

Non-motor effects of deep brain stimulation of the subthalamic nucleus in Parkinson's disease: preliminary physiological results

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Abstract Although deep brain stimulation (DBS) is a clinically effective therapy for patients with advanced Parkinson's disease (PD), its physiological effects on the brain and possible actions on non-motor functional systems remain largely unknown. This study evaluated the effects of DBS of the subthalamic nucleus (STN) on neurophysiological variables and on cardiovascular physiology. Nine patients affected by PD undergoing chronic DBS of the STN have been studied. We performed electroencephalography (EEG), somatosensory (SEPs) and visual evoked potentials (VEPs), exteroceptive masseteric silent period and sympathetic skin response (SSR) studies with DBS ON and OFF. To assess the effects of stimulation on the cardiovascular system the tilt test and plasma renin activity were studied. When we turned the DBS OFF, both SEP N20 and the VEP P100 component increased significantly in amplitude whereas the SSR decreased in amplitude and increased in latency. Although plasma renin activity tended to increase with DBS OFF, its modification induced by postural changes and blood pressure values did not significantly differ with DBS ON and OFF. We conclude that DBS of the STN in PD, besides inducing a clinical improvement, induces several non-motor effects.

In deep brain stimulation (DBS), an effective treatment for advanced Parkinson's disease (PD), stimulating electrodes are implanted in various anatomical structures of the motor system: the cerebellar thalamus, globus pallidus and subthalamic nucleus (STN) [1]. DBS functionally inactivates the target structure mimicking a surgical lesion. Despite the proven clinical efficacy of the technique, its physiological effects on the human brain remain unclear. The clinical effi-

cacy of the technique depends on its action on the motor system. The basal ganglia are also involved in several non-motor functions [2, 3]. The aim of this study was to evaluate the physiological changes produced by DBS on various functional systems of the brain and on the cardiovascular system.

Nine patients (mean age 59 years, range 51–65) implanted with bilateral DBS catheters in subthalamic nuclei have been studied. The time after surgery ranged from 3 to 24 months. Patients were investigated a day with the DBS stimulator ON and on the next day with the DBS stimulator OFF, while receiving their usual medications. All the subjects gave their informed consent.

We analysed the effects of DBS on EEG recorded using a longitudinal 8-channel montage arrangement. Somatosensory evoked potentials (SEPs) were used to assess the somatosensory pathway: the N20 component was obtained by stimulating the median nerve bilaterally with surface electrodes on the wrist and recording scalp responses from C3' and C4'. Pattern reversal visual evoked potentials (VEPs) at 30' and 15' spatial frequencies were used to assess the visual pathway: the P100 component was recorded from the scalp 2 cm above the inion. The excitability of brainstem inhibitory interneurons was investigated with the recovery cycle of the exteroceptive masseteric silent period using paired stimuli delivered to the mental nerve at 100, 250 and 500 ms intervals during voluntary contraction. The stimulus intensity was 10-times the patient's threshold. The ipsilateral and contralateral sympathetic skin response (SSR) was recorded after stimulating the ulnar nerve every 10 s with surface electrodes at a stimulus intensity 2.5-times the patient's threshold. The postural changes of arterial blood pressure and plasma renin activity during 20' clinostatism (basal position), 20' orthostatism at 60° (stress position), and 20' clinostatism (recovery position) were investigated. Values in the text are mean $\pm$ 1 SD. Results were analysed with Wilcoxon's signed rank test; values <0.05 were considered significant. All the data are expressed as percent of the DBS ON condition (= 100%).

With DBS OFF, the N20 SEP component remained unchanged in latency ($99.6 \pm 2.8\%$ of the on condition; $p > 0.05$; $n = 16$) while the amplitude increased significantly ($147.5 \pm 127.4\%$; $p = 0.020$).

With DBS OFF, the P100 VEP latency ($n = 18$) with both spatial frequencies remained unchanged (30'-check = $103 \pm 5.9\%$; $p > 0.05$; 15'-check = $101.5 \pm 7.4\%$; $p > 0.05$), whereas the amplitude increased (30'-check = $187.6 \pm 104.2\%$; $p = 0.002$; 15'-check = $209.3 \pm 123.5\%$; $p = 0.006$). At none of the intervals tested (100, 250, 500 ms), did the recovery cycles of the exteroceptive masseteric silent period differ significantly (100 ms, $104.5 \pm 45.1\%$; 250 ms, $95.1 \pm 17.7\%$; 500 ms interval, $93.7 \pm 25.8\%$; $p > 0.05$; $n = 7$). For SSR ($n = 33$) the threshold remained unchanged ($104.5 \pm 29.1\%$;

$p > 0.05$), but the latency increased ($113.0 \pm 19.5\%$; $p = 0.001$) and the amplitude decreased ($98.7 \pm 72\%$; $p = 0.023$) when DBS was turned OFF. No statistical differences were found between EEG variables recorded with the stimulator ON or OFF (frequency, $102.4 \pm 16.8\%$; max amplitude, $110.1 \pm 23.9\%$; $p > 0.05$; $n = 9$). Turning the stimulator OFF caused no significant changes in mean basal artery pressure and in its responses to tilt testing (baseline, $96.1 \pm 17.6\%$, $p > 0.05$; during stress, $97.1 \pm 15.6\%$, $p > 0.05$; on recovery, $94.6 \pm 19.9\%$, $p > 0.05$; $n = 8$). There were no significant differences during the various conditions of the tilt test (basal, $124.5 \pm 44.6\%$; $p > 0.05$; stress, $145.98 \pm 71.2\%$; $p > 0.05$; recovery, $151.8 \pm 57.1\%$; $p > 0.05$; $n = 8$) even though there was a clear trend to an increase in plasma renin activity during the recovery phase with DBS OFF.

Discussion

DBS induced no significant changes in the latencies of the SEP N20 or the VEP P100 component, in the recovery cycles of exteroceptive masseteric silent period, in the EEG, in the tilt test, or in plasma renin activity, whereas turning DBS OFF significantly increased the amplitude of the SEP N20 and, even more, the VEP P100 component. A previous study [4] in two patients with DBS of STN reported almost unchanged N20 component between DBS ON and OFF condition. But, in that study [4] besides the small sample size, the DBS "ON condition" was actually recorded soon after the stimulator was turned OFF, and therefore the results are methodologically not comparable. How DBS interacts with somatosensory and visual pathways remains conjectural. DBS-induced changes in SEPs and VEPs could be partly due to the DBS artefact that reduces the signal-to-noise ratio in the ON condition. Nonetheless a decrease of the signal-to-noise ratio would have induced changes of comparable magnitude both in VEPs and SEPs. In addition the N20 and P100 components increased in the DBS OFF condition also in patients with nearly artefact-free recordings in the ON condition. The amplitude reduction seems thus to be independent from the artefact generated by DBS and the reduction of signal-to-noise ratio cannot fully explain our findings. Changes in the evoked potential therefore likely originate also from physiological mechanisms. The STN is involved in somatosensory processing [5] and in visual motor function [6]. Its chronic functional inactivation elicited by DBS could arguably interfere with central processing of somatosensory and visual inputs.

The SSR is abnormal in PD [7]. Our data show that DBS improves the SSR, suggesting an effect of DBS on the autonomic nervous system. Importantly, turning DBS OFF

also increases, although not significantly, plasma renin activity. In essence, our preliminary data suggest that DBS of the STN also improves the sympathetic and cardiovascular reactivity. An attractive explanation is that these autonomic and cardiovascular effects arise from DBS spread to the zona incerta and/or to fibers passing through the subthalamic area and connecting the hypothalamus to the tegmentum as suggested by previous clinical and experimental observations [8, 9].

In conclusion, our preliminary results indicate, for the first time, that DBS of the human STN induces several non-motor effects, probably due to the interference with non-motor functions of the basal ganglia and from the stimulus spread to nearby pathways. Some of these effects might contribute to the clinical effects of DBS in PD.

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References

1. Caparros-Lefebvre D, Blond S, N'Guyen JP et al (1999) Chronic deep brain stimulation for movement disorders. *Adv Tech Stand Neurosurg* 25:61-138
2. Alexander GE, Crutcher MD, De Long MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and limbic functions. *Progr Brain Res* 85:19-146
3. Hikosaka O, Wurtz RH (1989) The basal ganglia. In: *The neurobiology of saccadic eye movement. (Reviews in oculomotor research, vol 2)*. Elsevier, Amsterdam, 2:257-281
4. Pierantozzi M, Mazzone P, Bassi A et al (1999) The effect of deep brain stimulation on the frontal N30 component of somatosensory evoked potentials in advanced Parkinson's disease patients. *Clin Neurophysiol* 110:1700-1707
5. Pinter MM, Murg M, Alesch MR et al (2000) Characteristics of somatosensory evoked potentials from the nucleus subthalamicus. *Mov Disord* 15[Suppl 3]:426
6. Matsumura M, Kojima J, Gardiner W et al (1992) Visual and oculomotor functions of monkey subthalamic nucleus. *J Neurophysiol* 67:1615-1632
7. Braune HJ, Kochunov AM, Schipper HJ et al (1997) Autonomic dysfunction in Parkinson's disease assessed by sympathetic skin response: a prospective clinical and neurophysiological trial on 50 patients. *Acta Neurol Scand* 95:293-297
8. Kim YK, Umbach W (1972) The effects of stereotaxic subthalamotomy on sympathetic tonus. *Confin Neurol* 34:156-160
9. Matsui H (1987) Effect of subthalamic stimulation of adrenal epinephrine and norepinephrine secretion in the rat. *Brain Res* 1:158-160