

Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Why so successful?

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Abstract

The subthalamic nucleus (STN), historically referred to as the corpus Luysii, is a relatively small nucleus located in the junction between the diencephalon and midbrain. An important discovery was made in the late 1980s by Miller and DeLong putting the focus on the STN demonstrating abnormal hyperactivity in this area in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated non-human primates. Shortly after, Benazzouz and colleagues showed STN deep brain stimulation (DBS) to significantly improve MPTP induced parkinsonian symptoms, including rigidity and bradykinesia in monkeys. In the same year, Pollak *et al.* were the first to publish a French case report describing the potential of STN DBS in a patient with advanced Parkinson's disease (PD) in whom they observed improvement of akinesia. Many other prospective studies showed similar improvements of motor symptoms and the lowering of required levodopa dosage. The great success of STN DBS for the treatment of advanced PD is underlined by the growing number of patients treated. STN DBS also provided additional insight into the role of the STN, which is important not only in motor control but also in cognitive and emotional functions.

Key Words: Corpus Luysii, deep brain stimulation, Parkinson's disease, subthalamic nucleus

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INTRODUCTION

The subthalamic nucleus (STN), historically referred to as the corpus Luysii, is a relatively small nucleus located in the junction between the diencephalon and midbrain.^[8,9,20] Now it is well established that the STN contains glutamatergic projection neurons essential for the regulation of the cortico-basal ganglia-thalamocortical circuit.^[6,15] In this historical review, we want to discuss key findings emphasizing the importance of the STN in motor function. We will

also highlight how these contributed to the clinical success of stereotaxic procedures targeting the STN for Parkinson's disease (PD) over the past two decades.

HOW THE STN BECAME A SUCCESS

Alexander and Crutcher introduced a model of the basal ganglia motor circuit where cortical motor information is processed in the basal ganglia via the "direct" and "indirect" pathways.^[1] In brief, the former promotes movement whereas the latter inhibits movement.

Interestingly, the STN is centrally located in the indirect pathway. It exerts a powerful excitatory influence on the basal ganglia output structures globus pallidus internus/substantia nigra reticulata (GPi/SNr), the activation of which inhibits thalamic projections to the motor cortex and inhibits movement.^[6,20] This model is widely applied in the context of movement disorders like PD. An important discovery was made in the late 1980s by Miller and DeLong putting the focus on the STN demonstrating abnormal hyperactivity in this area in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated non-human primates.^[14] This was the first evidence that abnormal STN activity may be responsible for the generation of parkinsonian motor symptoms like hypokinesia and formed the foundation for the current STN and PD related research.

Shortly after, Bergman and coworkers demonstrated that ibotenic lesions of the STN were effective in alleviating MPTP-induced motor impairment in the non-human primate.^[5] Similarly Aziz *et al.* reported that radiofrequency lesions of the STN improved the motor function of MPTP treated monkeys.^[3] They also described that chronic levodopa or apomorphine therapy was no longer necessary. Altogether STN lesions seemed to alleviate multiple parkinsonian symptoms.

Interestingly, Andy *et al.* published a series of 58 PD patients in 1963, who had undergone subthalamotomy surgery for PD-related tremor. Lesions of the posterior subthalamic region were effective in alleviating tremor.^[2] However, they did not describe the effect on other parkinsonian motor symptoms; neither did they elaborate about the rationale for this treatment. It was not until the electrophysiological findings of Miller and DeLong and the subsequent lesion experiments carried out in parkinsonian non-human primates that the interest for STN was regained for the treatment of PD. Simultaneously electrical stimulation [deep brain stimulation (DBS)] was re-introduced to replace lesion surgery. DBS is favorable over lesion surgery as it is adjustable to the individual patient's demands. Benazzouz and colleagues showed STN DBS to significantly improve MPTP-induced parkinsonian symptoms, including rigidity and bradykinesia in monkeys.^[4] In the same year, Pollak *et al.* were the first to publish a French case report describing the potential of STN DBS in a patient with advanced PD in whom they observed improvement of akinesia.^[16] Soon a small series of three patients with akinetic-rigid PD followed who underwent bilateral STN DBS.^[11] Stimulation reduced akinesia, rigidity, and levodopa usage substantially in all three patients. Despite these encouraging results, the success of STN DBS was still uncertain. Targeting the relatively small STN was challenging and was dealt with a Talairach diagram with ventriculography in combination with electrophysiological monitoring [Figure 1] and intraoperative stimulation.

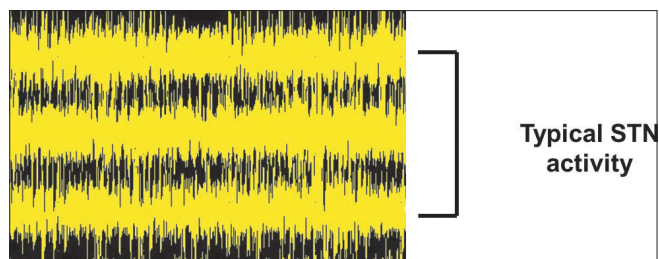


Figure 1: A picture of electrophysiological activity measured by the microelectrode during the subthalamic nucleus (STN) deep brain stimulation surgery in a patient with advanced PD. Activity of the STN was typically characterized by a neuronal firing pattern consisting of increased baseline activity and a strong increase of high-voltage spikes

Also, the effects of electrical stimulation on the STN and connected structures were unknown. Many clinical trials and experimental studies followed over the next two decades.

An elegant neurosurgical treatment was on the verge of bringing new perspectives to medically out-treated PD patients. Limousin *et al.* published a series of 24 patients with idiopathic PD. After a 1-year follow-up period, bilateral STN DBS dramatically improved motor scores (off medication; $\pm 60\%$). Also, the required levodopa was halved with concurrently less levodopa-induced dyskinesias.^[12] After few years, the same French group published a 5-year follow-up study of 49 patients, confirming and extending previous results. A relatively young age, good levodopa response, and no cognitive impairments were the favorable factors for a good outcome.^[10] Many other open-label prospective studies showed similar improvements of motor symptoms and the lowering of required levodopa dosage.^[7,17,24] Importantly, patients and their caregivers reported improvement in quality of life after surgery.^[21] Stimulation-induced side effects included dysarthria, weight gain, and paresthesias, but were mainly mild and temporary.^[7,25] Postoperative changes in cognitive and affective behavior, including depression and mania, have been observed and should be closely monitored.^[21]

Experimental studies have been utilized to further explore the role of the STN in PD neuropathophysiology and to elucidate the working mechanisms of STN DBS. Abnormal STN activity was recorded in PD patients and various animal models of PD. The exact relationship between STN activity and motor symptoms is still under debate. Although STN DBS clinically mimics a lesion, it is well established now that the influence of electrical stimulation on the targeted structure depends on the type of STN neurons and related areas, as well as the stimulation parameters.^[13]

Besides the direct effects on symptom relief, several lines of evidence suggest STN DBS to have neuroprotective properties on the remaining nigral dopamine neurons.^[18,22]

Although very interesting, this matter has remained controversial and it could be questioned whether saving the small remaining number of dopamine neurons is actually clinically relevant. The development of behavior changes after STN DBS has also emphasized the non-motor functions of this nucleus. The STN is involved in the upstream cognitive and limbic networks, as well as the modulation of the raphe serotonin system.^[19,23]

The great success of STN DBS for the treatment of advanced PD is underlined by the growing number of patients treated. Already more than 100,000 patients have been operated by this technique. STN DBS alleviates not only tremor, but also bradykinesia and rigidity. STN DBS also provided additional insight into the function of the STN, which is important not only in motor control but also in cognitive and emotional functions.

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