Mood and behavioural effects of subthalamic stimulation in Parkinson's disease

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Deep-brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for motor complications in Parkinson's disease. 20 years of experience with this procedure have contributed to improved understanding of the role of the STN in motor, cognitive, and emotional control. In Parkinson's disease, the pathological STN neuronal activity leads to motor, cognitive, and emotional inhibition. Deafferentation of the STN by DBS can reverse such behavioural inhibition. The release of this brake allows both motor and non-motor improvement, but can also be associated with excessive motor, cognitive, and emotional behavioural disinhibition. Conversely, the notable reduction in anti-parkinsonian drug dose allowed by motor improvement can unveil mesolimbic hypodopaminergic behaviours such as apathy, anxiety, or depression. Fine-tuning of stimulation parameters with dopaminergic drugs is necessary to prevent or improve pathological behaviours.

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Introduction

Subthalamic nucleus deep-brain stimulation (STN-DBS) is a well recognised treatment for motor complications of levodopa therapy in patients with Parkinson's disease. Patient selection, surgical technique, mechanisms of DBS, postoperative management, and motor outcomes have been extensively reviewed.[1–4] However, patients with Parkinson's disease can also have non-motor symptoms related both to the dopaminergic deficit affecting the mesolimbic system (such as fatigue, apathy, anxiety, depression, and pain—the so-called hypodopaminergic syndrome) and to a dopaminergic overdose (impulse control disorders, punding, and dopamine dysregulation syndrome—the so-called hyperdopaminergic syndrome).[5,6]

Since its first applications, much work has been published on the neuropsychiatric changes after STN-DBS, raising concerns over its safety. The reports are conflicting, ranging from new onset or worsening of pre-existing behavioural disorders to improvement of neuropsychiatric symptoms after STN-DBS. Therefore, after 20 years of STN-DBS use, improved understanding is needed of the mechanisms behind either worsening or improvement in mood and behavioural effects, which will eventually result in rational management and improved outcomes. Stimulation of the brain target can be switched on and off to study the pathophysiology of diseases, which is especially useful when combined with neuroimaging and neurophysiology studies. In this Review, we focus on the effects of STN-DBS on emotions and non-motor behaviour, summarising clinical observations and showing how the technique has contributed to progress in understanding the pathophysiology of dopamine-dependent behaviours.

STN function

The STN, or corpus Luysii, first described by J B Luys in 1865, is a lens-shaped, obliquely oriented nucleus, located at the diencephalon-mesencephalic junction. The average size of the human STN is 3×5×12 mm.[7–9] Despite this small size, the STN is thought of as one of the driving forces of the basal ganglia.[10] In 1927, J P Martin described the "syndrome of the body of Luys", based on clinicopathological observations after a lesion of the STN. This syndrome included not only severe hemichorea, but also emotional, cognitive, and behavioural abnormalities, which gave the first clue about the function of the STN.[11] Although hemiballism was retained as the most important sign of STN lesion, the non-motor effects were largely ignored, or were attributed to surrounding structures of the STN.[12] The description of behavioural effects noted with STN-DBS[13] has rekindled interest in the non-motor functions of the STN.

The STN is part of the basal ganglia, which is an integral part of a series of parallel but tightly linked cortico-basal ganglia circuitries involved in the regulation of motor, cognitive, and emotional behaviour.[14] Animal studies and post-mortem anatomical and neurochemical human data led to a new functional model of basal ganglia disorders in which the STN was thought of as the nexus of motor control activity (figure 1).[14–18] According to this model, the excitatory glutamatergic STN-globus pallidus pars interna (GPi) or STN-substantia nigra pars reticulata (SNr) projections drive the inhibitory basal ganglia outflow, resulting in decreased activation of the supplementary motor cortex involved in planning of movement. As such, hyperactive subthalamic neuronal activity can explain bradykinesia in Parkinson's disease. This model was confirmed by an improvement of bradykinesia after subthalamotomy in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated monkeys—a model of levodopa-sensitive Parkinsonism.[19] This discovery opened the way to successful STN-DBS in the parkinsonian monkey and, finally, in patients with Parkinson's disease.[20,21]

The present model of the basal ganglia proposes that two parallel projections originate from distinct populations of striatal neurons—the so-called direct and indirect pathways. These two pathways are thought to have opposite effects: the direct pathway enables the wanted movements, and the indirect pathway (from the

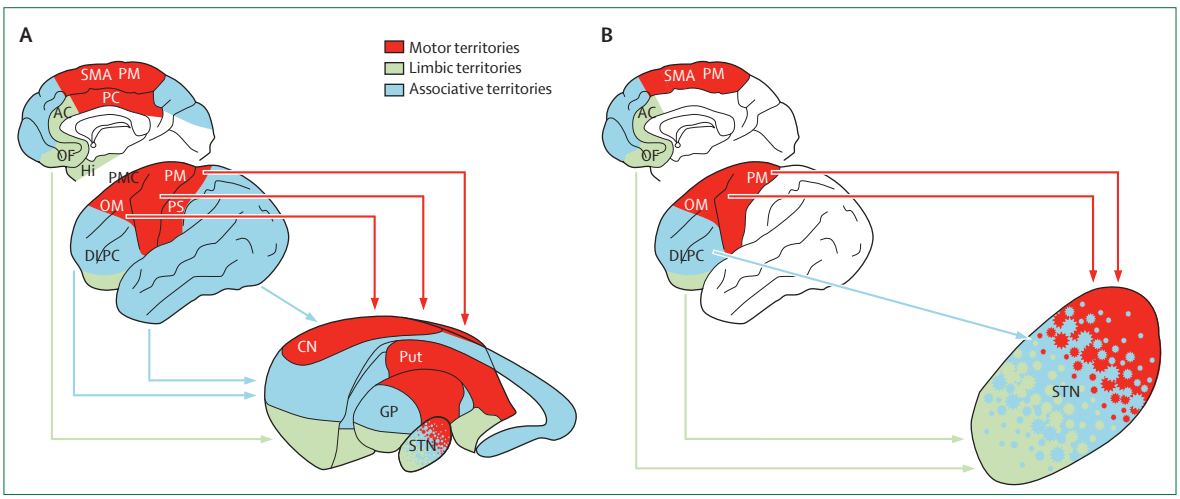

Figure 1: **Two different projection systems from the cortex to the basal ganglia allowing for convergence and integration of motor, associative, and limbic information at the level of the subthalamic nucleus (STN)**

Corticostriatal (A) and corticosubthalamic (B) entries into the basal ganglia. In the STN, widespread information from large areas of the cortex via the indirect cortico-striato-globus pallidus externus-STN (A) and strategic prefrontal cortical information via the fast hyperdirect corticosubthalamic pathways (B) converge in a nexus, putting the STN in a key position for behavioural control.[15,16] A high degree of functional overlap in the STN enables the fusion of motor, cognitive, and emotional information (B), enabling orchestration of complex behaviours.[15–17] Figure adapted from Yelnik,[15,16] integrating new information of a high degree of overlap between STN subterritories.[17] STN=subthalamic nucleus. SMA=supplementary motor area. PM=primary motor cortex. PC=posterior cingulate. AC=anterior cingulate. OF=orbitofrontal cortex. Hi=hippocampus. DLPC=dorsolateral prefrontal cortex. OM=oculomotor field. PMC=premotor cortex. PS=primary sensory cortex including sensorimotor function. CN=caudate nucleus. Put=putamen. GP=globus pallidus.

striatum via the external globus pallidus to the STN) inhibits the unwanted movements. In addition to the corticostriatal input (figure 1A), the basal ganglia also receive frontal cortical input through the hyperdirect corticosubthalamic projections (figure 1B).[17,22]

Like the striatum and pallidum, the STN is divided into sensorimotor, associative, and limbic territories, based on connections with specific functionally segregated regions of the striatum and pallidum.[23] The hyperdirect corticosubthalamic connections mostly have the same somatotopical organisation as the corticostriatal input into the basal ganglia.[17] A high degree of convergence exists for prefrontal corticosubthalamic projections. Unlike striatal territories, the borderlines between the functional territories at the level of the STN overlap.[17] Moreover, the subthalamic interneurons can cross the borders between functional territories.[15] Thus, this anatomical basis allows both convergence and integration of motor, associative, and limbic information at the level of the STN (figure 1).[17] The prefrontal cortex helps to regulate deliberate control over habitual behaviour. As the STN controls the inhibitory basal ganglia-thalamocortical outflow, the monosynaptic corticosubthalamic pathway places the STN at a strategic position to exert rapid control and integrate motor, cognitive, and emotional aspects of behaviour that modulate corticostriatal parallel processing (figure 1).[17,24] The STN seems to be a key player in inhibitory control of complex motivated behaviour.

If the action control via inhibitory processes is a function of the STN, then lesion or functional inhibition by DBS should induce motor and behavioural disinhibition.[25] STN lesions in non-parkinsonian rats induce impulsivity in a choice selection task.[26] The stop-signal paradigms measure reactive inhibition, which consists of stopping a prepared or already-initiated action when this is indicated by an external signal. In an imaging study in healthy individuals,[27] stop-signal inhibition was associated with activation of a fast-operating network between the inferior frontal gyrus, the presupplementary motor area, and the STN. In such a network, activation of the STN via the hyperdirect pathway is thought of as an emergency brake for last-minute action inhibition.[25,27] Compared with healthy controls, patients with Parkinson's disease take longer to inhibit ongoing responses in stop-signal tasks.[28] Reaction time in stop-signal tasks is ameliorated by STN-DBS (figure 2).[29] Clinically observed pathological behaviours that can be directly attributed to STN-DBS per se (ie, those that occur in the on-stimulation condition and disappear in the off-stimulation condition)[13,16,25,30–32] are compatible with release from executive control of so-called prepotent human behaviours—ie, powerful basic complex behaviours easily elicited by a stimulus that can be more strongly expressed in a particular individual according to genetic predisposition and environmental reinforcement.[32] Results of an electrophysiological study in patients with Parkinson's disease[29] directly implicated the STN in motor inhibition. STN neuronal activity recorded from implanted DBS electrodes during successful performance of a stop-signal task was modulated by dopaminergic treatment (figure 2). This result is compatible with the notion that dysfunction of the corticosubthalamic