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New Frontiers in Parkinson's Disease Therapy: Deep Brain Stimulation

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Introduction: Given the limitations of current drug therapies for most neurodegenerative diseases, a strong trend towards developing and implementing surgical interventions that provide adjustable and effective symptomatic relief is currently underway in the neurosciences. One surgical approach involves implanting electrodes into the brain to directly apply high-frequency electrical stimulation (>130 Hz) until the occurrence and severity of the disease-associated symptom is reduced. This anatomically discrete but highly invasive surgical intervention is called deep brain stimulation (DBS). In this review, we summarize our current understanding of DBS, especially its use in Parkinson's disease (PD) patients who no longer respond to conventional drug therapy.

The Disease: PD is a neurodegenerative disease characterized by the gradual and relentless demise of dopamine (DA) neurons in the substantia nigra pars compacta (SNPC), a nucleus of the midbrain (Rosenthal, 1998; Rothstein and Olanow, 2008). When a significant portion of DA cells die in PD, a number of debilitating symptoms emerge including, (1) rhythmic tremors at rest, (2) inability to initiate (akinesia) or complete (bradykinesia) voluntary movements and (3) cogwheel rigidity (increased motor tone). These untoward symptoms are manifested because loss of DA cells leads to excessive inhibitory stimuli within a group of forebrain nuclei (the basal ganglia) that play an important role in somatomotor control. Further, the neural or chemical deficiencies that underlie PD pathology also alter feedback loop signaling cues that exist between DA cells of the basal ganglia and the thalamus. The net result is an increased inhibition of thalamocortical neurons that are responsible in part for the movement disturbances of the disease (Fig. 1).

What Causes Cell Death in PD? Despite intensive research, it is not known what the causative pathological events are, or why midbrain DA neurons are selectively damaged by the disease. Headway on this point, however, has been made by identifying specific gene mutations in relatively rare familial forms of PD. For instance, people of Japanese and European descent who carry variants of five genes (PARK16, BST1, SNCA, LRRK2 and MAPT) may be at higher risk of developing PD than other population-specific individuals (Satake et al., 2009; Simon-Sanchez et al., 2009). Some of these genes code for proteins that have a critical role in degrading unwanted or toxic molecules that threaten cell function and viability (Shen and Cookson, 2004). Other gene(s) products are involved in protecting cell constituents from oxidative stress, thus raising the possibility that the selective vulnerability of DA neurons in the SNPC might be due to their intrinsic predisposition to generate reactive oxygen

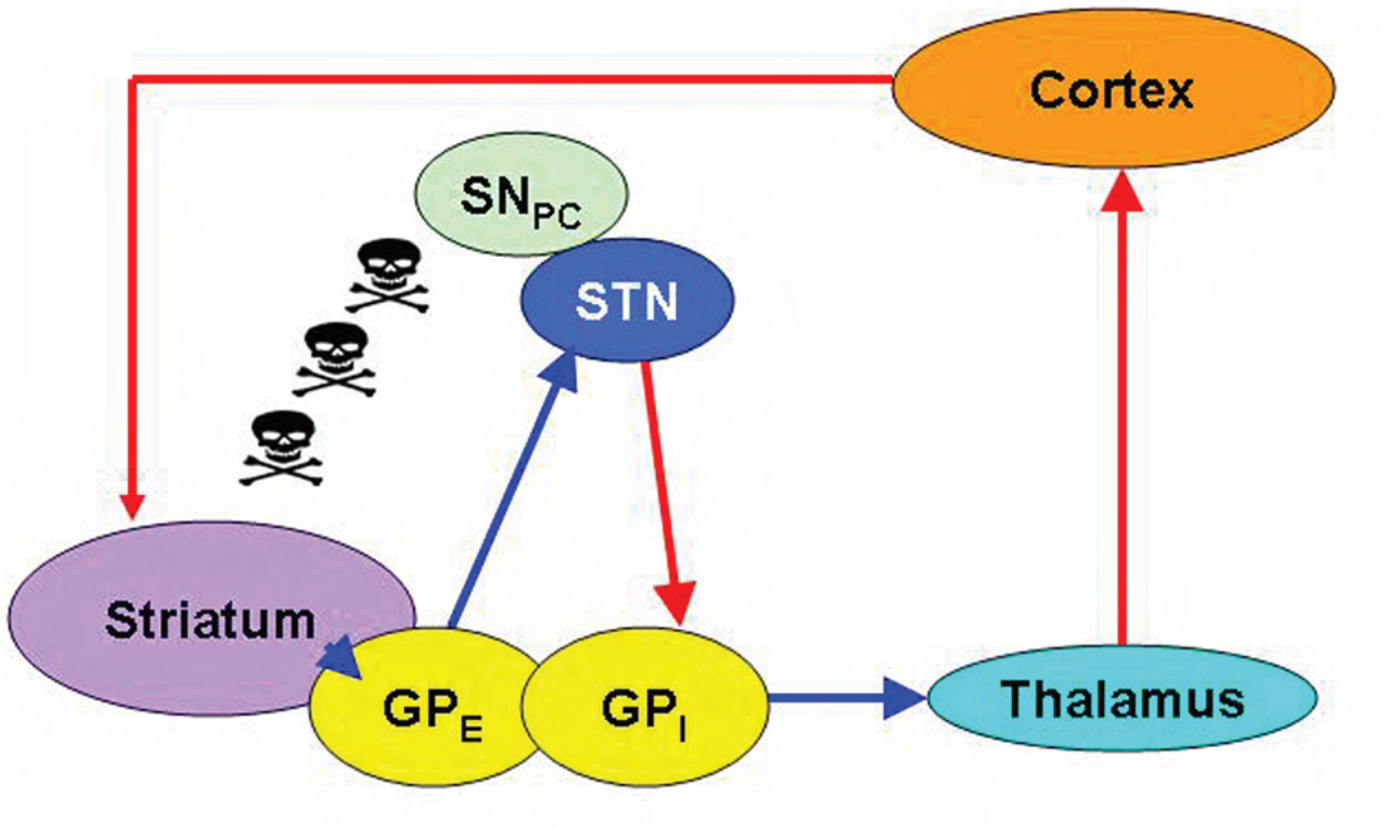

Fig. 1. A schematic and highly simplified description of the basal ganglia-thalamocortical motor circuitry affected by PD is shown. When DA cells of the SNPC face either internal or external death factors, the net result is a significant decrease in thalamocortical neuronal activity. In brief, loss of DA cells increases the firing activity of the corticostriatal glutamate neurons (red arrows) which in turn leads to increased activity of gamma-aminobutyric acid (GABA) cells (blue arrows) projecting from the striatum to the external globus pallidus (GPE). This causes a salient and persistent (glutamate) overactivity of the STN. There is also a (direct) reduction of GABA activity from the striatum to the internal globus pallidus (GPI). High-frequency electrical stimulation to the STN is thought to inhibit the overactive thalamic nucleus and restore normal basal ganglia output, thus providing a dramatic improvement in motor function.

species (Giasson and Lee, 2001). However, most cases of PD are diagnosed as idiopathic or sporadic. Thus, we are left with the conclusion that unknown pathogenic factors in the internal or external host environment might spontaneously affect DA cells in a unique property to initiate self-injury.

What Can Currently Be Done For PD Patients? The most prevalent therapy to counteract the neural or chemical deficiencies that underlie PD is levodopa (Sinemet® = carbidopa-levodopa). This drug compensates for the reduction of DA in the parkinsonian forebrain to consistently reverse akinesia, bradykinesia and rigidity. Unfortunately, levodopa is not effective in reducing mild tremors, nor does it prevent the invariably progression of the disease. In fact, most PD patients face a gradual decline of levodopa efficacy after 5 years of daily treatment, with induction of severe side effects known as dyskinesias. In addition, after long-term levodopa treatment, a constellation of non-DA symptoms emerge that contribute greatly to the disability of late-stage PD (Fox et al., 2008). These symptoms include choking and drooling, sleep disturbances, bowel dysfunction, mood disorders, dementia, and postural instabilities. As a result, most PD patients invariably reach a Hoehn and Yahr stage 5 of disability, which represents a bedridden state of pathology

(Maetzler et al., 2009). In light of this looming prognosis, there is a pressing need for developing both DA and non-DA therapies for the future management of sporadic PD.

What About DBS? DBS is a relatively new surgical procedure for PD patients with medically intractable motor symptoms. DBS often leads to striking improvements in bradykinesia and severe dyskinesias induced by long-term use of levodopa (Chang, 2004; Volkmann, 2004). Thus, DBS is an attractive alternative to DA therapies and their dramatic complications in advanced PD. Further, DBS is relatively safe, reversible and adjustable, if rather blunt, surgical procedure for treating an increasingly large number of neurological and psychiatric disorders, including dystonia, epilepsy and endogenous depression (Chang, 2004). The rationale for DBS grew out of experiments with animal models of PD in which discrete lesions to basal ganglia circuits, more specifically the thalamus (thalamotomy) and globus pallidus (pallidotomy), improved parkinsonian-like signs. These observations led to the delivery of pulsing electrical currents to highly specific brain regions such as the sub-thalamic nucleus (STN), thus mimicking the functional effects of pinpoint ablations. In particular, the STN has become the most sought out target for DBS because high-frequency electrical stimulation to this nucleus successfully restores thalamocortical activity feedback loops. Yet, empirical efficacy aside little is known of the mechanisms by which electrical stimulation to the thalamus disables abnormal rhythmic oscillations that seem to generate dyskinesias.

Surgical Procedure: Under local anesthesia, a craniotomy (or drilling holes in the skull) is performed on patients with advanced PD. Stimulating quadripolar electrodes are implanted bilaterally into the STN using stereotactic coordinates provided by ventriculography methods done at the onset of the surgical procedure (Dormont et al., 2010). The thin wire electrodes are then aimed at the STN where different currents are applied at varying depths until the desired effect (e.g., degree of rigidity) is found (Fig. 2). In most cases, the electrode leads are left outside the skull for a day or two to verify signal strength and final contact position to the STN before they are attached to a step- sized generator, implanted just under the left clavicle. Three-D computer tomography scans are also performed a few days later to confirm position of the electrodes. The Medtronic generators deliver electrical stimulation not in response to abnormal brain activity, but rather on a pre-programmed set schedule for 24 hours a day. Thus, electrical stimulation to the STN is delivered without feedback modulation (meaning, DBS is an open loop system).

How Does DBS Work? The exact mechanisms underlying DBS are still shrouded in mystery; no-one knows what actually happens at the cellular level when the STN is electrically stimulated. One possibility is that DBS affects neuronal membrane potentials and voltage-dependent Ca2+ channels surrounding the pathologic circuitry. Thus, DBS could be altering the firing pattern, not the firing rate, of STN neurons to immediately produce a therapeutic effect near the electrode's tip (Chang, 2004; Chan et al., 2007). Another tentative possibility is that DBS is not a localized event, but instead, high-frequency electrical stimulation affects the axons (not the cell bodies) that carry signals into the STN from other areas, including the primary motor cortex. Indeed, this hypothesis is supported by animal models of PD in which optically stimulated cortical neurons, whose axons reach down the STN, also diminish parkinsonian-like signs as efficiently as conventional DBS (Histed et al., 2009). These pre-clinical trials raise the possibility that DBS may differentially act on axons located within microns of the stimulation site, and point to the primary motor cortex as a crucial circuit in the therapeutic effects of DBS.

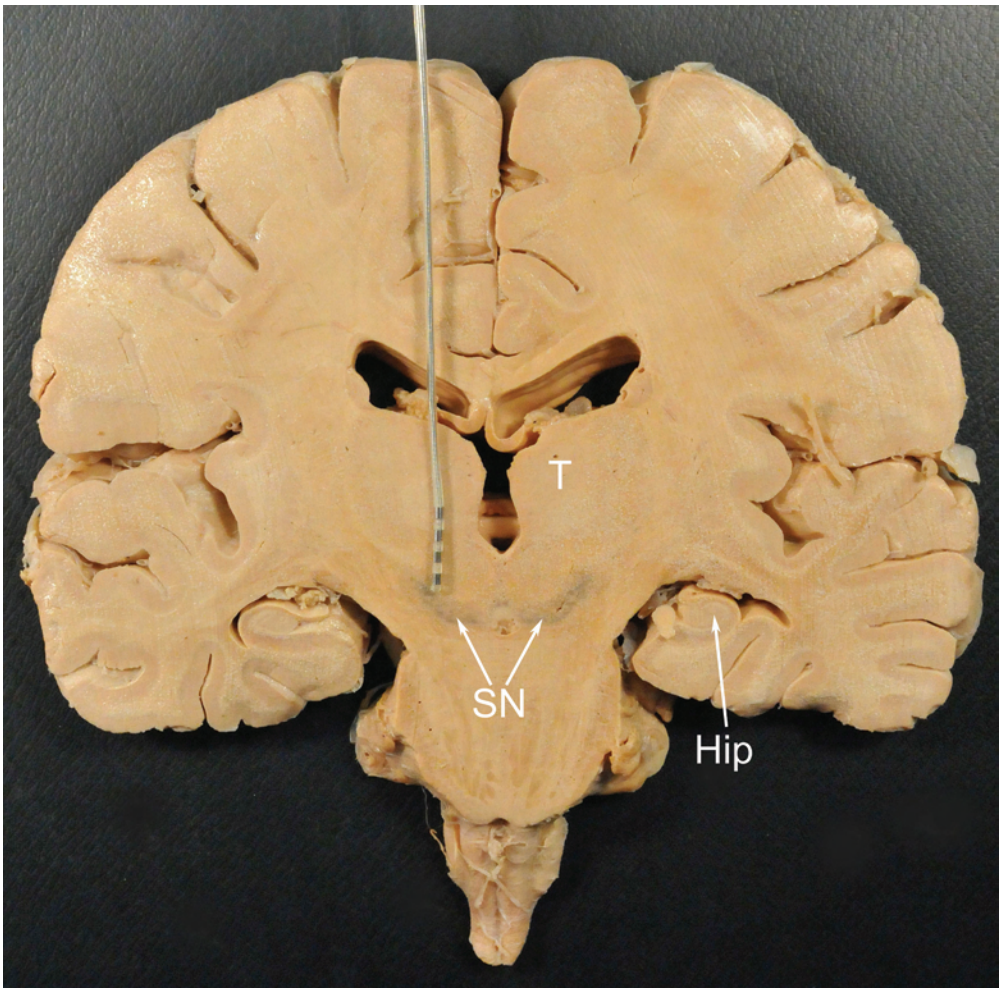

Fig. 2. This cross-sectional view of the human brain illustrates the positioning of the quadripolar electrode within the STN. The SN is ventral to the STN. The stimulation characteristics for most PD patients are as follows: mean frequency = ~135 Hz; mean voltage = ~2.3 V; mean pulse width = ~65 μs for either the right or left STN. Note that high stimulation parameters are required to maintain an optimal prophylactic effect. Nevertheless, levodopa medication is continuously reduced after DBS (mean equivalent dose before STN DBS = ~1066 mg and ~955 mg after STN DBS). Abbreviations: Hip = Hippocampus, T = Thalamus.

What Key Safety Issues Must Be Resolved in DBS? DBS is currently accepted as an adjunct therapy for end-stage PD; it dramatically reduces dyskinesias and decreases dependence on levodopa in some patients. However, DBS is not consistently effective in reducing tremors nor does it help with the non-DA symptoms of the disease (e.g., constipation or sleep disturbances). To further complicate this matter, inserting wired electrodes through the skull and into the brain can cause astrocytic gliosis, inflammation and cell dystrophy. This scarring process, in turn, is a major source of failure in chronically implantable electrodes. Long-term complications of DBS can also be observed. For instance, high-frequency electrical stimulation of the STN may lead to cognitive (e.g., reduction in verbal fluency performance) and psychiatric (e.g., mania and hypomania) disorders that can be a matter of concern to both patients and clinicians alike (Funkiewiez et al., 2004; Parsons et al., 2006; Marconi et al., 2008). Such examples illustrate the possible dramatic side-effects of DBS. It is noteworthy that these side-effects are remitted immediately

when the electrodes are moved away from the STN or when stimulation parameters are readjusted, thus suggesting that this particular parcellation of the thalamus is involved in a distributed network of synapses underlying associative and limbic functions. Indeed, anatomical and neuroimaging data demonstrate that the STN can be divided into sensorimotor (dorsolateral), limbic (medial) and cognitive-associative (ventromedial) areas (Parent and Hazrati, 1995). These findings are of particular interest to neuroscientists and of practical relevance to neurosurgeons.

Welcome to the Homonculus Machine: There is no doubt that DBS and other neural prostheses have an enormous future potential in neuroscience and neurosurgery. Brain-machine interfaces are clinically well-established in restoring motor function in PD and directing artificial limbs in amputees. Brain-implantable devices are also beginning to provide, for instance, a glimpse of integrated circuits involved in linguistic and motor function. Aside from brain-machine applications, there is a pressing need to ensure that risks are minimized during surgery, and to consider the ethical challenges that new therapies pose on the human brain.

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Editor's Column

Spring is coming as I write this in Columbus, Ohio. My wife and I, while maintaining our permanent home in Florida, are staying in our condominium here for three weeks visiting our son and his family who live nearby. It is great to be able to see the three grandchildren a lot. We will spend time a bit later just north of Detroit visiting our other son and his family (two grandchildren). Being retired from academics definitely has its upside.

There is certainly a lot going on in the neuroscience community. One of the most interesting areas just now is the research being done on the effects of human perception on physiological function. In a very recent research article in Psychological Science by Mark Schaller, Gregory E. Miller, Will M. Gervais, Sarah Yager, and Edith Chen, entitled "Mere Visual Perception of Other People's Disease Symptoms Facilitates a More Aggressive Immune Response"[1], the authors provide evidence that in humans, the mere act of observing pictures of disease symptoms produced a more aggressive immune response than observing scenes such as threatening acts. This is a very interesting and provocative finding. It provides more evidence that a person's thoughts and perceptions can play a real role in various physiological processes. As we understand more about how the brain functions, we obviously will have to become more attuned to not just the "wetware" function, but also the "software" function to understand the totality of how the brain controls the body (and visa-versa). We have come a long way, but have a long way to go.

The article in this 69th edition of the Kopf *Carrier*, presented here, was written by Drs. Torres, Fraley, Hallas, Lebeste and Philippens. Drs. Torres and Hallas have authored other *Carrier* articles of great interest, and this is no exception. In this article the authors review and speculate on how deep brain stimulation (DBS) aids in reducing the debilitating effects of Parkinson's disease. They explain the methods of DBS, the theories of how it may work, and touch on the ethical issues involved in such techniques. It is a fascinating field both from a practical and theoretical viewpoint. We appreciate their review and look forward to more in the future.

Should anyone reading this want to write an article for the *Carrier*, please contact me or David Kopf Instruments for any help. We will publish articles on various topics, including history of neuroscience, neuroethics, neuroscience techniques as well as interesting data based articles. David Kopf Instruments has generously supported the *Carrier* for over 36 years and continues to make the articles available to the entire community through their web site. All of us in the Neuroscience community are grateful for this support.

1. *Psychological Science* April 2010, first published online before print on April 2, 2010 doi:10.1177/0956797610368064, Author Affiliations: University of British Columbia. Mark Schaller, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia V6T 1Z4, Canada E-mail: schaller@psych.ubc.ca

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