Quantifying Decreases in Parkinsonian Rigidity with Surgical Intervention in the Subthalamic Nucleus

by

John Romas

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Physiology
University of Toronto

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QUANTIFYING DECREASES IN PARKINSONIAN RIGIDITY WITH
SURGICAL INTERVENTION IN THE SUBTHALAMIC NUCLEUS

John Romas, Master of Science 2001
Graduate Department of Physiology, University of Toronto

Electrical stimulation of the subthalamic nucleus (STN) has been shown to greatly improve rigidity, tremor and akinesia in MPTP-treated monkeys (Benazzouz et al. 1993), and more recently in parkinsonian patients (Kumar et al. 1998a; Limousin et al. 1995a). However, improvements remain subjectively evaluated using clinical rating scales like the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn 1989). A force- and displacement-sensing device (Prochazka et al. 1997) was used to quantify changes in arm rigidity in fourteen parkinsonian patients treated with levodopa or stereotactic surgery involving implantation of deep brain stimulation electrodes into the subthalamic nucleus (STN-DBS). These results show that electrical stimulation of the STN is as effective in alleviating parkinsonian rigidity as L-Dopa, and the insertion of micro- and DBS electrodes into the STN during surgery had a "microsubthalamotomy" effect, producing a measurable clinical benefit to rigidity.

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Acknowledgements

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<td>anterior commissure</td>
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<td>ANOVA</td>
<td>analysis of variance</td>
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<td>D1</td>
<td>dopamine receptor type 1</td>
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<td>DBS</td>
<td>deep brain stimulation</td>
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<td>EDC</td>
<td>extensor digitorum communis</td>
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<td>EMG</td>
<td>electromyography</td>
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<td>GAD</td>
<td>glutamic acid dehydrogenase</td>
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<td>GPe</td>
<td>globus pallidus, external segment</td>
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<td>GPi</td>
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<td>GTO</td>
<td>Golgi tendon organ</td>
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<td>HBN</td>
<td>habenular nucleus</td>
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<td>levodopa</td>
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<td>Limb Rigidity Analyzer</td>
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<td>primary motor cortex</td>
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<td>MEP</td>
<td>motor evoked potential</td>
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<td>MPTP</td>
<td>methylphenyltetrahydropyridine</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NRGC</td>
<td>nucleus reticularis gigantocellularis</td>
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<td>NRPC</td>
<td>nucleus reticularis pons caudalis</td>
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<td>PC</td>
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<td>Parkinson’s disease</td>
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<td>supplementary motor area</td>
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<td>SNC</td>
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<td>substantia nigra pars reticulata</td>
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<td>subthalamic nucleus</td>
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<td>tonic vibration reflex</td>
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<td>ventralis oralis anterior</td>
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<td>Vim</td>
<td>ventralis intermedius</td>
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<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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INTRODUCTION

Parkinson’s Disease

James Parkinson’s Essay on the Shaking Palsy provided the first comprehensive description of the features of Parkinson’s disease in 1817. In this historic account he described the symptoms of rest tremor, akinesia/bradykinesia, gait disturbance, postural instability and sleep disturbance typical of this disease (Weiner and Lang 1989). The inclusion of the other characteristic feature of the disease, rigidity, is usually attributed to Charcot, who named the disease for Parkinson several decades later.

Tremor at rest is a cardinal feature of PD. It is the presenting complaint in 60-70% of patients and is seen in the majority (70-80%) of patients (Germano and Olanow 1998). Frequencies between 3.5-7 Hz are characteristic, and EMG recordings of affected limbs show alternating rhythmic activity in antagonistic muscles (Findley et al. 1981). It usually begins in the distal part of one arm and spreads to the ipsilateral leg, and may eventually involve contralateral limbs as well as the jaw or lower facial muscles (Germano and Olanow 1998). Its amplitude is increased with stress or anxiety and decreased with voluntary movement and sleep (Delwaide and Gonse 1988).

Akinesia and bradykinesia refer to absence of movement or slowness of movement respectively. This feature is the most disabling feature of the disease. Patients have difficulty initiating movement, and in performing simple and/or rapid alternating movements (Germano and Olanow 1998). The mask-like face, decreased blinking, and difficulty rising from a chair are all components of this feature of the disease. Sudden “freezing” episodes can also occur in severely affected patients, rendering them immobile.
Gait disturbance and postural instability are another major cause of disability in PD. The characteristic PD patient has a stooped or flexed posture, flexion of the limbs and a decreased arm swing when walking. Gait consists of short, shuffling steps and patients tend to run forward to catch up to their center of gravity (Germano and Olanow 1998), known as a festinating gait. Patients also have difficulty maintaining balance and are prone to falling. Other features of PD include micrographia (small and illegible handwriting), impaired manual dexterity, hypophonia (diminution in speech volume), sialorrhea (excessive drooling), autonomic dysfunction (constipation or sexual dysfunction) and cognitive and psychiatric problems (dementia or hallucinations) (Germano and Olanow 1998).

Parkinsonian rigidity is classically defined as an increased resistance to passive stretch. It is observed equally in extensor and flexor muscles, does not vary greatly throughout the day, and is independent of the velocity of stretch (Weiner and Lang 1989). Rigidity is also clearly reinforced or “activated” by contralateral voluntary movement (Froment’s sign; see abstract) and can exhibit “cogwheeling”, a ratchet-like sensation appreciated by the examiner during passive extension/flexion of the limbs.

Epidemiologically, age appears to be the most prominent risk factor for Parkinson’s disease (Burton and Calne 1990). Symptoms typically appear after 50 years of age and age-specific prevalence increases afterward. Familial studies over the last century agree that 15-19% of patients report similarly affected family members (Duvoisin 1984; Hoehn 1976; Kurland 1958; Hart 1904; Gowers 1896), but low concordance rates of PD in monozygotic twins implicate environmental factors as a cause of PD (Ward et al. 1983). Viruses or toxins could be involved in the development of PD, given that models for both exist. The encephalitis lethargica epidemic of 1916 caused chronic
parkinsonism; this viral infection accounted for two thirds of patients attending neurology clinics between 1920 and 1930 (McKeigue and Marmot 1990). In addition to manganese and carbon monoxide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP for short), also causes parkinsonism (Montastruc et al. 1994). MPTP is a highly selective neurotoxin of dopaminergic cells of the substantia nigra pars compacta. This compound was discovered as a contaminant of a “homemade” opiate and caused a clinical syndrome indistinguishable from Parkinson’s disease in a group of young adults in California who ingested it (Langston and Palfieman 1995). Antipsychotic agents (neuroleptics, i.e. phenothiazines) can also induce a state resembling idiopathic PD (Montastruc et al. 1994) through their dopamine receptor binding properties.

**Historical**

The pathology of Parkinson’s disease was largely a mystery until the beginning of this century. In 1913, Lewy tried to identify the neurons whose loss would result in Parkinson’s disease. He described intracellular formations in degenerating neurons of the forebrain (which came to be known as Lewy bodies), but he failed to recognize the involvement of the substantia nigra (Lewy 1913). In 1925 Foix and Nicolesco identified the loss of neurons in the pars compacta of the substantia nigra (SNc) as critical to the development of Parkinson’s disease by examining the distribution of melanin-containing neurons in the brain (Foix 1925). Later, Lloyd and Hornykiewicz showed that the degeneration of these neurons created a deficit in dopaminergic innervation of the striatum (Lloyd Hornykiewicz 1970; Hornykiewicz 1966), and dopamine replacement therapy began soon after.
Before levodopa gained acceptance as a therapy for Parkinson’s disease, anticholinergic drugs were used for the treatment of PD (Burnham 1985). Although the theoretical basis was largely unknown, the degeneration of dopaminergic neurons was believed to cause an acetylcholine/dopamine imbalance and anticholinergic treatment (i.e. scopolamine, atropine) was thought to restore a more normal balance between these neurotransmitter systems. However, this class of drugs caused a wide variety of side effects. Blurred vision, dryness of the mouth, constipation, urinary retention and ataxia all occur at therapeutic doses (Burnham 1985).

Initial neurosurgical targets for the treatment of PD (Gildenberg 2000) involved interruption of the lateral pyramidal tract (Bucy and Case 1939; Bucy and Buchanan 1932) or, as the concept of an extrapyramidal system emerged, of structures within it (Meyers 1958; Meyers 1942). Meyers’s reports of substantial clinical improvement with interruption of the ansa lenticularis (pallidothalamic projections) and anterior limb of the internal capsule led to the exploration of these and other structures within the extrapyramidal system. A decade later Spiegel and Wycis confirmed the benefit of interruption of the ansa lenticularis in the treatment of PD (Spiegel and Wycis 1954). At about the same time, Narabayashi and Okuma began treating PD patients by injecting procaine oil into the globus pallidus (Narabayashi and Okuma 1953), thereby killing the cells that contribute to the ansa lenticularis.

While performing a pedunculotomy in 1952, Cooper accidentally interrupted the anterior choroidal artery. He ligated the artery and the procedure was aborted (Gildenberg 2000). Afterwards the patient experienced a significant improvement in his tremor with no neurological deficit. It was later shown that this procedure in fact caused ischaemic damage to GPi, supporting the results of previous reports. However, other investigators
were gravitating toward the ventrolateral thalamus (Benabid et al. 1998). Hassler et al. studied pallidal projections in pallidotomy autopsy cases and showed that pallidofugal fibres originating in the globus pallidus projected to the anterior lateral nuclei of the thalamus (Voa/Vop) (Hassler et al. 1965; Hassler et al. 1960). When one of Cooper’s successful patients later died and was autopsied, the lesion was found to be in the thalamus, prompting Cooper to endorse Vim as the preferred target as well (Cooper et al. 1958).

With the introduction of levodopa in the early 1960s, stereotactic surgeries declined. The risks of surgery became unacceptable compared to the safe and dramatic benefit achieved with levodopa therapy. However, within a few years the side effects of the drug became apparent. Disabling dyskinesias (involuntary movements) are estimated to occur in 80-90% of patients treated with levodopa, and in most cases this begins by the end of 1-2 years of treatment (Weiner and Lang 1989). Severe and rapid off/on fluctuations and hallucinations also appear after less than 10 years of treatment. The reintroduction of Leksell’s pallidotomy procedure by Laitinen in the early 1990’s provided relief from levodopa’s side effects and began a resurgence of stereotactic surgery for Parkinson’s disease and other movement disorders.

**Basal ganglia circuitry and models of PD**

Anatomically, the basal ganglia are a group of subcortical nuclei atop the brainstem. These are represented schematically in figure 1. The striatum is the input station of the basal ganglia, receiving afferents from widespread areas of the cortex. The output is from the internal segment of the globus pallidus (GPi) and the substantia nigra
Figure 1. Normal basal ganglia circuitry.

All excitatory projections are glutamatergic, inhibitory ones are GABAergic.

Dopaminergic nigrostriatal projections have both excitatory and inhibitory effects, mediated by D1 and D2 dopamine receptors respectively. STN-subthalamic nucleus, SNr-substantia nigra pars reticulata, SNC-substantia nigra pars compacta, GPi-globus pallidus internus, GPe-globus pallidus externus, Rt-reticular thalamus, PPN-pedunculopontine nucleus, HBN-habenular nucleus, SC-superior colliculus, RF-reticular formation.
pars reticulata (SNr), which histologically is similar to GPi but separated by the internal capsule. These efferents project to thalamic and brainstem targets.

The dopaminergic projections from SNc synapse onto two types of neurons within the striatum, based on the subtypes of dopamine receptor they express (Smith et al. 1998; Parent and Hazrati 1995). Striatal neurons expressing D2 receptors also express enkephalin, and project mainly to the external segment of the pallidum (GPe) comprising the “indirect” pathway. These neurons are inhibited by dopamine. Striatal neurons expressing D1 dopamine receptors are excited by dopamine and project mainly to GPi, comprising the “direct” pathway. These neurons also coexpress the neuroactive peptides substance P and dynorphin. Therefore a depletion of dopaminergic neurons in the substantia nigra increases activity of the indirect pathway via a disinhibition of D2-expressing neurons. The increased activity in the indirect pathway would excessively inhibit GPe neurons because the striatal neurons are GABAergic and inhibitory. A lower activity of GPe neurons (also GABAergic and inhibitory) would increase activity in the subthalamic nucleus by disinhibition. STN receives input from mainly premotor and supplementary motor areas, and its neurons project to GPi and SNr via excitatory glutamatergic synapses to increase activity in these nuclei (Nambu et al. 2000). Conversely, a dopamine deficit reduces excitatory drive to the D1 expressing neurons in the direct pathway in the striatum. Less inhibition of GPi from these GABAergic inhibitory neurons would also increase activity of GPi and SNr neurons. According to Marsden and Obeso (Marsden and Obeso 1994), the direct pathway facilitates cortically initiated movements while the indirect pathway inhibits unwanted programs; this would be analogous to inhibitory surround seen in other sensory systems. The net result of
dopamine depletion in the SNc is believed to be increased activity of the output nuclei of GPi/SNr. These changes in basal ganglia activity are summarized in figure 2.

A recent study by Aizman et al. (Aizman et al. 2000) has shown that D1 and D2 receptors are coexpressed in the striatum in vivo (with slices from neostriatum in rats) and in vitro (with cells cultured from embryonic rat striatum) via laser confocal microscopy. These results raise concern over the precise mechanism of action of dopamine in the striatum in models of the basal ganglia, both in the normal state and in PD. However, these models were derived primarily from primate and human data, and species differences could exist reflecting the increasing level of complexity in higher mammalian species. Furthermore, it is possible that direct vs. indirect pathways are distinguished by varying levels of D1 or D2 expression, i.e. striatal neurons comprising the direct pathway would have more D1 expression than D2, and vice versa.

Microelectrode studies from MPTP-treated monkeys confirm changes in resting firing rates and patterns of basal ganglia nuclei compared to the normal state. Recordings from the internal segment of the pallidum (GPi) (Wichmann et al. 1999; Filion and Tremblay 1991; Miller and DeLong 1987), substantia nigra pars reticulata (SNr) (Wichmann et al. 1999) and subthalamic nucleus (STN) (Guridi and Obeso 1997; Bergman et al. 1994; Miller and DeLong 1987) all show increased resting firing rates. A study by Hutchison et al. in PD patients did find high firing rates in STN but not in SNr (Hutchison et al. 1998), but this structure might be primarily involved with oculomotor and axial musculature, which may not have been as affected in his group of patients (personal communication). Furthermore, there are no studies of firing rates in these structures in normal patients, for obvious reasons. These abnormal rates are believed to
Figure 2. Basal ganglia circuitry in Parkinson's disease.

All abbreviations the same as in figure 1. Alterations are denoted by the thickness of the arrows connecting the various nuclei.
be downstream effects of the deficit in dopaminergic innervation of the striatum, as mentioned above.

**Rationale for surgical intervention from BG models**

Conventional therapy for parkinsonian patients is dopamine replacement (levodopa/carbidopa). Increasing the levels of dopamine within the striatum is thought to restore a more normal balance between the two pathways and reduce the resting firing rates of the basal ganglia output nuclei (Lozano et al. 1998a; Wichmann and DeLong 1996). Recent studies reveal apomorphine (a non-specific D1/D2 agonist which improves PD symptoms) can lower spontaneous firing rates of cells recorded in GPi, STN and SNr in PD patients (Levy et al. 1999; Hutchison et al. 1997).

Similarly, lesioning these structures is also thought to remove some of the excessive inhibition of thalamic and brainstem targets. Removing this inhibition of the thalamus could then allow more adequate facilitation of cortical circuitry required for movement. In addition to therapies aimed at reducing activity in these nuclei (lesioning or high frequency electrical inhibition, discussed later), some of the newer strategies include the use of growth factors, gene therapy, and transplantation of allogenic or xenogenic (porcine) fetal tissue into the caudate and putamen (Lozano et al. 1998a). However these therapies remain in the experimental stage and are not in widespread clinical use.

**Pathophysiology of parkinsonian rigidity**

Current models of basal ganglia dysfunction do not adequately explain the pathophysiology of parkinsonian rigidity. The increased activity in GPi and SNr is GABAergic and inhibitory upon the ventral anterior and ventral lateral thalamic nuclei.
and pedunculopontine nucleus (PPN) in the brainstem. In this pathologic state the thalamus is presumed to be excessively inhibited, preventing it from activating cortical areas responsible for the planning and initiation of movement (e.g. premotor cortex, supplementary motor area) and leads to a hypokinetic state (akinesia Bradykinesia) via an inadequate facilitation of agonist muscle groups (Wichmann and DeLong 1998). The decreased facilitation of thalamocortical circuitry predicted by current basal ganglia models predicts a decrease, not an increase in rigidity. The increased muscle tone at rest is commonly thought of as a hyperkinetic disorder, i.e. increased agonist drive, but imaging studies suggest cortical motor areas are less active in PD patients (Sakatani et al. 1999; Davis et al. 1997; Hirato et al. 1993). Although rigid patients can have an increased tone (higher EMG activity at rest), this correlates poorly with clinically assessed rigidity (Berardelli et al. 1983) and casts doubt on the idea that rigidity is simply a result of an enhanced supraspinal drive to motor neurons.

Short latency reflexes are normal in PD

When researchers demonstrated early on that removal of peripheral input by surgically sectioning dorsal roots also abolished rigidity in PD patients (Pollock and Davis 1930; Foerster 1921), it was assumed that parkinsonian rigidity resulted from an increased gain of the stretch reflex as well. By analogy to the decerebrate animal, it was proposed that this increased gain was due to an enhanced fusimotor drive. In the 1920s, Walshe showed that an intramuscular injection of procaine (a local anaesthetic initially thought to be selective for smaller diameter \(\gamma\)-efferents) abolished the tendon jerk/monosynaptic stretch reflex and reduced rigidity in PD patients (Walshe 1924). Injections into or around the nerve had the same effect (Matthews and Rushworth 1957).
However, since the selectivity of procaine for γ-efferents is now believed to be poor (Gassel and Diamantopoulos 1964), the decreases cannot be attributed solely to decreased fusimotor activity. Muscle spindle activity in PD patients is similar to a normal patient whose muscles are contracting; although direct recordings from muscle spindle afferents can reveal an increased activity it appears appropriate for the underlying level of muscle contraction in resting patients (Burke et al. 1977; Wallin et al. 1973).

Vibration, like tendon taps, strongly excites muscle spindle afferents (Matthews et al. 1990). This stimulus elicits the tonic vibration reflex or TVR, and has the advantage of allowing reflex pathways to be studied during a maintained increase in Ia input (as opposed to phasic tendon taps or electrical stimuli). If an enhanced fusimotor drive alone was sufficient to cause rigidity, increasing spindle activity with vibration in normal subjects should reproduce this condition. In fact, vibration is such a powerful stimulus for spindle afferents it increases their activity far beyond what is induced by passive stretch in PD patients. Despite this, normal subjects do not become rigid when their muscles are vibrated, so although the TVR often develops it can be controlled voluntarily (Burke, Hagbarth, and Wallin 1977).

The tendon jerk/stretch reflex has been studied extensively in PD patients, usually by examining tendon taps or by the Hoffman reflex (H-reflex) (Hoffman 1922). In this technique, the peripheral nerve is electrically stimulated with an intensity large enough to preferentially activate large afferent Ia fibres, and the evoked muscle response via the spinal reflex loop is monitored with EMG (refer to figure 4). It is now generally accepted that the monosynaptic/short latency reflex in PD (the M1 response of Lee and Tatton) is not increased above controls (Bergui et al. 1992; Cody et al. 1986; Tatton et al. 1984; Berardelli, Sabra, and Hallett 1983; Rothwell et al. 1983; Lee and Tatton 1975), so a
mechanism other than simple enhanced segmental stretch reflexes must be involved in PD rigidity.

When stimulus intensities are increased during H-reflex testing, efferent motorneurons in the peripheral nerve become directly activated and evoke a muscle contraction at a shorter latency than the H-reflex (the M-response). At maximal intensity, all the motorneurons in the nerve are recruited and a maximal muscle contraction is seen in the EMG record. In theory, the ratio of the maximal elicitable reflex (H-max) to the maximal direct response of a muscle (M-max) indicates the fraction of the motor neuron pool that can be excited monosynaptically (H-max/M-max ratio) (Dietrichson 1971). In PD patients this ratio appears normal (Delwaide 1985; Angel and Hoffman 1983; Dietrichson 1971).

When a muscle is being passively stretched, the opposing muscle or its “antagonist” is shortened. The reflex contraction of the shortened muscle is known as the Westphal phenomena, or shortening reaction. For example, during passive extension of the elbow, the triceps shows a shortening reaction, manifested by a burst of EMG activity (Angel 1982). The mechanism responsible is autogenic; stimulation of Ib joint afferents originating in the Golgi tendon organ (GTO) of the contracting muscle synapse onto Ib inhibitory interneurons in the spinal cord, and these in turn inhibit the motorneurons of the homonymous muscle (Delwaide et al. 1991; Katz and Rondot 1978). In support of this circuitry (figure 3), perfusion of procaine into the stretched muscle fails to abolish this response, which is exaggerated in PD patients (Berardelli and Hallett 1984; Angel 1983; Andrews et al. 1972). In a recent study by Burne et al. electrical stimuli were delivered via electrodes placed over tendons in the extensor digitorum communis (EDC) muscle (Burne and Lippold 1996). This resulted in an inhibition of voluntary EMG
Figure 3. “Autogenic” inhibition.

Afferents originating in the tendon organs inhibit homonymous muscle contraction via the Ib inhibitory interneuron and facilitate contraction in the antagonist muscle.

Directions of axonal conduction are denoted by arrows.
activity in the EDC. In fact, this group claims 100% discrimination between control and PD patients based on latency, threshold and form of tendon organ inhibition. The exaggeration of this response observed in PD would then likely reflect a decreased activity of the Ib interneuron downstream of the dysfunction in the basal ganglia.

Another type of cell closely coupled with motor neurons in the spinal cord is the Renshaw cell. Before exiting the gray matter, motor neuron axons send collaterals to these cells, which then inhibit the neurons that drive them (Mackay 1995). This system is known as Recurrent or Renshaw inhibition. Investigations into recurrent inhibition in PD patients use the method described by Pierrot-Deseilligny et al. (Pierrot-Deseilligny et al. 1976), in which regular electrical stimuli are delivered from electrodes over the popliteal fossa for stimulation of the posterior tibial nerve. Muscle responses are recorded with surface EMG electrodes over the soleus muscle. Two different stimuli are delivered to the posterior tibial nerve. The first stimulus is at the threshold intensity for an H-reflex and is increased to an intensity capable of eliciting the maximal H-reflex without an M-response. The second stimulus is at an intensity sufficient to obtain the supramaximal M response. H-reflexes are obtained under two conditions, recorded either after the first stimulus alone or after both stimuli with an interstimulus delay of 15 ms. In this case, the H-reflex recorded after the first stimulus is blocked by collision with the antidromic volley in the motor fibres from the second stimulus. The H-reflex recorded after the first and second stimuli is produced by the orthodromic volley in the afferent fibres from the second stimulus, which can evoke an H-reflex in those fibres where the prior collision has cleared the motor nerve (Lelli et al. 1991). The second H-reflex contraction is then smaller due to Renshaw cell-mediated inhibition of motor neurons excited by the first
stimulus. These studies found no differences between PD patients and normal subjects (Lelli, Panizza, and Hallett 1991; Delwaide 1985).

In addition to projecting to homonymous motor neurons, muscle spindle afferents also project to Ia inhibitory interneurons in the spinal cord. These interneurons then inhibit the motorneurons of the antagonistic muscle, a process called reciprocal inhibition (Mackay 1995) (see figure 4). A recent study by Tsai et al. examined the inhibition of the median nerve H-reflex by conditioning stimuli on the radial nerve at various time delays (Tsai et al. 1997). Three phases of reciprocal inhibition in normal subjects and patients with an asymmetric manifestation of PD features were seen. The first phase, with a latency of 1-4 ms was attributed to the disynaptic pathway through the Ia interneuron. The second phase of latency 4-50 ms, was attributed to presynaptic Ia inhibition. For the first two phases, there was no difference between normal subjects and patients. The third inhibitory phase, of latency 50-500 ms, was replaced by a mild potentiation on the symptomatic side. On the asymptomatic side, there was still an inhibition in the third phase but it was less than the control group, suggesting there is some dysfunction in the ipsilateral basal ganglia of unilaterally affected PD patients.

Therefore, the enhanced response to stretch observed in PD patients is unlikely to originate from segmental reflexes. Excitability of motor neurons in the spinal cord in PD patients are normal, based on the observations that fusimotor drive, monosynaptic reflexes and Renshaw inhibition appear to be normal. Reflexes that consistently showed abnormalities (reciprocal inhibition, autogenic inhibition) are regulated by spinal Ia and Ib interneurons respectively, which are under a descending supraspinal influence.
Figure 4. Reciprocal inhibition.

Muscle spindle afferents monosynaptically facilitate contraction in the stretched muscle but also inhibit the contraction of the antagonist via the Ia inhibitory interneuron. Directions of axonal conduction are denoted by arrows.
Ia fibre

Muscle spindles

Excitatory

Inhibitory
Alterations in long latency reflexes in PD and descending control

In addition to the short latency monosynaptic pathway, H-reflex studies also reveal a longer latency (M2/3) EMG response in PD patients. A study by Lee and Tatton illustrates the evoked responses to sudden upper limb displacements using a precision torque motor. The short latency (M1) component occurred at 28-32 ms (presumably monosynaptic), the M2 at 55-60 ms and the M3 at 85-95 ms (Lee and Tatton 1973). It is widely accepted that this late response is under supraspinal regulation, probably involving the motor cortex (Cantello et al. 1996; Mortimer and Webster 1979; Burke, Hagbarth, and Wallin 1977; Tatton and Lee 1975; Lee and Tatton 1975; Marsden et al. 1973). The responses of a PD patient attempting to remain passive during an imposed stretch resemble the responses obtained in normal subjects who voluntarily resist the stretching movement. When a normal subject relaxes and does not try to impede the movement, the M2/3 components disappear (Burke, Hagbarth, and Wallin 1977). These results suggest that it is the parkinsonian patients' inability to relax which is causing their rigidity; pathways normally activated in voluntary movement but inactive at rest are inappropriately stimulated by some upstream control mechanism.

Muscle afferents project to the spinal cord but also relay to the sensorimotor cortex via thalamus. Cortical potentials can be evoked by stimulation of muscle afferents (Gandevia et al. 1984; Starr et al. 1981), suggesting the long latency reflex could be due to a transcortical activation of the corticospinal tract (Cheney and Fetz 1984). Sensory evoked potentials (SEPs) and stimulation of motor cortex and the corticospinal pathway were initially shown to give normal responses (Dick et al. 1984). However, contemporary methods using magnetic stimulation suggest a hyperexcitability of the cortical motor system on the more rigid side, based on lower stimulus thresholds and enhanced motor
evoked potentials (MEPs) (Cantello et al. 1996). Additionally, the post-MEP silent period, presumed to reflect cortical inhibitory or suppressing phenomena (Cantello et al. 1992), was shortened on the more rigid side. According to Cantello et al. (Cantello et al. 1996), these findings advocate a disinhibition of the cortical motor system, which appears to be confirmed by other investigators (Valls-Sole et al. 1994; Meyer and Conrad 1992; Maertens de Noordhout et al. 1991; Marsden 1990).

Convincing evidence for involvement of the cortex in the long loop reflex comes from a more recent study by Palmer and Ashby (Palmer and Ashby 1992). Short and long latency EMG responses in flexor pollicis longus (FPL) were elicited by extension of the terminal phalanx of the thumb. Magnetic stimulation of the contralateral motor cortex produced strong, short latency facilitation of FPL motor neurons. When the stimulation-induced facilitation was timed to coincide with the long latency component of the stretch reflex, the FPL EMG responses were greater than the sum of the responses from either stimulus alone, suggesting the afferent fibres mediating the long latency stretch reflex converge on cortical motor neurons.

The question then remains, how can modifications to “phasic” reflexes contribute to a “tonic” condition of rigidity? It has been shown that muscle spindle afferents at least continue to fire throughout the course of the imposed movement (Burke and Eklund 1977), so these feedback mechanisms are operating continuously to control muscle tone.

**Hypotheses of PD rigidity: cortical vs. brainstem origins**

Marsden speculates that muscle spindle input to the sensorimotor cortex is disinhibited by abnormal SMA control, secondary to abnormal basal ganglia input to SMA in PD (Marsden 1990). While there is sufficient evidence to show that the increased
long-latency response is transcortical, the correlation between the gain of this response and degree of rigidity in PD patients is questionable (Cody et al. 1986; Rothwell et al. 1983). Additionally, patients with lesions to SMA do not exhibit rigid syndromes, they can show a loss of control of sensory driven movement; e.g. Alien Hand syndrome (Chan and Ross 1997; Chan et al. 1996). The SMA has been implicated in the temporal organization of multiple movements (Clower and Alexander 1998; Shima and Tanji 1998), both "higher" functions.

Delwaide offers an alternative explanation for the origin of rigidity, involving primarily the brainstem. His argument is based on a series of studies in which he found increased reciprocal inhibition (Delwaide et al. 1993) and decreased autogenic inhibition (Delwaide, Pepin, and Maertens 1991). The activity of the interneurons involved in these responses (Ia and Ib, respectively) is modulated by reticulospinal neurons via the reticulospinal tract (Delwaide et al. 1996; Burne and Lippold 1996; Delwaide et al. 1990). The STN sends axons back to GPe, and also to the basal ganglia output nuclei, GPi and SNr. The output of the GPi/SNr is not only directed to the thalamus, but also to brainstem structures such as the pedunculopontine nucleus (PPN) and parvicellular reticular formation (RF). Furthermore, it is well established the PPN projects to the nucleus reticularis pontis caudalis (NRPC) and nucleus reticularis gigantocellularis (NRGC) at the junction of the pons and medulla. Since these nuclei contribute to the pontine reticulospinal tract, Delwaide speculates that a reduced activity of pontomedullary reticular nuclei could contribute to parkinsonian rigidity by modifying the excitability of both the Ia and Ib interneurons (Delwaide et al. 1996; Delwaide, Pepin, and Maertens de Noordhout 1993).
As mentioned previously, other authors have also found an enhanced shortening reaction (decreased autogenic inhibition) (Berardelli and Hallett 1984; Angel 1983; Andrews, Burke, and Lance 1972), but this has also been observed in dystonic patients (Marsden 1990), suggesting this is not specific to parkinsonian rigidity. Furthermore, it is not intuitively obvious how his finding of an increased reciprocal inhibition could contribute to rigidity (Delwaide, Pepin, and Maertens de Noordhout 1993); other authors found a decreased reciprocal inhibition (Tsai, Chen, and Lu 1997; Lelli, Panizza, and Hallett 1991). Delwaide’s work involved electrophysiological studies in the leg, whereas the studies that found a decreased reciprocal inhibition were done in the arm, suggesting at least different limbs may have different influences in the development of PD rigidity.

**PD rigidity and the STN**

As mentioned previously, the pallidum was the first target for neurosurgeons in treating PD. Due to the relatively large size and distributed circuitry of the pallidum, the accuracy and size of the lesion is critical in providing relief, since there are believed to be at least five segregated loops connecting different regions of cortex, striatum and pallidum. They are the limbic loop, motor loop, oculomotor loop, dorsolateral/associative and lateral loops (Alexander et al. 1990). Therefore, it is conceivable that although a lesion may be within the anatomical boundaries of GPi, it may not be within the appropriate motor circuitry to provide relief of PD symptoms. A recent study by Gross et al. (Gross et al. 1999) examined the relationship of lesion location to clinical outcome in microelectrode guided-pallidotomy patients. Within the posteroventral GPi, anteromedial lesions were associated with greater improvement in “off” period contralateral rigidity and “on” period dyskinesia, whereas more centrally located lesions correlated with better
postoperative scores of contralateral akinesia and postural instability/gait disturbance. Improvement in contralateral tremor was weakly related to lesion location, being greater with posterolateral lesions. Similarly, while Vim has traditionally been the best target for tremor relief, lesions here are not as beneficial to rigidity or akinesia/bradykinesia (Benabid et al. 1996; Burchiel 1995). It is likely that more anterior pallidal-receiving regions of the thalamus (Voa/Vop) must be involved to improve akinesia/bradykinesia and rigidity, but according to basal ganglia modelling lesions or electrical inhibition here should exacerbate PD symptoms (by decreasing activity in an already hypoactive structure).

The STN is a relatively small structure located below the thalamus in the white matter of the internal capsule. Its boundaries can be accurately determined with microelectrode mapping (see Methods). According to the anatomical connections, it should play a critical role in regulating basal ganglia output activity as described in the basal ganglia models (figures 1 and 2) (Lozano et al. 1998a; DeLong 1990). The STN receives inputs from cortical areas SMA, PMC and M1, as well as an input from PPN in the brainstem. The STN output is directed to GPe, GPI and SNr.

Lesions in the STN improved all of the features of PD in MPTP-treated monkeys (Bergman et al. 1990) in contrast to pallidotomy (Gross et al. 1999) or thalamotomy (Benabid et al. 1996; Burchiel 1995), as mentioned above. Since the STN projects to both GPI and SNr, removing or lowering the excessive activity in STN could affect activity in both of these downstream nuclei. Furthermore, the high degree of convergence in this structure, i.e. the “funneling” of inputs through a small area could also increase the likelihood of affecting the appropriate circuitry. Why interventions in the STN appear to
improve all PD symptoms is unknown, but recently the subthalamic nucleus has emerged as the optimal target for treating PD patients.

Recently, high-frequency deep brain electrical stimulation (DBS) of Vim (Benabid et al. 1996), GPi (Kumar et al. 1998b; Pahwa et al. 1997; Siegfried and Lippitz 1994), and STN (Kumar et al. 1998a; Limousin et al. 1995a) has emerged as a potentially safer and reversible alternative to ablation. Lesioning and high frequency stimulation appear to have the same effect, so DBS is presumed to inhibit neurons in the affected structure. While the mechanism of DBS is unknown (Ashby et al. 1999), current theories include depolarization block of target neurons (Burbaud et al. 1994) or inhibition via presynaptic GABA release (Dostrovsky et al. 2000; Boraud et al. 1996). Effects could also be mediated by the stimulation of fibre systems around the electrodes, at least with regards to the STN (Ashby et al. 1999). Surrounding the STN are the ansa lenticularis (ventrally) and lenticular fasciculus (dorsally), which fuse in Forel’s Fields. Therefore, dorsal or ventral contacts could affect pallidothalamic outflow as well (refer to figure 7). Nevertheless, electrically-induced inhibition of the hyperactive structures in PD is in agreement with current models of basal ganglia dysfunction.

Other “rigid” syndromes:

Spasticity-Decerebrate and decorticate rigidity

Although parkinsonian rigidity is perhaps the best known, an increased muscle tone is seen in other neurologic and/or pathologic states. One example of this is Sherrington’s decerebrate rigidity. His monumental work Integrative Action of the Nervous System (Sherrington 1947) first published in 1906, described this artificial condition in cats induced by bilateral cerebral ablation. It is characterized by an extended
posture of the neck, upper and lower limbs sufficient to support the animal in a standing position.

Decorticate rigidity, a similar condition, results from cortical lesions more rostral to those that cause decerebrate rigidity (Kandel et al. 1991). In decerebrate rigidity the lesion is above the level of the vestibular nuclei but below the red nucleus, releasing vestibulospinal and reticulospinal neurons from cortical inhibition. These neurons activate α and γ motorneurons of extensor muscles, resulting in the decerebrate posture. Conversely, the lesion must be above the red nucleus to cause decorticate rigidity. In this case, the rubrospinal tract and other midbrain projections to the spinal cord are intact. These neurons act to oppose the vestibulospinal and reticulospinal efferents, so disinhibition of these neurons predominantly facilitates flexor muscles. In humans the rubrospinal system only projects as far as the cervical cord, so only the upper limbs assume a flexed posture while the lower limbs are extended due to the influence of vestibulospinal and reticulospinal activity (Kandel, Schwartz, and Jessell 1991).

While decerebrate and decorticate rigidity share the characteristic of an increased muscle tone with parkinsonian rigidity, clinically and physiologically these conditions are different. Decerebrate and decorticate rigidity are known as spasticity, and involve damage to upper motorneurons. Like rigidity, there is an increased resistance to passive stretch, but it may not be over the full range of movement, and the resistance is proportional to the velocity of stretch (Dimitrijevic 1993). Sudden releases of resistance also occur, known as the “clasp-knife” phenomenon. Spasticity is believed to be caused by an exaggerated stretch reflex, as removal of afferent input by surgical sectioning of the dorsal roots abolishes decerebrate rigidity. Furthermore, this rigidity subsides with a
selective blockade of γ-efferents with local anaesthetic (Matthews and Rushworth 1957), suggesting an enhanced fusimotor activity is responsible for the higher gain of the reflex.

**Stiff-Person Syndrome**

Stiff-man or stiff-person syndrome is another condition characterized by an increased tone, in this case mostly in axial and proximal muscles. This type of rigidity is enhanced by anxiety or other external stimuli which can cause painful muscle spasms (Gershanik 1997). However, this condition is believed to have an autoimmune origin; antibodies to glutamic acid dehydrogenase (GAD), an enzyme involved in GABA synthesis have been found in stiff patients. Suprasegmental GABAergic activity would be impaired, shifting the balance of inhibitory and excitatory influences to drive increased motorneuron activity (Gershanik 1997).

**Clinical assessment of rigidity: qualitative vs. quantitative methods**

Currently, Parkinson’s disease symptoms are assessed with clinical rating scales like the Unified Parkinson’s Disease Rating Scale (UPDRS) (Lang and Fahn 1989). Rigidity is only a small subset of this assessment, where the rater manipulates the limbs of the patient and assigns a score from 0 to 4, with zero corresponding to an absence of rigidity and 4 corresponding to a rigidity sufficient to prevent the manipulation of the limb. This method is subjective and the reliability between raters can be poor (Prochazka et al. 1997). A sensitive and reliable method of quantifying parkinsonian rigidity would be useful in evaluating drug or neurosurgical therapies, or tracking the course of the disease. Agate (Agate et al. 1956) and Webster (Webster 1959) were among the first to try to quantitatively assess rigidity, and recently other “engineering” attempts have been
made. Torque motors were used to deliver transient perturbations to the wrist (Fung et al. 2000; Teräväinen et al. 1989), elbow (Relja et al. 1996; Kirollos et al. 1996) or fingers (Caligiuri and Galasko 1992), but these artificially imposed movements do not accurately emulate a standard clinical exam. The force- and displacement-sensing device (Limb Rigidity Analyzer, or LRA) developed by Prochazka et al. (Prochazka et al. 1997) allows the limbs to be moved normally by the examiner and thus more accurately reflect a clinical exam.

**Prochazka’s Limb Rigidity Analyzer**

Briefly, the LRA consists of a balanced pair of air pads and gyroscope. Any imposed movements on the limb by the examiner require an applied force, and the air pads transmit this force via a pressure-sensitive diaphragm to a computer interface. Since the force is applied at a distance to the point of rotation, the torque is calculated. The gyroscope calculates the angular velocity (in degrees/sec) and its integral, angular displacement (in degrees). Prochazka’s examination showed the ratings of patients by independent evaluators to be poorly correlated and could vary up to 2 points on the UPDRS scale. However, the impedance measurements induced by different evaluators across subjects were very similar, demonstrating the reliability of this device.

**The physics of rigidity and mechanical impedance**

There are at least three forces resisting an externally applied movement to a limb, and in order to move the limb these forces must be overcome. First, the mass of the limb generates an inertial component, proportional to the mass of the limb and the acceleration of the applied movement ($F = m \times a$, Newton’s second law). Second, the drag is a
frictional force proportional to the applied movement velocity. Third, since the stretch is applied to spring-like muscles, an elastic force resisting the applied movement is generated, proportional to the displacement of the limb. Rigidity in PD could involve changing any or all of these resistive forces, so they all must be considered when modelling the mechanical impedance of the limbs.

According to models of basal ganglia dysfunction in PD and recent qualitative studies (Kumar et al. 1998a; Limousin et al. 1995a), an inhibition of STN activity should decrease parkinsonian rigidity. This technique was applied to quantify the decreases in rigidity due to interventions in the subthalamic nucleus. The effects of high frequency STN-DBS on parkinsonian rigidity were also compared to the standard pharmacological treatment of L-Dopa. Furthermore, the changes in rigidity during surgery for the mapping of the STN (and GPi) and implantation of these electrodes were measured to determine if a "microsubthalamotomy" effect was present in our patients.

This device also permitted rigidity measurements intra-operatively while simultaneously recording cellular activity within the STN or GPe, and during a reversible pharmacologic block of STN neurons. The effect of these interventions on the activation phenomena, evoked by voluntary contralateral hand movement, was also measured in an effort to determine the contribution of basal ganglia structures involved in the regulation of resting and activated rigidity in PD.
METHODS

Calculating Prochazka’s mechanical impedance

Basically, a second order mathematical model was fitted to the torque and displacement data (the complete derivation of Prochazka’s mechanical impedance is given in Prochazka et al. 1997). The imposed movements were of low enough frequency (< 1 Hz, 0.3 - 0.8 Hz used in this study) that the inertial component (second derivative of displacement) could be ignored in the calculation of the torque response. The equation then is:

\[ T = Kx + Bv + C \quad (1), \]

Where \( T \) is torque, \( x \) is displacement, \( v \) is velocity (by differentiating \( x \)), \( K \) is the stiffness, \( B \) is viscosity and \( C \) any constant offset in torque or length. A linear least-squares estimation was used to fit the parameters \( K \), \( B \), and \( C \) to 4 seconds of data preceeding any given point in time. This 4-second window was moved along the torque and displacement data, and the time courses of elastic and viscous components of impedance were obtained. (A four second window was found by trial and error to give the best correlation between computed and verbalized ratings)

The net torque experienced by the rater is due to the elastic \((Kx)\) and viscous \((Bv)\) stiffnesses (torque proportional to displacement and velocity, respectively). For sinusoidal movements of frequency \( \omega \). equation 1 reduces to:

\[ T = (K + B\omega)x + C \quad (2), \]

by substitution. Since raters imposed near-sinusoidal movements, the elastic and viscous stiffnesses were resolved by estimating a mean value of \( \omega \) and calculating \( B\omega \). The mechanical impedance is then calculated as the vectorial sum of elastic and viscous
stiffnesses, expressed in Newton-metres per degree of displacement (Nm/deg, see figure 5).

**Rigidity Assessment**

During measurements, patients were either seated comfortably in a chair or supine on the OR table. The device was attached to the wrist proximal to the base of the thumb with a Velcro strap. The examined limb was fully supported by the examiner, and patients were then instructed to relax and not to help or hinder the movements that were imposed on the arm. Rigidity measurements were obtained from slow flexion and extension movements (70-100°) of the elbow at a frequency of 0.3-0.7 Hz and each measurement lasted 50 seconds. Twenty-five seconds into each measurement, the patients were instructed to repetitively open and close the opposite hand as quickly as possible (in some patients this was measured with an accelerometer on the dorsal surface of the contralateral hand), and this point was indicated on the LRA with a marker function. This method gave a 25 second sample of resting or “baseline” rigidity +/- S.E and 25 seconds of an “activated” rigidity +/- S.E (see figure 5). Measurements were usually performed in duplicate and averaged. If the two measures were dissimilar, a third measurement was taken and the two most similar were averaged. Rigidity assessments were either performed alone, with the examiner (J.R.) simultaneously verbalizing UPDRS rigidity ratings (figure 7a), with accelerometry of the contralateral hand and/or simultaneous bicep and tricep EMG recordings of the manipulated arm, or simultaneously recording cellular activity during microelectrode mapping (figure 15).
Figures 5a-e. Limb Rigidity Analyzer output.

a) illustration of the LRA b) mechanical impedance trace, calculated in Nm/deg (see Methods). Regions used for calculations of mean baseline and activated impedances are indicated. Activation procedure begins at ~25s, indicated by dashed vertical line. c) Force trace, in N, d) angular velocity in deg/second, and e) angular displacement (integral of angular velocity in d). The impedance calculations begin after 4s of data has been gathered, shown by the straight line at the beginning of the trace. Note the larger force amplitudes after activation.
Output to interface box, computer

**Graphs:**

- **b**: Impedance (N/m/deg) over time
  - Baseline
  - Activated

- **c**: Force (N) over time

- **d**: Angular velocity over time

- **e**: Angular displacement over time
Concurrent UPDRS rigidity ratings

During rigidity measurements in two patients, the examiner (J.R.) simultaneously reported UPDRS rigidity ratings (see example in figure 7a). These ratings were inputted to the LRA through a marker function (W.D.H.) and were plotted against mechanical impedance figure 7b to determine if there was a correlation between UPDRS ratings and measured mechanical impedance.

Microelectrode recording and implantation of DBS electrodes

The DBS electrodes (Medtronic Model 3387) were implanted in the STN as previously described by Lozano et al. (Lozano et al. 1998b) using magnetic resonance imaging (MRI) and microelectrode recordings for localization. Briefly, on the morning of surgery a Leksell stereotactic frame is attached to the skull under local anaesthetic. The patient is then scanned with MRI imaging to determine the 3 dimensional (x, y, z) coordinates of the anatomical landmarks, the anterior and posterior commissures, with respect to the frame. A custom-designed computer program (TGHx or SNS: Solve-it. Toronto) then customizes (scales) a series of Schaltenbrand-Wahren sagittal sections to these landmarks. Surgical targets are selected at the ventral and posterior border of the STN; in these sagittal sections the STN is oval-shaped, angled upwards to the anterior at roughly a 60° angle with respect to the horizontal plane of the stereotactic frame (see figure 6). Therefore at a parallel entry angle, electrodes are presumed to pass through the long axis of the nucleus. Once the targets have been determined, burr holes are drilled into the skull (2-3 cm rostral to the coronal suture and 20 mm lateral to the midline) at a location which allows several microelectrode trajectories through the STN and surrounding region. The dura mater is incised and cauterized, and the burr hole filled with
Figure 6. Typical electrode placement in STN.

Electrode is to scale, drawn on a Schaltenbrand-Wahren 12 mm sagittal section.

Electrodes are placed with the most ventral contact at the presumed border of STN/SNr to maximize the number of electrode contacts within the STN. STN-subthalamic nucleus, SNR-substantia nigra pars reticulata, ZI-zona incerta, IC-internal capsule, Hpth-hypothalamus, Rt-reticular nucleus, Voa-ventralis oralis anterior, Vop-ventralis oralis posterior, Vim-ventralis intermedius. Anterior direction is indicated by the arrow, as well as approximate angle of insertion.
Surgiseal Tisseal® compound or fibrin glue. Parylene-C coated, gold and platinum-plated tungsten microelectrodes (Hutchison 1998) (~25 μm tip exposure, ~300k Ω impedance) were advanced through the brain through a guide tube via a hydraulic microdrive.

The microelectrode signal was fed through a headstage preamplifier, and output was directed to further amplifiers, filters, audio speakers and oscilloscope. The data were digitally converted and stored on VCR tape (Instrutech VR-100 B digital recorder) for subsequent off-line analysis. The tapes were played back on a VCR and outputted to oscilloscopes and a data acquisition computer interface system (CED 1401. Cambridge Electronic Design). Action potentials were isolated with window discriminators; these events were then converted to logic pulses and recorded by a data capture and analysis computer program (Spike 2, also CED).

A physiologic map of the area was composed based on recorded cellular activity (Hutchison et al. 1998) (see figures 14 and 18). In the area surrounding the STN, three cell types are typically encountered. At the top the track, thalamic reticular neurons can be recorded. These neurons typically are slow, bursting cells with a frequency of ~20 Hz. The second cell type encountered are STN cells, typically ~35 +/- 10 Hz. Finally, SNr cells are recorded at the bottom of the tracks and are easily distinguished by their much higher firing rates (~72 Hz). Once the boundaries and motor territory of the STN were determined (population of neurons responding to axial or limb movement), the DBS electrodes were inserted with the most ventral contact at the presumed border of STN/SNr, verified with fluoroscopy. Once in place, the electrode contacts were systematically tested to find combinations that were effective in alleviating PD symptoms and to avoid placements that would cause adverse effects. Once satisfied, the surgeon then secures the electrodes in place with a plastic cap.
Patients:

**STN-DBS group**

Six patients with idiopathic Parkinson’s disease with deep brain stimulation (DBS) electrodes implanted in STN participated in the study. Post-operative MRI was available in five of the six patients and confirmed the location of the electrodes within STN (figure 8). The electrodes in the patient without the MRI are presumed to be within STN from the microelectrode-guided physiologic map during surgery and from a sustained and dramatic clinical benefit from stimulation.

In the STN-DBS group all measurements reported are on the more rigid arm (without and with activation, off vs. on), the right arm for patients 1-5 and the left arm for patient 6. Patients 1, 4 and 5 were assessed with both stimulators turned on (bilateral); patients 2,3 and 6 were assessed in response to unilateral stimulation, contralateral to the arm being measured. Three patients had undergone previous pallidotomies; patients 4 (▼) and 6 (○) had previous left pallidotomies (4 in Sept/97, 6 in Feb/95), and patient 5 (●) had a right pallidotomy Mar/95 (these symbols for figure 8). Rigidity was measured at least three weeks post surgery and all patients were assessed by the same examiner.

All patients were measured 12 h “off” medication and “off” stimulation. The stimulators were then switched on, and rigidity was re-measured within 1 to 5 mins. In patients 1 to 4, the settings were already “optimized” for the alleviation of tremor, rigidity and bradykinesia (parameters which yielded the best results). Patients 5 and 6 were measured during the optimization of DBS parameters; these settings were not the final combination used and may not have produced the best results. The voltages used were in the range 1.3-4.5 V (volts), pulse durations of 60-180 μs (microseconds), and frequencies
130 – 180 Hz (Hertz). Using an average electrode impedance of 1.4 kΩ (kiloOhms), the range of current delivered was 0.92 - 3.21 mA (milliAmperes).

Statistical analysis consisted of a One Way Repeated Measures Analysis of Variance (ANOVA) on normalized impedances (log10) and subsequent multiple comparisons between groups (without/with activation, off/on DBS, Student-Newman-Keuls Method).

Electrode position reconstructions

Electrode positions were determined in 5 of the 6 patients from post-surgery MRI imaging (T2, FSE, 256X256, 2mm contiguous sections, TR 3000. TE 90. TR 3.29khz, J.A. Saint-Cyr, personal communication) based on distances to AC and PC landmarks in sagittal, axial and coronal series images (L.C.M. Perreira, personal communication). The positions are scaled and redrawn on Schaltenbrand-Wahren sagittal sections throughout the medial-lateral span of the STN (figure 9).

L-Dopa group

The L-dopa group consisted of four patients with idiopathic PD. Initial examination was performed in the clinically defined “off” state, 12h without antiparkinsonian medication. The patients’ regular medication was then given and they were re-examined clinically “on” (with improvement to rigidity and other symptoms assessed with the UPDRS) from 30 mins to 3h later. Measurements were done bilaterally (without and with activation, off vs. on), and only patient 4 had a previous right pallidotomy (in May/96; ◆-ipsilateral arm, ◇-contralateral arm in figure 10).
Statistical analysis consisted of a One Way Repeated Measures Analysis of Variance (ANOVA) on normalized impedances \( \log_{10} \) and subsequent multiple comparisons between groups (without/with activation, before/after L-Dopa, Student-Newman-Keuls Method).

Microsubthalamotomy group

The introduction of microelectrodes and DBS electrodes into the STN creates microlesions and can often produce an improvement in symptoms, a "microsubthalamotomy". We measured rigidity changes due to the introduction of micro- or DBS electrodes to observe the magnitude of these effects in 5 PD patients undergoing surgery. Measurements were carried out before surgery (patients had withdrawn from medications for at least 12h) and were repeated either after microelectrode mapping in 1 patient (▲ figure 11) or after insertion of DBS electrodes in the remaining 4 patient (same figure). Measurements were on the more rigid arm in these patients.

Statistical analysis consisted of a One Way Repeated Measures Analysis of Variance (ANOVA) on normalized impedances \( \log_{10} \) and subsequent multiple comparisons between groups (without/with activation, before/after surgery, Student-Newman-Keuls Method).

Controls:

Limb impedance in normal subjects

Rigidity measurements were applied bilaterally to six age-matched controls without PD or other conditions (i.e. arthritis or joint pain) that might cause an increased resistance of the arms to passive manipulation to determine a normal range of mechanical
impedance. The range of normal impedances (mean +/- SEM) in baseline and activated states are plotted over figures 8 and 10-12.

**Surgical control group**

Since the surgical procedures can cause a variable amount of anxiety and stress or fatigue, it is conceivable these factors may play a role in altering limb impedance. To control for these effects, rigidity measurements were also performed on three patients undergoing similar stereotaxic procedures, bilaterally for the implantation of a DBS electrode into ventralis intermedius (Vim) of the thalamus for treatment of Essential tremor in two patients (circles and triangles, figure 12) and contralaterally to implantation of a DBS electrode into Vim for Multiple Sclerosis in one patient (*, same figure).

Statistical analysis consisted of a One Way Repeated Measures Analysis of Variance (ANOVA) on normalized impedances \( \log_{10} \) and subsequent multiple comparisons between groups (without/with activation, and before/after surgery, Student-Newman-Keuls Method).

**Intra-operative and other experiments:**

To better understand the contribution of STN. GPi and GPe neurons to rigidity we measured changes in rigidity (and of its activation) with a reversible pharmacologic block in STN. We also measured the increase in rigidity with activation simultaneously to recording a neuron in the pallidum (later determined to be in GPe).
Lidocaine injection into the STN

During microelectrode mapping in one patient for bilateral implantation of DBS electrodes, we injected 23 µL of 2% lidocaine (a non-specific Na+ channel blocker) at a site presumed to be in the STN based on movement-evoked potentials in recorded activity. Injections were made in 10 µL and 13 µL increments, less than a minute apart. Rigidity measurements were performed at regular intervals in the contralateral arm until impedance returned to its initial magnitude (see figure 13). The injection site is shown in figure 14.

Rigidity assessment with simultaneously recorded neuron

On one occasion we had the opportunity to measure rigidity changes with activation simultaneous to microelectrode recordings in GPe in a patient undergoing a pallidotomy (Figure 15). This cell responded to passive movements, suggesting it was involved in sensorimotor control of the contralateral arm. The LRA output was directed to the analog/digital converter and stored on magnetic tape for off-line analysis. Off-line analysis included spike averaging of activity during 14 cycles of alternating flexion/extension movements (8 baseline, 6 activated), triggered to the end of the biceps stretch as obtained from the gyroscope trace. Thus, cell and EMG activity was determined in the 1 s interval preceding the end of the biceps stretch and the 1 s interval during the onset of the triceps stretch (see figure 16a). Histograms of changes in cell activity were then constructed and analysed by t-tests (figures 16b and 17). The location of the recorded cell in GPe during microelectrode trajectory is shown in Figure 18.
Subthalamotomy vs. pallidotomy: effects on rigidity

Isolated observations and measurements during surgical procedures in STN and GPi provided the opportunity to compare the effects of lesions in these structures. Rigidity measurements were performed before and after microelectrode recording, and immediately or ~30 minutes after the lesions were made in three patients, one undergoing a unilateral subthalamotomy (STN) and two patients undergoing unilateral pallidotomies (GPi) (figure 19). Due to the large range of impedances in these patients, the data are reported as ratios to the baseline rigidity measured before procedures began. The lesions were made with a thermistor-coupled electrode; the typical procedure is to heat the electrode tip from 60° C to 90°C in 10° increments for 60 seconds at each temperature (Lozano and Hutchison 1998).

Time course of STN-DBS induced changes in rigidity

During optimization of parameters in one PD patient with a unilaterally implanted STN-DBS electrode, rigidity measurements were performed with the stimulator on (at parameters pre-determined to reduce rigidity and abolish tremor), and repeated at regular intervals as the stimulators were switched off and on again. Tremor was monitored via accelerometry of the tremulous hand, contralateral to the DBS electrode (see figure 20).
RESULTS

UPDRS rigidity ratings correlated poorly with mechanical impedance

The simultaneous UPDRS rigidity ratings generally did not agree with the measures of mechanical impedance. An example of this is illustrated in Figure 7a. Baseline impedance was reported as a score of 1 on the UPDRS scale (slight rigidity detectable with activation procedures); when a slight decrease in the impedance occurred the rigidity was thought to have dissipated. Furthermore, activation procedures increased impedance nearly threefold (175%) but rigidity was still rated at 1. The results of simultaneous ratings during various assessments in two patients are shown in figure 7b. There was significant overlap between ratings of 0, 0.5 and 1 at similar impedances, and generally ratings did not correspond well to the impedance measures ($r = 0.454$). The simultaneous assessments were thus abandoned.

Patients:

STN-DBS group

All PD patients showed decreases in arm rigidity with STN-DBS at voltages from 1.3-4.5 V, pulse durations of 60-180 μs (microseconds), and frequencies 130-180 Hz (figure 8). STN-DBS decreased baseline rigidity from $64 \pm 19.3$ mNm/deg to $26 \pm 11$ mNm/deg and activated rigidity from $112 \pm 37.2$ mNm/deg to $51 \pm 7$ mNm/deg, corresponding to decreases of 60% and 54% respectively ($p<0.05$, One Way RM ANOVA). Activation caused a 71% increase in impedance when stimulators were off and a 96% increase with stimulators on ($p<0.05$, One Way RM ANOVA).

Of the six patients treated by STN-DBS, three patients had a previous pallidotomy ($\blacktriangledown, \bullet, \bigcirc$, Figure 8). These patients showed results similar to the non-lesioned patients.
Figure 7. UPDRS ratings correlate poorly with mechanical impedance measures.

a) example of simultaneous UPDRS ratings during rigidity assessment. A rating of 1 was given in both baseline and activated states although with activation impedance increased threefold. b) linear regression of concurrent UPDRS ratings with measured impedances shows a poor correlation, r= 0.484.
Impedance Verbalized Rating

![Graph a: Impedance and Verbalized Rating Over Time](image)

![Graph b: Impedance vs. UPDRS Rating](image)

$$r = 0.454$$
Figure 8. STN-DBS decreases rigidity.

Filled symbols bilateral stimulation, open unilateral. Grey symbols/bold line = mean.

Range of control impedances (mean – SEM to mean + SEM) are indicated by dashed lines on both baseline and activated impedance plots. Baseline rigidity was decreased to within the control range of impedance in three patients. DBS also resulted in a similar decrease in activated rigidity.
most likely because the rigidity was measured in the arm ipsilateral to the pallidotomy in two of these three patients (● and ○, same figure). The patient whose rigidity was measured contralateral to the pallidotomy (▼) showed a decrease which paralleled the mean decrease (grey symbols/bold line), but the small number of patients precludes observing any difference between these patients.

**Effective vs. ineffective STN-DBS contacts**

The positions of effective (black circles) and ineffective contacts (open circles) in decreasing rigidity are shown in figure 9. All “optimized” effective contacts were located in the medial STN or slightly dorsal (possibly in the lenticular fasciculus, pallidothalamic projections) and produced significant therapeutic benefit. The non-optimized (grey circles) contacts also improved rigidity, but these contacts may not have provided the best relief from PD symptoms. In one patient the effective contact was very dorsal to the STN, presumably in the ventral anterior thalamus (Voan/Vop).

**L-Dopa group**

L-Dopa decreased the baseline and activated rigidity in all PD patients. Mean baseline rigidity was reduced from 64 +/- 11.7 mNm/deg to 26 +/- 5.8 mNm/deg and activated rigidity from 112 +/- 19.5 mNm/deg to 43 +/- 6.4 mNm/deg, corresponding to decreases of 59% and 62% respectively (p<0.05, One Way RM ANOVA), shown in figure 10. Activation increased rigidity by 75% in the off state (p<0.05, One Way RM ANOVA) and by 63% when on, but this was not significant (p>0.05). Rigidity was decreased to within the control range in only one patient. The patient with the previous pallidotomy showed similar decreases in both arms, regardless of whether it was ipsi- or
Figure 9. Positions of electrode contacts used in STN-DBS patients.

Contact positions were determined from MRI imaging with respect to AC-PC coordinates and superimposed on Schaltenbrand-Wahren sagittal sections spanning the STN. Distances to midline are shown in mm, medial to lateral. “Optimized” contact locations are black circles, non-optimized but effective contacts are grey, and ineffective contact locations are open circles.
Figure 10. Rigidity changes with L-Dopa.

Each patient is represented by a different symbol, filled symbols right arm, open symbols left arm. Grey symbols/bold line = mean. Range of control impedances (mean – SEM to mean + SEM) are indicated by dashed lines on both baseline and activated impedances. L-Dopa produced similar decreases to both baseline and activated rigidity, and decreased baseline rigidity to within the control range of impedance in two patients.
contralateral to the lesion (◆, ◊ decreases parallel, see figure 10). However, the arm contralateral to the previous pallidotomy did have lower baseline and activated rigidity (◊).

Microsubthalamotomy group

The perioperative results are shown in figure 11. Here baseline and activated rigidity were decreased from 49 +/- 14.6 mNm/deg to 22 +/- 6.4 mNm/deg and from 91 +/- 28.4 mNm/deg to 43 +/- 17.7 mNm/deg, or 55% and 43% respectively (p<0.05, One Way RM ANOVA). Activation increased rigidity by 86% before surgery and 95% after (p<0.05, One Way RM ANOVA).

Controls:

Limb impedance in normal subjects

The range of impedances in the control group was 6 +/- 0.8 mNm/deg for baseline impedance, and 13 +/- 1.9 mNm/deg with activation. This range is displayed in figures 8 and 10-12. There was no significant increase with activation in normal subjects (p>0.05, One Way RM ANOVA).

Surgical control group

The ET/MS patient results are shown in figure 12. Changes in baseline (5 +/- 0.4 mNm/deg to 7 +/- 1.6 mNm/deg) and activated limb impedance (9 +/- 1.7 mNm/deg to 10 +/- 2 mNm/deg) were insignificant; the rigidity was within or below control values before and after surgery and was not affected by the stress, anxiety or fatigue the
Figure 11. Effects of microsubthalamotomy on rigidity.

Each symbol is a different patient. Grey symbols/bold line = mean. Range of control impedances (mean – SEM to mean + SEM) are indicated by dashed lines on both baseline and activated impedances. Here baseline rigidity was decreased to within the control range of impedance in one patient. Again, similar decreases occurred in both baseline and activated rigidity.
Figure 12. Effects of surgery on ET/MS patients.

Each symbol is a different patient, filled symbols contralateral to surgery. open ipsilateral. Grey symbols/bold line = mean. Range of control impedances (mean – SEM to mean + SEM) are indicated by dashed lines on both baseline and activated impedances. Impedance was unchanged after surgery, and there was no increase in impedance with activation.
procedure may have caused. Again, there was no significant increase with activation in these subjects (p>0.05, One Way RM ANOVA).

Intra-operative and other experiments:

Lidocaine injection into the STN reduces rigidity

Baseline and activated rigidity decreased within 5 and 12 minutes of the injection of lidocaine, respectively (paired t-tests, p< 0.05; see figure 13, 14 for injection site). Activated rigidity recovered within ~44 minutes, while baseline rigidity recovered after ~71 minutes. There was also a "rebound" effect in the activated rigidity; it was higher than before the injection, but this effect was less obvious in the baseline rigidity.

GPe cell activity indicates its involvement in the activation of rigidity

The activation procedure (see accelerometer trace in Figure 15d) resulted in increased EMG responses in the triceps and biceps muscles (parts b and c) with a resultant increase in mechanical impedance throughout the activation (37 +/- 4.6 mNm/deg to 261 +/- 33.4 mNm/deg, figure 15a). The cell had a lower mean firing rate during biceps stretches (86.5 Hz) than triceps stretches (121.3 Hz) before activation (t-tests p<0.05, figures 16b and 17). With activation this difference was exaggerated (28.3 Hz vs. 111 Hz, t-tests p<0.05). The activity remained roughly the same during triceps stretches (t-tests, p>0.05). The location of the cell is shown in figure 18.
Figure 13. Lidocaine injection into STN decreases rigidity.

Two injections of 10 µL and 13 µL into the STN (2% lidocaine) were made 5 minutes prior to the first measurement. Measurements were repeated at regular intervals until rigidity returned to pre-injection levels. Baseline rigidity decreased within five minutes of injection, activated rigidity decreased within 20 minutes.
Injection @ -5 minutes

Time (min)

Baseline
Activated
Figure 14. Lidocaine injection site.

Lidocaine injections were made at the beginning of a region rich in movement-evoked activity (presumed STN cells, responded to passive manipulation of limbs). Regions of characteristic bursting cells, STN cells and SNr cells are superimposed on a Schaltenbrand & Wahren 12 mm sagittal section.
In this diagram, the following labels and annotations are present:

- **S1** and **S2**
- **Rt**
- **Voa**
- **Vop**
- **Vim**
- **bursting cells**
- **Injection site ~23 uL**
- **STN cells**
- **SNr cells**
Figures 15a-f. GPe neuron simultaneously recorded during rigidity assessment.

a) mechanical impedance output from the LRA, in Nm/deg, b) and c) rectified triceps and biceps EMGs, respectively in volts, sampled at 250 Hz, bandpass filtered 50-2000 Hz, amplified 100x; d) activation procedure, measured by accelerometry on the dorsal surface of contralateral hand in volts, sampled at 250 Hz, amplified 100x. e) gyroscope (angular velocity) output in volts, and f) GPe cell activity, bin width is 100 ms, signal amplified 5,000 –10,000x.
Figure 16. Triggered averaging of cellular and EMG activity of recorded neuron.

a) gyroscope output (deg/s), b) cell activity (100 ms bin widths), c) rectified biceps EMG, and d) rectified triceps EMG in volts. Each cycle of flexion/extension movements was aligned to the end of the biceps stretch, the biceps stretch preceding from −1 to 0 seconds, the triceps stretch from 0 to 1. Cell activity and EMG responses were averaged over these intervals across the 14 cycles (8 baseline, 6 activated). Note an enhanced biceps and triceps response after activation.
Figure 17. Mean firing rates of GPe neuron during biceps and triceps stretches.

During baseline rigidity (part a), firing rates were 121.3 Hz and 86.5 Hz during triceps and biceps stretches, respectively. With activation (part b), the firing rate during biceps stretch fell to 28.3 Hz, while the rate during triceps stretch was not affected (111 Hz).
Triceps stretch

Counts/100 ms
Without activation

Counts/100 ms
With activation

b

Triceps stretch

Biceps stretch
Figure 18. The position of the GPe cell recorded in Figure 15.

Regions of “signature” cellular activity are displayed (GPe-like vs. GPi-like cells), as well as cells which displayed changes in activity with passive manipulation of various joints (movement-evoked activity). The microelectrode results from one trajectory are superimposed on a Schaltenbrand & Wahren 20 mm sagittal section. The recorded cell is at the end of the region where GPe-like cells were encountered.
GPi-like cells
(low frequency, irregular)

GPe-like cells
(high frequency, regular)
Subthalamotomy vs. pallidotomy

These results are shown in figure 19. Baseline rigidity was decreased in one pallidotomy patient and in the subthalamotomy patient. The activated component remained in the pallidotomy patients (top trace) and was totally abolished in the subthalamotomy patient (bottom trace). Decreases in baseline and activated rigidity were a consistent feature of interventions in the STN (via DBS or subthalamotomy). An activation component also remained in measurements from insertion of a DBS electrode into the Gpi (results not shown here).

Time course of STN-DBS induced changes in rigidity

As the stimulator was switched off, the tremor returned almost immediately (< 10 seconds, see figure 20). This is a consistent clinical observation when parameters have been optimized to provide maximal therapeutic benefit. However, there was a gradual increase in the rigidity of the limb contralateral to the electrode over the course of ~20 minutes. As the electrode was switched on again, the tremor and rigidity were decreased immediately.
Figure 19. Effects of pallidotomy vs. subthalamotomy on rigidity.

a) Pallidotomy results. b) Subthalamotomy results. Measurements were taken prior to surgery, after microelectrode mapping, immediately following lesion (pallidotomy) and 30 minutes post lesion. Impedance measurements are plotted as the ratio to baseline rigidity before surgery.
Before After -30 mins
recordings recordings, lesion

Baseline Activated

a

Ratio to baseline Impedance

Before recordings After recordings, before lesion After lesion ~30 mins after lesion

b

Ratio to baseline Impedance

Baseline Activated
Figure 20. STN-DBS induced changes in rigidity follow a slower time course than changes in tremor.

Periods with/without tremor are displayed by the shaded/non-shaded boxes above the time axis. While tremor returned almost immediately after the electrode was switched off, the rigidity increase followed a slower time course. Both rigidity and tremor were abolished once the electrode was switched on again.
No Tremor | Tremor | No Tremor

Time (min) | 0 | 20 | 40 | 60 | 80 | 100 | 120 | 140 | 160

Impedence (Nm/deg)

- DBS ON
- DBS OFF
- DBS ON

Baseline | Activated
DISCUSSION

STN-DBS significantly decreases rigidity

This study is the first to quantify the immediate and profound decrease in rigidity in both baseline and activated states with STN-DBS, as reported qualitatively in clinical studies (Kumar et al. 1998a; Limousin et al. 1995b). These results, combined with the novel observation that lidocaine injections into the STN decrease rigidity and that electrical stimulation inhibits neurons in GPi and SNr (Dostrovsky et al. 2000) in PD patients and STN in rats (Benazzouz et al. 2000) provide further evidence that DBS inhibits ongoing neuronal activity in the STN. At least with regards to rigidity, inhibition of STN activity (via STN-DBS, L-Dopa administration or microsubthalamotomy) appears to decrease the overall gain of the response to muscle stretch, as baseline and activated rigidity showed similar proportional decreases (Figures 7-9). STN-DBS therapy often allows for a decrease in L-Dopa dosage (Molinuevo et al. 2000; Limousin et al. 1995b) further suggesting similar physiological effects.

In four of the five patients the contacts that decreased rigidity were shown to be within the STN. However, there is some uncertainty in the reconstruction of electrode positions. First, it is possible for the electrodes to shift between the time of rigidity assessment and post-op MRI imaging. For example, the contact that appeared to be dorsal (in Voa or Vop) could have been lower at the time of assessment and have subsequently moved up. However, a reduction in rigidity can be achieved with lesions in this region of the thalamus (it receives the pallidal projections), but this is paradoxical since this region is already hypoactive. Second, the DBS electrodes can cause some distortion in the MRI image and the STN is not as clearly seen as the pallidum, making visualization of the structure and contacts more difficult.
Possible mechanism of action of DBS in decreasing rigidity

Electrical stimulation of the pontomedullary reticulospinal tract (Kohyama et al. 1998; Iwakiri et al. 1995) or PPN in decerebrate cats (Lai and Siegel 1990), or of PPN in rats (Kelland and Asdourian 1989) has been shown to decrease muscle tone, suggesting STN-DBS could reduce rigidity via disinhibition of downstream descending reticulospinal systems. In this study, 4 of the 5 effective contacts were within the STN (figure 9), but there is no direct evidence to support this scheme. An interesting experiment would be to look at the effects of STN-DBS on the long latency responses to muscle stretch or electrical stimulation, to see if it in fact disappears when rigidity is alleviated. In addition, the STN-DBS effects on rigidity most likely follow a different mechanism than for the effects on tremor. As stimulation was interrupted, tremor returned immediately but rigidity required a longer interval of time to increase to initial baseline levels (see figure 20).

Quantifying L-dopa mediated decreases in rigidity

As mentioned, the mean decreases evoked by STN-DBS and L-dopa in baseline rigidity were the same (both 59%). While it is widely accepted that PD symptoms are alleviated by oral administration of L-dopa, evaluation of results has been made qualitatively or with respect to EMG activity in rigid limbs, which may not correlate well with clinically assessed rigidity (Berardelli, Sabra, and Hallett 1983). Quantitative studies examining the L-Dopa-mediated decreases in rigidity via artificially induced movements have been carried out on the hand (Caligiuri and Galasko 1992) or around the knee (Knutsson and Märtensson 1971), but to our knowledge this is the first attempt to compare changes evoked by L-Dopa and STN-DBS. The extents of these changes were
similar, as were the effects of lesions in the STN from microelectrode mapping or DBS insertion.

Possible mechanism of activation of rigidity

The increases in baseline rigidity with activation ranged from 71% to 96% in the “off” states of the three groups (before surgery, pre L-Dopa, STN-DBS off). With treatment or surgery activation still increased rigidity from 63% to 105%. A recent study by Fung et al. (Fung, Burne, and Morris 2000) also reported significant increases in rigidity with activation in PD patients, although their methodology was different in that they calculated angular impulse and work required to move the wrist via a torque motor. Furthermore, in normal subjects these increases were not significant, again in agreement with our results.

A curious observation from the mechanical impedance traces was the appearance of an initial “peak” as activation procedures began (see figure 5b). These peaks did not appear in all patients (see figure 7a or 15a), and did not give the impression of being consistent with the level of rigidity, as one might expect. These peaks might reflect an initial contribution of “mental stress” or anxiety to rigidity (Delwaide and Gonce 1988) when the subject attempts to remain passive, but other authors disagree as to whether stress or anxiety influences rigidity in PD (Weiner and Lang 1989). It is also possible these peaks might more accurately reflect the level of akinesia in these patients, but parameters such as movement time or velocity for activating movements were not measured in these patients.

The activation phenomenon has been known since Webster (Webster and Mortimer 1977) and appears to be a consistent feature in PD. Inducing or “activating”
rigidity with voluntary contralateral movement is a standard clinical technique for assessing patients with little or no resting rigidity. The mechanism is not known, but it could involve SMA input to the contralateral striatum. PET studies of repetitive movements with an intermovement interval of <1s (frequencies similar to activation procedures used in this study) have consistently shown increases in rCBF in contralateral SMA (Sadato et al. 1996; Kawashima et al. 1996; Kawashima et al. 1993; Fox et al. 1985). A recent study by Inase et al. (Inase et al. 1999) using anterograde tracers injected into the SMA forelimb region in macaque monkeys has confirmed contralateral SMA-striatal projections. A possible mechanism is illustrated in figure 21. Part a) outlines the pathophysiological changes already proposed in the basal ganglia. Part b) illustrates the possible contribution of the contralateral SMA in activating or reinforcing rigidity. For example, the left SMA (contra SMA in part b of figure) would be activated in voluntary movement of the right hand, which could then change activity in the right striatum and right STN via the indirect pathway through GPe or possibly direct corticosubthalamic projections (thus affecting left arm rigidity).

Microstimulation of SMA decreased the firing frequency of cortical motor neurons evoked in response to muscle stretch (Hummelsheim et al. 1986; Wiesendanger et al. 1975), suggesting the SMA “gates” input from the periphery. Therefore, an inhibition of SMA activity would increase the muscle response to stretch. This process would normally be inhibited by other cortical areas (i.e. prefrontal or premotor cortex), but these are less active in PD patients (Sakatani et al. 1999; Davis et al. 1997; Hirato et al. 1995; Hirato et al. 1993). While the SMA seems a likely site for activating contralateral rigidity, there are other levels of the neuraxis where bilateral influences on
Figure 21. Basal ganglia activity involvement in rigidity.

a) simplified version of figure 2, showing changes that could contribute to baseline rigidity, and b) during activation of rigidity with contralateral hand movements. SMA input to the contralateral striatum could activate rigidity by further increasing activity in STN and GPi via the indirect pathway.
Activating hrnd muscles

Sensorimotor cortex

Striatum

GPe

STN

D2

D1

GPi

SNr

Thalamus

Rigid arm

PPN

RF

Spinal cord

Contra Sensorimotor cortex

Striatum

GPe

STN

D2

D1

GPi

SNr

Thalamus

MORE Rigid arm

PPN

RF

Spinal cord

Activating hand muscles

M1

SMA
rigidity such as cortico-cortical via callosal pathways and brainstem areas such as PPN may also be involved.

In one patient we had the opportunity to record from a neuron in GPe during a rigidity measurement (see figure 15). As outlined in the introduction, GPe is reciprocally connected to the STN and activity in this structure might reflect STN or striatal input. Activation of rigidity by voluntary contralateral hand movements appeared to cause more inhibition in the cell’s activity during bicep stretches, consistent with the mechanism mentioned above. Further simultaneous recordings from the STN (or GPi) during this activation procedure could provide valuable insight into the role of this and other nuclei in the activation of rigidity. We had the opportunity to measure the changes in rigidity during a unilateral subthalamotomy and compare these to a unilateral pallidotomy. Interestingly, activated rigidity appeared to be more affected by subthalamotomy than it was by pallidotomy (see figure 19). After pallidotomy, the baseline rigidity was decreased in one patient and a significant activation component remained in both (a similar result was obtained after insertion of a DBS electrode in GPi of another patient, results not shown), while in the subthalamotomy both baseline and activated rigidity were decreased.

These results support the notion that STN/GPi may have different contributions to resting and activated rigidity, but further experimentation is needed. Activation was a consistent feature of our patients, and is a useful feature in the diagnosis and assessment of Parkinsonian patients.
Cortical vs. brainstem origins of rigidity

As outlined in the introduction, sufficient evidence exists to support that the long-latency response to stretch is transcortical. However, one criticism of the transcortical model is that the amplitudes of these responses do not correlate well with clinically assessed rigidity. This is most likely due to differences in procedures used by experimenters, since the amplitude of the M2/3 response may depend on the preload (background EMG activity) of the stretched muscle (Evarts et al. 1979). An opposing, but not mutually exclusive explanation for the origin of rigidity is a change in activity of descending reticulospinal systems. Vestibulospinal activity is clearly affected in PD; postural instability is a hallmark of the disease and is demonstrated by the inability of the PD patient to maintain balance in a standard clinical "pull test". Delwaide demonstrated that the activity of at least one of these reticular nuclei, the nucleus reticularis pons caudalis (NRPC) was altered in PD patients. The NRPC is the last supraspinal relay for the audiogenic startle reaction, the generalized muscle response following an unexpected loud sound. In Delwaide's group of patients, this reaction was reduced (Delwaide, Pepin. and Maertens 1996).

In this explanation, the activity of Ia and Ib inhibitory interneurons is regulated by reticulospinal control, and these dysfunctional reflexes could contribute to rigidity by increasing co-contraction of antagonistic muscles or by decreasing the ability of a contracting muscle to relax. However, decreased autogenic inhibition is also found in dystonic patients (Marsden 1990) without the basal ganglia dysfunction, so the contribution of this to parkinsonian rigidity cannot be certain. While Burne et al. (Burne and Lippold 1996) claim 100% discrimination between normal subjects and PD patients by examining tendon organ inhibition, the correlation between parkinsonian rigidity and
degree of reciprocal inhibition is less clear. Can decreases in rigidity (from L-Dopa or DBS) correlate with a reversal of activity of these reflexes (i.e. increases in autogenic inhibition or increases in reciprocal inhibition)?

It is also likely that different muscles (proximal vs. distal, arm vs. leg) could have different origins of rigidity. Arm and proximal muscles, which presumably have a finer control of muscle tone, may be more influenced by cortical or long-loop modification of these reflexes than leg or antigravity muscles. The regulation of tone in these muscles could be more sensitive to spinal reflexes under reticulospinal control. These factors could account for the difficulty in correlating changes in reflexes in different limbs to rigidity. At this time however, neither explanation can be refuted. There is evidence to support both schemes, but there may also be an interaction between the two. In addition to the abnormal basal ganglia output, direct projections from cortex to spinal interneurons could be involved in modifying reflex activity, since Golgi tendon organ reflexes are depressed in decerebrate animals (Chan and Ross 1997).

**Other possible contributors to the enhanced long latency response in PD**

However, one cannot ignore other possible contributors to the long-latency reflex. Segmentation of afferent discharges into groups (Hagbarth et al. 1981) or slower conducting secondary muscle spindle afferents (Matthews 1984) have also been proposed as mechanisms for an enhanced M2/3 response, since their conduction velocities fit well with the latency of the long-latency reflex. Any facilitory input arriving at the motor neurons of the stretched muscles with the appropriate latency after the stretch (transcortical loop, slower secondary spindle afferents) could theoretically contribute to rigidity by enhancing the evoked muscle response.
Furthermore, the contribution of cutaneous afferents has not been sufficiently addressed. A study by Fuhr et al. (Fuhr et al. 1992) examined the contribution of these afferents to muscle tone in PD patients. The index finger was electrically stimulated (four times the sensory threshold) while simultaneously recording EMG activity from the first dorsal interosseous muscle. Not only was the first inhibitory reflex component less pronounced in the PD patients, but this effect was partially reversed with dopaminergic therapy, suggesting cutaneous afferents could also be involved. Quantifying rigidity or EMG responses recorded in the index finger before and after removing the contribution of cutaneous afferents (with a ring block of the cutaneous nerves at the base of the finger) could shed some light on their contribution to rigidity in PD.

Value of the LRA in clinical investigation

UPDRS ratings generally did not agree with mechanical impedance (figure 7), as Prochazka et al. already demonstrated (Prochazka et al. 1997). The UPDRS scale only allows ratings of rigidity in four intervals. Clearly, this is not sensitive enough to detect often small changes in rigidity with therapeutic interventions (or with activation). In fact, some clinicians use added intervals of .5 to accommodate a wider range of assessed rigidity. These results clearly demonstrate the usefulness of this device, especially in optimizing lesion location, in the optimization of DBS parameters or in titrating antiparkinsonian medications. However, one limitation of the device is that the impedance of flexor vs. extensor muscles cannot be separated, since the impedance measurements are averages over several cycles of imposed movement. Although most authors suggest that rigidity is equally expressed in flexors and extensors, separate impedance measurements of flexors vs. extensors would be valuable in supporting this
issue. Furthermore, the contribution of the inertial term to the impedance model may be underestimated. Although Prochazka et al. suggest that imposed movements of frequencies <1 Hz produce a negligible acceleration, faster movements or larger patients (increased arm mass) could potentially contribute to mechanical impedance of the arm \( F = m \times a \).

The present study shows that STN-DBS dramatically reduces both baseline and activated Parkinsonian rigidity, and outlines the critical role the STN plays in mediating the pathophysiology expressed by the basal ganglia. Furthermore, rigidity is abolished with mechanical interventions without electrical stimulation, casting doubt on the validity of clinical procedures that use ongoing subjective ratings of rigidity to localize the STN (Pollak et al. 1996). Additionally, preliminary evidence suggests the involvement of the basal ganglia in mediating the activation of rigidity. Clearly, there is a complex interaction between central (basal ganglia and cortex) and peripheral (spinal reflex) mechanisms and further work needs to be done to elucidate these interactions.

**Future directions**

Further microelectrode recordings in the STN and GPe/GPi during rigidity assessment in surgery could confirm the involvement of the basal ganglia in the activation of rigidity. Additionally, an expanded study comparing the acute effects of lesions in GPi vs. STN on rigidity would be invaluable in substantiating (or refuting) the proposed model for the activation of rigidity.

Another interesting experiment would be to investigate the role of reciprocal or autogenic inhibition in rigid patients undergoing STN-DBS therapy. As mentioned, the
correlation between changes in clinically assessed rigidity and changes in reciprocal inhibition has been questionable; it would be valuable to determine if STN-DBS could reduce rigidity via changes in activity of reciprocal or autogenic inhibition. These experiments could help define the role of these reflexes in mediating changes in rigidity in PD.

Lastly, the time course of DBS effects on rigidity could be further substantiated by DBS stimulation during rigidity assessment in a larger group of patients. Initial measurement could be performed with the stimulators off, and subsequent measurements with previously optimized stimulation parameters could outline the time course of rigidity changes with DBS and confirm these effects have a longer latency than DBS effects on tremor.
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