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Editor's Comment: Deep brain stimulation is nowadays an established and important therapeutic resource for the treatment of several movement disorders. Sometimes, though, the stimulation might be associated with the emergence of novel, unwanted types of movement disorders. Here, Drs. Baizabal-Carvallo and Jankovic present a comprehensive review of this complex topic, divided by the site of deep brain stimulation (subthalamic nucleus, globus pallidus, thalamus, and pedunculopontine nucleus), and including frequency, phenomenology, pathophysiology and management approaches. This review is particularly interesting and timely as scientific and technological advances are being translated into novel devices and paradigms for deep brain stimulation, which are expected to enable soon a more precise and versatile control of the targeted circuitries.

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Review article

Movement disorders induced by deep brain stimulation

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ABSTRACT

Deep brain stimulation represents a major advance in the treatment of several types of movement disorders. However, during stimulation new movement disorders may emerge, thus limiting the positive effects of this therapy. These movement disorders may be induced by: 1) stimulation of the targeted nucleus, 2) stimulation of surrounding tracts and nuclei, and 3) as a result of dose adjustment of accompanying medications, such as reduction of dopaminergic drugs in patients with Parkinson's disease. Various dyskinesias, blepharospasm, and apraxia of eyelid opening have been described mainly with subthalamic nucleus stimulation, whereas hypokinesia and freezing of gait have been observed with stimulation of the globus pallidus internus. Other deep brain stimulation-related movement disorders include dyskinesias associated with stimulation of the globus pallidus externus and ataxic gait as a side effect of chronic bilateral stimulation of the ventral intermediate nucleus of thalamus. These movement disorders are generally reversible and usually resolved once the stimulation is reduced or turned off. This, however, typically leads to loss of benefit of the underlying movement disorder which can be re-gained by using different contacts, changing targets or stimulation parameters, and adjusting pharmacological therapy. New and innovative emerging technologies and stimulation techniques may help to prevent or overcome the various deep brain stimulation-induced movement disorders. In this review we aim to describe the clinical features, frequency, pathophysiology, and strategies for treatment of these iatrogenic movement disorders.

1. Introduction

Deep brain stimulation (DBS) has proven effective in the treatment of several hyper- and hypokinetic movement disorders (MDs), such as Parkinson's disease (PD) [1,2], and many other MDs [3–8]. However, during stimulation of different anatomical targets other movement disorders may emerge, hampering the efficacy of the stimulation and posing new therapeutic challenges for the DBS programmer (Table 1). In this review, we aim to identify the frequency, phenomenology, pathophysiology and potential treatments of DBS-related hypo- and hyperkinetic MDs, including parkinsonism, chorea, dystonia, tremor, myoclonus, abnormal ocular movements, gait and balance disturbances.

2. Subthalamic nucleus DBS related movement disorders

2.1. Dyskinesias

Hemiballism and other hyperkinesias may follow a variety of lesions in previously intact contralateral subthalamic nucleus (STN)

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Table 1
Summary of DBS-induced movement disorders.

Nucleus	MDS induced by stimulation of the nucleus itself[a]	MDS possibly induced by stimulation of surrounding tracts[b]
STN	Dyskinesias:	Blepharospasm, AEO, and contralateral muscle contractions (corticobulbar and corticospinal tracts)
	Chorea	Ataxia and gait disorder (cerbellothalamic tract)
	Athetosis	Monocular deviation (oculomotor fibers)
	Dystonia	Ipsilateral mydriasis (sympathetic fibers in ZI)
	Hypotonia	Dysarthria (cerebellothalamic tract)
	Gait disorder with FOG	Gait disorder and FOG (pallidothalamic fibers)
	Akinesia	
	Contraversive conjugated ocular deviation	
GPi	Dyskinesias:	Contralateral muscle contractions (corticobulbar and corticospinal tracts-internal capsule)
	Chorea	Dysarthria (cerebellothalamic tract)
	Dystonia	Gait disorder and FOG (pallidothalamic fibers)
	Parkinsonism	Contraversive eye deviation (internal capsule)
	Gait disorder with FOG	
	Stuttering	
GPe	Dyskinesia:	–
	Chorea	
Vim	Tremor (with LFS)	Dysarthria (cerebellothalamic tract, internal capsule)
	Gait disorder	Contralateral muscle contractions (corticobulbar and corticospinal tracts-internal capsule).
	Hypotonia	
	Dysarthria	
	Dysmetria	
PPN	Akinesia (with HFS)	Abnormal ocular movements (oculomotor fibers)
		Myoclonus (thalamic projections)
		Tremor (subthalamic area)

AEO: apraxia of eyelid opening; FOG: freezing of gait; GPe: globus pallidus externus; GPi: globus pallidus internus; HFS: high frequency stimulation; LFS: low frequency stimulation; PPN: pedunculopontine nucleus; STN: subthalamic nucleus; VIM: ventral intermediate nucleus; ZI: zona incerta.

[a] The movements and motor phenomena are usually not strictly time-locked to the stimulation; they tend to habituate and may respond to pharmacological therapy in some cases.

[b] These phenomena are more time-locked to the stimulation and usually do not habituate with chronic stimulation.

[9]. Although the STN is one of the main targets to treat several manifestations of PD including rigidity, bradykinesia, tremor, and levodopa-related motor fluctuations [10]; STN DBS can also improve levodopa-induced dyskinesias (LID), with the most robust effect on levodopa "off" dystonia, followed by diphasic dyskinesia and peak-dose dyskinesia [11,12]. Despite this well-known suppressive effect on LID, several types of dyskinesias can be actually induced by STN stimulation. These dyskinesias can resemble hemiballism and other hyperkinetic disorders associated with acute lesions of the STN [12,13]. As the STN stimulation is turned on the first effect typically observed is disappearance of off-period dystonia, but with higher voltage and as the rigidity decreases, diphasic dyskinesia may appear and with further voltage increase choreic dyskinesia can emerge along with hypotonia, similar to what is observed with increasingly higher doses of dopaminergic drugs [11]. Although the anti-dyskinetic effect of STN stimulation is mainly attributed to reduced dose of levodopa, STN stimulation alone can decrease the intensity and duration of diphasic and peak-dose dyskinesias [11]. Dyskinesias, usually in the form of contralateral hemiballism or hemichorea, can occur immediately after electrode implantation into the STN, presumably as a lesioning effect [11]. More typically, they are observed within the first three months following surgery [14,15]. These dyskinesias may appear within a few seconds to several hours after turning the stimulator on, but usually disappear immediately upon turning the stimulator off [13]. Although DBS-induced dyskinesias are usually transient, some patients experience persistent dyskinesia that cannot be treated without inducing an "off state," so-called "brittle" dyskinesia [16]. In one study, "brittle" dyskinesia were identified in 4 out of 197 patients (2%) treated with STN DBS but in none of the 75 patients treated with pallidal DBS [16].

Although the mechanism of DBS-induced dyskinesia is not well understood, the involuntary movements have been attributed to disruption of the normal basal ganglia circuitry. In some cases, however, the relationship between DBS and the associated disorder is even more speculative. For example, one patient, a 76 year-old man treated with STN DBS, developed severe dyspnea and stridor associated with fixed epiglottis involving the top of the larynx documented with fiber-optic examination, requiring emergency tracheostomy [17,18]. The authors suggested that the improvement of the fixed epiglottis and of the accompanying lower limb dystonia after reducing the stimulation voltage provided evidence that these phenomena were related to the STN DBS [17].

While the pathophysiology of DBS-induced dyskinesias is not well understood, several risk factors have been suggested for the development of STN DBS-induced dyskinesias such as severe dyskinesias preoperatively, young onset PD, and contact location within the sensorimotor part of the STN [14,16]. Increased neuronal activity in the STN and globus pallidus internus (GPi) leading to excessive inhibition of thalamo-cortical and brainstem nuclei is one of the pathophysiological hallmarks of PD [19]. Evidence from primates and humans shows a neuronal glutamatergic hyperactivity of the STN, with marked improvement after lesioning the STN and the GPi [20]. In the medication off-state, the STN of PD patients shows a maximal power or amount of activity in the beta band (11–30 Hz), which is shifted mainly to the gamma (>60 Hz) band after dopaminergic therapy, associated with normal voluntary movements [21], and theta (4–10 Hz) band which coincides with the appearance of dyskinesia [22]. It is, therefore, possible that in DBS-induced dyskinesias the power activity in the STN is shifted mainly to the theta band range, coincident with the abnormal involuntary movement. Furthermore, experimental studies have shown that suppression of strongly synchronized local field potentials (LFPs) below 30 Hz in the pallidum of PD patients correlates with LID [23].

Glutamate has been postulated to play a key role in the pathogenesis of LID and possibly DBS-induced dyskinesias. High frequency stimulation (HFS) of the STN in parkinsonian rats induces a significant increase in the expression of vesicular glutamate transporters 1 to 3 (VGLUT1-3) in the basal ganglia [24]. This is