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REVIEW

Deep brain stimulation and multiple sclerosis: Therapeutic applications

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Abstract
Deep brain stimulation is a neurosurgical technique that can be used to alleviate symptoms in a growing number of neurological conditions through modulating activity within brain networks. Certain applications of deep brain stimulation are relevant for the management of symptoms in multiple sclerosis. In this paper we discuss existing treatment options for tremor, facial pain and urinary dysfunction in multiple sclerosis and discuss evidence to support the potential use of deep brain stimulation for these symptoms.

Contents

Abbreviations: DBS, deep brain stimulation; EDSS, expanded disability status scale; IASP, International Association for the Study of Pain; LUTS, lower urinary tract symptoms; MCS, motor cortex stimulation; MS, multiple sclerosis; MS-TN, multiple sclerosis associated trigeminal neuralgia; MVD, microvascular decompression; NICE, National Institute of Clinical Excellence; PD, Parkinson's disease; PMC, pontine micturition centre; PVG/PAG, periventricular grey area/periaqueductal grey area; STN, subthalamic nucleus; VIM, nucleus ventralis intermedius; Vop, nucleus ventralis oralis posterior; VPL, ventral posterior lateral thalamic nucleus; VPM, ventral posterior medial thalamic nucleus; ZI, zona incerta

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1. Introduction

Effective management of symptoms arising from multiple sclerosis (MS) is a major and important challenge for clinicians responsible for the care of patients with MS. Common symptoms, which arise from one or a combination of lesions within the central nervous system, include sensory disturbances such as parasthesiae, dysaesthesiae and chronic pain, motor disturbances, including weakness, spasticity, tremor and ataxia, sphincter dysfunction, which can affect bowel, bladder or both, sexual dysfunction, fatigue and cognitive symptoms (Lindsat et al., 2010). Many of these complications lead to significant disability and have a marked impact on the patient's quality of life, ability to remain in employment and his/her mental and physical wellbeing. In most cases, complete restoration of function is not possible, and the aim of the health care provider is to minimise the impact of symptoms as far as possible. Usually, low cost, low risk, conservative treatments are attempted first, such as physiotherapy or pharmacological therapies. However, if these prove to be ineffective, alternative approaches may be necessary.

Deep brain stimulation (DBS) surgery is a form of neuromodulation that involves the implantation of electrodes into selected target regions of the brain. Electrodes may be implanted bilaterally or unilaterally into a given nucleus, and occasionally into two different areas of the brain. Although its precise mechanism of action is not known with certainty, possible effects include stimulation of neurotransmitter release, blockage of local circuits by preventing action potential generation, stimulation of axonal firing in afferent/efferent axons or fibres of passage, or a combination of these effects in sections of neural tissue at different degrees of separation from the stimulating electrode. Mechanism of action may also depend on the properties of the tissues being stimulated and the stimulus duration (pulsewidth) and intensity (voltage or current) delivered by the DBS device (Kringelbach et al., 2007).

DBS implantation usually involves either one or two operations. In the first operation, electrodes are guided to the target nucleus using stereotactic techniques based on radiologically planned trajectories (and in some cases, additional real-time analysis of neurophysiological signals from the advancing electrode). Efficacy of stimulation is often tested in the operating theatre itself, where the patient is asked to evaluate the response of their symptoms to stimulation. If the operation is being carried out over two stages, the deep brain electrodes are then externalized via temporary extension leads and attached to an external battery and the patient undergoes a period of assessment (usually for up to 1 week), during which time the intensity of stimulation is varied by the clinical team and the responses to different stimulation intensities evaluated. If the patient experiences benefit from stimulation, a second operation is carried out to attach the wires to an internal pacemaker, which is normally placed either under the clavicle or in the abdomen. After the entire system has been implanted, stimulation parameters can be altered telemetrically. Pacemaker life depends on the chosen stimulation parameters but is normally between 2 and 4 years, and a small operation is required to remove and replace the pacemaker after this time. In some cases, the whole procedure described above can be carried out as a single operation, although this means that the patient is not able to undergo a week of trialling to confirm that the stimulator is effective.

DBS was initially pioneered for the management of pain and became a mainstream therapy in the 1990s. Since, then, many different target nuclei have been explored, and new therapeutic interventions have been established (Hariz et al., 2013). Certain applications of DBS are relevant for patients with MS, including the use of DBS for movement disorders and chronic pain syndromes, which are discussed in the following text, using tremor and facial pain as key examples. We also present evidence for the possible use of DBS for control of bladder function, which, although still at an experimental stage, may prove to be a significant tool for neurogenic bladder control in the future.

2. DBS for MS tremor

2.1. MS tremor: background and pathophysiology

Movement disorder in MS may be composed of various elements, including tremor, proximal postural instability and dysmetria (Bain et al., 2009). MS tremor has been defined as "*intermittent or continuous involuntary movements of a body part that [appear] rhythmic and oscillatory to visual inspection in a patient with clinically definite MS*" (Pittock et al., 2004). Accurate estimates of tremor prevalence and severity in MS are difficult to make due to the relapsing and remitting pattern of disease and the fact that tremor can be difficult to distinguish from other elements of the movement disorder, such as ataxia. One study based on 100 patients randomly selected from an MS clinic in London, UK, found a clinically detectable tremor in 58% of participants. Only 37% of participants had symptoms associated with the tremor, implying that asymptomatic tremor is relatively common. 27% had tremor related disability and 10% were described as having an incapacitating tremor (Alusi et al., 2001b). A population study based in Olmsted County, Minnesota found clinically evident tremor in 26% of

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