8	21.6 (0.17)
cZi stimulation	23.5 $\pm$ 2.1	52.5 (0.047 ^a)	17.5 $\pm$ 4.5	36.9 (0.067)
Combined PPN/cZi stimulation	21.0 $\pm$ 4.5	57.6 (0.025 ^a)	13.8 $\pm$ 6.2	50.5 (0.02 ^a)
		% Change from cZi stimulation alone		% Change from cZi stimulation alone
		5.1 (0.155)		13.6 (0.03 ^a)

Abbreviations: cZi = caudal zona incerta; PPN = pedunculo pontine nucleus; UPDRS-III = Unified Parkinson's Disease Rating Scale motor subscale.

^a Significant.

Specific effects were investigated by using appropriate contrasts to create maps of Z scores.¹⁵ We used a blocked analysis of covariance with global counts as a confound to remove the variance due to global from regional changes in perfusion across scans. Statistical maps were displayed at a threshold $p < 0.01$ (Z score = 2.33), and all resulting activation clusters at a $p < 0.05$ corrected threshold are reported.

The following within-group analyses were performed: PPN stimulation alone compared to no stimulation, cZi stimulation alone compared to no stimulation, and combined PPN/cZi stimulation compared to no stimulation.

For each analysis, both decreases and increases in rCBF were interrogated.

Standard protocol approvals, registrations, and patient consents. Both the Frenchay and Hammersmith Hospital ethical committees approved the study. Permission to administer [¹⁵O]-H₂O was obtained from the Administration of Radioactive Substances Advisory Committee, UK. Informed written consent was obtained from all participating subjects. The clinical trial identifier number is ISRCTN16511360.

RESULTS Clinical examination. The mean changes in UPDR-III scores and axial subscores following DBS are detailed in tables 2 and 3. Combined PPN/cZi stimulation produced greater improvement in UPDRS-III scores and axial subscores in comparison with isolated cZi and PPN stimulation, in both "off" and "on" states. However, the magnitude of clinical improvement induced by combined PPN/cZi was only significantly greater than that induced by cZi stimulation alone when the patients were medicated.

PET findings. Concomitant PPN/cZi stimulation resulted in significantly increased rCBF in multiple brain areas including those activated by isolated PPN stimulation (midbrain, thalamus, globus pallidus, and cerebellum) and those activated by cZi stimulation only (putamen, Brodmann area [BA] 10) (figure). Combined PPN/cZi stimulation induced significant rCBF

Table 3 Changes in UPDRS-III axial subscore following deep brain stimulation

	UPDRS-III axial subscore (derived from items 27, 28, 29, and 30 [arising from chair, posture, gait, and postural stability])			
	"Off" medication		"On" medication	
	Mean $\pm$ SD	% Change from baseline (p value)	Mean $\pm$ SD	% Change from baseline (p value)
Baseline ("off" stimulation)	9.8 $\pm$ 3.1	—	4.0 $\pm$ 0.8	—
PPN stimulation	6.5 $\pm$ 3.7	33 (0.12)	2.5 $\pm$ 1.7	38 (0.10)
cZi stimulation	4.8 $\pm$ 0.5	51 (0.05 ^a)	3.3 $\pm$ 1.5	19 (0.44)
Combined PPN/cZi stimulation	3.0 $\pm$ 1.4	69 (0.03 ^a)	2.0 $\pm$ 1.4	50 (0.041 ^a)
		% Change from cZi stimulation alone		% Change from cZi stimulation alone
		18 (0.16)		31 (0.19)

Abbreviations: cZi = caudal zona incerta; PPN = pedunculo pontine nucleus; UPDRS-III = Unified Parkinson's Disease Rating Scale motor subscale.

^a Significant.

Figure Cumulative effect on regional cerebral blood flow (rCBF) by concomitant caudal zona incerta (cZi) and pedunculopontine (PPN) stimulation

Projections of statistical parametric maps showing areas of significant rCBF increases compared to baseline induced by deep brain stimulation of the cZi alone, of the PPN alone, and of combined PPN and cZi. The figure shows the cumulative effect on rCBF by concomitant PPN and cZi stimulation. The areas are superimposed on axial and coronal sections of the averaged T1 MRI in Montreal Neurological Institute space available in SPM. The colorstripe indicates t values.

decreases in sensorimotor cortical areas (bilateral BA 4, bilateral BA 6, and left BA 5) similar to those observed with cZi DBS (bilateral BA 4, left BA area 5, and left BA 6) but more extensive than those observed with PPN stimulation alone (left BA 5).

SPM5 results are summarized in table 4 and more fully described in tables e-2 and e-3.

DISCUSSION Our findings suggest that concomitant PPN/cZi stimulation induces cumulative functional changes in motor areas which is associated with an improved control of PD symptoms.

As previously reported,^{6,10} the combination procedure seems to be particularly useful in alleviating symptoms still present in the “on” state—the magnitude of clinical improvement in UPDRS-III induced by combined PPN/cZi was significantly greater than that induced by cZi stimulation alone only after levodopa administration. In the “on” state, combined PPN/cZi stimulation improved the axial subscore by 31% compared to cZi stimulation, but this did not reach significance, probably reflecting our low power due to the few patients. The reason why combined PPN/cZi stimulation is more effective

when patients are in “on” state remains unclear but it may increase the efficacy of exogenously administered therapy by influencing the intrastriatal dopamine and acetylcholine balance.⁶

In line with our clinical observations, we found an additive effect on rCBF when combining PPN with cZi stimulation. Concomitant stimulation of both targets resulted in effectively combining the subcortical and cortical rCBF changes induced by stimulation of either target in isolation.

Our patients had PET withdrawn from medication, whereas the best effect of additional PPN stimulation on UPDRS-III score was observed when medicated. The effect of levodopa administration on the changes in rCBF observed with combined PPN/cZi stimulation needs to be assessed in future investigations.

It should also be noted that in this study cZi was stimulated at 60 Hz. When stimulating cZi at high frequency (130 Hz) in combination with PPN stimulation at 60 Hz or below we found that postural stability became impaired, whereas cZi stimulation to 40 Hz or below worsened tremor, rigidity, and bradykinesia. Therefore a compromise setting of 60

Table 4 Summary of statistical parametric mapping results

Increases from baseline ^a				Decreases from baseline ^a			
Area	cZi on	PPN on	cZi and PPN on	Area	cZi on	PPN on	cZi and PPN on
L putamen	+	–	+	L BA4	+	–	+
R putamen	+	–	+	R BA 4	+	–	+
L GP	+	–	+	L BA5	+	+	+
R GP	+	+	+	L BA6	+	–	+
L thalamus	–	+	+	R BA6	–	–	+
R thalamus	+	+	+	L BA13	–	+	+
L cerebellum	–	+	+				
R cerebellum	–	+	+				
L midbrain	+	+	+				
R midbrain	+	+	+				
L BA8	+	–	–				
L BA10	+	–	+				
R BA10	+	–	+				

Abbreviations: + = Yes; – = no; BA = Brodmann area; cZi = caudal zona incerta; GP = globus pallidus; PPN = pedunculo-pontine nucleus.

^a Baseline = all stimulators off.

Hz at both targets was selected. We acknowledge that cZi stimulation in this study might be suboptimal and a direct comparison with the results of other studies where the subthalamic region was stimulated at higher frequencies should be done with caution.

The rCBF changes following PPN stimulation in our patients were less widespread than those previously reported. rCBF increases in prefrontal areas have been noted during unilateral PPN stimulation.¹⁶ The discordance between the patterns of rCBF changes following PPN stimulation may reflect the few patients in both studies giving reduced power to detect subtle changes. Alternatively, the lack of prefrontal activation in our patients may represent degeneration in the ascending cholinergic projections from the PPN to the frontal cortex, which has been described in advanced PD, especially in patients with axial symptoms.^{17,18}

AUTHOR CONTRIBUTIONS

S. Khan: research project: conception, organization, execution including clinical assessments and analysis of clinical data; manuscript: writing of the first draft together with Dr. Pavese. S.S. Gill: research project: conception; manuscript: review and critique. L. Mooney: research project: execution including clinical assessments and assistance during PET scanning; manuscript: review and critique. Dr. White: research project: statistical analysis; manuscript: review and critique. Dr. Whone: research project: clinical assessments; manuscript: review and critique. Dr. J Brooks: research project: conception; manuscript: review and critique. Dr. Pavese: research project: conception, organization, execution including PET scanning and analysis; manuscript: writing of the first draft together with S. Khan.

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DISCLOSURE

S. Khan reports no disclosures. S.S. Gill serves as a consultant to Renishaw plc. L. Mooney, Dr. White, and Dr. Whone report no disclosures. Dr. Brooks has received funding for travel or speaker honoraria from GlaxoSmithKline, Genzyme, and Teva Pharmaceutical Industries Ltd.; serves on the editorial boards of *Brain*, *Synapse*, *Journal of Neural Transmission*, and *Clinical Neurology and Neurosurgery*; is employed part-time by and holds stock/stock options in GE Healthcare; serves as a consultant for Shire plc; and receives research support from the Clinical Sciences Centre, Medical Research Council UK. Dr. Pavese serves as a consultant for GE Healthcare.

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