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REVIEW/MISE AU POINT

Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review

Effets de la stimulation cérébrale profonde sur l'équilibre et la marche chez les patients atteints de la maladie de Parkinson : une revue systématique neurophysiologique

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Summary Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and internal globus pallidus (GPi) deep brain stimulation (DBS) provides an efficient treatment for the alleviation of motor signs in patients with Parkinson's disease. The effects of DBS on gait and balance disorders are less successful and may even lead to an aggravation of freezing of gait and imbalance. The identification of a substantia nigra pars reticulata (SNr)-mesencephalic locomotor region (MLR) network in the control of locomotion and postural control and of its dysfunction/lesion in PD patients with gait and balance disorders led to suggestion that DBS should be targeting the SNr and the pedunculopontine nucleus (part of the MLR) for PD patients with these disabling axial motor signs. However, the clinical results to date have been disappointing. In this review, we discuss the effects of DBS of these basal ganglia and brainstem structures on the neurophysiological parameters of gait and balance control in PD patients. Overall, the data suggest that both STN and GPi-DBS improve gait parameters and quiet standing postural control in PD

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patients, but have no effect or may even aggravate dynamic postural control, in particular with STN-DBS. Conversely, DBS of the SNr and PPN has no effect on gait parameters but improves anticipatory postural adjustments and gait postural control.

MOTS CLÉS
Stimulation cérébrale profonde ;
Marche ;
Équilibre ;
Posture ;
Maladie de Parkinson

Résumé La stimulation cérébrale profonde du noyau sous-thalamique (NST) ou du globus pallidum interne (GPi) représente un traitement efficace des troubles moteurs de la maladie de Parkinson. Les effets de la stimulation cérébrale profonde (SCP) sur les troubles de la marche et de l'équilibre sont moins probants avec parfois une aggravation postopératoire du *freezing* de la marche et/ou des chutes. L'identification du circuit substantia nigra pas reticulata (SNr) — région locomotrice mésencéphalique (RLM), qui comprend le noyau pédunculopontin (NPP) comme ayant un rôle majeur dans le contrôle postural et la locomotion et de leur dysfonctionnement/lésion chez les patients parkinsoniens souffrant de troubles de la marche et de l'équilibre a permis d'envisager la SCP de ces régions cérébrales pour améliorer ces signes moteurs invalidants. Toutefois, les résultats cliniques ont été assez décevants. Dans cette revue, nous rapportons les effets de la SCP des ganglions de la base et du NPP sur les paramètres neurophysiologiques de la marche et du contrôle postural chez les patients parkinsoniens. En moyenne, la SCP du NST et du GPi améliore les paramètres locomoteurs et le contrôle postural en position statique, mais semble avoir peu ou pas d'effet sur le contrôle postural dynamique avec peut-être une aggravation, en particulier avec la SCP-NST. Inversement, la SCP de la SNr ou du PPN ne modifie pas les paramètres locomoteurs mais pourrait améliorer les ajustements posturaux anticipatoires et le contrôle postural dynamique.

Introduction

In 1987, high frequency stimulation of the thalamus was first proposed as a treatment for patients with tremor [7]. In accordance with experimental data obtained in animal models of Parkinson's disease (PD) [8], deep brain stimulation of the internal part of the globus pallidus (GPi-DBS), one of the major basal ganglia outputs, and subthalamic nucleus (STN-DBS) was employed for the treatment of PD and proved an efficient means of improving parkinsonian symptoms and alleviating levodopa-induced motor complications [111], with in addition significant decrease of dopaminergic drug treatment with STN-DBS [135]. Whereas the efficacy of DBS on segmental motor symptoms, i.e. rigidity, tremor and peripheral akinesia, is well established, its effect on axial disability remains controversial [36]. Published data mainly report an improvement of posture, gait and balance control after GPi or STN-DBS, with a greater improvement with STN-DBS providing that these symptoms were responsive to levodopa treatment before surgery [36,102,130]. However, the effects of DBS on balance (postural instability) and gait tend to decrease with time [23,38,105]. Moreover, some authors suggest that DBS may induce or aggravate freezing of gait and postural instability with falls in PD patients with DBS [46], but also in non-parkinsonian patients [139]. The role of stimulation parameter settings, in particular the frequency of stimulation has been suspected, freezing of gait being reported to be improved with low frequency STN stimulation (60—80 Hz) [88,103,138].

Besides the loss of dopaminergic nigrostriatal neurons, the neuropathological hallmark of PD, the role of additional brain dysfunction and/or lesions in the occurrence of balance and gait disorders has been recently pointed out. In PD patients, a loss of cholinergic neurons in the pedunculopontine nucleus (PPN), in the mesencephalic tegmentum, has been reported in those PD patients with a tendency to fall, with a decrease in thalamic cholinesterase activity [12,13,60,67]. In normal and parkinsonian monkeys, lesioning cholinergic neurons in the PPN induces gait and postural deficits resistant to levodopa treatment [51,67]. In line with these experimental data, low frequency PPN stimulation, thought to increase neuronal activity, has been tested in a few patients to improve freezing of gait and falls resistant to levodopa treatment and/or STN-DBS with disappointing and controversial results. In open label studies, PPN-DBS improved gait and balance in patients previously operated for STN-DBS, but also parkinsonian symptoms [69,121]. These first results have not been consistently confirmed in double-blind assessments [42,91,133]. However, a subjective improvement in the number of falls or freezing episodes has been frequently reported [42,127,133]. Lastly, high frequency stimulation of the substantia nigra pars reticulata (SNr), the other major basal ganglia output, has also been recently tested in PD patients to alleviate gait and balance disorders [25,132]. The combination of STN and SNr-DBS might specifically improve freezing of gait, whereas balance impairment remains unchanged [132].

In this review, we summarise the effects of DBS on neurophysiological parameters of balance and gait in PD patients. For this purpose, we first briefly describe the different DBS targets used in PD patients from an anatomical and functional point of view in relationship with known neural structures and networks involved in balance and gait control in humans. We then report the changes induced by DBS from a neurophysiological point of view on these two distinct, but interconnected, motor processes.