Perhaps a more direct explanation for the finding in this case report is that STN DBS does not alter all the striatal DA-mediated abnormalities in PD, but produces only a partial correction which in most patients is sufficient to suppress the cardinal parkinsonian symptoms that are mediated by dopamine loss. Thus, STN DBS patients could still rely on some residual function of nigrostriatal DA circuits, even if STN DBS itself does not affect striatal dopamine release in humans. This scenario is consistent with the observation that most PD patients receiving STN DBS experience optimal motor function with a combination of DBS and dopaminergic pharmacotherapy. A further blockade of striatal DA transmission could then worsen parkinsonian symptoms beyond the ability of STN DBS to compensate, as illustrated in this case report.

References

- 1 Abosch A, Kapur S, Lang AE, Hussey D, Sime E, Miyasaki J, Houle S, Lozano AM: Stimulation of the subthalamic nucleus in Parkinson's disease does not produce striatal dopamine release. *Neurosurgery* 2003;53:1095–1102.
- 2 Lee KH, Chang SY, Roberts DW, Kim U: Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. *J Neurosurg* 2004;101:511–517.
- 3 Oueslati A, Sgambato-Faure V, Melon C, Kichidian P, Gubellini P, Amri M, Kerkerian-Le Goff L, Salin P: High-frequency stimulation of the subthalamic nucleus potentiates L-dopa-induced neurochemical changes in the striatum in a rat model of Parkinson's disease. *J Neurosci* 2007;27:2377–2386.

Prof. Philip A. Starr
University of California San Francisco and
Veteran's Affairs Medical Center
779 Moffitt Hospital, 505 Parnassus Avenue
San Francisco, CA 94143 (USA)
Tel. +1 415 502 3744, Fax +1 415 753 1772
E-Mail starrp@neurosurg.ucsf.edu

Stereotact Funct Neurosurg 2008;86:188–190
DOI: 10.1159/000126944

The Paradoxical Role of Dopamine after Subthalamic Nucleus Deep Brain Stimulation – Downstream Is Upstream in a Circuit Diagram

Comment on 'Does Dopamine Still Have a Leading Role in Advanced Parkinson's Disease after Subthalamic Stimulation?' (Stereotact Funct Neurosurg 2008;86: 184–186)

Robert E. Gross

Department of Neurosurgery, Emory University School of Medicine, Atlanta, Ga., USA

Is anyone else as troubled as I am by the fact that patients must have a good response to levodopa to have a good response to subthalamic nucleus (STN) stimulation? It does not bother me that – in patients that have a good response to levodopa – the ef-

fects of STN stimulation and levodopa are similar in magnitude: they both ostensibly rectify the circuit dysfunction at the globus pallidus internus (GPi) level and beyond caused by the dopaminergic (DA) deficit. What bothers me is that patients who *do not* have a good levodopa response *do not* respond well to STN stimulation. I thought that poor levodopa response was due to insufficient numbers of DA terminals in the putamen to take up and metabolize levodopa to DA but that STN stimulation works 'downstream' of the putamen. Indeed, this observation came as a surprise to many movement disorder specialists as well, as evidenced by the overall lower levodopa responsiveness (and STN benefits) in some centers that adopted STN stimulation the earliest [see 1]. They apparently did not predict, based on the prevalent DeLong model of basal ganglia circuitry, that response to STN stimulation (whether you believe it is inhibitory or excitatory) would require that patients respond to levodopa. So why is this the case? The potential explanations cut right to the central question that to this day remains incompletely understood: what is the mechanism of action of STN stimulation? Although in this issue Jabre et al. [2] present only a single case, their finding is quite provocative and may shed light on the question of how STN deep brain stimulation (DBS) works and the role of levodopa in its effectiveness.

Jabre et al. [2] describe the acute deterioration in parkinsonian symptoms of a patient with ongoing confirmed functioning STN stimulation triggered by a single dose of fluphenazine, a potent D1/D2 antagonist (in addition to its effects on other neurotransmitter systems). The patient had a 75% response to levodopa challenge before surgery, and similarly STN stimulation led to a 73% reduction in the Unified Parkinson's Disease Rating Scale motor subscale score. All parkinsonian medication was initially withdrawn but non-motor findings of apathy prompted the institution of cabergoline, a mixed D1/D2 agonist, i.e. this was not ostensibly to treat motor symptoms. After the inadvertent fluphenazine dose, the patient's motor score response deteriorated – on STN stimulation and on cabergoline – to 58%, including increased akinesia, rigidity, tremor and axial symptoms. The patient's preoperative levodopa-induced dyskinesia was 83% alleviated by STN stimulation and withdrawal of levodopa treatment. However, the patient experienced mild STN stimulation – evoked facial and right upper extremity dyskinesia, and after fluphenazine this temporarily disappeared. Thus, as the authors point out, it appeared that fluphenazine blocked the effects of STN stimulation and/or blocked the effects of ongoing DA activity. These possibilities are intriguing or seemingly mundane, respectively, but both are actually instructive with regard to mechanisms of STN stimulation.

Is there ongoing DA activity that contributes to clinical performance during 'downstream' STN stimulation? This would seem at first glance not to be the case when one considers that STN stimulation leads to clinical improvements in the 'off' medication state (off medication/on stimulation) that are similar in magnitude to the response to medication (on medication/off stimulation) and that adding levodopa to STN stimulation leads to essentially no greater response (on medication/on stimulation) [see 1]. The lack of additivity of levodopa and STN stimulation implies that they operate by the same mechanism (e.g. rectification of circuit activity at and beyond GPi). However, is the off medication/on stimulation state the same as the fluphenazine/on stimulation state? No! In the 'off' medication state, it is perhaps overlooked

Fig. 1. Downstream is upstream in the basal ganglia ‘circuit’ diagram. **a** The standard depiction of the model where it is easy to see that STN is ‘downstream’ of the striatum (and its DA deficit). **b** If one presents the model upside down, it is easier to see that in a ‘circuit’ the STN is also ‘upstream’ of the striatum, by following the arrows leading out of STN/GPi to the striatum. GPe = Globus pallidus externus; SN = substantia nigra.

that what remains of the patient’s DA system is still functioning, albeit poorly. This is why phenothiazines are so disastrous for Parkinson’s disease patients: they are worse than being ‘off’. So, the patient scores of Jabre et al. [2] in the fluphenazine/on stimulation state may simply reflect the STN-mediated increase in Unified Parkinson’s Disease Rating Scale motor scores above a lower ‘no DA activity’ baseline as compared to a somewhat higher ‘off medication’ baseline. Except that, as the authors point out, STN stimulation is supposed to work downstream of striatal DA activity, which should mitigate the effects of even no DA activity. Thus, it appears that fluphenazine indeed blocks the effects of ongoing DA activity, but more importantly that this activity is necessary for the effects of STN stimulation, and STN stimulation does not simply work to rectify circuitry downstream of the DA deficit in the putamen. This begs the question: by what mechanism is DA activity necessary for the effects of STN stimulation?

One explanation that the authors proffer is that extrastriatal DA function is necessary for STN DBS actions, for example mid-brain DA projections to the STN, but there are several difficulties with this proposal. First, although they are present normally, as was shown many years ago [3], they may be lost in Parkinson’s disease to a similar degree as striatal projections. Second, D5 dopamine receptors appear to predominate in STN, where they potentiate burst firing [4, 5]. Therefore, their blockade – if indeed fluphenazine were an antagonist at D5 receptors – might be predicted to decrease STN activity, not increase it. Finally, even if STN stimulation activated DA afferents to the STN acting via D1 or D5 receptors, this would lead to activation of STN at the cell body, not inhibition [4]. Were this pathway blocked by fluphenazine, STN stimulation-mediated activation of STN efferents [6] would remain intact, i.e. STN stimulation is still downstream of midbrain afferents to STN. What of DA receptors in GPi? These are D2/3 (presynaptic) and D4 receptors (postsynaptic), and it has been shown that via these receptors DA reduces GPi activity evoked by stimulation of subthalamo-pallidal fibers [7]. Since fluphenazine potently blocks D2 receptors, it is conceivable that in the reported patient this led to increased GPi activity acting downstream of STN stimulation. However, since Hashimoto et al. [6] demonstrated that STN stimulation activates GPi in MPTP (1-

methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkeys, and we have observed this in a patient intraoperatively as well [R.E. Gross, M.R. DeLong, K. Mewes, unpublished observations], the result of this fluphenazine-induced GPi activation in the face of ongoing STN stimulation is at best hard to predict.

A second explanation for the DA requirement of STN stimulation that the authors discuss is activation of the nigrostriatal pathway (by en passant stimulation and/or release of glutamate from STN efferents to the nigra region) [8]. As they discuss, 2 PET studies failed to find evidence of increased DA release in the putamen by competition for radioactive raclopride binding, but these were small studies and ‘absence of evidence is not evidence of absence’. In contrast, Nimura et al. [9] found that STN stimulation, while minimally affecting absolute DA binding in the putamen, led to stabilization of fluctuations of DA binding potential in the putamen. This is consistent with the long-term antidyskinetic effects of STN stimulation and the thinking that dyskinesias result from rapid temporal and spatial fluctuations in synaptic DA levels associated with pulsatile levodopa administration in the setting of decreased uptake and storage by degenerating DA terminals. The findings of Nimura et al. [9] do not address the question of how this is mediated, but 2 possibilities are that (1) STN stimulation indeed directly affects the nigrostriatal pathway, or (2) that it leads to downstream rectification of the circuit which includes effects on the recurrent thalamo-cortical-striatal projections. Consistent with the latter, Oueslati et al. [10] showed in rats that STN DBS modulates the responsiveness of the striatum to the effects of levodopa.

In either case, when one considers that these are circuits we are discussing, the resolution of the paradoxical role of DA in STN DBS is that STN is downstream of the striatum, but it is also upstream of the striatum (fig. 1). Thus, whatever the explanation for the effects of fluphenazine in the single case report of Jabre et al. [2], including other neuropharmacological explanations not addressed here, the report serves to focus the discussion on the role of levodopa in the effects of STN stimulation, and the answer to the question they raise is: DA maintains its leading role in Parkinson’s disease even after STN DBS.

References

- 1 Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G: Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 2006;21(suppl 14):S290–S304.
- 2 Jabre M, Nohra G, Damier P, Bejjani B-P: Does dopamine still have a leading role in advanced Parkinson's disease after subthalamic stimulation? *Stereotact Funct Neurosurg* 2008;86:184–186.
- 3 Brown LL, Makman MH, Wolfson LI, Dvorkin B, Warner C, Katzman R: A direct role of dopamine in the rat subthalamic nucleus and an adjacent intrapeduncular area. *Science* 1979;206:1416–1418.
- 4 Baufreton J, Garret M, Rivera A, de la Calle A, Gonon F, Dufy B, Bioulac B, Taupignon A: D5 (not D1) dopamine receptors potentiate burst-firing in neurons of the subthalamic nucleus by modulating an L-type calcium conductance. *J Neurosci* 2003;23:816–825.
- 5 Svenningsson P, Le Moine C: Dopamine D1/5 receptor stimulation induces c-fos expression in the subthalamic nucleus: possible involvement of local D5 receptors. *Eur J Neurosci* 2002;15:133–142.
- 6 Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL: Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci* 2003;23:1916–1923.
- 7 Ibanez-Sandoval O, Hernandez A, Floran B, Galarraga E, Tapia D, Valdiosera R, Erlij D, Aceves J, Bargas J: Control of the subthalamic innervation of substantia nigra pars reticulata by D1 and D2 dopamine receptors. *J Neurophysiol* 2006;95:1800–1811.
- 8 Bergmann O, Winter C, Meissner W, Harnack D, Kupsch A, Morgenstern R, Reum T: Subthalamic high frequency stimulation induced rotations are differentially mediated by D1 and D2 receptors. *Neuropharmacology* 2004;46:974–983.
- 9 Nimura T, Yamaguchi K, Ando T, Shibuya S, Oikawa T, Nakagawa A, Shirane R, Itoh M, Tominaga T: Attenuation of fluctuating striatal synaptic dopamine levels in patients with Parkinson disease in response to subthalamic nucleus stimulation: a positron emission tomography study. *J Neurosurg* 2005;103:968–973.
- 10 Oueslati A, Sgambato-Faure V, Melon C, Kachidian P, Gubellini P, Amri M, Kerkerian-Le Goff L, Salin P: High-frequency stimulation of the subthalamic nucleus potentiates L-dopa-induced neurochemical changes in the striatum in a rat model of Parkinson's disease. *J Neurosci* 2007;27:2377–2386.

Robert E. Gross, MD, PhD
 Department of Neurosurgery, Center for Neurodegenerative Diseases
 Emory University School of Medicine
 Atlanta, GA 30322 (USA)
 Tel. +1 404 727 2354, Fax +1 404 778 4472
 E-Mail Robert.gross@emoryhealthcare.org