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Quantification of Limb Stiffness and Bradykinesia and Application to the Clinical and Surgical Setting

by

Susan Kathleen Patrick

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Division of Neuroscience

Edmonton, Alberta

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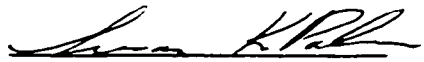

c/o Division of Neuroscience
513 HMRC
Edmonton, Alberta
T6G 2S2

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Versions of Chapters 2, 3, 4, and 5 will be submitted for publication to various journals. The authors for each chapter are listed here:

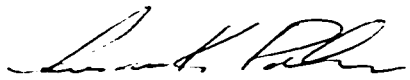
Chapter 2: Quantification of the UPDRS and modified Ashworth scales of rigidity and hypertonus. authors: S.K. Patrick, A. Denington, M.J.A. Gauthier, D.M. Gillard, A. Prochazka

Chapter 3: Quantification of rigidity and bradykinesia before, during, and after stereotactic surgery for Parkinson's disease. authors: S.K. Patrick, M.F. Wilkinson, J. Krcek, D.M. Gillard, O. Suchowersky, A. Prochazka

Chapter 4: Quantified effects of deep brain stimulation on bradykinesia and upper limb rigidity. authors: S.K. Patrick, M.F. Wilkinson, K.J. Burchiel, F.B. Horak, A. Prochazka

Chapter 5: Activity-induced changes in tone of normal and spastic finger flexors. authors: S.K. Patrick, D.M. Gillard, R. Sustrik, A. Prochazka

All co-authors have given verbal consent for the use of this material in this thesis.



Susan K. Patrick

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Quantification of limb stiffness and bradykinesia and application to the clinical and surgical setting submitted by Susan K. Patrick in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dr. Arthur Prochazka
Supervisor

Dr. Richard B. Stein

Dr. Jack Jhamandas

Dr. Dave Bennett

Dr. Jaynie Yang

1 Oct 1999
Date

Dr. John C. Rothwell
External Examiner

ABSTRACT

Accurate evaluation of motor symptoms is required to determine progression of disease and response to treatment. This thesis presents four studies pertaining to the development and application of simple quantification devices designed for the clinical setting. The first study dealt with the technical aspects of a device to quantify parkinsonian rigidity in the arm, and examined the reliability of the device in the clinical setting. Characterization of the non-linear relationships found between quantified measures and clinical ratings permits expression of the quantified measures in clinically-accepted terms. In the second study, changes in upper limb rigidity and in parameters of volitional movement during simple repetitive tasks were quantified during and following pallidotomy or thalamotomy for Parkinson's disease. The study established the feasibility of application of the device to both the clinical examination and intraoperative assessments. In the process, inconsistencies were observed in the intraoperative administration of clinical tests. Several recommendations are put forth to improve the quality and reliability of quantified measures acquired in this setting. In the third study, the effects of deep brain stimulation on rigidity and performance of repetitive movements were quantified in post-operative assessments of subjects with Parkinson's disease. Stimulation of the subthalamic nucleus or the internal segment of the globus pallidus resulted in significant reduction of rigidity at the elbow and increases in speed and amplitude of repetitive movements in most subjects. In the final set of experiments, the rigidity quantification device was applied to measurement of tone in the hand in subjects with hemiplegia due to stroke. Most subjects demonstrated gradual decreases in tone over the course of a test session as well as within sets of six quantification trials. Increases in tone measured *during* movement did not necessarily occur more often in subjects with hemiplegia than in control subjects, but the level of tone attained was usually higher and in some cases took longer to subside. The quantification methods developed and utilized during the course of this thesis work provide objective assessments of established clinical tests, and are

appropriate for application to the clinical, intraoperative, and research environments. Their use may enhance clinical assessments of therapeutic intervention for Parkinson's disease and spastic hypertonus.

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CHAPTER 1

General Introduction

1.1 INTRODUCTION

Impairments of muscle tone and motor function are symptomatic of disease or injury of the central nervous system (CNS). Deficiencies in motor performance can be very debilitating. Hypertonicity may also contribute to functional impairment. Monitoring of both muscle tone and motor function is used to determine progression of disease state, and response of the condition to medical intervention. However, clinical assessment is generally based on rating scales, and is thus reliant on the subjective interpretation of the examiner. The need for more reliable and sensitive methods of evaluation has often been expressed.

This thesis is primarily concerned with the development and use of methods to quantify hypertonicity in the arm as well as some aspects of volitional movement of the limbs. The main focus is on measuring rigidity and bradykinesia in Parkinson's disease, and the application of the measurement techniques to the clinical and surgical setting. Quantification of hypertonicity of the hand in hemiplegia is also investigated. This introductory chapter presents some background information on the pathophysiology of Parkinson's disease, and on the history, techniques, and results of stereotactic surgical procedures. Clinical evaluation of rigidity and bradykinesia, and other efforts to quantify these symptoms, are outlined. A brief introduction to spasticity and assessment of spastic hypertonus is also presented.

1.2 PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

Parkinson's disease, first formally described by James Parkinson in 1817 (Tyler, 1992) is a progressive, debilitating neurological disorder characterized by rigidity, bradykinesia, resting tremor, and postural instability. It is predominantly a motor disorder, although the scope of the effects may encompass severe emotional, cognitive, and systemic problems (Jankovic, 1992). The disease is associated with pathological degeneration of the substantia nigra pars compacta (SNc) and consequent depletion of dopamine in the basal ganglia (Hornykiewicz, 1966).

The symptoms usually initially appear on one side of the body, but gradually become bilateral (Jankovic, 1992). The presence of specific symptoms, their intensity, and distribution throughout the body vary between individuals. Rigidity, a resistance of the limbs to passive movement, generally affects antagonistic muscle groups equally and may involve "cogwheeling", a clinical change in resistance. Rigidity may be reinforced by voluntary or even passive movement of the contralateral side (Delwaide and Gonce, 1993). Tremor typically occurs only at rest, but may also occur during voluntary movement (action tremor) with progression of the disease. Execution of voluntary movements is typically slow (bradykinesia). Complex, simultaneous, or sequential tasks may be especially affected (Benecke *et al.*, 1986; Benecke *et al.*, 1987). Initiation of movements, especially those that are internally generated, may also be delayed. Associated with bradykinesia are fatigue and hesitations or arrests during repetitive movements. By contrast, festination, a progressive increase in the cyclic frequency of movements accompanied by a decrease in amplitude may occur during repetitive movements and gait (Lang and Fahn, 1989). Akinesia is often used to describe a poverty of movement; there is a decrease in spontaneous movements, including those of facial expression (hypomimia), and a lack of associated movements such as swinging of the arms while walking. Patients often demonstrate "freezing", a sudden arrest in ongoing activity or the inability to initiate movements such as locomotion. Treatment with levodopa to augment low levels of dopamine often results in dramatic

amelioration of symptoms such as bradykinesia and rigidity, but also leads to side effects such as generation of involuntary movements (dyskinesias), and motor fluctuations.

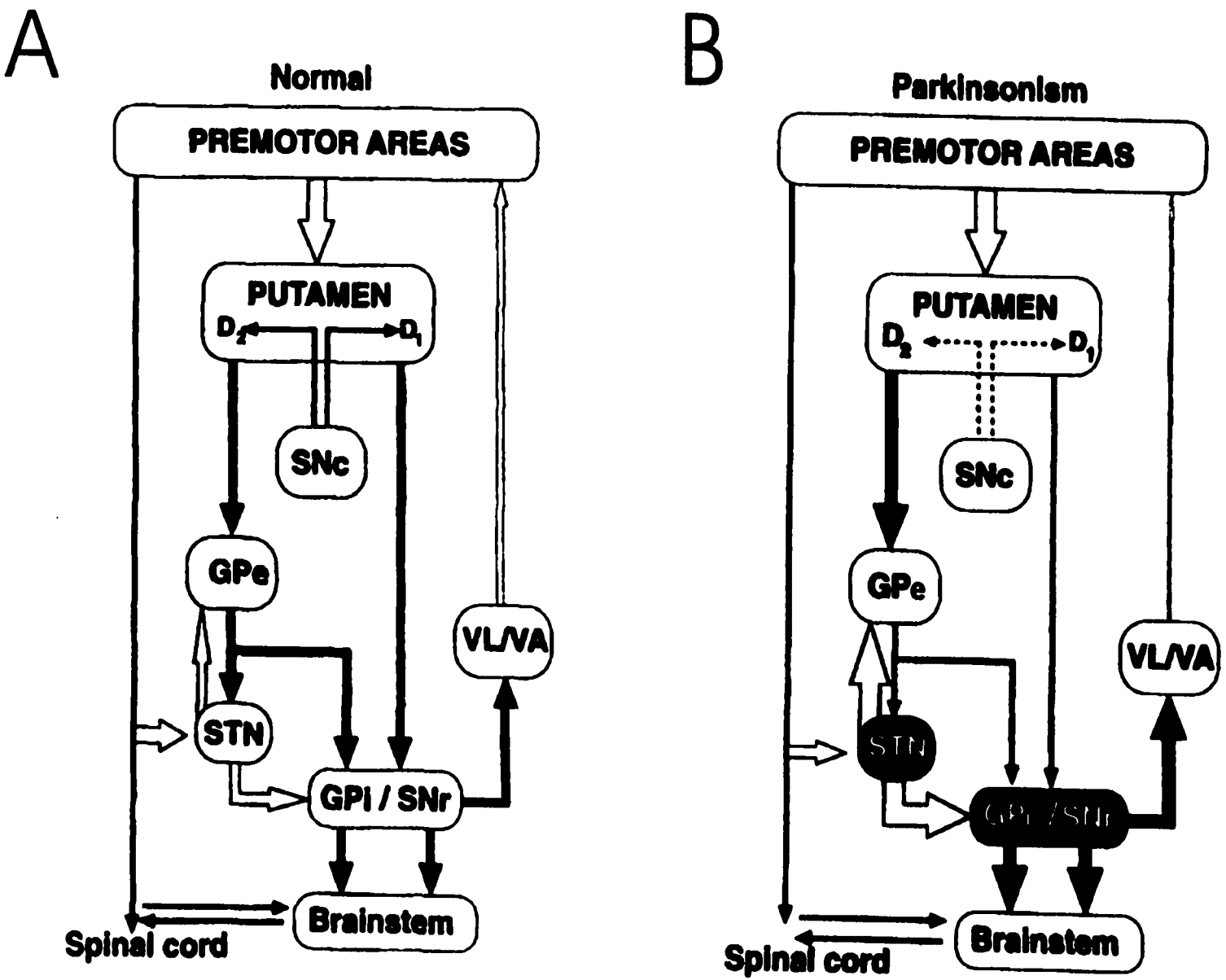
This section reviews current theories of basal ganglia function with respect to motor activity and the consequences of dopamine depletion. Some hypotheses regarding the pathophysiology of rigidity and bradykinesia will also be presented.

1.2.1 Role of basal ganglia in Parkinson's disease

The basal ganglia are composed of five bilaterally-paired nuclei: the putamen and caudate nucleus which together constitute the striatum, the substantia nigra (SN), globus pallidus (GP) and subthalamic nucleus (STN). In the current version of the most widely-accepted model, there are at least five parallel circuits running through the basal ganglia, subserving motor, oculomotor, cognitive, and limbic functions (Alexander and Crutcher, 1990). Motor deficits in Parkinson's disease are thought to be due to a pathological imbalance of opposing pathways within the motor circuit, as described below (see Alexander and Crutcher, 1990; Obeso *et al.*, 1997; Wichmann and DeLong, 1996)).

The connections within the motor circuit are outlined in Figure 1-1. Briefly, cortical input from motor and somatosensory areas is received mainly by the putamen. Basal ganglia output is from the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GPi), and is directed mainly at the ventral lateral (VL) and ventral anterior (VA) nuclei of the thalamus as well as areas of the brainstem including the pedunculopontine nucleus (PPN). VL and VA send axons back to the motor cortices. There are two pathways from the striatum to the output nuclei. The direct pathway consists of GABAergic inhibitory connections from the putamen to the GPi and SNr. In the indirect pathway, striatal neurons send inhibitory projections to the external segment of the globus pallidus (GPe), which in turn has inhibitory connections to the STN and GPi. Neurons of the STN have glutamatergic (excitatory) projections onto the output

Figure 1-1. *Model of the motor circuit of the basal ganglia in the normal state and in Parkinson's disease* A) Connections within the motor circuit are shown with activity levels as they are hypothesized to occur in normal functioning. Open arrows represent excitatory (glutamatergic) connections and filled arrows represent inhibitory (GABAergic) connections. B) Loss of dopamine in Parkinson's disease results in excessive inhibitory output of the GPi and SNr. See text for details. (Adapted from Obeso *et al.*, 1997)


A
Normal
PREMOTOR AREAS
PUTAMEN
D2
D1
SNc
GPe
VL/VA
STN
GPI / SNr
Brainstem
Spinal cord
B
Parkinsonism
PREMOTOR AREAS
PUTAMEN
D2
D1
SNc
GPe
VL/VA
STN
Brainstem
Spinal cord

nuclei. Dopaminergic neurons of the substantia nigra pars compacta (SNc) synapse onto two different populations of striatal neurons, exerting an excitatory effect on one population (direct pathway) through D_1 receptors, and inhibiting the other (indirect pathway) through D_2 receptors.

Functionally, tonic firing of the output nuclei (GPi, SNr) results in inhibition of VL activity, and therefore inhibition of movement. Cortical glutamatergic excitation of striatal neurons facilitates motor activity via the direct pathway, and inhibits it through the indirect pathway. Dopamine from the SNc acts to shift the balance between these two pathways to favor motor activity by exerting inhibitory and facilitatory effects on the indirect and direct routes, respectively. Conversely, a loss of dopamine results in the removal of inhibition of the indirect pathway and reduction in excitation of the direct pathway. The net result is increased inhibition of the thalamocortical neurons, and a poverty of motor activity. This theory is likely a gross simplification. For instance, tremor (involuntary movement) often accompanies akinesia (lack of movement). However, the model serves as a useful testbed and has many features that are consistent with known pathology and connections.

1.2.2 Parkinsonian rigidity

Rigidity is a resistance of the joints to passive movement due to increased tone of the muscles. Although several factors may contribute to rigidity (Lee, 1989), observations that it may be abolished by dorsal root section or anaesthesia of the muscles implicate a role of afferent input (Meara, 1994). It is generally accepted that the stretch reflex is involved (Lee, 1989; Meara and Cody, 1992). It is postulated that decreased activity of the supplementary motor area (SMA) due to decreased facilitation from thalamocortical projections results in a reduction of tonic inhibition of transcortical or spinal reflex pathways (Meara, 1994).

The amplitude of the long-latency (LL) component of the stretch reflex has been shown to be enhanced in subjects with Parkinson's disease compared to control subjects (Tatton and Lee,

1975; Berardelli *et al.*, 1983; Meara and Cody, 1993; Rothwell *et al.*, 1983), and a causal relationship with rigidity has been suggested. Tatton and Lee (Tatton and Lee, 1975) observed an increase in amplitude of the LL reflex of Parkinsonian patients with clinical rigidity over those without, and Mortimer and Webster (Mortimer and Webster, 1979) showed a positive correlation with quantified measurements of rigidity. However, other studies have found large inter-subject variability in the amplitude of the LL reflex (Berardelli *et al.*, 1983; Rothwell *et al.*, 1983) and less definite relationships between this measure and clinical ratings of rigidity (Berardelli *et al.*, 1983; Meara and Cody, 1993; Rothwell *et al.*, 1983). The current understanding is that, while LL reflexes may have a role in parkinsonian rigidity, other reflex activity must also be involved (Rothwell, 1994).

1.2.3 Bradykinesia

Basically, bradykinesia in Parkinson's disease is attributed to decreased facilitation of motor cortices from thalamocortical projections due to the pathological increase in inhibitory output of the GPi to its thalamic targets. Results observed with stereotactic surgery have led some to propose that the inhibitory output of the GPi to the PPN of the brainstem may also contribute to bradykinesia (Iacono *et al.*, 1995b; Wichmann and DeLong, 1996). The details of the mechanism in either case, however, are unknown. One hypothesis is that decreased facilitation of motor cortices may result in inadequate descending motor commands (Wichmann and DeLong, 1993). Additionally, normal changes in activity of GPi neurons may be obscured by the high level of tonic output (Meara, 1994). A "comparator" role for the basal ganglia has been suggested; the basal ganglia may use sensory input to monitor ongoing movement in order to compare it to the motor command. The unusually heightened response of pallidal neurons to proprioceptive input, as seen in parkinsonian animals, may be misinterpreted by the basal ganglia as an indication that the movement has progressed further than it actually has. On this view, the basal ganglia then

send the signal to terminate the movement prematurely (Meara, 1994; Wichmann and DeLong, 1993).

Normal ballistic movements are executed with a distinct triphasic agonist-antagonist-agonist pattern of EMG activity. In subjects with Parkinson's disease the timing and sequence of the components of this pattern were found to be unchanged (Hallett and Khoshbin, 1980). However, it appears that the first agonist EMG burst is insufficient for execution of the desired movement (Berardelli *et al.*, 1986). Multiple repetitions of the pattern are needed to complete the task (Hallett and Khoshbin, 1980). Although the size of the EMG bursts were similar to that recorded in control subjects (Berardelli *et al.*, 1986), the rate of increase in EMG was slower (Godaux *et al.*, 1992). Similarly, the rate of production of force has been shown to be impaired (Brown *et al.*, 1999), and it has been suggested that deficits of production and termination of force may have a role in difficulties with repetitive movements seen in Parkinson's disease (Brown *et al.*, 1999).

The precise role of the basal ganglia in controlling normal, volitional movement is unknown, but evidence suggests involvement in promotion of desired activity with suppression of unwanted movement, assistance in the execution of routine movements, and response to novel stimuli (Marsden and Obeso, 1994). The difficulty in Parkinson's disease appears to lie in the initiation and execution of motor programmes (Delwaide and Gonce, 1993). It has been suggested that bradykinesia in Parkinson's disease is due to an inability to automatically execute sequences of movements, as well as difficulty in switching from one motor pattern to the next (Delwaide and Gonce, 1993).

1.3 STEREOTACTIC SURGERY FOR PARKINSON'S DISEASE

Present-day stereotactic surgery for Parkinson's disease most commonly involves lesioning of the GPi (pallidotomy) or ventral intermediate (Vim) nucleus of the thalamus (thalamotomy). (This nucleus is called the Vim by Hassler's nomenclature, which is generally used in the surgical

literature. It corresponds to part of the posterior VL nucleus (VLp). Alternatively, and more recently, implantation of a chronic deep brain stimulation (DBS) electrodes may be used to mimic lesions in either of these sites, as well as in the subthalamic nucleus (STN). While thalamotomy can ameliorate rigidity with extension of the lesion to include parts of the anterior VL nucleus (VLa) (Grossman and Hamilton, 1993), the best indication for this procedure is the presence of tremor as the main symptom (Grossman and Hamilton, 1993). Pallidotomy, on the other hand, has been effective in reducing a broader spectrum of symptoms, most notably levodopa-induced dyskinesias. Recent reports suggest that bilateral DBS of the STN can ameliorate tremor, bradykinesia, and rigidity (Limousin *et al.*, 1998).

The procedures are performed as non-invasively as possible though a small hole made in the skull. A coordinate system defined by a metal frame fixed to the skull allows for precise localization of the target using a combination of imaging and electrophysiological techniques. For a more detailed description of surgical techniques, see the methods paper by Lozano (Lozano *et al.*, 1996). The initial coordinates are calculated based on the location of anatomical landmarks as determined by magnetic resonance imaging (MRI), ventriculography, or computed tomography (Starr *et al.*, 1998). These coordinates must be subsequently adjusted to accommodate for individual anatomical variations. Microelectrode recording is employed by several groups to identify neurons with characteristics, such as firing pattern and frequency and response to passive or active movement, of target and nearby non-target areas. Stimulation via micro- or macroelectrodes transiently simulates the effect of a would-be lesion, including unwanted side effects. In ablative procedures, lesioning is usually produced by radiofrequency thermocoagulation (Starr *et al.*, 1998). The procedures are performed under local anaesthetic, with the patient awake and alert so that physiological responses and parkinsonian symptoms can be monitored.

The current model of the motor circuit of the basal ganglia predicts abnormal activity of its components as a result of dopamine depletion in the SNc in Parkinson's disease. The hypothesis

that lesions in the overactive pathways should help restore the normal balance in the motor circuit and thus reduce pathological symptoms is the basis of the understanding of effects of stereotactic surgery in Parkinson 's disease (Starr *et al.*, 1998). (Note that output from the basal ganglia is not directed at the Vim, which instead receives input from the cerebellum (Macchi and Jones, 1997). Vim thalamotomy is believed to relieve rigidity by disrupting the connections from the GPi to the VL nucleus (Grossman and Hamilton, 1993)). Microelectrode recordings from animals rendered parkinsonian by administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and from human patients undergoing stereotactic surgery suggest elevated levels of activity in the GPi and STN, as predicted by the model (Obeso *et al.*, 1997; Wichmann and DeLong, 1996). However, they have also contributed to the growing concept that abnormal patterns of activity in the GPi, as opposed to simply elevated activity, may play an important part in motor dysfunction (Bergman *et al.*, 1998; Marsden and Obeso, 1994; Obeso *et al.*, 1997).

Although the effects of DBS on parkinsonian symptoms are similar to those of a lesion in the same location, the mechanism whereby these effects are produced is different. The most prevalent theory is that high-frequency (over 100 Hz) stimulation inhibits neuronal activity in the target by inducing depolarization block (Gross *et al.*, 1997a; Starr *et al.*, 1998). Other possibilities include stimulation of fibres or "overriding" of irregular firing patterns (Starr *et al.*, 1998).

1.3.1 Pallidotomy

The first pallidotomy-like surgical intervention was a resection of the ansa lenticularis (pallidofugal fibres connecting to the thalamic targets) credited to Russel Meyers in the late 1930s or early 1940s (Speelman and Bosch, 1998). Following their introduction for use with human patients by Spiegel and coworkers in 1947, stereotactic techniques were applied by Spiegel and Wycis, Narabayashi, and others to produce lesioning, by chemicals or electrocoagulation, of the pallidum or ansa lenticularis in patients with Parkinson's disease (Baron *et al.*, 1996). In 1952

Leksell moved the target from the anterodorsal pallidum to the posteroventral pallidum and achieved better clinical outcome (Svennilson *et al.*, 1960). However, with the initiation of lesions of the ventrolateral nuclei of the thalamus by Hassler and Riechert in 1954 and the concomitant success in tremor reduction, thalamotomy became the surgery of choice, replacing pallidotomy (Baron *et al.*, 1996; Speelman and Bosch, 1998). Dramatic alleviation of parkinsonian symptoms by levodopa, introduced in 1968, resulted in the near complete abandonment of stereotactic surgery for treatment of Parkinson's disease. Shortly thereafter, however, the limitations of the miracle drug, including motor fluctuations and induction of dyskinesias, became evident (Marsden and Parkes, 1977; Sweet and McDowell, 1975). In 1985, Laitinen began performing pallidotomy, using Leksell's posteroventral target, in subjects demonstrating a poor response to pharmacological treatment, and in 1992 published the seminal report that sparked the resurgence of stereotactic surgery for Parkinson's disease that continues today (Laitinen *et al.*, 1992).

There is general agreement that pallidotomy ameliorates drug-induced dyskinesias (Golbe, 1998; Quinn and Bhatia, 1998; Weiner, 1998). Most pallidotomy studies report additional positive effects on rigidity, tremor, and at least some aspects of bradykinesia (e.g. Baron *et al.*, 1996; Dogali *et al.*, 1996; Iacono *et al.*, 1995b; Laitinen *et al.*, 1992; Lozano *et al.*, 1995), although Sutton's study of five patients concluded that there was little overall functional benefit of the surgery (Sutton *et al.*, 1995). There is considerable disagreement, however, as to the degree of reduction of bradykinesia (compare Iacono *et al.*, 1995b; Johansson *et al.*, 1997; Samuel *et al.*, 1998), as well as conflicting reports concerning the amelioration of symptoms during the "on" state of drug therapy (Iacono *et al.*, 1995b vs. Samuel *et al.*, 1998), bilateral effects (Dogali *et al.*, 1996; Lozano *et al.*, 1995 vs. Samuel *et al.*, 1998) and the duration of benefit (Fazzini *et al.*, 1997 vs. Samuel *et al.*, 1998).

1.3.2 Deep Brain Stimulation (DBS)

Chronic DBS was first applied to the treatment of Parkinson's disease by Benabid in 1987. The idea came from intraoperative observations that stimulation of the Vim nucleus of the thalamus during thalamotomy reversibly arrested tremor (Benabid *et al.*, 1987). In light of this success, DBS of the pallidum was investigated as a therapeutic strategy with very promising results (Siegfried and Lippitz, 1994). Around the same time, Bergman, Wichmann, and DeLong demonstrated that MPTP-induced parkinsonism in monkeys could be reversed by ibotenic acid lesions to the STN (Bergman *et al.*, 1990). Their findings inspired animal studies into the effects of stimulation of the STN (Benazzouz *et al.*, 1993), and finally the introduction of STN DBS in humans (Pollak *et al.*, 1993). Despite some disadvantages of DBS, such as risk of infection, cost of the stimulator, and necessity of surgical intervention for replacement of batteries, it is the reversibility of the procedure that makes it potentially more attractive than a lesioning approach, especially for bilateral procedures or procedures involving the STN (Benabid *et al.*, 1998; Ghika *et al.*, 1998; Starr *et al.*, 1998; Volkmann *et al.*, 1998).

The majority of the albeit limited number of published studies on the effects of chronic DBS of the GPi or STN report highly favorable results. Unilateral or bilateral stimulation of the GPi has been found to significantly and often dramatically reduce parkinsonian motor symptoms, including rigidity, tremor, bradykinesia, gait, and freezing, with noted improvement in activities of daily living, and reduction in motor fluctuations (Ghika *et al.*, 1998; Gross *et al.*, 1997a; Iacono *et al.*, 1995a; Kumar *et al.*, 1998; Merello *et al.*, 1999; Siegfried and Lippitz, 1994; Volkmann *et al.*, 1998). The most consistent finding is a dramatic reduction in levodopa-induced dyskinesias. Excluding symptoms resulting from levodopa treatment, effects were mainly detected while the patients were "off" medication, but some groups also report benefits of stimulation with levodopa (e.g. Gross *et al.*, 1997a). In contrast, stimulation has been shown to diminish the beneficial effect of levodopa on akinesia (Bejjani *et al.*, 1997; Krack *et al.*, 1998a;

Krack *et al.*, 1998b; Tronnier *et al.*, 1997b); this aggravation of "on" period akinesia appears to be dependent on task as well as on stimulation parameters and the precise location of the field of stimulation within the GPi (Bejjani *et al.*, 1997; Krack *et al.*, 1998a; Krack *et al.*, 1998b). Despite the generally positive results, one group failed to detect any significant benefit accorded to patients by the procedure outside amelioration of levodopa-induced dyskinesias (Tronnier *et al.*, 1997a).

Improvement in motor performance with chronic stimulation of the STN has also been documented, again involving many of the same symptoms reported improved with GPi DBS (Brown *et al.*, 1999; Kumar *et al.*, 1998; Limousin *et al.*, 1998; Moro *et al.*, 1997; Rodríguez *et al.*, 1997). It is speculated that observed amelioration of levodopa-induced dyskinesias is due to a reduction in medication made possible with DBS (Krack *et al.*, 1997). Two non-randomized comparative studies suggested that the benefits of stimulation of the STN may be greater than those accorded with bilateral pallidal DBS (Krack *et al.*, 1998c; Kumar *et al.*, 1998); this was not as evident in a recent report employing quantified measures of, among other parameters, movement time and strength in the upper limb (Brown *et al.*, 1999).

1.4 ASSESSMENT OF PARKINSONIAN RIGIDITY AND BRADYKINESIA

The assessment of Parkinson's disease is complicated by the diversity of symptoms as well as by their variability, whether inherent or resulting from pharmacological treatment (Lang and Fahn, 1989; Marsden and Schachter, 1981; Martínez-Martín, 1993; Teräväinen *et al.*, 1989a). These same characteristics make treatment of the patient very individual (Giovannini *et al.*, 1986). The need exists for reliable, sensitive, and valid methods of determining the response of the symptoms to current and new treatments (Martínez-Martín, 1993). A variety of subjective and objective methods have been used for monitoring parkinsonian symptoms (Marsden and Schachter, 1981). The following section deals with some of the shortcomings concerning the

evaluation tools employed in the clinical setting, as well as a description of efforts to quantify the symptoms of rigidity and bradykinesia. The role of these tools in relation to stereotactic surgery will also be outlined.

1.4.1 Clinical assessment

Although clinical rating scales, such as the Hoehn and Yahr staging system, were in use prior to the introduction of levodopa, the remarkable effect of the new drug emphasized their importance and accelerated their proliferation (Lang and Fahn, 1989; Marsden and Schachter, 1981; Martínez-Martín, 1993). The development of scales evolved along with the appearance of new symptoms consequent to levodopa therapy (Marsden and Schachter, 1981; Martínez-Martín, 1993).

In 1984, the multiplicity of existing scales and the need for uniformity inspired the collaborative effort of a group of researchers to create the Unified Parkinson's Disease Rating System (UPDRS) (Lang and Fahn, 1989). The scale combines components of several other scales, and includes assessment of motor function, activities of daily living, and pharmacologically-induced complications. Most items consist of five-point (0-4) ordinate scales, each rating point accompanied by a fairly precise description. Rigidity of the limbs is assessed by passive manipulation of the patient's arm or leg by the examiner, who then rates the evoked resistance. Bradykinesia of the limbs is assessed by evaluating the performance of the patient in a number of repetitive tasks: finger taps, hand opening/closing, hand pronation/supination, and a test of leg agility. There is a separate item for rating body bradykinesia.

Since its induction, the UPDRS has achieved widespread use (Goetz *et al.*, 1995; Starr *et al.*, 1998). However, its subjective nature makes it susceptible to examiner bias (Gross *et al.*, 1997b) and open to individual interpretation (Hely *et al.*, 1993; Richards *et al.*, 1994). Studies investigating inter-rater reliability of the scale, while in general favorable, vary in the details of

their findings. Inter-rater reliability for rapid repetitive movements such as hand pronation/supination and leg agility ranged from moderate to excellent (Martínez-Martín *et al.*, 1994; Rabey *et al.*, 1997; Richards *et al.*, 1994). Reports of moderate to excellent reliability of the rigidity component by these same three studies are in conflict with two studies which found only fair reliability of the scale (tested under its original name of the Columbia University rating system) (Geminiani *et al.*, 1991; Ginanneschi *et al.*, 1988). Concerns pertaining to the subjectivity and sensitivity of the UPDRS remain (Obeso *et al.*, 1996; Teräväinen *et al.*, 1989a).

In attempt to include more objective measures, several groups have supplemented the motor section of the UPDRS with timed tasks of repetitive movements and walking, such as those outlined in the Core Assessment Program for Intracerebral Transplantations (CAPIT) (Langston *et al.*, 1992). However, these offer a limited amount of information about the patient's performance of the movements (Lang and Fahn, 1989), and in fact for some tasks may themselves be open to the subjective interpretation of the examiner (Lang *et al.*, 1995).

The need for simple methods of quantification of symptoms has often been expressed and is evidenced by the large number of tests and protocols that has been developed. Few of these have actually been incorporated into regular clinical examinations and fewer still provide quick and simple measures based on routinely employed clinical evaluations. The following section reviews some of the methods that have been applied to quantify parkinsonian rigidity and bradykinesia.

1.4.2 Quantification of rigidity and bradykinesia

The earliest documented method for quantifying muscle tone was developed by Mosso in 1896. His technique involved measuring the amount of dorsiflexion of the foot that was produced, through a pulley system, by placing weights on a pan (Walsh, 1992). Using a similar weight-pulley approach, La Joie and Gersten determined the minimum amount of force required to extend the elbow 1.5° in control subjects and subjects with hemiplegia (La Joie and Gersten,

1952). Shortly thereafter, electric motors were engaged to study parkinsonian rigidity at the elbow, the measurements expressed in terms of torque at constant-velocity displacement (Agate and Doshay, 1956; Boshes *et al.*, 1960). Torque motors have been employed in a number of approaches quantifying tone in the arm, measuring parameters such as work (Kirollos *et al.*, 1996; Teräväinen *et al.*, 1989b; Webster, 1959), compliance and stiffness (Wiegner and Watts, 1986), and resonant frequency (Lakie *et al.*, 1984). Some of the more recent methods more closely resemble the clinical examination in that displacements of the limb are imposed by the examiner, as opposed to a motor (Caligiuri, 1994; Ghika, 1993; Halpern *et al.*, 1979; Prochazka *et al.*, 1997).

Other methods that have been used to assess rigidity use electromyography (EMG), specifically to quantify characteristics of the LL reflex. As mentioned before, changes in rigidity are not always accompanied by changes in the LL reflex (Brown *et al.*, 1999). Marsden and Schachter concluded that changes in the LL reflex with parkinsonian rigidity are too variable to constitute a good measure of rigidity (Marsden and Schachter, 1981).

Quantification of bradykinesia is a difficult task since several aspects of movement, such as reaction time, movement time, frequency, and precision, may be implicated (Marsden and Schachter, 1981). Furthermore, deficits may not be universal to all tasks (Lang and Fahn, 1989).

Reaction time has been measured by a variety of methods generally requiring the subject to perform a movement of the upper limb (press a key, turn a handle, move from one touch pad to another) in response to an auditory, visual, or kinaesthetic stimulus (Evarts *et al.*, 1981; Heilman *et al.*, 1976; Teräväinen and Calne, 1981). Movement time, which has been found to correlate more closely with clinical assessments of bradykinesia (Marsden and Schachter, 1981), can often be measured with the same protocol. Tracking tasks, in which the subject may use a mouse, joystick, or manipulandum to follow a target on a display, have been used to assess precision, amplitude, and speed of movement (Johnson *et al.*, 1994; Jones and Watson, 1993). In one study, speed, frequency, and amplitude of rapid alternating pronation/supination movements were

measured as the subject rotated spheres connected to optical sensors (Beuter *et al.*, 1994). Force and kinematic parameters have been quantified to assess performance of complex simultaneous (Benecke *et al.*, 1986) or sequential tasks (Benecke *et al.*, 1987), and these revealed deficits additional to those measured in simpler tasks. Techniques able to monitor movement in 3-dimensions have also been introduced (Johansson *et al.*, 1997).

The clinical setting demands that evaluation methods be simple to use, quick, and relatively inexpensive (Teräväinen *et al.*, 1989a). Although some quantification techniques have been adapted to the clinical setting (e.g. MM-1 Movement Monitor, Axon Instruments, Inc., for measurement of reaction time, movement time, and finger dexterity), many others have failed to meet these criteria (Lang and Fahn, 1989).

1.4.3 Role of assessment in stereotactic surgery

Obviously, evaluation of clinical results of pallidotomy and DBS is important in order to determine the usefulness of these surgical procedures; there is no point in subjecting individuals to risks inherent in the surgery if the outcome shows no benefit. Differences between results of pallidotomy studies have been attributed in part to the method of assessment used (Baron *et al.*, 1996; Gross *et al.*, 1997b; Hariz, 1997; Ondo *et al.*, 1998; Vitek and Bakay, 1997), including insufficient standardization, and subjectivity of rating scales. In addition, several unanswered questions remain concerning the optimal targets and surgical techniques, the indications and effects of the different procedures, and additionally the outcome of these treatments relative to other surgical or pharmacological intervention (Kumar *et al.*, 1998; Ondo *et al.*, 1998; Quinn and Bhatia, 1998; Starr *et al.*, 1998). Sensitivity, objectivity, and standardization of methods of assessment are required to properly address these issues (Favre *et al.*, 1996 (commentaries by Kelly, Penn, and Bakay); Merello *et al.*, 1999; Starr *et al.*, 1998; Vitek and Bakay, 1997). Although quantified measures other than timed tasks have been used in the assessment of the

effects of stereotactic surgery (Benabid *et al.*, 1996; Blond *et al.*, 1992; Brown *et al.*, 1999; Iacono *et al.*, 1995a; Johansson *et al.*, 1997; Robertson *et al.*, 1999; Volkmann *et al.*, 1998; Walsh, 1992), this remains more the exception than the rule.

Evaluation of rigidity and bradykinesia is frequently employed during the course of stereotactic surgery itself in order to guide decisions regarding lesion site (Scott *et al.*, 1998; Vitek *et al.*, 1998) or extent (Iacono *et al.*, 1994; Vitek *et al.*, 1998), as well as final placement of DBS electrodes into the pallidum (Gross *et al.*, 1997a; Kumar *et al.*, 1998; Tronnier *et al.*, 1997b) or STN (Limousin *et al.*, 1995; Moro *et al.*, 1997). Usually the assessments are limited to clinical evaluation of the symptom. A few objective techniques employing EMG (Benabid *et al.*, 1994), fibre-optics (Iacono *et al.*, 1995a) and even torque motors (Walsh, 1992) have been applied intraoperatively. Timed tapping was found to be too fatiguing for subjects under intraoperative conditions (Limousin *et al.*, 1995).

1.5 SPASTIC HYPERTONUS

Spasticity frequently accompanies damage to motor components of the CNS (Noth, 1991), due to, for example, cerebral vascular accident (stroke) or traumatic brain injury. Between settings and investigators, the definition of spasticity variably includes multiple symptoms associated with the clinical condition (Noth, 1991), such as increased tendon jerk, associated reactions, incoordination, and weakness. Almost universal, however, is the description of a pathological increase in tone (Noth, 1991), and this is often accompanied by mention of hyperreflexia.

The characteristics and pathophysiological mechanisms of spastic hypertonus are distinct from those of parkinsonian rigidity. Unlike in rigidity, the resistance to stretch in spastic hypertonus is generally claimed to be velocity-dependent (Noth, 1991), although this has been recently disputed (Powers *et al.*, 1989). Further, antagonistic muscle groups are not equally affected in spastic hypertonus; in subjects with hemiplegia, for example, flexors are more affected in the arms, and

extensors are more affected in the legs (Rothwell, 1994). As with rigidity, the stretch reflex is implicated in the resistance to passive stretch in hemiplegia (Powers *et al.*, 1988; Thilmann *et al.*, 1991), but it is the short latency component that is often claimed to be exaggerated (Hallett, 1985). Increases in tone in hemiplegia due to stroke may be caused by other factors including synergies and unmasked reflexes evoked by volitional movement (Bobath, 1990; Brennan, 1959), mechanical changes to muscle (Dietz *et al.*, 1991) and contracture, i.e. physical shortening of the muscle (O'Dwyer *et al.*, 1996)

Regardless of its pathophysiological origin, hypertonicity can have serious consequences, including discomfort and problems of hygiene. More importantly, the resistance to stretch of certain muscles is often implicated in impairment of volitional movement (Ashby *et al.*, 1987; Bobath, 1990; Haley and Inacio, 1990), although the exact contribution to functional disability is debatable (Allison and Abraham, 1995) and varies between individuals (Haley and Inacio, 1990). In addition, the effectiveness of functional electrical stimulation (FES) devices aimed at enhancing function may be compromised by high levels of muscle tone. The argument is that contraction of an agonist muscle, whether by volitional activity or FES, is of little functional consequence if pathological tone of the antagonist prevents movement at the joint.

Clinical assessment of tone, as with rigidity, tends to rely on the application of rating scales, the most popular being the modified Ashworth scale (Ashworth, 1964; Bohannon and Smith, 1987). The subjectivity of these scales makes them susceptible to the same problems encountered with the UPDRS rigidity scale. Indeed, the studies investigating the reliability of the original or modified Ashworth scale have produced conflicting results (Allison *et al.*, 1996; Bohannon and Smith, 1987; Haas *et al.*, 1996; Lee *et al.*, 1989). Several methods have been used to quantify spasticity, including EMG recording, the Wartenberg pendulum test, and assessment of the Hoffmann reflex (Haas and Crow, 1995). Quantification of tone in subjects with spasticity has involved measurement of resistance to passive movement, using similar approaches to those employed with quantification of parkinsonian rigidity (Chabal *et al.*, 1991; Firoozbakhsh *et al.*,

1993; Halpern *et al.*, 1979; Long *et al.*, 1964). These have met with little clinical acceptance (Haas and Crow, 1995).

1.6 DEFINITION OF MECHANICAL IMPEDANCE

Sinusoidal (angular) displacement of a mass, such as the relaxed forearm, requires sinusoidal variations in the force (torque) needed to move the mass. When an additional load is added, such as that caused by active resistance of the muscles to imposed stretch, more force is required, i.e. the amplitude of the force sinusoid increases. The relationship between the displacement and force traces is dependent on the viscoelastic properties of the net load. The force required to move a purely elastic load is proportional to displacement; the common analogy is that of stretching a spring. Thus, as the spring is extended, the force increases proportionally. In this case, changes in force are *in phase* with changes in *displacement*, and both can be represented by a sine wave. By contrast, in a viscous stiffness force depends upon velocity; a faster velocity results in a greater force. This is analogous to stirring honey or running under water – the task is easier, i.e. requires less force, when performed slowly. In this case, changes in force are in phase with changes in *velocity*. Since the displacement is represented by a sine wave, the velocity, the derivative of the displacement, is represented by a cosine function. This trace is 90° *out of phase* (phase advanced) with respect to the displacement trace. A resistance that exhibits both elastic and viscous properties will produce a force sinusoid that is the sum of the sine wave produced by the elastic resistance and the cosine wave produced by the viscous resistance. This resultant force sinusoid is phase advanced on the displacement sinusoid; the amount of phase shift is dependent on the relative contribution of the elastic and viscous stiffnesses to the total force, that is, the magnitudes of the sine and cosine waves. The inertial force required to move the load is proportional to the product of the mass of the load and its acceleration. This component of force contributes to the

resultant force sinusoid. If the frequency of movement is low and the magnitude of the mass is relatively small, this component is therefore also relatively small (Prochazka *et al.*, 1997).

The elastic and viscous stiffness components of the resistance can be plotted as vectors on a Cartesian plane. The length of the vector represents the magnitude of the stiffness, and the direction represents the phase with respect to the displacement signal. The sum of these two vectors is the *mechanical impedance*. It is this measure that is used as a measure of tone, resistance to passive stretch, in this thesis.

1.7 OBJECTIVES OF THE THESIS

The main objectives of this thesis were to develop simple methods to quantify tone and movement and to explore their potential in the clinical and surgical settings. The specific goals of each chapter are outlined separately:

CHAPTER 2. The rigidity quantification device described in this thesis was originally developed by Drs. Arthur Prochazka and David Bennett. A considerable amount of time was spent in developing a Windows-based user interface to control data collection and analysis, integrating all the steps involved in the original procedure, and in testing, modifying, and adopting different sensors to increase the simplicity and reliability of the device. The experiments in Chapter 2 were aimed at characterizing the sensors employed by the rigidity quantification device, and determining the validity and reliability of the measures of mechanical impedance. The other main objective was to describe the relationships between the quantified measures of impedance and UPDRS ratings of rigidity at the elbow and wrist. Additionally, we wished to explore the application of the device to quantification of hypertonus in the hand following stroke, and to relate impedance measures to modified Ashworth scale ratings.

CHAPTER 3. In this study, the rigidity device was used to quantify rigidity in subjects with Parkinson's disease before, during, and after pallidotomy. Sensors employed by the rigidity quantification device also provided a method of quantifying the simple tasks commonly employed in clinical assessment of bradykinesia. The main purpose of this study was to establish the utility of the quantification techniques with respect to assessment of the outcome of stereotactic surgery, and to investigate their potential for intraoperative use.

CHAPTER 4. In this study, the methods for quantifying rigidity and bradykinesia were employed in post-operative assessments of subjects who had had DBS stimulators implanted into the GPi or STN. The objective was to quantify the effects of DBS on rigidity and some aspects of bradykinesia.

CHAPTER 5. In this set of experiments, tone in the hands of subjects with hemiplegia was measured before and after periods of volitional movement or FES. A second study quantified changes in tone in the hand *during* movement or with short trains of FES in these subjects with hemiplegia as well as in control subjects. The objectives were to test the application of the rigidity quantification device to measurement of tone in the hand, as well as to determine immediate effects of volitional movement and FES on tone in the hands of these two subject groups.

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CHAPTER 2

Quantification of the UPDRS and modified Ashworth scales of rigidity and hypertonus

2.1 INTRODUCTION

Treatment of Parkinson's disease can be difficult and very individual due to variation in symptoms between patients, progression of the disease, and changing responses to medications (Lang and Fahn, 1989; Marsden and Schachter, 1981; Martínez-Martín, 1993). Rigidity is one of the cardinal symptoms of Parkinson's disease that responds well to levodopa and is one of the parameters monitored to evaluate the effectiveness of this and other pharmacological treatments, as well as the benefits of new surgical approaches and graft implantation. However, there is currently no standardized objective method of measuring rigidity. Presently, the clinician manipulates the limb of the patient and rates the evoked stiffness according to an ordinal rating scale, often but not always that of the Unified Parkinson's Disease Rating System (UPDRS). The subjective nature of this scale makes it open to the interpretation of the examiner. Studies of the UPDRS have found inter-rater reliability of the rigidity component to be "excellent" (Rabey *et al.*, 1997), "very good" (Martínez-Martín, 1993), and "moderate" (Richards *et al.*, 1994). Other studies of the Columbia University rating scale (on which the motor component of the UPDRS was based), the Webster rating scale, or a recently-developed custom scale, have reported poorer levels of inter-rater agreement, which in some cases was not more than what would be expected by chance (Geminiani *et al.*, 1991; Ginanneschi *et al.*, 1988; Van Dillen and Roach, 1988). Our own observations have shown disagreement between clinicians as to the effectiveness of medication (Prochazka *et al.*, 1997), which may be in fact explained by the tendency of different raters to concentrate to different extents on the minimum, maximum, or mean rigidity evoked. It

has also been recognized that the severity of one symptom may affect the assessment of another (Lang and Fahn, 1989; Ward *et al.*, 1983). A need for more precise methods has often been expressed (Obeso *et al.*, 1996; Ondo *et al.*, 1998; Teräväinen *et al.*, 1989a; Ward *et al.*, 1983).

Several groups have recognized the shortcomings of the subjective methods of assessment of rigidity and have developed methods of quantifying, among other parameters, the work involved in moving a limb (Kirollos *et al.*, 1996; Teräväinen *et al.*, 1989b; Webster, 1959), or the stiffness (Ghika, 1993; Wiegner and Watts, 1986), resonant frequency (Lakie *et al.*, 1984) or activation-induced increases in stiffness (Caligiuri, 1994; Caligiuri and Galasko, 1992) of the limb. Several of the earlier methods involved the use of torque motors which put unnatural constraints on movement of the limb. Some of the more recent measurement devices were designed to be used in ways that more closely resemble a clinical examination (Caligiuri, 1994; Halpern *et al.*, 1979). The most often quoted reasons for lack of general acceptance of objective methods of quantification into the clinical setting are the expense, complexity, and time involved (Lang and Fahn, 1989).

We have previously introduced a device for the quantification of limb stiffness, and applied it to the measurement of parkinsonian rigidity (Prochazka *et al.*, 1997). This device is based on the method of assessment of rigidity used routinely in the clinical setting, that is, the passive manipulation of the joint in question by the examiner. Two air-filled pads connected to a differential force transducer act to measure the force imposed by the examiner in moving the limb; a gyroscope mounted on the force pads is used to monitor the displacement of the limb. Elastic and viscous stiffness, as well as mechanical impedance is calculated from these two parameters. The device is inexpensive, simple to use, and allows the examiner to feel and thus rate the evoked rigidity simultaneous with its quantification. We found that a 50-second trial length allows for a better description of a fluctuating level of stiffness than would a brief 10-second examination.

Although the characteristics and physiological mechanisms of spastic hypertonus are distinct from those of parkinsonian rigidity, the manifestation of the symptom is fundamentally the same, that is, an increase in mechanical impedance (Dimitrijevic, 1993). Evaluation of spastic hypertonus of the limbs usually involves a rating scale such as the modified Ashworth scale (Bohannon and Smith, 1987), and is thus subject to the same difficulties encountered with the UPDRS (Haas and Crow, 1995; Ragnarsson, 1992). It is reasonable, then, to propose that methods to quantify parkinsonian rigidity may also be adaptable to measurement of spastic hypertonus.

Any method of assessment of clinical symptoms must be valid, sensitive to changes in the level of the symptom, and reliable (Martínez-Martín, 1993). Because clinicians are accustomed to ordinal rating scales, we suggest that quantitative measures additionally be expressible in terms of such ratings. We have previously determined a preliminary conversion factor between values of mechanical impedance and the UPDRS rigidity scale (Prochazka *et al.*, 1997). Since that time, the quantification device has undergone substantial changes to the hardware. Here we characterize the sensors employed by the current version of the device, and validate the algorithm used to calculate stiffness. In addition, we propose a formula for the conversion of quantified stiffness measures to UPDRS rigidity scores for the elbow based on recent data, and compare this to the conversion factor previously introduced (Prochazka *et al.*, 1997). A similar conversion formula for the wrist will also be introduced. Finally, we describe modifications of the device to make it suitable for measurement of tone in the hand, and compare preliminary measures to modified Ashworth scale ratings.

Parts of this paper have been presented elsewhere and appear in abstract form (Patrick *et al.*, 1997; Patrick *et al.*, 1998; Patrick *et al.*, 1995; Patrick and Prochazka, 1996)

2.2 METHODS

2.2.1 Stiffness quantification device

The device to quantify impedance was originally designed to measure parkinsonian rigidity. The original version has been described in detail elsewhere (Prochazka *et al.*, 1997); the more recent modifications of the current version are described in Chapter 3. A brief description is given here.

To quantify rigidity of a particular joint, the examiner repeatedly flexes and extends the joint in a manner similar to that employed during a regular clinical examination. The movements are imposed through two air-filled pads held distal to the joint. The pads are connected to a differential force transducer (Motorola MPX10-DP) and measure the force applied by the examiner. A solid state piezoelectric gyroscope (Murata ENC05E) mounted on the force pads is used to monitor the imposed angular displacement. Both signals are fed into a data acquisition box where they are filtered (9.6 Hz second order low-pass Sallen-Key), and digitized. A Motorola 68HC11 microprocessor samples the signals at 20 s^{-1} and sends the result to a laptop computer. Alternatively, the filtered analogue signals can be obtained from a DB-9 connector on the side of the box for external display or sampling. In addition, a keypad on the box allows input of clinical ratings or event markers.

Data collection is controlled via a user interface written in Visual Basic™ (Miscrosoft®). This program invokes Matlab® (Version 4.2c.1, The MathWorks, Inc.) to perform the analysis. Briefly, the first approximately 0.5 second of the gyroscope signal is used to determine the offset of the sensor. The first four seconds of all signals are discarded to avoid analyzing data collected before the rigidity testing is actually underway. The gyroscope signal is integrated using Euler's method with a step size of 0.5 ms, and detrended. Calibration of the raw data signals is then

performed using linear interpolation. Calibration values are obtained by applying a 1 kg weight to each force pad individually, and by rotating the gyroscope through 90 degrees.

Calculation of stiffness values is performed by using a least-squares parametric method to solve the following equation for K and B over a four-second moving window of data:

$$T = Kx + Bv + C \tag{1}$$

where T is the torque measured, x and v are the angular displacement and angular velocity, respectively, K is the elastic stiffness, B is the viscosity, and C is the constant offset of the sensors. The viscous stiffness is $B\omega$, where ω equals 2π * the mean frequency of the cyclical displacement. The output of the device includes approximately 46-second traces of torque, angular displacement, and event markers, as well as approximately 42-second traces of K and $B\omega$. Mechanical impedance (Z) is the magnitude of the vectorial sum of K and $B\omega$.

For purposes of statistical analysis, independent samples of Z can be obtained from a single trial by selecting one data point every four seconds (every 80^{th} point). Since negative K or $B\omega$ values imply that the subject was assisting the movements imposed by the examiner, data points falling within a segment of the trace where either K or $B\omega$ is negative are excluded; the point immediately after such a segment is selected instead.

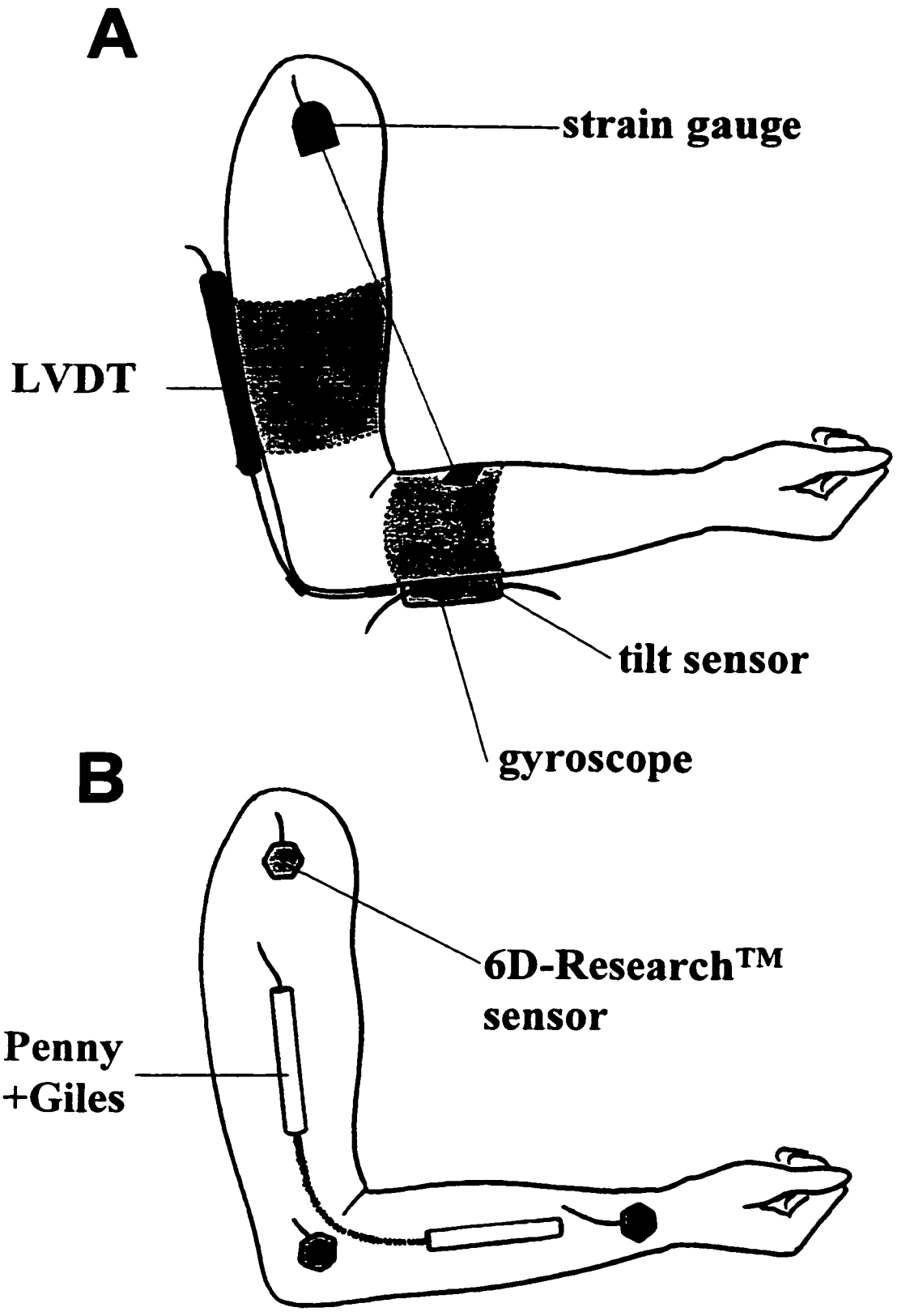
2.2.2 Gyroscope validation

We compared the performance of the gyroscope to that of five other sensors that have been or could be used to monitor limb displacement. The sensors tested were: (1) a strain gauge to which was attached a piece of silastic tubing which spanned the elbow joint; this sensor employed by the original version of the rigidity quantification device (Prochazka *et al.*, 1997); (2) a linear variable

displacement transducer (LVDT) with a flexible cable; (3) a tilt sensor comprised of two orthogonal single-axis accelerometers (Silicon Designs Model 1210). The performance of each sensor was tested against that of a Penny and Giles goniometer (Biometrics Ltd.) (P+G), as well as against that of an electromagnetic three-dimensional movement analysis system (6D-Research™, Skill Technologies, Inc.)(6D).

The sensors were affixed to the right arm of a human subject with no known neurological impairment. The examiner (SP) applied passive flexion and extension to the elbow joint at varying speeds and through a variable range. The subject was asked either to relax or, less frequently, to provide some resistance. Positioning of each of the sensors is shown in Figure 2-1. The strain gauge was attached to the shoulder, with the silastic tubing spanning the elbow and taped approximately one third of the distance between elbow and wrist. The LVDT was positioned along the back of the elbow over the olecranon. The tilt sensor and gyroscope were placed along the ulna, just distal to the elbow. The P+G goniometer was positioned along the elbow on the ulnar side of the arm. Three electromagnetic sensors of the 6D system were placed over the styloid process of the radius, and lateral epicondyle of the humerus, and on the shoulder. Because the placement of the sensors on the arm overlapped, not all of the sensors could be tested simultaneously. Consequently, up to two of the tested sensors (gyroscope, strain gauge, LVDT, or tilt sensor) were compared with one or (usually) both of the P+G and 6D system at one time. Data from the gyroscope and tilt sensor were collected through the data acquisition box of the rigidity quantification device (9.6 Hz second order low-pass Sallen-Key filter). The LVDT signal was low-pass filtered at 2.9 Hz (first order) and 10 Hz (second order Sallen-Key), and that of the strain gauge was filtered at 10 Hz (second order Sallen-Key). Signals from all sensors were digitized at 20 s^{-1} (Cambridge Electronic Design (CED) 1401 interface with 12 bit resolution, and SIGAVG (version 5.42) software). Data from the 6D electromagnetic sensors were sampled at 40 Hz using the 6D software. Off-line, angular displacement was calculated from the strain gauge, LVDT, tilt sensor, P+G goniometer, and integrated gyroscope signals using linear interpolation.

Figure 2-1. *Comparison of sensors to monitor angular displacement of the arm: sensor placement* The performance of a gyroscope, LVDT, strain gauge and tilt sensor comprised of two orthogonal accelerometers (shown in **A**) was compared to that of a Penny+Giles goniometer (P+G), and three-dimensional movement analysis system ((6D-Research) (6D) (shown in **B**). Note that because there was overlap in the placement of the sensors, not all sensors could be tested simultaneously.


A
strain gauge
LVDT
tilt sensor
gyroscope
B
6D-Research™
sensor
Penny
+Giles

The 6D system produced its own calculations of absolute joint angle based on vectorial projections. The strain gauge, LVDT, tilt sensor, P+G goniometer, and 6D system were calibrated on the arm of the subject; the gyroscope was calibrated by moving it through 90° independent of the arm. The calibrated signals were detrended and aligned to reduce any observed phase shift as much as possible, and the amplitudes of the signals were compared by calculating the root mean square (RMS) error from the P+G or 6D signals.

2.2.3 Characterization of force sensors

As mentioned above, the force sensors of the device consist of two air-filled pads connected to a differential force transducer. To test the linearity of the voltage output of this arrangement, combinations of weights were applied to one force pad at a time. Each force pad was filled with 20 mL of air, and placed concave-side downward on a plaster cast of an arm which was supported on a tabletop. The weights ranged from 500 g to 3630 g and were applied in increasing order within a 50-second time period, with complete removal of one weight before application of the next so that a baseline (0 g) voltage was obtained between weight applications. Data were collected through the data acquisition box via the Visual Basic user interface. Three trials were performed on each force pad. The voltage deflection from baseline (0 g) at the commencement of the trial, the voltage deflection from baseline (0 g) immediately preceding application of the weight, and the absolute voltages attained at each weight application were all determined for each trial. Correlation coefficients between the magnitude of the weight applied and the absolute voltage attained were determined for individual trials. Correlation coefficients were also determined between the magnitude of the weight applied and the average resultant voltage deflections over the three trials for each force pad. Finally, the correlation coefficients between the magnitude of the weight applied and the average voltage deflections were calculated for both pads together. This same procedure was used to test the linearity of the force sensors at the

extremes of the ranges of force used in testing patients or control subjects, but here only one trial per force pad was performed. The lower weights ranged from 10 g to 500 g, while the larger weights tested ranged from 1000 g to 4630 g.

To test the frequency response and phase shifting of the force sensors, sinusoidal variations in force were applied to one of the force pads using a custom-made moving-coil electromagnetic force servo-motor with a 4-strain-gauge proving-ring force transducer. A signal generator (Feedback Function Generator FG600) was used to drive the servo-motor; the frequency of the sinusoidal input was incremented from 0.2 Hz to 10 Hz over 60 seconds. The signal from the force sensor was collected through the data acquisition box. Both this signal and the output of the force transducer of the servo-motor were digitized at 100 s^{-1} (CED 1401 and SIGAVG). A 6000-point Fast Fourier Transform was performed in Matlab on the raw voltage signals using a 1500-point Hanning window with a 750-point overlap. The frequency response and the amount of phase shift were determined by dividing the cross spectral density by the power spectrum of the output of the servo-motor force transducer.

2.2.4 Phase shifting investigation

The elastic stiffness (K) of a joint is the ratio of the component of torque in phase with the angular displacement of the joint and the displacement itself; the viscous stiffness ($B\omega$) is the ratio of the component of torque in phase with the angular velocity of the movements imposed and the velocity itself. The algorithm employed by the device to calculate mechanical impedance first estimates the contributions of elastic and viscous stiffnesses to the torque measured. The mechanical impedance is then the vectorial sum of K and $B\omega$. If the net torque measured is due entirely to the viscous stiffness, then the raw force signal will be in phase with the angular velocity signal. Conversely, in a purely elastic system, the force signal will be in phase with the

angular displacement signal, i.e. 90° phase lagged from the angular velocity signal. Since any phase shifting of the displacement or force signals with respect to each other will affect the relative proportion of K and $B\omega$ calculated by the algorithm, it is important that the relative time course of force and displacement signals be as accurate as possible.

This accuracy was tested for the force sensors as described above. To test this accuracy for the gyroscope, the output of the gyroscope was compared to signals obtained from the displacement transducers attached to angular servo-motors. Gyroscope signals were collected via the data acquisition box.

Two gyroscopes were attached to the arm of one of two different angular servo-motors (Cambridge Technologies 310B muscle lever system, and Printed Motors Ltd. "Servalco" servo-motor) which was controlled by a function generator (Feedback FG600) to move sinusoidally through a range of 10° (two trials), 201°(two trials), or 91.5°(one trial) for 50 to 60 seconds. The frequency of the sinusoid was 0.2 Hz at the beginning of each trial, and was incremented during the trial to 1.0 Hz (one trial) or 1.5 Hz (four trials). The length transducers of the servo-motors were calibrated using 0.2 or 0.5 Hz sinusoidal movements at the same angular displacements (10°, 91.5°, 201°) used during the corresponding trials. The gyroscopes were calibrated through a 90° range independent of the servo-motors. Outputs from the data acquisition box and displacement transducers of the servo-motors were digitized at 100 or 20 s^{-1} (CED 1401 and SIGAVG). Data sampled at 100 s^{-1} were later reduced to 20 s^{-1} by taking every fifth data point. Calibration files were collected at 20 s^{-1} for 20s. Analysis of the signals was performed in Matlab, using the same procedures invoked by the Visual Basic user interface of the quantification device: gyroscope signals were integrated, and both the length transducer and integrated gyroscope signals were detrended and calibrated by linear interpolation using Matlab. The calibrated signals were plotted and compared graphically in Matlab.

2.2.5 Validation of system and test-retest reliability on a model arm

In order to validate the results of the stiffness calculations, we quantified the elastic stiffness of a model constructed from a prosthetic arm. The model is depicted in an inset of Figure 2-4A. Different levels of stiffness were created by attaching different combinations of elastic cords across the elbow. To calculate the stiffness of this system, the arm was repeatedly flexed and extended via a load cell at a rate of 0.5 Hz over a constant range measured by a goniometer. Angular displacement was measured using an LVDT. This signal was low-pass filtered at 2.9 Hz (first order) and 10 Hz (second order Sallen-Key). LVDT and load cell signals were digitized at 20 s^{-1} (CED 1401 and SIGAVG). Five tests of 50 seconds were performed at each of four stiffness settings. The first four seconds of data were removed from each trace to emulate the analysis software of the quantification device. The "actual stiffness" was taken as the slope of the regression line of the Lissajous plot of angular displacement versus imposed torque over the remaining 46 seconds of the trial. Calibration of the sensors was performed at the completion of each set of five trials. The LVDT was calibrated while mounted on the model arm, at the limits of the range tested. The load cell was calibrated by taking the average of two calibration trials using weights of 500 g and 1 kg.

After each set of five trials of a particular stiffness setting, the stiffness was tested using the rigidity quantification device. The gyroscope was mounted on the ulnar side of the model forearm, just distal to the elbow. The force sensors were filled with 24 mL of air and strapped to the anterior and posterior sides of the wrist. Data collection was performed through the device hardware and software. Five trials were carried out, at the same range and frequency as those used during the trials with the load cell. For each trial, the elastic stiffness was determined using two methods. First, the average value of K for the trial was estimated by the analysis software as described above. In addition, the output signals of torque and angular displacement were plotted against each other and the slope of the regression line of the resultant Lissajous plot taken as a

measure of K. These values were compared to the measures of K calculated using the load cell and LVDT using Pearson's correlation coefficient as well as one-way ANOVA with Dunnett's test post-hoc. Calibration of the gyroscope was performed upon completion of all trials by rotating it through 90° (independent of the model arm). The force pads were calibrated with a 1 kg weight at the beginning of the experiment.

This set of experiments also allowed evaluation of the test-retest reliability of the system, as five quantification trials were carried out at each level of relatively constant stiffness. By taking every 80th data point of the Z trace, 11 independent samples of Z were obtained for each trial. One-way ANOVA with Student-Newman-Keuls test post-hoc was used to test for significant differences between the trials for each stiffness setting. When the data sets failed tests of normality or equal variance, non-parametric versions of the statistical tests were used (Kruskal-Wallis ANOVA and Student-Newman-Keuls test).

Alpha was set at 0.01 for ANOVA, and 0.05 for the post-hoc tests.

2.2.6 Clinical testing and determination of relationship of mechanical impedance to qualitative UPDRS ratings

Clinical testing of the device was used in order to test the numerical conversion factor between Z and the clinical ratings for rigidity at the elbow that had been established using an older version of the device (Prochazka *et al.*, 1997), as well as to determine such a factor for rigidity at the wrist. In addition, we wished to investigate the intra- and inter-rater relibility of the measures of mechanical impedance produced by the device, and to compare this reliability to that of the rigidity scale of the UPDRS.

Four patients with idiopathic Parkinson's disease consented to participate in this study. The average age of the subjects was 58 years (range 52 to 64 years), and the average duration since onset of symptoms was 8 years (range 6 to 10 years). One subject (GM) had undergone a right

unilateral pallidotomy two years prior to this study. All subjects were tested without alteration of their daily medication routine; thus, at the time of testing, subjects were not necessarily receiving maximal pharmacological benefit, nor was medication withheld.

Four examiners also participated in this study. JJ and WM are neurologists, and MW is a physiotherapist who works regularly with WM; all three had extensive experience in clinical evaluation of parkinsonian rigidity. AP is one of the authors of this paper, as well as one of the original initiators of the quantification device, and was less experienced in the clinical evaluation of rigidity at the elbow. JJ and AP both had participated in a previous study involving the quantification device to measure mechanical impedance at the elbow (Prochazka *et al.*, 1997).

The rigidity of each patient was evaluated by each of all four examiners. The wrist and elbow of the right arm were assessed, separately, in all cases. The examiner would first rate the rigidity of the joints using his or her regular method. Then two (or one for AP's examination of GM and WD) quantification trials would be performed on each joint. The examiners were requested to instruct the patient to perform a reinforcement manoeuvre for roughly half of each trial; the examiner could decide which reinforcement manoeuvre to use. For the quantification trials, the forearm was supinated while the elbow was tested, and pronated while the wrist was tested. Each quantification trial lasted 50 seconds. Every few seconds over the course of each trial, as well as when the rigidity level was felt to change, the examiner verbally rated the rigidity according to the UPDRS; this rating was recorded by SP using the keypad. For all subjects except one, the order of examiners was: JJ, WM, MW, AP; for subject WD, the order of JJ and WM was switched.

For each trial with the quantification device, the Z trace was subsampled to obtain independent samples, using the method described above. Points falling in segments where either K or $B\omega$ were negative were omitted, and the point immediately after such a segment taken instead. The corresponding data points from the keypad trace were also selected and used as independent samples of the clinical rating. The selected data points are referred to as the "samples" of Z and of

the clinical rating. These samples were grouped according to whether or not they were collected during periods of reinforcement. Any samples from non-reinforced segments occurring after a reinforced segment in the same trial were omitted, as effects of reinforcement may still have been present.

To determine the mathematical relationship between Z and the clinical rating (UPDRS), the average of the samples of non-reinforced or reinforced Z obtained from *one trial* was plotted against the average of the corresponding samples of clinical rating. The linear conversion factor was the slope of the regression line passing through the origin and fitted to data from all trials performed during the study. A non-linear relation was also determined by fitting a two parameter power function to the data (SigmaPlot® Version 4.01, Jandel Scientific).

Usually an examiner performed two trials of impedance quantification on each subject. Scores of non-reinforced or reinforced rigidity (Z or clinical rating) of one subject by one examiner could be calculated by taking the average of all such samples obtained from *both trials*. A combined rigidity score (Z or clinical rating) was obtained by taking the average of the non-reinforced and reinforced scores; this allowed equal weighting of either score so that the final measurement was not contingent on the amount of time allotted to reinforcement manouevres.

The Spearman rank order correlation coefficient (r_s) was used as a measure of test-retest reliability, by calculating r_s between the results of the first and second trials performed on the same subject by the same examiner. All such paired trials for all examiners and subjects were tested together. The results from non-reinforced and reinforced segments of the test were tested separately as well as pooled, and the combined rigidity scores for each test were also compared. Agreement between examiners was estimated by comparing the magnitude of the standard deviation of rigidity scores for individual patients across examiners.

Upper limb impedance of four control subjects with no known neurological disorder was measured by SP using the quantification device. Subjects ranged in age from 46 to 74 years (mean 58.5 years) and included three males and one female. Both wrists were tested in three

subjects, and both elbows in all four. Three 50-second tests were performed on each joint. The subjects were asked to perform reinforcement manoeuvres (tap the knee with the other hand) for roughly the last half of the second and third trials. Impedance and clinical rating traces were subsampled as described above. Scores of non-reinforced and reinforced impedance were calculated for each subject using the data from all trials for one joint combined.

2.2.7 Measurement of tone in the hand following stroke

Spastic hypertonus, like rigidity, results in resistance to passive movement, although characteristics of this resistance are different. In order to measure this resistance in the hand, the force pads of the rigidity quantification device were modified to fit around the first and second interphalangeal joints of all four fingers simultaneously. Mechanical impedance about the metacarpophalangeal (MCP) joints was then measured by flexing and extending the hand through the force pads.

Tone in the hand was measured for six subjects who had suffered a cerebrovascular accident at least one year prior to the study[1]. The subjects ranged in age from 13 to 57 years (mean 35.7), and consisted of four males and two females. The examiners participating in this study were two students in Occupational Therapy. They received training in the modified Ashworth scale from a professor of Occupational Therapy for the purposes of this study.

Tone was measured in these subjects as part of an investigation into the effects of Functional Electrical Stimulation on spasticity and hand function. Each subject was tested by only one of the examiners. A brace held the wrist flexed at an angle of approximately 20° from neutral (referred to as "neutral") or 35° from neutral (referred to as "flexed"). The examiner first rated the tone

1. The term "tone" may sometimes be used by clinicians to refer to muscle activity that is not necessarily due to stretch of the muscle. In this thesis, "tone" is used to describe the force encountered upon passive movement of a joint.

about the MCP joint on the modified Ashworth scale without the use of the quantification device. Three or four 50-second trials using the quantification device were then performed; during these trials the examiner voiced the modified Ashworth rating every few seconds or whenever the level of tone was felt to change. The tests were carried out at both "neutral" and "flexed" wrist positions, and only the hand of the affected side was tested. Three subjects were examined on more than one occasion; the same examiner performed the tests on each occasion.

Impedance and clinical rating traces were subsampled as described above. Linear and non-linear conversion formulae were determined using the same methods employed for the elbow and wrist data.

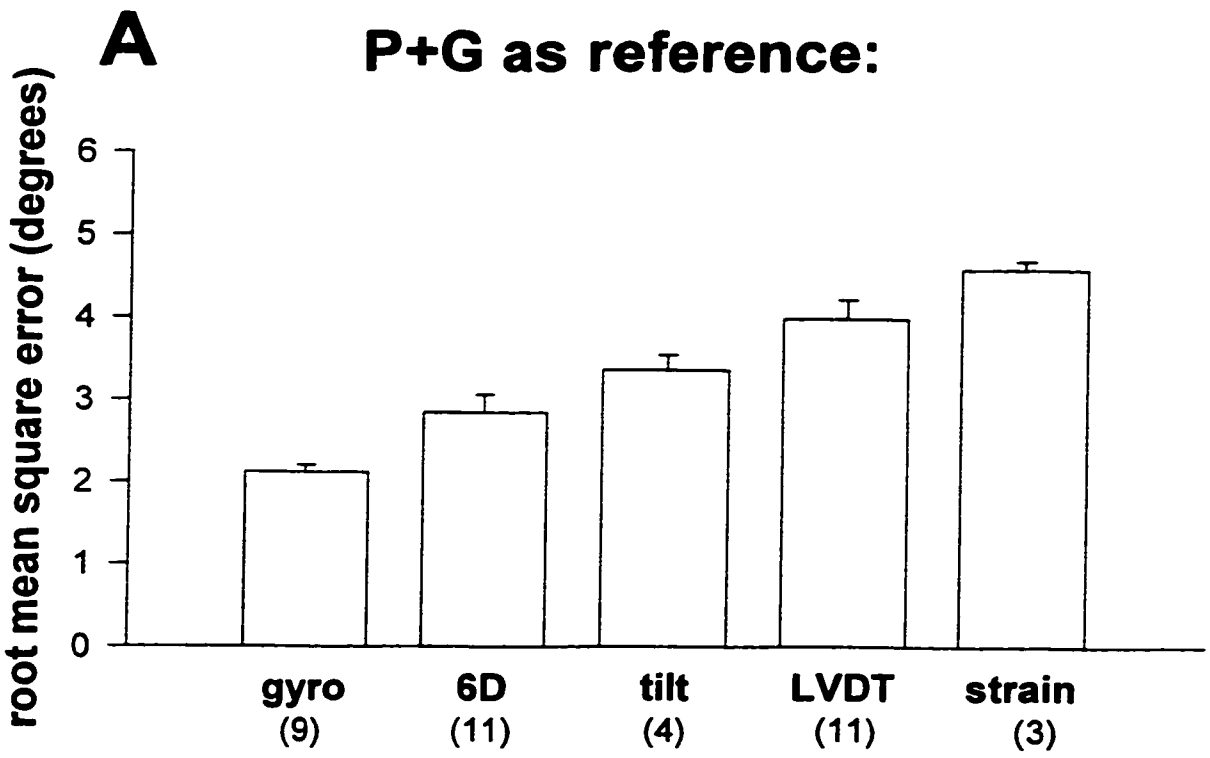
Unless otherwise stated, statistical analysis for all of the above methods was performed using SigmaStat™ Version 1.0 (Jandel Scientific).

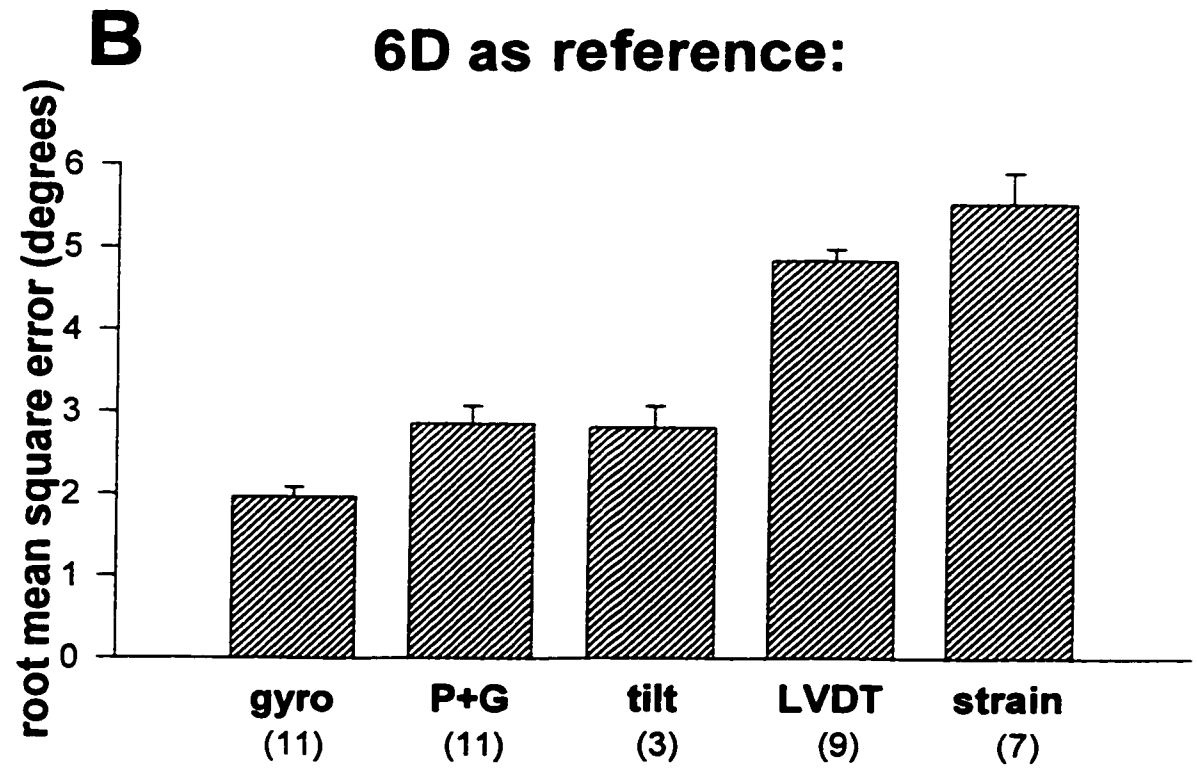
2.3 RESULTS

2.3.1 Gyroscope validation

Passive angular displacement of the elbow joint of one subject was measured using a gyroscope, strain gauge, LVDT, and tilt sensor. Whether compared to a P+G goniometer or a three-dimensional movement analysis system (6D), the gyroscope performed best overall with RMS error (mean ± SEM) of 2.1 ± 0.09° and 1.9 ± 0.12°, respectively (Figure 2-2). The RMS error was the largest for the strain gauge (4.6 ± 0.10 ° vs. P+G, 5.5 ± 0.38° vs. 6D). The error of the gyroscope represented less than 3% of the total range tested, and was similar when the gyroscope was calibrated on, rather than independent of, the arm of the subject.

Figure 2-2. *Comparison of sensors to monitor angular displacement of the arm: RMS error* The performance of a gyroscope, LVDT, strain gauge and tilt sensor comprised of two orthogonal accelerometers was compared to that of a Penny and Giles goniometer (P+G) (**A**), and three-dimensional movement analysis system ((6D-Research) (6D) (**B**). The gyroscope performed the best whether compared to the P+G or 6D system. Numbers in parentheses indicate the number of 20-second trials performed. Note that because there was overlap in the placement of the sensors, not all sensors could be tested simultaneously. Bars represent mean ± SEM.


A
P+G as reference:
root mean square error (degrees)
0
1
2
3
4
5
6
gyro
(9)
6D
(11)
tilt
(4)
LVDT
(11)
strain
(3)

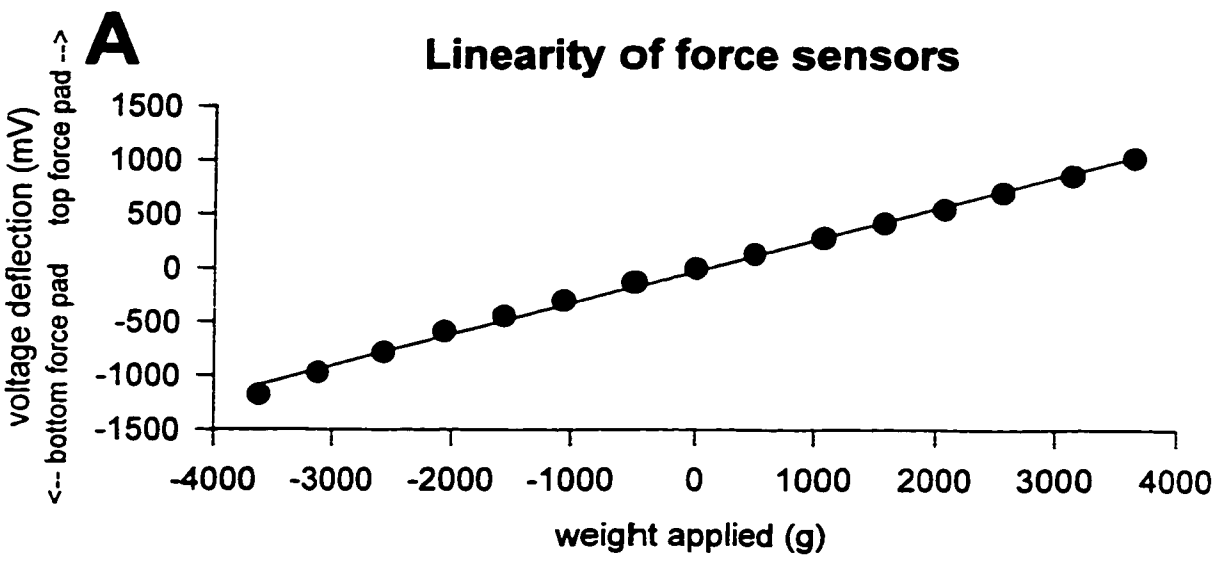

B
6D as reference:
root mean square error (degrees)
0
1
2
3
4
5
6
gyro
(11)
P+G
(11)
tilt
(3)
LVDT
(9)
strain
(7)

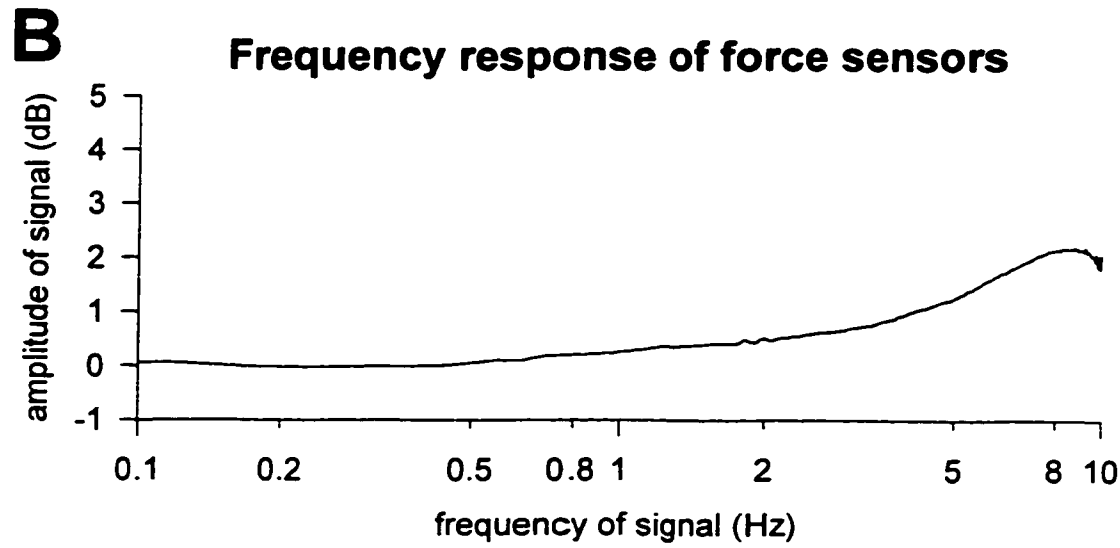
2.3.2 *Characterization of force sensors*

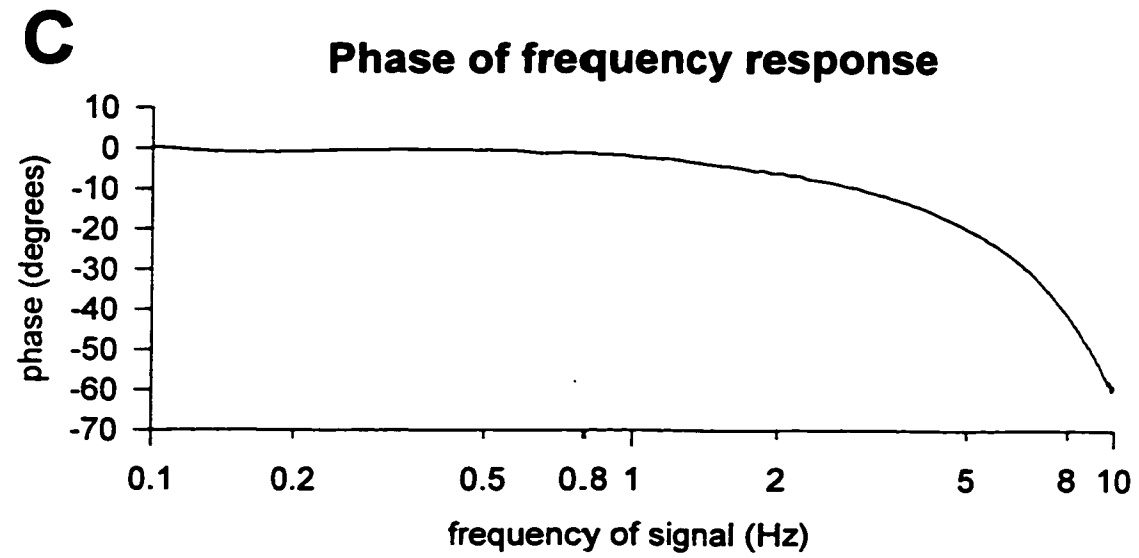
The linearity of the force sensors, which consisted of two air-filled pads connected to a differential force transducer, was tested by applying weights of increasing magnitude to each of the force pads. Correlation between the magnitude of the weights applied and the resultant absolute voltage or average voltage deflection was excellent, coefficients ranging from 0.997 to 1.000 for the trials using weight combinations ranging from 500 g to 3630 g (Figure 2-3A). The deviation of voltage deflections from the regression line was 3% over ± 3630 g. Correlation coefficients were equally good when the smaller weights were applied (10 g to 500 g, r = 0.998 to 1.000), as well as when the larger weights were investigated (1000 g to 4630 g, r = 0.988 to 0.999). The range of weights applied corresponds to the range of forces employed in the passive manipulation of wrist and elbow joints of control subjects or subjects with mild to severe parkinsonian rigidity. There was little difference in the baseline immediately preceding application of a weight compared to the baseline at the beginning of the trial; over a 50-second trial the change in the offset of the signal was equivalent to approximately 0 to 15 g, equivalent to about 10% of the minimum forces used in manipulation of the hand about the MCP joint in our studies.

The frequency response and phase shifting of the force sensors was tested by applying sinusoidal variations in force to one of the force pads via a linear servo-motor in force feedback mode. Compared to the output of the proving-ring force transducer of the servo-motor, the change in gain of the pad force sensor was 2 dB in the range of 0.2 to 10 Hz, and 0.5 dB over 0.2 to 2.0 Hz (Figure 2-3B). The force pad signal lagged that of the force transducer of the servo-motor strain gauge by 0.5° at 0.5 Hz, and 2° at 1 Hz (Figure 2-3C). This was opposite to the lead expected based on the frequency response, and is thought to be caused by a delay due to the time

Figure 2-3. *Characteristics of force sensors employed by the stiffness quantification device* **A)** Linearity of the force sensors was tested by applying increasing levels of weight to the two force pads individually. Shown here is the voltage deflection from the baseline (0 g) immediately preceding weight application. Pearson's regression coefficient (r) in this case was 0.997, and the deviation from the regression line was 3% over ± 3630 g. **B,C)** Quasi-sinusoidal variation in force was applied to one of the force pads by a linear servo-motor driven by a signal generator. The results shown here were obtained by dividing the cross spectral density of both signals by the power spectrum of the output of the proving-ring force transducer of the servo-motor. Note the logarithmic scale of the x-axes. The change in gain of the force sensor was 2 dB in the range of 0.2 to 10 Hz, and 0.5 dB over 0.2 to 2.0 Hz (**B**). Phase lag of the force pad signal was 0.5° at 0.5 Hz and 2° at 1 Hz (**C**); this is comparable to the 4.5° and 9° lag of the integrated gyroscope signal at 0.5 Hz and 1 Hz, respectively (not shown).


A
Linearity of force sensors
voltage deflection (mV)
<-- bottom force pad top force pad -->
1500
1000
500
0
-500
-1000
-1500
-4000 -3000 -2000 -1000 0 1000 2000 3000 4000
weight applied (g)


B
Frequency response of force sensors
amplitude of signal (dB)
5
4
3
2
1
0
-1
0.1 0.2 0.5 0.8 1 2 5 8 10
frequency of signal (Hz)


C
Phase of frequency response
phase (degrees)
10
0
-10
-20
-30
-40
-50
-60
-70
0.1 0.2 0.5 0.8 1 2 5 8 10
frequency of signal (Hz)

taken for the air to move through the tube connecting the force pad to the differential force transducer. We conclude that the force pad transducers are linear and have a flat frequency response over the range of frequencies of movements that would be imposed during rigidity evaluation.

2.3.3 Phase shifting investigation

Potential phase shifting of the integrated gyroscope signal with respect to the output of length transducers of servo-motors was investigated. Shifting of the force sensor signal was discussed above.

When the gyroscope was tested over a 91.5° or 201° range and its signal sampled at 20 s^{-1}, the integrated signal (angular displacement) generally lagged the output of the length transducer of the servo-motor by 20 to 30ms (equivalent to about 4.5° phase lag at 0.5 Hz, and 9° phase lag at 1 Hz testing frequencies). The phase shift was negligible when the gyroscope signal was sampled at 100 s^{-1}, and this suggests that the observed phase shift at 20 s^{-1} was a result of integration at low frequency sampling and not an artifact of the sensor itself. When the gyroscope was moved through a 10° range and sampled at 20 s^{-1}, the phase shift was slightly greater than that observed at the larger ranges, being approximately 4.5° to 7.2° at a 0.5 Hz test frequency; when the signal was sampled at 100 s^{-1}, small phase shifts (0° to 2.2°) were still observed.

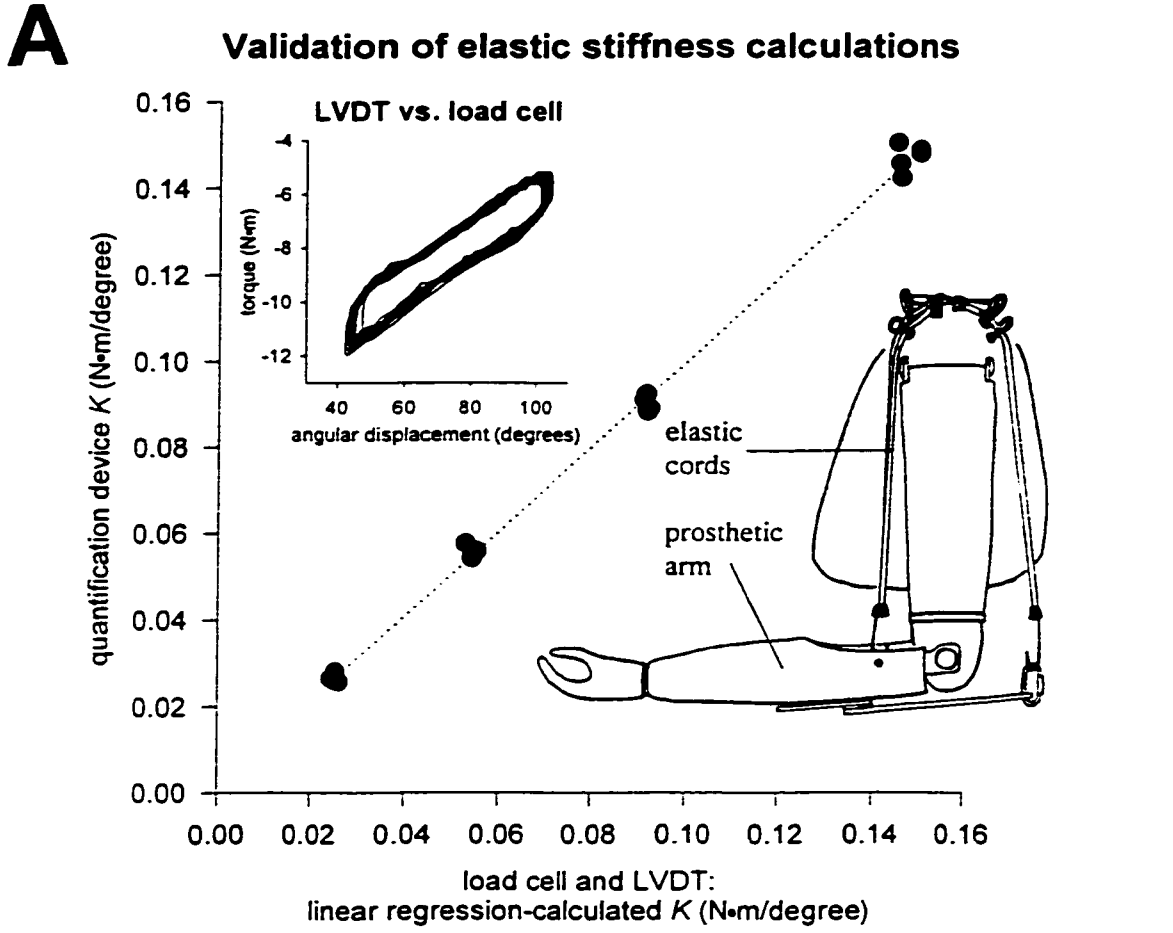
During evaluation of rigidity, the joint is generally tested over an approximately 90° range, at a rate of 0.5 to 1 Hz. When these ranges are considered, it is expected that the relative phase shift between the force and angular displacement signals will be quite small (4° to 7°), and the effect on estimates of K and $B\omega$ minimal.

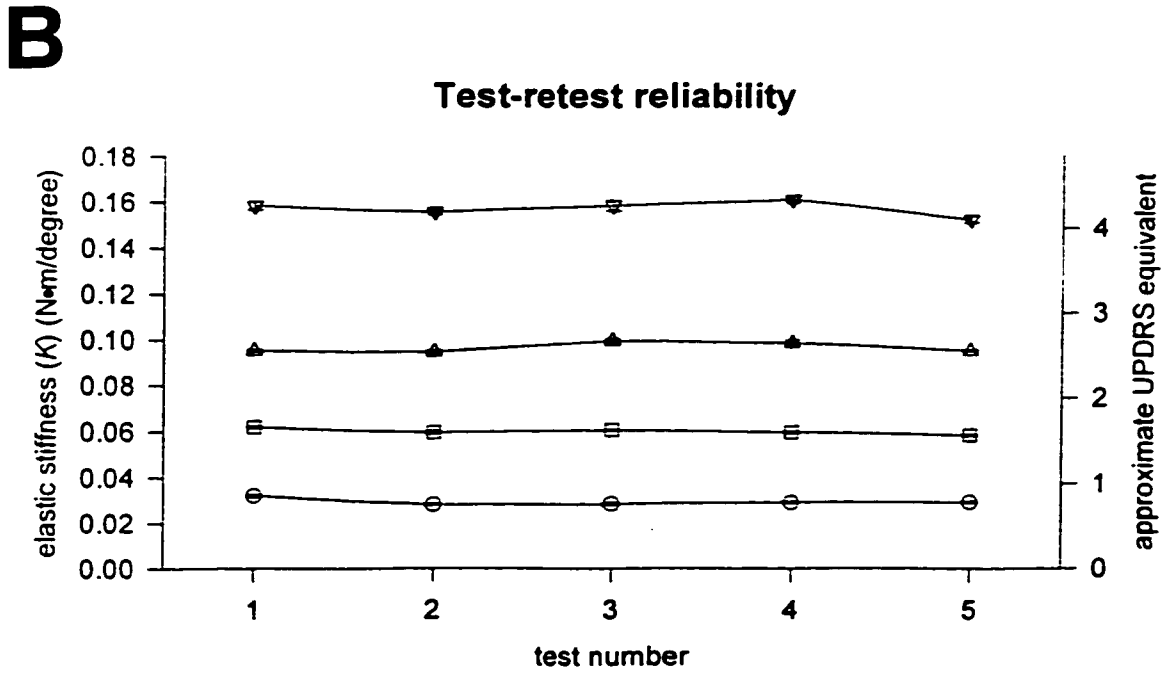
2.3.4 Validation of system and test-retest reliability on a model arm

The stiffness calculations of the quantification device were validated by comparing device-generated estimates of K to the stiffness of a model arm measured in separate tests with other transducers (Figure 2-4A). Four stiffness settings were tested, covering the general range of elbow stiffnesses we have encountered in patients with parkinsonian rigidity. The "actual stiffness" was computed from the slope of the regression line of a Lissajous plot of the angular displacement derived from an LVDT-like length gauge versus the torque calculated using a load cell. Excellent correlation was obtained when these values were compared to estimates of K ($r = 0.999$) computed by the device software (shown in Figure 2-4A), or to the slopes of the regression lines of Lissajous plots generated from the output of the device ($r = 0.998$, not shown). Absolute values were very similar; small differences were attributed to non-linearity of the elastic cords used to produce the stiffness of the model arm. Estimates of K were never statistically different from actual values (ANOVA, α set at 0.01); estimates of K derived from the Lissajous generated by the device were statistically different from actual values for only one of the stiffness settings (stiffness setting 3, ANOVA ($\alpha = 0.01$) with Dunnett's test post-hoc ($\alpha = 0.05$)).

Since 11 independent samples of Z could be obtained from each trial that employed the quantification device, this set of experiments presented an opportunity to evaluate the test-retest reliability of the device at each of four relatively constant stiffness levels. Individual trials within a stiffness setting were usually statistically different from each other (ANOVA or Kruskal-Wallis ANOVA, $\alpha = 0.01$, and Student-Newman-Keuls test post-hoc, $\alpha = 0.05$), suggesting poor test-retest reliability. However, the standard error of each test was very small; although the values were different statistically, they were not different in a practical sense given that the variability corresponded to a small fraction of one point on the UPDRS scale (see Figure 2-4B).

Figure 2-4. *Validation of calculations of elastic stiffness using a model arm* The quantification device was tested on a prosthetic limb to which were attached combinations of elastic cords to produce different levels of constant stiffness (schematic inset of **A**). Stiffness of the system was measured by repeatedly flexing and extending the arm over a period of 50 seconds using a load cell and monitoring the angular displacement with an LVDT. The elastic stiffness (K) was taken as the slope of the regression line of the Lissajous plot of the two signals (graph inset of **A**). Stiffness of the system was subsequently measured using the quantification device. Comparison of the estimates of K calculated by the software of the device to the values determined using the load cell and LVDT yielded a regression coefficient of 0.999. Absolute values of K were the also the same (**A**). These data also offered a check of test-retest reliability of the quantification device on a system of constant stiffness. Shown are the mean of samples of K ($\pm$ SEM) of individual trials (**B**). Statistically significant differences between some of the measurements of the same stiffness level are attributed to the small standard errors, and are negligible on the UPDRS scale. The scale factor used to create the UPDRS axis was: UPDRS rating = 27 * K.


A
Validation of elastic stiffness calculations
LVDT vs. load cell
torque (N•m)
angular displacement (degrees)
elastic cords
prosthetic arm
quantification device K (N•m/degree)
load cell and LVDT:
linear regression-calculated K (N•m/degree)


B
Test-retest reliability
elastic stiffness (K) (N•m/degree)
approximate UPDRS equivalent
test number

2.3.5 Clinical testing and determination of conversion factor to UPDRS

Four examiners (two neurologists, one physiotherapist, and one neuroscientist (see Methods)) measured the mechanical impedance (Z) of the right arm and wrist of four patients with idiopathic Parkinson's disease using the quantification device. They also rated the rigidity of the joints on the UPDRS scale both during the quantification trials ($UPDRS_{quant}$) as well as separately using their usual method before the trials ($UPDRS_{clin}$). Reinforcement manoeuvres varied between examiners and subjects and were chosen by the examiner. When the quantification device was employed, the period during which the subject performed reinforcement manoeuvres ranged from one third of the trial to the entire test period, as decided by the examiner. One of the subjects (GM) experienced medication-induced dyskinesias throughout the session.

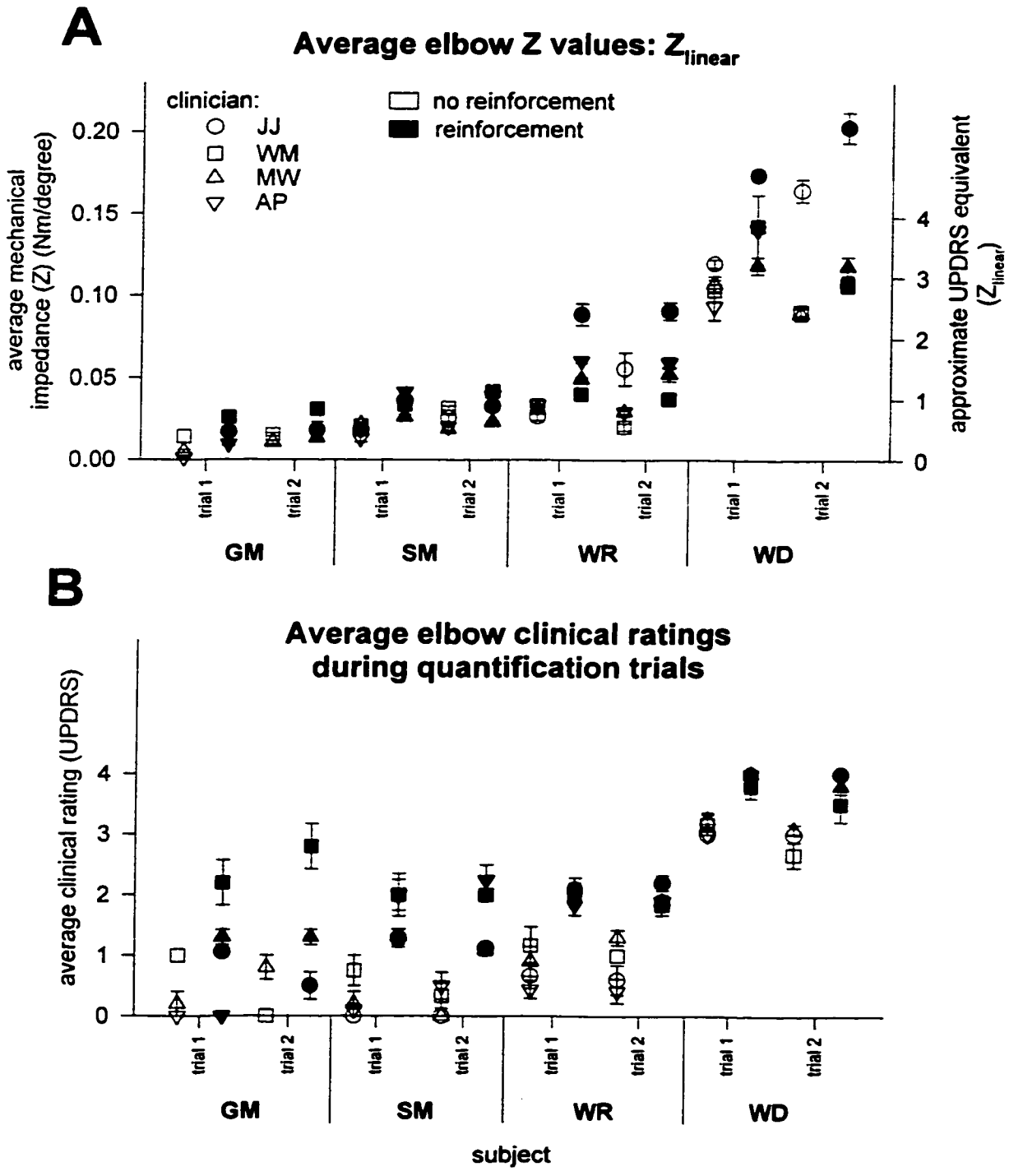
Quantified measures (Z) of reinforced and non-reinforced rigidity from each trial performed were plotted against corresponding $UPDRS_{quant}$ scores obtained during the trial; a linear conversion factor to allow expression of the Z scores in terms of the UPDRS rigidity scale was determined by taking the slope of the regression line fitting the data from all trials. For data obtained from the elbow, the slope was 27.4. A rounded-off value of 27 will be used as the conversion factor in this paper, i.e.

$$\text{UPDRS rating}_{elbow} = 27 * Z \qquad (2)$$

Multiple y-axes (Z and clinical rating) appearing on graphs are scaled accordingly unless otherwise specified. Scores of Z_{linear} refer to Z scores that have been converted to an approximate UPDRS score using this formula.

Z values for non-reinforced and reinforced rigidity as measured in individual trials are presented in Figure 2-5A. The corresponding $UPDRS_{quant}$ measurements are presented in Figure 2-5B. Test-retest reliability, as indicated by Spearman's rank order correlation coefficients (r_s)

Figure 2-5. *Quantified and subjective measures of non-reinforced and reinforced rigidity at the elbow: individual trials* Each point represents a measure of non-reinforced (open symbols) or reinforced (filled symbols) rigidity from a single trial (mean ± SEM of subsamples). Quantified measures (*Z*) are shown in **A**; the linear conversion factor was used to approximate UPDRS equivalents. At low levels of rigidity, quantified measures indicate that changes in impedance evoked by reinforcement are smaller than suggested by clinical ratings assigned during the trial ($UPDRS_{quant}$, **B**). Test-retest reliability, as estimated by Spearman rank order correlation coefficients (r_s), are comparable (see text for details) for both measures. Note that there are no measures of non-reinforced rigidity for subject GM from examiner JJ. Note also that examiner AP performed only one test of quantification on subjects GM and WD.

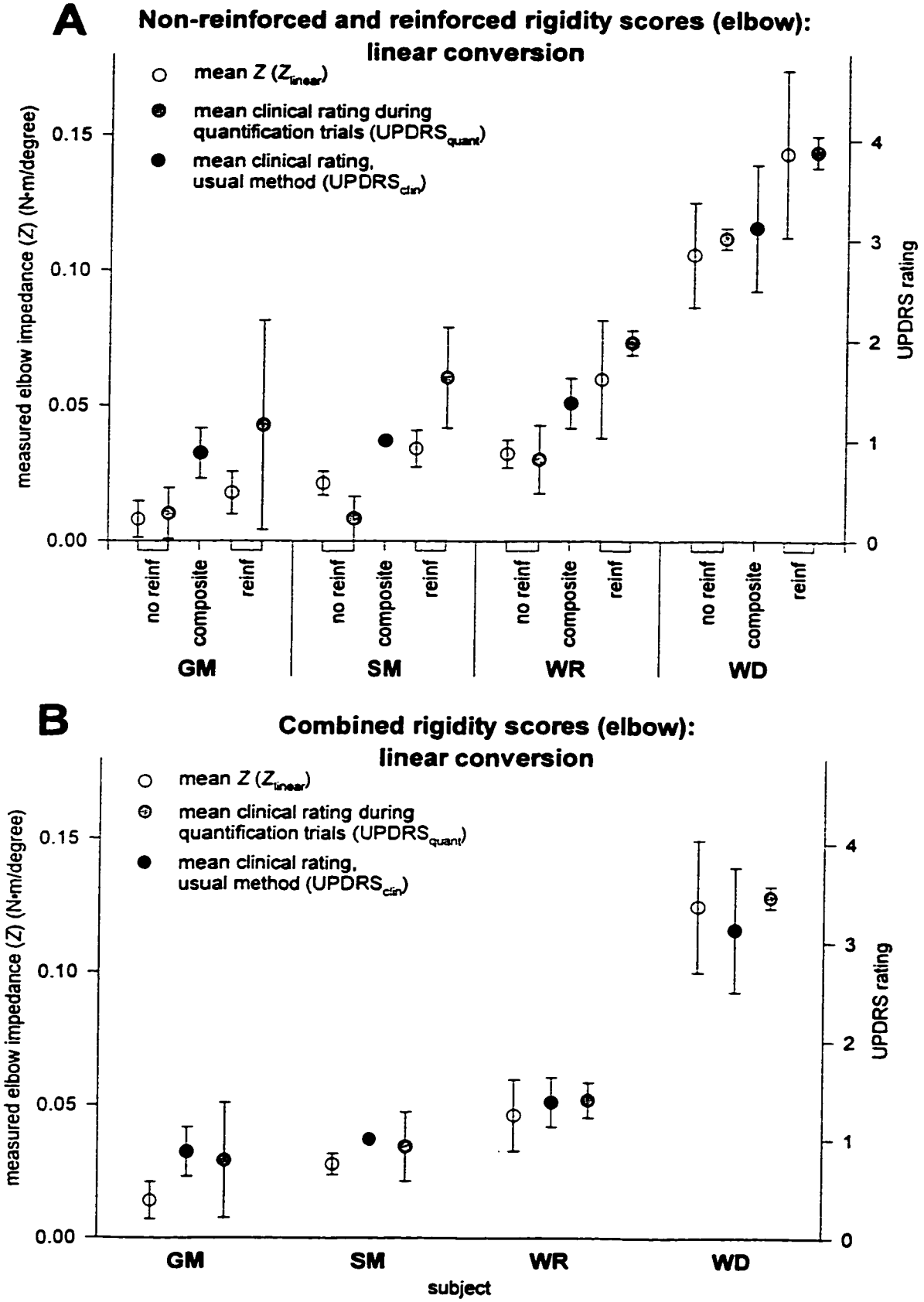

A
Average elbow Z values: Z_{linear}
clinician:
JJ
WM
MW
AP
no reinforcement
reinforcement
average mechanical impedance (Z) (Nm/degree)
0.20
0.15
0.10
0.05
0.00
approximate UPDRS equivalent (Z_{linear})
4
3
2
1
0
trial 1
trial 2
GM
SM
WR
WD
B
Average elbow clinical ratings during quantification trials
average clinical rating (UPDRS)
4
3
2
1
0
subject

was greatest for combined rigidity scores (r_s = 0.95 (Z_{linear}) or 0.94 ($UPDRS_{quant}$)), when non-reinforced and reinforced rigidity scores were pooled (r_s = 0.91 or 0.94), or when reinforced rigidity scores were considered separately (r_s = 0.96 or 0.93). Reliability was less for measures of non-reinforced rigidity (r_s = 0.78 or 0.71). Based on the results in Figure 2-5, it is proposed that the Z score may offer more accurate discrimination of changes in low levels of rigidity; $UPDRS_{quant}$ scores often suggested that reinforcement augmented rigidity by more than was indicated by the Z_{linear} measurements.

Inter-examiner agreement was comparable for Z_{linear} values and UPDRS ratings. The rigidity scores for each subject across examiners are shown in Figure 2-6. Each point represents the mean ± standard deviation of four scores (one score from each examiner). The magnitude of the standard deviation, expressed in terms of the UPDRS scale, was used as an estimate of inter-examiner agreement. When scores of non-reinforced rigidity are considered (Figure 2-6A), the agreement between Z_{linear} scores was greater than that between $UPDRS_{quant}$ scores for three of the four subjects. In either case, the magnitude of the standard deviation was ≤ 0.52; that of the Z_{linear} scores was usually below 0.2 (three of four subjects). Agreement was usually worse for both measures when only reinforced scores were considered (Figure 2-6A). Interestingly, larger (s.d. ≥ 0.50) variance of the Z_{linear} scores for reinforced rigidity was accompanied by small (s.d. ≤ 0.21) variance of $UPDRS_{quant}$ scores (two subjects), and vice versa (two subjects). $UPDRS_{clin}$ scores were not assigned for reinforced and non-reinforced rigidity separately and are assumed to take both into account.

The combined rigidity score of an examiner for a subject is the average of the non-reinforced and reinforced rigidity scores; these are plotted in Figure 2-6B. The standard deviation of Z_{linear} scores for each subject was within 0.12 of the standard deviation of the $UPDRS_{clin}$ scores and was smaller for one of the subjects. The largest standard deviation for the Z_{linear} scores was ±0.66, while the largest for the $UPDRS_{clin}$ was ±0.63. The standard deviation of $UPDRS_{quant}$ scores was

Figure 2-6. *Inter-examiner agreement of Z_{linear} and UPDRS scores of elbow rigidity* Each data point represents the mean ± standard deviation of four scores of rigidity (one from each examiner). **A)** Z (open circles) and $UPDRS_{quant}$ (grey filled circles) measures for non-reinforced and reinforced rigidity were plotted separately; $UPDRS_{clin}$ (black filled circles) scores were only taken for the combined assessment. **B)** Combined scores were plotted for all measures (Z_{linear}, $UPDRS_{quant}$, $UPDRS_{clin}$). In both **A** and **B** the y-axes are scaled according to the linear conversion factor. The size of the error bars reflects the level of inter-rater agreement. Note that there are no measures of non-reinforced rigidity for subject GM from examiner JJ. Note also that examiner AP performed only one test of quantification on subjects GM and WD.


A
Non-reinforced and reinforced rigidity scores (elbow): linear conversion
mean Z (Z_{linear})
mean clinical rating during quantification trials ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured elbow impedance (Z) (N•m/degree)
0.00
0.05
0.10
0.15
UPDRS rating
0
1
2
3
4
no reinf
composite
reinf
GM
SM
WR
WD
B
Combined rigidity scores (elbow): linear conversion
mean Z (Z_{linear})
mean clinical rating during quantification trials ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured elbow impedance (Z) (N•m/degree)
0.00
0.05
0.10
0.15
UPDRS rating
0
1
2
3
4
GM
SM
WR
WD
subject

larger than for either $UPDRS_{clin}$ or Z_{linear} for two subjects, and smaller than for either for two subjects. In our small sample of four subjects, it appears that inter-rater agreement according to Z_{linear} and $UPDRS_{clin}$ values was best at lower impedance levels while agreement of $UPDRS_{quant}$ scores was best at higher impedance values.

For combined rigidity scores, the maximum difference in $UPDRS_{clin}$ for any subject was 1.5, comparable to the maximum difference between $UPDRS_{quant}$ or Z_{linear} scores (1.4). The number of examiners in agreement according to the Z_{linear} scores (agreement defined either as a difference of ≤ 0.4 points, or as an exact match after rounding Z_{linear} scores to the nearest 0.5) was similar to the number in agreement according to the $UPDRS_{clin}$ scores (agreement between $UPDRS_{clin}$ scores was defined as exact match of scores).

A non-linear relation between clinical ratings and mechanical impedance was evident in the plot of quantified measures (Z) of reinforced and non-reinforced rigidity versus the corresponding $UPDRS_{quant}$ scores of individual trials (Figure 2-7A). In attempt to produce a more accurate means of expressing Z in terms of UPDRS ratings, the data of this plot were fitted with a power function instead of with a linear regression line (Figure 2-7B):

$$\text{UPDRS rating}_{elbow} = 15 * Z^{0.7} \qquad (3)$$

Z scores converted to UPDRS equivalents using this formula are notated by Z_{power}. Figure 2-8 shows the same results shown in Figures 2-5 and 2-6 except that the power function was employed instead of the linear conversion factor. Test-retest reliability, as indicated by Spearman correlation coefficients (r_s), was the same for Z_{power} scores as for Z_{linear} scores (Figure 2-8A). As expected, at low levels of impedance, Z_{power} scores are more distributed along the UPDRS scale than the equivalent Z_{linear} scores, resulting in greater resolution of Z_{power} at the lower end of the scale (while still retaining the apparent greater accuracy of the quantified measures over $UPDRS_{quant}$ scores in discriminating changes in low levels of impedance); the opposite is true at

Figure 2-7. *Power function relationship between quantified measures and clinical ratings of elbow rigidity* UPDRS ratings obtained during quantification trials ($UPDRS_{quant}$) were plotted against simultaneously-obtained quantified measures of mechanical impedance (Z) to reveal a non-linear relationship. The data were fitted by the line plotted in **B**; the equation of this line (inset) was used as a conversion formula for expressing Z in terms of the UPDRS rigidity scale. Each point represents the mean of samples of non-reinforced or reinforced rigidity from one trial.

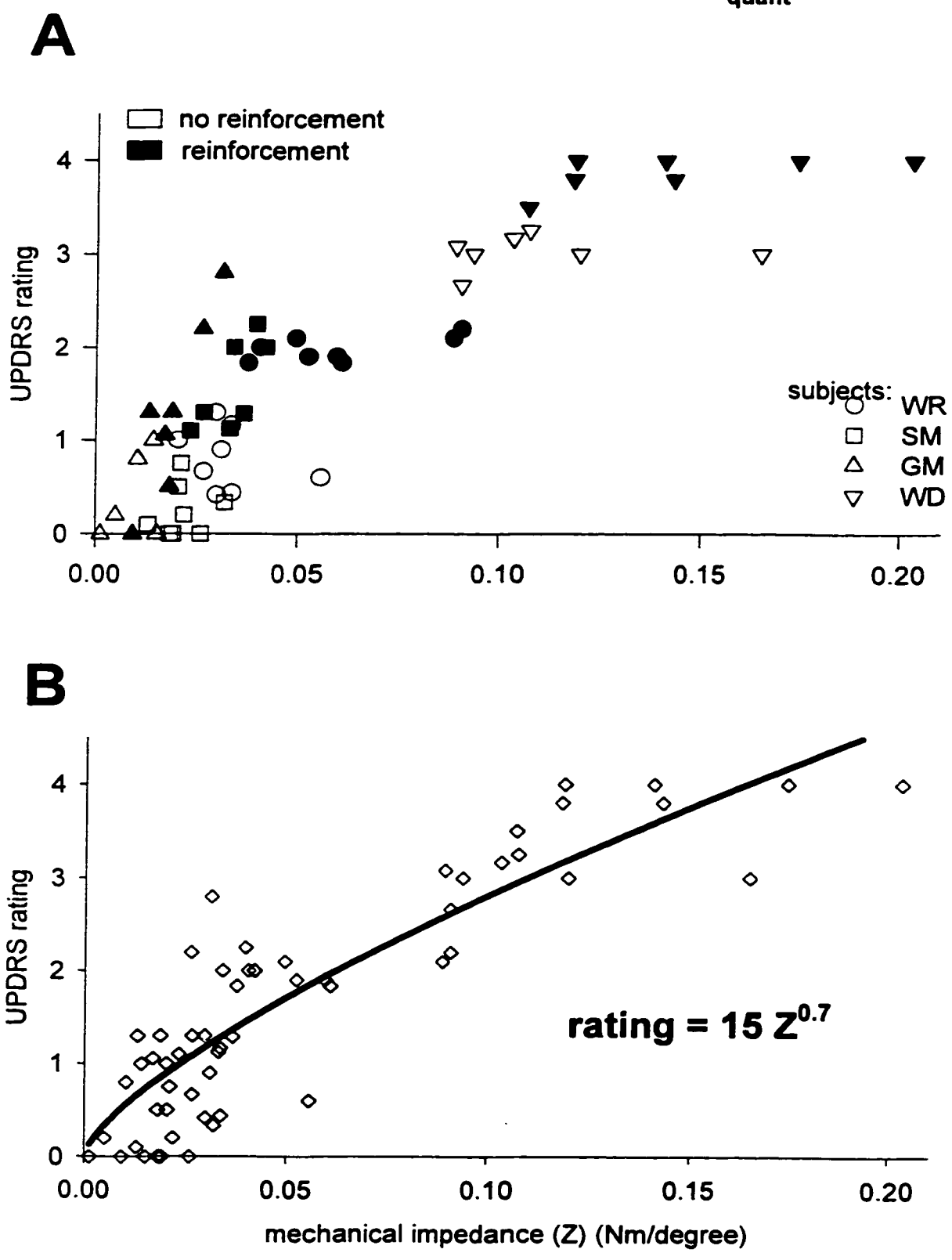
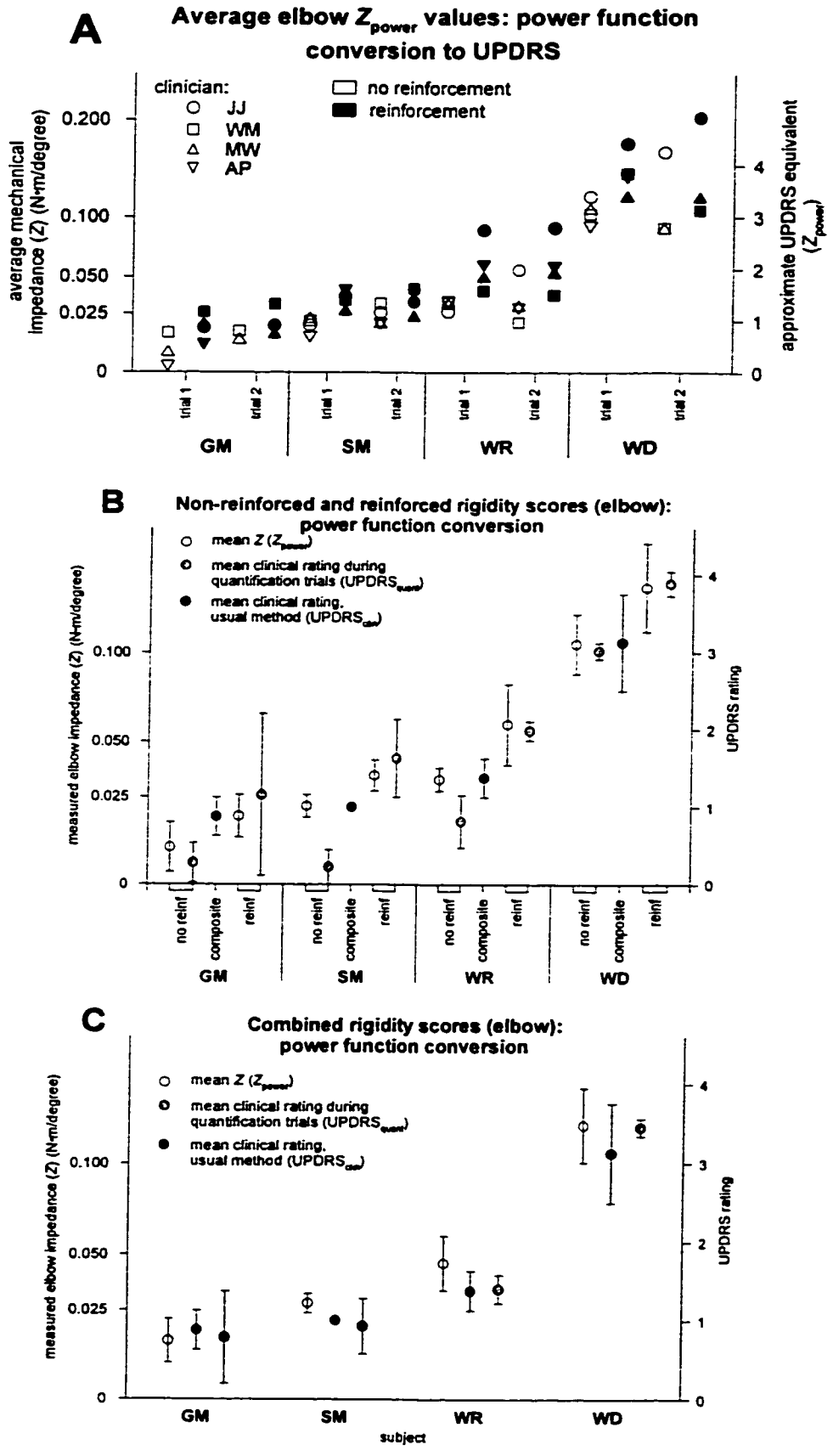

Elbow rigidity: Z vs. UPDRS quant
A
no reinforcement
reinforcement
UPDRS rating
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
subjects:
WR
SM
GM
WD
B
UPDRS rating
rating = 15 Z^0.7
mechanical impedance (Z) (Nm/degree)

Figure 2-8. *Test-retest reliability and inter-examiner agreement of Z_{power} scores of elbow rigidity* This figure shows the same data presented in Figures 2-5 and 2-6 except that here the power function was used to relate Z and UPDRS scores instead of the linear conversion factor. In **A** there are no error bars because raw Z values were converted to Z_{power} scores after averaging of samples for a trial (as opposed to converting the individual samples). In parts **B** and **C**, scores for each examiner (combined rigidity scores, or separate scores of non-reinforced or reinforced rigidity) were converted to Z_{power}. The error bars in these plots represent standard deviation and reflect the level of inter-rater agreement for that subject. Note that the scale on the axis for Z is logarithmic.


A
Average elbow Z_{power} values: power function conversion to UPDRS
clinician:
JJ
WM
MW
AP
no reinforcement
reinforcement
average mechanical impedance (Z) (N•m/degree)
approximate UPDRS equivalent (Z_{power})
0.200
0.100
0.050
0.025
0
4
3
2
1
0
trial 1
trial 2
GM
SM
WR
WD
B
Non-reinforced and reinforced rigidity scores (elbow): power function conversion
mean Z (Z_{power})
mean clinical rating during quantification trials ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{usu}$)
measured elbow impedance (Z) (N•m/degree)
UPDRS rating
no reinf
composite
reinf
C
Combined rigidity scores (elbow): power function conversion
subject

the higher end. A consequence of this is that inter-examiner agreement of Z_{power} scores, relative to that of Z_{linear} scores, is better at higher impedance levels and worse at lower levels. The result is a level of agreement (magnitude of standard deviation) intermediate to the range demonstrated with Z_{linear}, yet somewhat more consistent across the levels of impedance tested. In the data presented here, the standard deviation for Z_{power} scores ranged from 0.15 to 0.39 (mean 0.25) for non-reinforced rigidity, from 0.20 to 0.57 (mean 0.39) for reinforced rigidity (Figure 2-8B), and from 0.12 to 0.47 (mean 0.31) for the combined scores (Figure 2-8C). The average standard deviation for the combined rigidity scores was similar to that for Z_{linear} and $UPDRS_{clin}$ scores, although the magnitude of the standard deviation for these latter measures covered a larger range (Z_{linear}: 0.11 to 0.66, $UPDRS_{clin}$: 0 to 0.63).

The maximum difference in Z_{power} scores between examiners for any subject (combined rigidity) was 1.0 (compared to 1.5 for $UPDRS_{clin}$ and 1.4 for $UPDRS_{quant}$ and Z_{linear}). The average maximum difference in scores across subjects was comparable for all methods used (0.63 – 0.73). The average number of examiners in agreement according to Z_{power} values was slightly less than for Z_{linear}. This number was roughly equivalent to that observed for $UPDRS_{clin}$, and depended on the method of determining agreement of Z_{power} scores. Table 2-1 compares the four methods of measuring upper limb rigidity.

In general, the observations from the measurements of rigidity at the elbow hold for those at the wrist, although the picture is not as clear with the wrist data. Scores of reinforced and non-reinforced rigidity from individual trials are shown in Figure 2-9. The large variation in scores for reinforced rigidity for subject WR is attributed to two things. First, examiner AP instructed a stronger reinforcement manoeuvre than had the other examiners. Second, WR assisted the limb movements imposed by examiner MW for most of the two trials, the result being that only a few data samples were obtained from each trial.

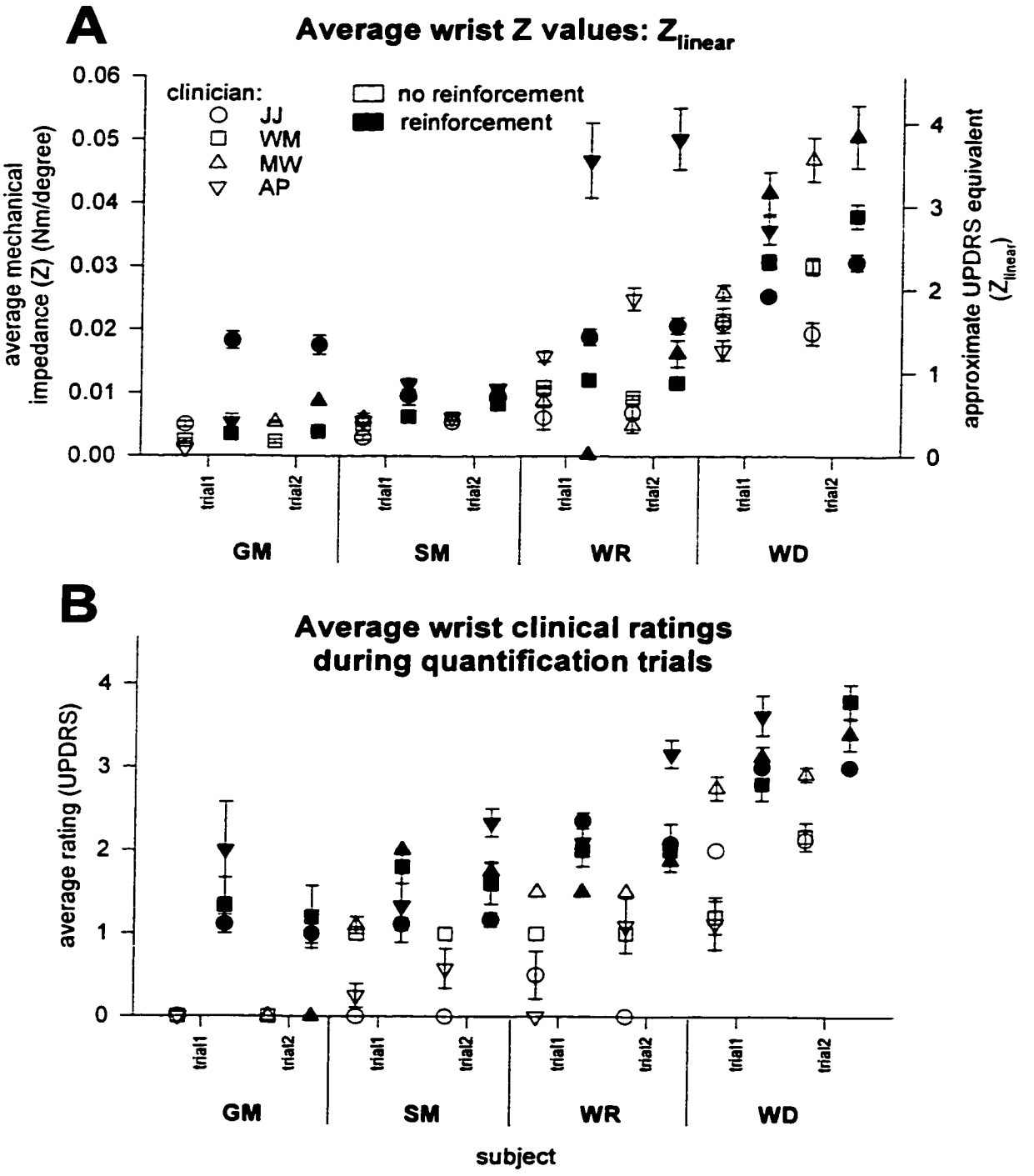
The linear conversion factor determined for converting Z values to UPDRS equivalents for the wrist was 76 (the slope of the regression line was 76.2); the equation

TABLE 2-1: *Comparison of methods of measurement of limb impedance (combined scores of rigidity)*

	elbow impedance				wrist impedance			
	$UPDRS_{clin}$	$UPDRS_{quant}$	Z_{linear}	Z_{power}	$UPDRS_{clin}$	$UPDRS_{quant}$	Z_{linear}	Z_{power}
test-retest (r_s)	not measured	0.94	0.95	0.95	not measured	0.84	0.91	0.91
average number of examiners in agreement across subjects	3	3[a] 2.75[b]	3.25[a] 3[b]	3.25[a] 2.5[b]	2.25	3[a] 2.75[b]	3[a] 2.75[b]	3[a] 2.75[b]
maximum difference in scores for a subject	1.5	1.4	1.4	1.0	1.5	1.0	1.9	1.6
average maximum difference in scores across subjects	0.63	0.68	0.73	0.68	1.13	0.76	1.04	0.88
inter-examiner agreement (standard deviation of 4 scores for a subject (one score from each examiner)): mean ± SEM across subjects	0.28 ± 0.13	0.31 ± 0.11	0.33 ± 0.12	0.31 ± 0.07	0.55 ± 0.03	0.32 ± 0.06	0.48 ± 0.18	0.41 ± 0.13

a: agreement between Z scores defined as a difference between Z_{linear} or Z_{power} scores of ≤ 0.4 points on the UPDRS scale
b: agreement between Z scores defined as an exact match of Z_{linear} or Z_{power} scores rounded to the nearest 0.5 on the UPDRS scale

Figure 2-9. *Quantified and subjective measures of non-reinforced and reinforced rigidity at the wrist: individual trials* Symbols represent mean ± SEM of samples of non-reinforced (open symbols) or reinforced (filled symbols) rigidity from individual trials. The linear conversion factor for the wrist (76) was used to scale the axes for impedance and UPDRS scores with respect to one another. Note that for examiner JJ, there are no data for non-reinforced rigidity for the second trial of subject GM. For examiner MW, there are no data from the first trial for subject GM, and no data for non-reinforced rigidity for the second trial of subject SM. Examiner AP performed only one test of quantification on subjects GM and WD.


A
Average wrist Z values: Z_{linear}
clinician:
JJ
WM
MW
AP
no reinforcement
reinforcement
average mechanical impedance (Z) (Nm/degree)
approximate UPDRS equivalent (Z_{linear})
0.06
0.05
0.04
0.03
0.02
0.01
0.00
4
3
2
1
0
trial1
trial2
GM
SM
WR
WD
B
Average wrist clinical ratings during quantification trials
average rating (UPDRS)
4
3
2
1
0
subject

$$UPDRS_{wrist} = 76 * Z \quad (4)$$

was used to convert Z values to Z_{linear}. The resultant concordance between $UPDRS_{clin}$ and Z_{linear} was not as good as seen with the elbow data (Figure 2-10). Again, the relation between Z and $UPDRS_{quant}$ appeared to be non-linear and the equation

$$UPDRS_{wrist} = 22 * Z^{0.6} \quad (5)$$

was fitted to the data and employed to calculate Z_{power} scores (Figure 2-11). Again, as expected, this increased the disparity between scores of low impedance and decreased the variation in scores of higher impedance. The result was a better association of $UPDRS_{clin}$ and quantified measures (Figure 2-12).

Spearman rank order correlation coefficients between scores obtained from first and second trials, reflecting test-retest reliability, were good for all methods of measurement, but better for quantified measures than for $UPDRS_{quant}$ scores (rs = 0.88 to 0.91, and 0.80 to 0.89, respectively). Inter-rater agreement, as estimated by the magnitude of the standard deviation of scores for an individual subject across examiners, was frequently not as good as that observed for the elbow for any of the measurements, including $UPDRS_{clin}$. Agreement between quantified measures (Z_{power} and Z_{linear}) was generally better at lower levels of impedance whereas $UPDRS_{quant}$ scores demonstrated slightly higher agreement at higher levels of impedance. Although inter-examiner agreement of $UPDRS_{clin}$ scores was overall not as good as for the other measures of wrist impedance, it was the most consistent across subjects. With the exception of subject WR, agreement of Z_{power} and Z_{linear} scores was comparable to or better than agreement between $UPDRS_{clin}$ ratings.

Figure 2-10. *Inter-examiner agreement of Z_{linear} and UPDRS scores of wrist rigidity* Each data point represents the mean ± standard deviation of four scores of rigidity at the wrist (one score from each examiner). The size of the error bars reflects the level of agreement between examiners. **A)** Z (open circles) and $UPDRS_{quant}$ (grey filled circles) measures for non-reinforced and reinforced rigidity were plotted separately; $UPDRS_{clin}$ (black filled circles) scores were only taken for the combined assessment. **B)** Combined scores were plotted for all measures (Z_{linear}, $UPDRS_{quant}$, $UPDRS_{clin}$). In both **A** and **B** the y-axes are scaled according to the linear conversion factor for the wrist (76). Note that for examiner JJ, there are no data for non-reinforced rigidity for the second trial of subject GM. For examiner MW, there are no data from the first trial for subject GM, and no data for non-reinforced rigidity for the second trial of subject SM. Examiner AP performed only one test of quantification on subjects GM and WD.

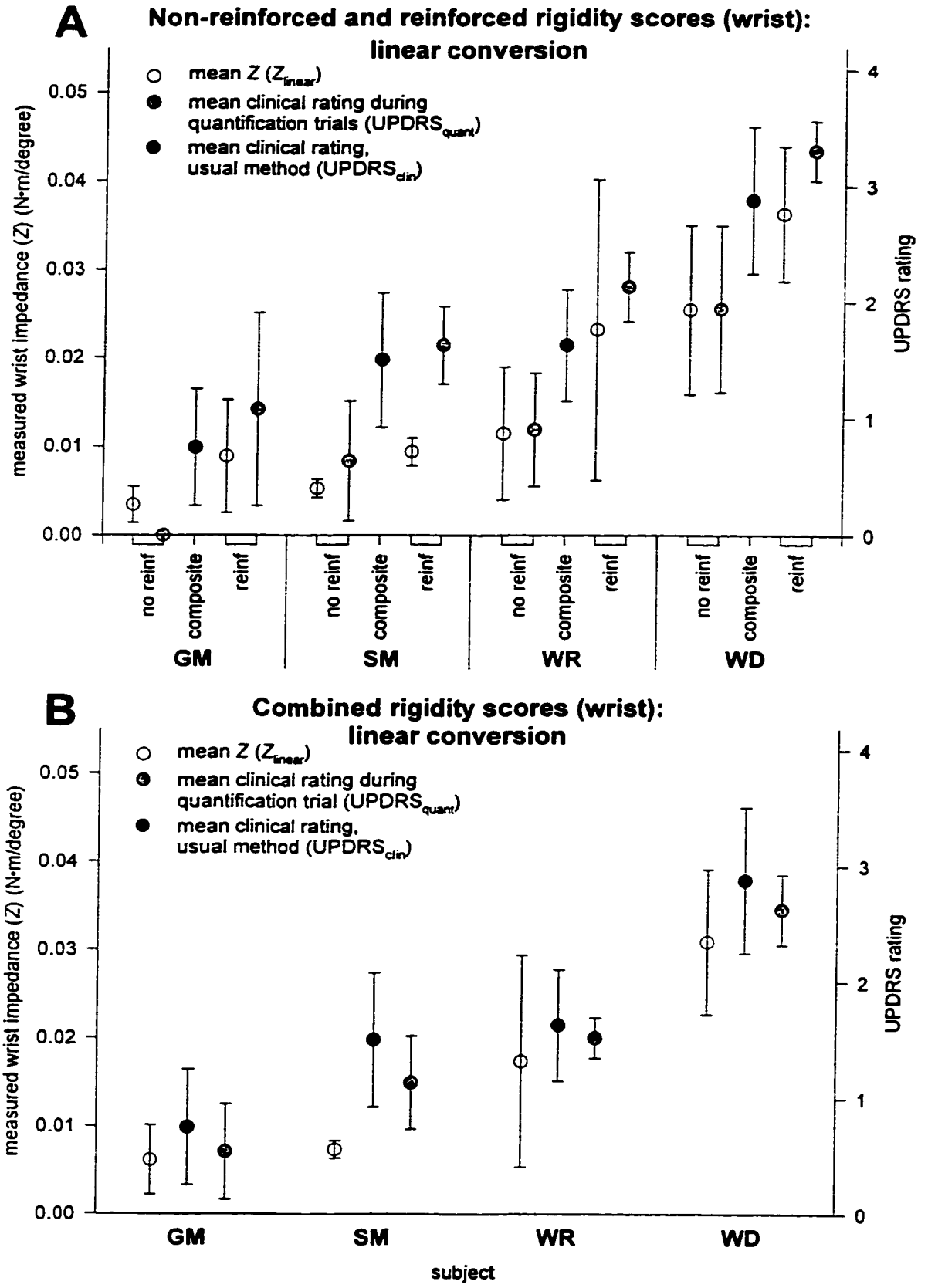

A
Non-reinforced and reinforced rigidity scores (wrist): linear conversion
mean Z (Z_{linear})
mean clinical rating during quantification trials ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured wrist impedance (Z) (N•m/degree)
UPDRS rating
0.00
0.01
0.02
0.03
0.04
0.05
0
1
2
3
4
no reinf
composite
reinf
GM
SM
WR
WD
B
Combined rigidity scores (wrist): linear conversion
mean Z (Z_{linear})
mean clinical rating during quantification trial ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured wrist impedance (Z) (N•m/degree)
UPDRS rating
subject
GM
SM
WR
WD

Figure 2-11. *Power function relationship between quantified measures and clinical ratings of wrist rigidity* As with the elbow, a power function was fitted to the plot of raw Z values versus simultaneously-obtained $UPDRS_{quant}$ scores of rigidity at the wrist. Each symbol represents the mean of samples of non-reinforced or reinforced rigidity from one trial. The equation of the fitted power function (inset) was used as a conversion formula for expressing mechanical wrist impedance in terms of the UPDRS rigidity scale.

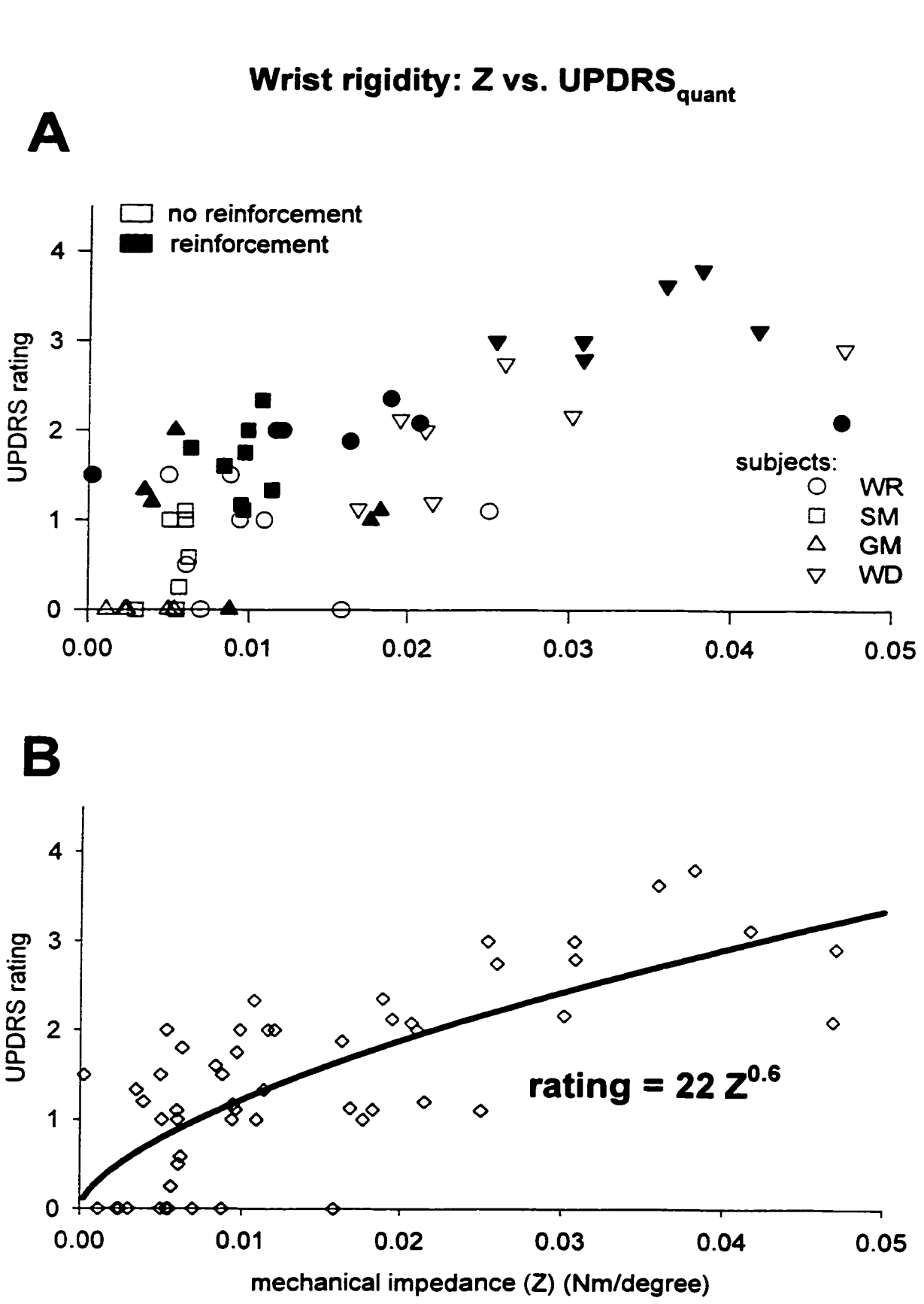
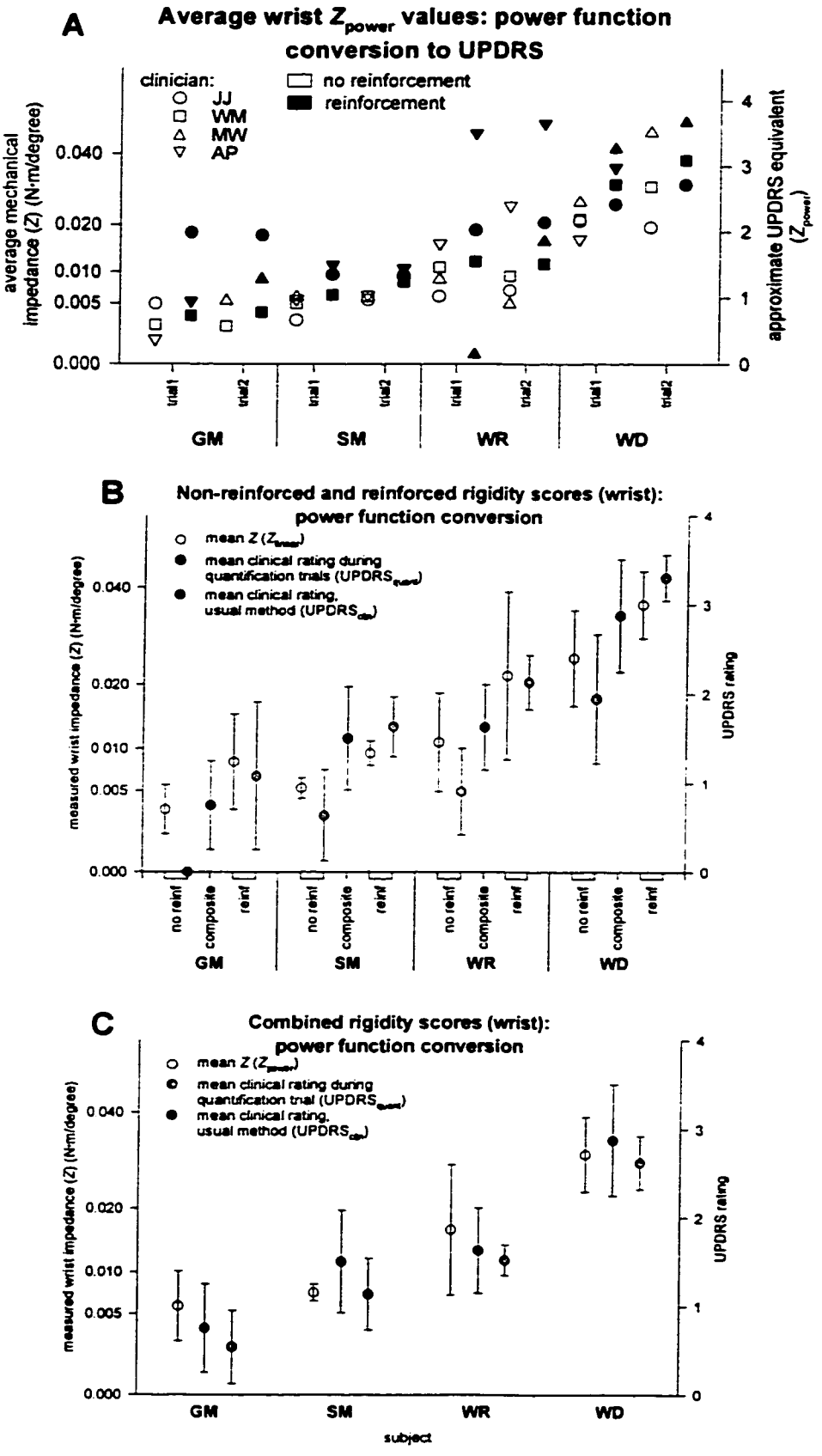

Wrist rigidity: Z vs. UPDRS quant
A
no reinforcement
reinforcement
UPDRS rating
0
1
2
3
4
0.00
0.01
0.02
0.03
0.04
0.05
subjects:
WR
SM
GM
WD
B
UPDRS rating
rating = 22 Z^0.6
mechanical impedance (Z) (Nm/degree)

Figure 2-12. *Test-retest reliability and inter-examiner agreement of Z_{power} scores of wrist rigidity* The same data represented in Figures 2-9 and 2-10 are represented here, but here the power function for the wrist was used to relate raw measures of mechanical impedance to the UPDRS scale. Note that the scale on the axis for Z is logarithmic. As with the elbow, there are no error bars in part **A** because the average Z value from a trial, as opposed to individual samples, was converted to Z_{power}. In parts **B** and **C**, the error bars represent the standard deviation of Z_{power} scores for a subject, and therefore reflect the level of inter-rater agreeement for that subject.

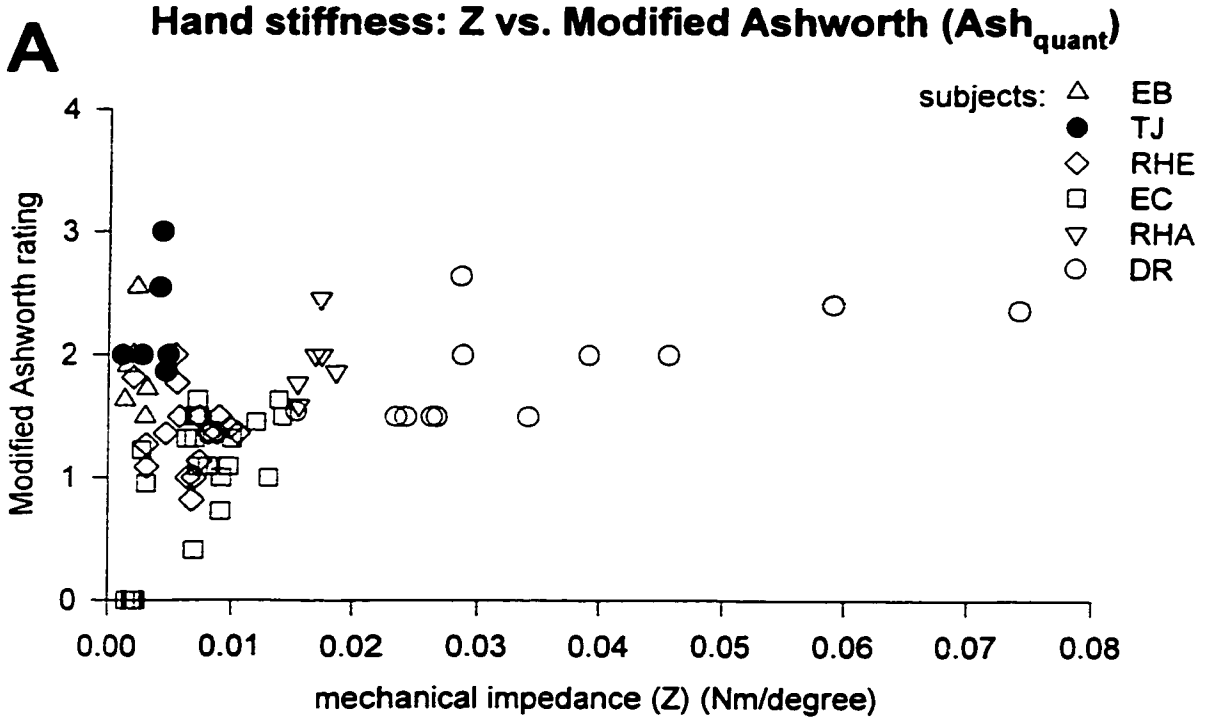

A
Average wrist Z_{power} values: power function conversion to UPDRS
clinician:
JJ
WM
MW
AP
no reinforcement
reinforcement
average mechanical impedance (Z) (N·m/degree)
approximate UPDRS equivalent (Z_{power})
0.000
0.005
0.010
0.020
0.040
0
1
2
3
4
trial1
trial2
GM
SM
WR
WD
B
Non-reinforced and reinforced rigidity scores (wrist): power function conversion
mean Z (Z_{power})
mean clinical rating during quantification trials ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured wrist impedance (Z) (N·m/degree)
UPDRS rating
no reinf
composite
reinf
C
Combined rigidity scores (wrist): power function conversion
mean Z (Z_{power})
mean clinical rating during quantification trial ($UPDRS_{quant}$)
mean clinical rating, usual method ($UPDRS_{clin}$)
measured wrist impedance (Z) (N·m/degree)
UPDRS rating
subject

Non-reinforced impedance values for control subjects ranged from 0.0062 to 0.0216 N•m/degree (mean ± SEM: 0.0122 ± 0.0031) for the elbow and 0.000396 to 0.00264 N•m/degree (mean ± SEM: 0.00146 ± 0.00038) for the wrist. When the power functions determined above are employed, these measures translate to 0.43 to 1.0 (mean ± SEM: 0.67 ± 0.12) and 0.2 to 0.62 (mean ± SEM: 0.42 ± 0.07), respectively, on the UPDRS scale. That the mean scores were not 0 is not surprising since often subjects had difficulty in relaxing the arm, resulting sometimes in resistance to the passive movements imposed. Reinforcement had no effect on impedance at the wrist. At the elbow, impedance was seen to increase by as much as 273% with reinforcement, but this was inconsistent; across subjects, reinforced impedance was slightly higher but statistically insignificant than non-reinforced impedance. Note that because negative values of K or $B\omega$ resulted in exclusion of data, the values presented above represent the results from five elbows (three subjects) and five wrists (three subjects). Data of reinforced impedance at the wrist was only available from four joints (two subjects).

2.3.6 Measurement of tone in the hand following stroke

Tone in the affected hands of six subjects who had suffered cerebrovascular accidents was evaluated by one of two students in Occupational Therapy. Tone was assessed at the MCP joint first according to the modified Ashworth scale (Ash_{clin}), then using a version of the rigidity quantification device modified to accommodate the hand. Modified Ashworth ratings were also given during quantification trials (Ash_{quant}). Results from individual trials are shown in Figure 2-13. Impedance values for subjects EB and TJ were lower than anticipated based on the Ashworth scores, the reasons for which are uncertain and will be discussed later. If data from subjects EB and TJ are excluded, then the data are fitted with the following power function:

Figure 2-13. *Power function relationship between quantified measures and clinical ratings of tone in the hand* The relationship between quantified measures of mechanical impedance (Z) and simultaneously-assigned clinical ratings (modified Ashworth) of tone about the MCP joint is similar to that observed between Z and $UPDRS_{quant}$ measures obtained at the wrist and elbow. Data from subjects TJ and EB (filled symbols in **B**) were questionable and were therefore not used to estimate the power function. Symbols represent the mean of samples obtained from one trial.


A
Hand stiffness: Z vs. Modified Ashworth (Ash quant)
subjects:
EB
TJ
RHE
EC
RHA
DR
Modified Ashworth rating
0
1
2
3
4
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
mechanical impedance (Z) (Nm/degree)

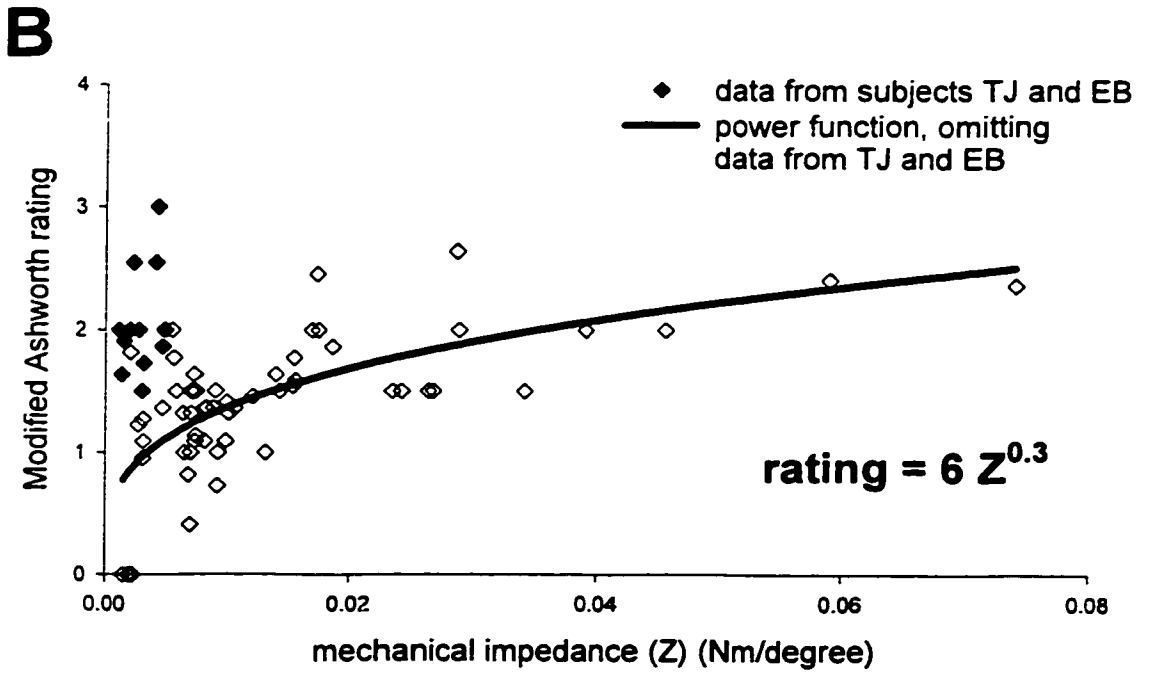
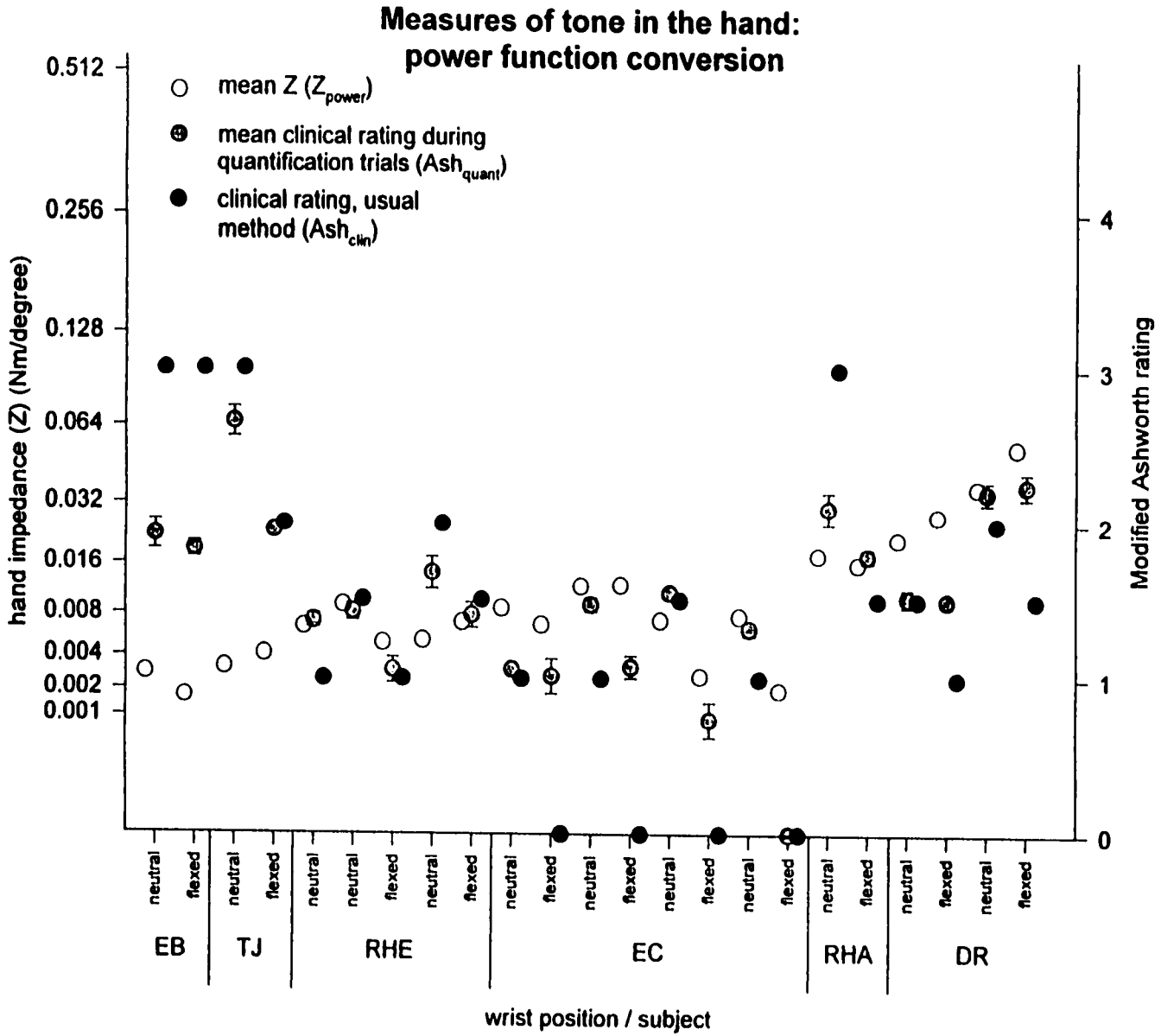

B
data from subjects TJ and EB
power function, omitting
data from TJ and EB
rating = 6 Z^0.3
Modified Ashworth rating
0
1
2
3
4
0.00
0.02
0.04
0.06
0.08
mechanical impedance (Z) (Nm/degree)

Figure 2-14. *Clinical and quantified measures of tone in the hand following stroke* There was a closer association to Z_{power} scores of Ash_{quant} scores than Ash_{clin}. Unfilled symbols represent the mean of samples of mechanical impedance acquired during all trials performed while the wrist was neutral or flexed. This mean was converted to Z_{power} using the power function for the hand. Grey filled symbols represent the mean ± SEM modified Ashworth score obtained during quantification trials (Ash_{quant}). Black filled symbols represent the scores of tone according to the modifed Ashworth scale, and obtained prior to quantification trials (Ash_{clin}); each point is one score.


Measures of tone in the hand:
power function conversion
mean Z (Z_{power})
mean clinical rating during quantification trials (Ash_{quant})
clinical rating, usual method (Ash_{clin})
hand impedance (Z) (Nm/degree)
0.512
0.256
0.128
0.064
0.032
0.016
0.008
0.004
0.002
0.001
Modified Ashworth rating
4
3
2
1
0
neutral
flexed
EB
TJ
RHE
EC
RHA
DR
wrist position / subject

$$rating_{hand} = 6 * Z^{0.3} \quad (6)$$

A linear regression line through the origin had a slope of 63.1 but described the data poorly. When the power function was used, Ash_{quant} scores were much more closely associated with Z_{power} than were Ash_{clin} ratings (Figure 2-14).

2.4 DISCUSSION

The data presented here demonstrate that a device introduced previously (Prochazka *et al.*, 1997) provides a valid and effective means of quantifying rigidity and hypertonus of the upper limb.

The gyroscope, used to monitor angular displacement of the limb, is accurate within 5%. The force sensors are linear with a frequency response that is flat over the maximum range of frequencies of passive limb movement anticipated under the conditions of clinical evaluation of tone. Although the change in the baseline of the signal from the force sensors was equivalent to approximately 10% of the lowest forces used to manipulate the hand about the MCP joints, it should be pointed out that this drift was obtained under somewhat artificial conditions and would be expected to be smaller when force was applied alternately to two force pads instead of just to the one. Of course, these artificial circumstances may also reflect what may occur when resistance is encountered largely only when the joint is moved in one direction and not the other, as can be the case with spastic hypertonus.

Results obtained from the quantification device were validated with those of another measure of stiffness on a model arm, suggesting that the device is indeed quantifying stiffness. Trials performed using this model arm as well as clinical trials on subjects with Parkinson's disease demonstrated excellent test-retest reliability of quantified measures.

In clinical trials, measures of mechanical impedance corresponded well to clinical ratings of parkinsonian rigidity, both in individual trials and across the data set as a whole. The linear conversion factor obtained from this study to describe the relation between Z and clinical ratings (27.4) was remarkably close to that obtained in our previous study (22.9) (Prochazka *et al.*, 1997). Two examiners (AP, JJ) had participated in the earlier trials, but all subjects were unique to the present study. When the measures of mechanical impedance were expressed in terms of the UPDRS rigidity scale using this conversion factor, the inter-examiner agreement was comparable to that of the examiners' clinical ratings.

The clinical ratings assigned by each examiner are a reflection of the examiner's perception of the evoked rigidity, or more basically, the resistance to the imposed movements. Based on Weber's observation that the size of the smallest detectable difference between two stimuli is dependent upon the magnitude of the stimuli, Fechner determined that the relation between sensation and stimulus is non-linear, and expressed this relation in terms of a logarithmic function (Snodgrass *et al.*, 1985). Stevens later determined that the relationship was better described by a power law, which could be applied to noxious as well as neutral stimuli (Snodgrass *et al.*, 1985).

Noticing an apparent non-linear relationship between the Z values and corresponding UPDRS ratings from individual trials, we took Stevens' observations into account and fitted the data with a power function. When the raw Z values were expressed in terms of the UPDRS using this function, the result was a better association between clinical ratings and quantified measures than had been achieved when the linear conversion factor was used.

Linearity of measurement has been listed as an advantage of quantification systems (Caligiuri, 1994): a joint twice as stiff produces a measure with twice the magnitude. However, if the absolute value of the exponent of Stevens' power law is less than 1.0 for perception of stiffness, as we have preliminarily determined it is, then what feels twice as stiff actually is not (Snodgrass *et al.*, 1985). Application of the power law to express quantified measures of mechanical impedance is then more *perceptually* intuitive than a linear conversion.

Though the linear conversion factor is more logical and simpler to apply, the power function offers a more accurate picture of the relation between Z and the UPDRS rigidity scale. Inter-examiner agreement of Z_{linear} scores was very good at low levels of impedance, but suffered somewhat at higher levels. On the other hand, agreement according to Z_{power} scores was in general more consistent across the range of impedance levels measured. We suggest that a power function may therefore offer the more appropriate method of conversion, but that more trials involving a larger number of subjects and an international representation of clinical specialists are necessary to establish with certainty this relationship.

Studies evaluating the hand after stroke tend to rely on functional tests (e.g. Frenchay, Jebsen). The effectiveness of functional electrical stimulation (FES) devices designed to produce hand opening in people who have suffered spinal cord injury or stroke depends critically upon the level of tone present in the finger flexors. Thus, measurement of stiffness becomes important in a hand with limited function. However, there is currently no effective method of measuring hand stiffness. Although a few attempts of quantification have been made (Brand, 1995; Long *et al.*, 1964), most studies estimating levels of spastic hyperreflexia employ electromyography (Mathiowetz *et al.*, 1983), passive range of motion, or subjective rating systems (Weingarden *et al.*, 1998). Haas and Crow (Haas and Crow, 1995) discuss the reliability and validity problems with some of these techniques.

Our application of the rigidity quantification device to the evaluation of tone in the hand met with reasonable success. Again a non-linear relationship between mechanical impedance and clinical ratings was observed. However, there were large discrepancies between Z values and modified Ashworth ratings for two of the subjects, TJ and EB. Although the exact cause is not yet known, possible reasons for this include the inexperience of raters in the use of the clinical scale, or improper use of device (i.e. if not all of the force imposed by the examiner was imposed through the force pads). In an informal survey, we have found that the Ashworth scale is not as familiar in clinical and rehabilitation circles as the UPDRS rigidity scale. This was a preliminary

study, but the results are promising and encourage further investigation into this application of the device.

It was observed that measurement of mechanical impedance of the elbow of a completely relaxed subject without hypertonus will produce negative values of K. This is likely due to the varying action of gravity on the mass of the forearm as it is rotated. Our current method of discarding any segment of Z containing negative values of either K or $B\omega$ does not accommodate for situations of low stiffness with complete relaxation. Testing our model arm without elastic cords (i.e. no stifness) produced negative values of K ranging from –0.0018 to –0.0083; the mean value of –0.0045 corresponded to a UPDRS rating of 0.34 using the power function. As the weight of this arm was comparable to that of a human arm, it is speculated that negative values of K within the range observed for the model arm and accompanied by positive values of $B\omega$ may be substituted by values of 0. This needs to be tested on human subjects showing no electromyographic activity of the muscles of the upper arm.

In the current study, inter-rater agreement and test-retest reliability of quantified measures of impedance were similar to those of UPDRS ratings of rigidity. The conclusion may then be drawn that these measures are redundant and that clinical evaluation alone would suffice. However, it is important to keep in mind that the examiners involved in this study had worked together previously, and three of them had been involved in the first clinical assessments of the quantification device. Some studies have reported moderate to excellent inter-rater reliability of the rigidity component of the UPDRS scale (Martínez-Martín *et al.*, 1994; Rabey *et al.*, 1997; Richards *et al.*, 1994). It is important to note, however, that in at least two of these studies comparisons were made between examiners from the same centre. On the other hand, another study evaluating the Columbia University scale (on which the motor component of the UPDRS was based) and the Webster scale involved four examiners from different centres (Geminiani *et al.*, 1991). The relatively poor reliability reported was attributed not only to the inexperience of

the raters, but also to differences in technique employed and interpretation of the scales. However, another study evaluating these same two scales with six neurologists from the same centre reported only "fair" to "moderate" inter-rater reliability (Ginanneschi *et al.*, 1988), perhaps an indication of shortcomings in the scales themselves. In any case, differences in the method of rigidity assessment is one source of disagreement between clinicians.

In an unpublished clinical trial of our quantification device in London, UK, five neurologists from three countries assessed rigidity at the elbow and wrist of seven subjects with Parkinson's disease. While initial UPDRS ratings differed between clinicians by as much as 2 points, and frequently by 1.5 points, clinical ratings collected over 50-second trials with the device demonstrated less inter-rater variance for some of the subjects. Thus, agreement was improved by specification of the plane of movement of the joint and prolongation of the length of the test. The need for uniformity in methods of application of rating scales has been recognized (Goetz *et al.*, 1995; Lang and Fahn, 1989; Langston *et al.*, 1992). It has been recommended that clinicians involved in a study establish agreement on the technique to be used and interpretation of scales (Geminiani *et al.*, 1991; Montgomery *et al.*, 1985). However, this does not remedy the problem of comparing results between studies by different groups.

Quantification of rigidity can help by removing the subjective element of the scales. In the London study above, persisting inter-rater discrepancies between $UPDRS_{quant}$ scores obtained under the more controlled conditions of quantification of rigidity were attributed largely to individual interpretation of the scale. Despite technical difficulties which have since been corrected, further improvement in the level of agreement was observed for quantified measures of impedance (Z).

It is important to note that standardization of technique is also required when a quantification device is employed, since many variables can affect the level of muscle tone observed (Lang and Fahn, 1989). In the present study, occasional large variability in measures of mechanical impedance was most likely due to actual differences in the level of rigidity evoked. For example,

examiner AP instructed subject WR to perform a reinforcement manoeuvre that was stronger than requested by the other examiners.

In this paper, we have demonstrated validity and reliability of a device for the quantification of parkinsonian rigidity, and applied this device to the measurement of tone in the hand following stroke. The device fulfills the requirements demanded by a clinical setting, that is, it is inexpensive, time-efficient, and simple. The way in which this device is used more closely emulates the clinical examination than other methods of quantitative assessment. Measurements are sensitive to changes in impedance levels due to reinforcement, as well as to fluctuations in rigidity which occur spontaneously during the course of a trial and which are detectable by the clinician.

The relationships between measures of mechanical impedance of the elbow and wrist to UPDRS scores of rigidity obtained were described. Measures of impedance at the MCP joints of the hand showed a similar relationship to simultaneously-acquired ratings on the modified Ashworth scale. The conversion formulae determined were based on data from a small number of subjects examined by a small number of local raters, and are thus only preliminary. Because differences in technique of tone assessment and interpretation of rating scales appear most evident when clinicians from different centres are compared, a study involving a large, international sample of clinicians would be desirable to test the conversion parameters we have proposed in this paper.

The quantification device evaluated here is currently in use in several clinical and research settings in North America and Europe and the number is slowly growing. If the device achieves widespread acceptance, then the choice will need to be made as to whether to communicate the measures of rigidity as raw measures of mechanical impedance or as scores relating to the UPDRS scale. Scientifically, the former approach is preferable, but it may be that the method will gain better initial acceptance if measures are expressed in terms of the familiar clinical rating scales. Conversion formulae such as those determined here may subsequently allow a gradual

transition to the expression of rigidity and hypertonus in the standard physical units of the Système International (SI).

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CHAPTER 3

Quantification of rigidity and bradykinesia before, during, and after stereotactic surgery for Parkinson's disease

3.1 INTRODUCTION

Despite reports of excellent outcomes, there is still considerable disagreement concerning the effectiveness of stereotactic surgery in ameliorating symptoms of Parkinson's disease, as well as the overall functional benefit accorded the patient (Hariz, 1997; Ondo *et al.*, 1998; Samuel *et al.*, 1998; Vitek and Bakay, 1997). The debate has applied mainly to pallidotomy (Hariz, 1997), but the recent proliferation of procedures for chronic deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus may quickly lead to equal controversies (e.g. Iacono *et al.*, 1995b vs. Tronnier *et al.*, 1997; see also Quinn and Bhatia, 1998).

While the beneficial effect of thalamotomy on tremor is largely accepted, some hold that there is a detrimental effect of thalamotomy on bradykinesia (Laitinen *et al.*, 1992), whereas others claim no effect (Grossman and Hamilton, 1993).

There is general agreement that pallidotomy ameliorates drug-induced dyskinesias (Golbe, 1998; Quinn and Bhatia, 1998; Weiner, 1998). Most pallidotomy studies report additional positive effects on rigidity, tremor, and at least some aspects of bradykinesia (e.g. Baron *et al.*, 1996; Dogali *et al.*, 1996; Iacono *et al.*, 1995c; Laitinen *et al.*, 1992; Lozano *et al.*, 1995), although Sutton's study of five patients concluded little overall functional benefit of the surgery (Sutton *et al.*, 1995). The degree of change of symptoms appears the biggest question, and the debate is largely focussed on bradykinesia. Reports variously describe "dramatic" contralateral improvement (Iacono *et al.*, 1995c Shima, 1996), moderate contralateral improvement (Samuel *et*

al., 1998), significant bilateral effects (Lozano *et al.*, 1995 Fazzini, 1997), and essentially ineffectual outcomes (Johansson *et al.*, 1997).

Additionally, there are conflicting reports as to whether or not there is improvement while the patient is experiencing maximal pharmacological benefit ("best on") (e.g. Iacono *et al.*, 1995c; vs. Samuel *et al.*, 1998). Several studies have found bilateral improvement in bradykinesia or timed manual tasks (e.g. Dogali *et al.*, 1996; Fazzini *et al.*, 1997; Lozano *et al.*, 1995), while other reports specify ipsilateral amelioration of rigidity alone (Samuel *et al.*, 1998). Finally, the duration of effects of surgery is uncertain. One group has reported that most benefits were no longer significant one year following surgery (Samuel *et al.*, 1998), whereas another still found substantial benefits after four years (Fazzini *et al.*, 1997); only a few patients were available for the long-term assessments in either case.

Accurate perioperative assessment is important not only for the precise establishment of the clinical benefits of stereotactic surgery on symptoms of Parkinson's disease, but also for the evaluation of the different surgical and imaging techniques employed, determination of the best indications for the surgery, and comparison with alternative surgical or pharmaceutical treatment options (Favre *et al.*, 1996 (commentaries by Kelly, Penn, and Bakay); Hariz, 1997; Kumar *et al.*, 1998; Quinn and Bhatia, 1998; Vitek and Bakay, 1997). Conflicting results have been attributed not only to differences in surgical techniques, target site, and patient characteristics, but also to the method of assessment of clinical outcome (Baron *et al.*, 1996; Gross *et al.*, 1997; Hariz, 1997; Ondo *et al.*, 1998; Vitek and Bakay, 1997), including insufficient standardization, and subjectivity of rating scales. The Unified Parkinson's Disease Rating System (UPDRS) is likely the most common evaluation tool currently employed in the clinical assessment of severity of parkinsonian symptoms. Reported inter-rater reliability for the individual components of bradykinesia, rigidity, and tremor has ranged from moderate to excellent (Goetz *et al.*, 1995; Martínez-Martín *et al.*, 1994; Richards *et al.*, 1994). However, there are concerns regarding the subjective nature of the UPDRS and sensitivity of the scales (Iacono *et al.*, 1995c (commentary

by Kelly); Obeso *et al.*, 1996; Ondo *et al.*, 1998; Teräväinen *et al.*, 1989); more precise methods are required. Our own observations concerning rigidity assessment (Prochazka *et al.*, 1997) revealed inconsistencies in scores between clinicians, possibly resulting from differences in the importance placed on maximum, minimum, and average rigidity as well as the examiner's training and experience. Significantly, our results demonstrated disagreement among clinicians as to the effectiveness of medication on the rigidity of individual patients.

Some groups of researchers have attempted to rid the evaluation process of unconscious expectation bias of the examiner by adopting blinded videotape assessments (Lozano *et al.*, 1995; Ondo *et al.*, 1998). While removing as much subjectivity as possible given the nature of the scales utilized, this method has its shortcomings in that rigidity cannot be evaluated from videotaped records, and differences in interpretation of the rating scales are still not addressed. The need for simple methods of quantification of symptoms has often been expressed and is evidenced by the large number of tests and protocols that have been developed. Few of these have actually been incorporated into regular clinical examinations and fewer still provide quick and simple measures based on routinely employed clinical evaluations.

Quantitative assessment of symptoms in current studies of pallidotomy, thalamotomy, and DBS is largely limited to timing of volitional tasks to evaluate bradykinesia, of which those described in the Core Assessment Program for Intracerebral Transplantations (CAPIT: Langston *et al.*, 1992) are most widespread. However, Iacono and co-workers (Iacono *et al.*, 1995b) have used a fibre-optic "data glove" to measure speed, amplitude, and frequency of joint movements during simple tasks. Also, accelerometers have been employed to quantify the effects of DBS on tremor. In one case, tremor was characterized on an ordinal scale on the basis of amplitude (Blond *et al.*, 1992). In another case, however, surgical benefits were still reported according to a subjective scale of improvement (Benabid *et al.*, 1996). A recently-patented system of movement monitoring using solid-state gyroscopes mounted on the back of the hands was designed for the clinical setting (Felsing, 1996). Objective assessment combined with adequate standardization

would make it possible to compare results between centres more reliably (Favre *et al.*, 1996; Gross *et al.*, 1997).

In addition to its role perioperatively, qualitative monitoring of symptoms is currently performed throughout surgery, especially during the lesioning process. Assessments of symptomatic response may influence decisions of lesion site (Scott *et al.*, 1998; Vitek *et al.*, 1998) or extent (Iacono *et al.*, 1994; Vitek *et al.*, 1998), as well as final placement of DBS electrodes into the pallidum (Kumar *et al.*, 1998) or subthalamic nucleus (Limousin *et al.*, 1995). It is reasonable to expect that sensitive, objective measures would help clarify responses that are not easily detected visually or with the usual clinical evaluation methods. For a device to be effective during surgery, it is imperative that the results of the measurements be immediately available (Walsh, 1992), and that the procedures be as unobtrusive as possible. The "data glove" (Iacono *et al.*, 1995b) and accelerometers (Benabid *et al.*, 1996; Benabid *et al.*, 1993) discussed above have been used intraoperatively to augment clinical evaluation, as have timed tests (Limousin *et al.*, 1995) and EMG (Benabid *et al.*, 1994). Felsing's (Felsing, 1996) gyroscope system could also conceivably have intraoperative value, although there are no published reports of such an application.

In this study, we apply small sensors to monitor clinical tests of rigidity and bradykinesia in order to assist in the evaluation of motor deficits before, during, and after stereotactic procedures.

Parts of this paper were presented at the Fifth International Congress of Parkinson's Disease and Movement Disorders, and appear in abstract form (Patrick *et al.*, 1998).

3.2 METHODS

3.2.1 Patient population

All experiments were performed with the informed consent of the subjects according to the Declaration of Helsinki Guidelines on Human Experimentation, and with local ethical board approval.

Five patients with idiopathic Parkinson's disease enrolled in the surgical programme at the Foothills Hospital in Calgary, Alberta participated in the study of postoperative effects of stereotactic surgery. Three others agreed to participate but did not complete the study; one of these suffered an intraventricular hemorrhage and died 49 days following his pallidotomy. Surgery was cancelled for the other two. The preoperative bradykinesia scores for these three patients are included in the interpretation of quantified measures of hand pronation/supination with respect to UPDRS ratings. Characteristics of the five patients who completed the study are listed in Table 3-1. The mean age at the time of surgery was 65.4 years (range 48-77), and the average duration since onset of Parkinson's disease was 13.4 years (range 6-21). The average preoperative Hoehn and Yahr stage while off medication was 3.6 (range 2.5-5). One patient (JL), whose principal symptom was tremor, underwent a Vim (ventralis intermedius) thalamotomy. The other four patients underwent unilateral pallidotomy and demonstrated, preoperatively, absent to severe rigidity, mild to extreme bradykinesia, absent to moderate tremor, as well as dyskinesias, off periods, freezing, and some degree of postural and gait deficits.

Nine patients, including all five participating in the perioperative study, took part in a study evaluating the use of quantification devices intraoperatively. Eight of the surgeries were performed at the Foothills Hospital; one (LH) was performed at the Toronto Hospital. Characteristics of these patients are also listed in Table 3-1. The mean age at the time of surgery was 64.7 years (range 48-77), and the mean duration since disease onset was 14.6 years (range 6-

TABLE 3-1 : *Patient characteristics**

subject	age	sex	duration of disease (years)	Hoehn and Yahr, off med (1 month preop)	Hoehn and Yahr, on med (1month preop)	DOPA dose (mg/day)	other anti-parkinson medication (trade name)	lesion site	symptoms quantifed** pre-op	intra-op	post-op
MG	65	F	11	3	3	950-1000	Symmetrel Tasmar	right GPi	R,B	B	R,B
GC	48	M	11	5	3	800	Mirapex	right GPi	R,B,T	R	R,B,T
JL	72	M	6	2.5	2	600	Eldepryl	right Vim	R,B,T	T	R,B,T
BT	77	F	18	5	4	600	--	left GPi	R,B,T	B	R,B,T
RS	65	M	21	2.5	2.5	562.5	Artane Permax Tasmar	left GPi	R,B,T	B	R,B,T
HH	74	F	18	2.5	not scored	500	Requip	left GPi	--	R,T	--
LH	52	F	10	4-5	not scored	325	Permax	right GPi	--	R	--
AS	64	M	21	5	3	1000	Permax	right GPi	--	R,B	R
PM	65	M	15	3	2	500	Parlodel Parsitan Tasmar	right GPi	--	B	B

*age and duration of disease at time of surgery, medications and H&Y staging at time of 1-month pre-op
** R: rigidity; B: bradykinesia; T: tremor

21). The surgery performed was unilateral pallidotomy for eight patients, and Vim thalamotomy for the other one (JL).

3.2.2 Quantification methods

The devices used to quantify limb rigidity and bradykinesia are depicted in Figure 3-1. Force and angular velocity data obtained from sensors applied to the limb were sampled using a Motorola 68HC11 microprocessor. Data collection was controlled by a Windows™-based user interface written in Visual Basic™. On- and off-line analysis was performed with the use of Matlab® software.

The method used to quantify limb rigidity has been described in detail elsewhere (Prochazka *et al.*, 1997). Briefly, the examiner imposed cycles of flexion and extension on the patient's wrist or elbow joint over a 50-second trial. The examiner held the distal limb segment (i.e. hand if wrist rigidity was measured, or wrist if elbow rigidity was measured) through a cuff comprised of two air-filled pads connected to a differential force transducer (Figure 3-1A). This arrangement allowed for recording of the force applied to move the extremity. A solid-state gyroscope mounted on the force pads simultaneously monitored the angular velocity of the movements. Signals were low-pass filtered at 9.6 Hz (second order Sallen-Key) and sampled at 20 Hz. Torque, angular velocity, and angular displacement values derived from the sensors were used to calculate elastic (K) and viscous ($B\omega$) stiffnesses. A rough estimate of elastic stiffness was calculated and displayed on-line. More accurate measures of K and $B\omega$ were produced off-line. Analysis was performed using a least-squares parametric method to solve the following equation over a four-second moving window of data:

Figure 3-1. *Schematic of devices used to quantify limb rigidity and bradykinesia* **A)** Wrist or elbow rigidity was calculated as the examiner applied passive flexion and extension of the joint through force sensors held around the hand or wrist, respectively. A gyroscope mounted on the force pads was used to monitor movement. **B)** Repetitive pronation/supination of the hands was measured using gyroscopes attached to the wrist or hand. Foot taps were monitored by gyroscopes taped to the dorsum of the foot (not shown). See text for details.

B
A

$$T = Kx + Bv + C \quad (1)$$

where T is the torque, K is the elastic stiffness, x is the angular displacement, B is the viscosity, v is the angular velocity of movements, and C is a constant offset due to the sensors. The first four seconds of data were used to determine gyroscope offset, and were thus omitted from stiffness calculation. The result was two 42-second traces of K and $B\omega$, both consisting of 20 values per second. Mechanical impedance (Z), the vectorial sum of K and $B\omega$, was calculated at each point of the traces using the equation

$$Z = \sqrt{K^2 + (B\omega)^2} \quad (2)$$

where $\omega=2\pi$ * frequency. In order to obtain independent samples of impedance from the time-course of impedance, we selected every 80th data point of the trace beginning with the first data point of each segment. Data points falling within regions where either K or $B\omega$ were negative were disregarded; the point immediately after such a region was selected instead. (Negative values of K or $B\omega$ indicate that the subject was assisting the imposed movements.)

Voluntary movements employed as tests of bradykinesia were monitored using solid-state gyroscopes. Signals were low-pass filtered at 9.6 Hz (second order Sallen-Key) and sampled at 40 Hz. The gyroscopes were attached either to the back of the hand or radial side of the dorsum of the wrist to measure hand pronation/supination (Figure 3-1B), or to the dorsum of the foot to measure foot taps. Sensors were calibrated with respect to angular displacement. Signals were integrated off-line and converted into degrees based on the calibration, and detrended to reduce any drift imposed by the integration procedure. Calibrated displacement signals were then differentiated to obtain angular velocity. To express irregularity of the repetitive movements, we computed Edwards and Beuter's "harmonicity value" (Edwards and Beuter, 1999) of the

displacement signal. This method entails calculating the power spectrum of the signal, and then replotting the power spectrum values in descending order of magnitude along the x-axis. This creates a non-symmetrical shape with its highest point adjacent to the y-axis. The harmonicity value is defined as the x-coordinate of the centre of mass of this shape (Hcm). The higher the value, the more irregular the movement. We calibrated this Hcm value to be between 0 and 1, 0 representing the Hcm value of a pure sinusoid (2.3 Hz, amplitude of 1), and 1 representing the Hcm value of random noise (Matlab random number generator "randn", 800 points). The result is referred to as the normalized harmonicity (nHcm) value. The power spectrum for a trial was obtained by performing a Fast Fourier Transform (FFT) on the displacement signal of the trial using an 80-point (2-sec) Hanning window with a 40-point overlap. The normalized spectrum from 0 to 10Hz was used in the nHcm calculation. One nHcm value was calculated per trial. The power spectrum was also used to determine the principal frequency component of the movements for each trial. Amplitude and speed of repetitive movements are also assessed in the clinical setting. We therefore determined the mean peak-to-peak amplitude ($2\sqrt{2}$ * root mean square (RMS) of displacement) and mean speed (mean rectified angular velocity) of one-second intervals of the bradykinesia test trials. The values reported under each condition (i.e. pre-surgery "off" medication, pre-surgery "on" medication, post-surgery "off" medication, post-surgery "on" medication) are the mean values of all one-second intervals from all trials under those conditions.

3.2.3 Pre- and postoperative examinations

Measurement of symptoms took place in conjunction with the regular pre- and postoperative clinical examinations scheduled at approximately one month pre- and one and six months post-surgery. At these times, one of two registered nurses evaluated the patient first while the patient was "off" medication ("practically defined off" according to CAPIT (Langston *et al.*, 1992): not having taken medications for a minimum of 12 hours), and then at "best on" ("best on" was when

the patient was receiving maximal benefit from the medication, as agreed upon by patient and examiner; the presence of dyskinesias was often taken as an indication of this state). Each evaluation comprised the entire UPDRS, Hoehn and Yahr staging, Mini–Mental Status Examination, timed walking, and Schwab and England Activities of Daily Living Scale. The tremor of subject JL was also evaluated with the Purdue peg board and drawing of spirals. Each examination session generally lasted three to four hours. Usually the same registered nurse administered the test series at each examination of a given patient.

Quantified measurement of elbow or wrist rigidity took place immediately after the examiner completed the rigidity section of the UPDRS. One to three 50-second trials were carried out. The patient was asked to tap their leg with the contralateral hand in order to reinforce the rigidity for roughly half of the trial. This reinforcement was divided into two shorter segments for patients who had difficulty performing the task. The limb tested (right or left or both) as well as the orientation of the limb (supinated or pronated) was kept consistent for each patient. The examiner was not permitted to see the results of the tests. If the examiner had also performed the clinical test of rigidity, she was allowed to change her UPDRS rating after completing the quantification tests, but without knowledge of the outcome.

Bradykinesia was quantified by monitoring repetitive voluntary movements. Hand pronation/supination was measured concurrently with UPDRS test administration. This task was performed with both hands simultaneously, the hands held vertically. One to five tests lasting approximately 4 to 18 seconds were separated by short rest periods. UPDRS ratings were assigned without knowledge of the results of the quantified measures. Foot taps, in which the patient tapped the toes while keeping the heel on the ground, were also measured, one foot at a time. This task is not part of the UPDRS, and therefore was not rated. Leg agility ratings were used as a rough comparison of lower-limb function. Again, one to five tests lasting three to 19 seconds were performed for each foot; tests were separated by short rest periods.

Tremor was recorded with a single-axis accelerometer taped to the hand. Results of tremor quantification are not included in this paper.

3.2.4 Intraoperative evaluations

At most, two of the symptoms rigidity, bradykinesia, and tremor were quantified during the course of the stereotactic surgery. Rigidity was measured between microelectrode penetrations (subjects AS, GC), during microelectrode recording (subject LH), during macrostimulation (subjects AS, GC, LH), between lesions (subjects AS, HH), and after completion of all lesions. The electrophysiologist (MW) performed the intraoperative rigidity measurement tests for subjects AS and GC. Tests performed on the same subjects by other examiners were omitted from the analysis to try to keep tests as consistent as possible. The graduate student (SP) performed all tests during surgery for LH. MW and one of the nurses involved in pre- and postoperative examinations performed the measurements during the surgery for HH. Sensors were applied to the patient only during rigidity testing; they did not remain on the patient for the entire surgical procedure.

Bradykinesia was quantified during microelectrode recording which occurred during the mapping procedure (subjects AS, RS, PM, BT). During this time the electrophysiologist or a neurologist instructed the patient as to what task to perform (hand pronation/supination or foot dorsi/plantarflexion), and when to start and stop the movements. Pre-lesion measurements were taken between microelectrode penetrations for subject MG. Movements were also quantified during the lesioning process (subjects AS, RS, PM) as well as after completion of all lesions. The same instructions were given by the same instructors during all tests for MG. For the other patients there was invariably a change in instructor during the surgery, often resulting in a change of instruction. Sensors for quantification of bradykinesia remained on the subject throughout the surgery for all subjects except MG; MG preferred that the sensors be removed when no testing

occurred. Hand pronation/supination was tested for all subjects; foot tapping (foot dorsi- and plantarflexion) was tested for all but MG. For all subjects except MG, movement tests were performed only when the electrophysiologist, a neurologist, or a nurse instructed the patient; no tests extra to what is normally carried out during the surgical procedure were performed. At some points in the surgery this testing became very fast-paced, notably during the lesioning process, and the timing of tests was not necessarily synchronized with the computer data collection software. For these reasons tests are of different lengths, and some trials were either not fully recorded or missed completely. Any trial less than two seconds in duration was rejected, as this was the length of the FFT window used in the off-line analysis.

3.2.5 Control subjects

The quantification devices were used to measure elbow and wrist impedance, and to monitor hand pronation/supination and foot taps in three subjects with no known neurological disorder, ranging in age from 46 to 74 years (average 56). Impedance was measured for three 50-second trials for each joint tested. Three approximately 10-second trials were collected for each voluntary repetitive task performed.

3.2.6 Statistical analysis of rigidity and bradykinesia quantified measures

Independent samples of mechanical impedance were divided into groups according to the conditions under which they were collected (i.e., off medication with no rigidity reinforcement manoeuvres, off medication with reinforcement, on medication without reinforcement, on medication with reinforcement.) Student's t-tests were used to compare impedance values under a set of conditions post-operatively with impedance values obtained under the same conditions pre-operatively. One-way ANOVA was used in cases where more than one post-operative assessment

had been performed, or when comparing intraoperative measures (pre-lesion, macro stimulation, post-lesion), or when comparing intraoperative with perioperative measures. Data were tested for significant difference from pre-lesion or pre-operative measures using Dunnett's Test post-hoc. If the data set did not show equal variance or normal distribution, a non-parametric test was employed instead (Mann-Whitney Rank Sum Test was used in place of Student's t-test, Kruskal-Wallis one-way ANOVA with Dunn's Test post-hoc was used in place of the parametric one-way ANOVA and Dunnett's Test). The same procedure was used to analyze bradykinesia test measures of frequency, irregularity, mean speed, and displacement amplitude. Alpha was set at 0.05.

3.2.7 Surgical procedure

Surgery took place at the Foothills Hospital in Calgary, or at the Toronto Hospital (subject LH). The surgical procedures were essentially those described elsewhere (Lozano *et al.*, 1996). Briefly, a Leksell stereotactic frame was applied under local anesthesia and magnetic resonance images of the brain were generated in the horizontal plane. Based on coordinates for the anterior and posterior commissures, customized neuroanatomy software determined an initial anatomical target for pallidotomy using the coordinates suggested by Laitinen (Laitinen *et al.*, 1992). For thalamotomy, the initial target was set at 2mm anterior to the posterior commissure. This was usually in the sensory thalamus, allowing for determination of laterality of the track; in such cases the target position was always subsequently modified. Target locations were confirmed physiologically using microelectrode recordings in conjunction with micro- and macro-stimulation. Sensorimotor afferent input to a recorded cell was determined with passive and active joint manipulation, including fingers, wrist, elbow, shoulder, ankle and knee. Oral-facial, jaw and eye movements were also assessed. Manipulations were performed on limbs ipsilateral and contralateral to the electrode for subsequent comparison. Each set of manipulations was

repeated to rule out non-specific effects as an explanation for the results. For pallidal surgeries, microelectrode detection of action potentials evoked by strobe light stimulation helped determine the location of the optic tract, as did microelectrode stimulation. Potential lesion sites were re-assessed using macrostimulation delivered through a thermocoupled lesion probe (tip diameter 1mm). Macrostimulation (Radionics RFG-3CF) consisted of 0.2 msec square pulses at 185 or 200 Hz from 0.1 to 10 mA. Visual and motor responses were assessed by the clinical team. Lesions were performed only after visual and motor responses were absent following macrostimulation at thresholds of 2 - 4 mA. Incremental radiofrequency lesions were performed to a maximum of 90°C for 90 seconds. From 1 to 3 lesions were made depending on the results of physiological mapping.

3.3 RESULTS

3.3.1 Pre- and Postoperative assessments

Eight patients with Parkinson's disease who were scheduled to undergo unilateral thalamotomy (subject JL) or pallidotomy (all other subjects) participated in the preoperative quantified assessments of rigidity and bradykinesia. Three of these did not complete the postoperative examination: surgery was cancelled for two, and the other suffered a ventricular hemorrhage postoperatively and died 49 days following his surgery.

Daily doses of medication at the time of the one-month postoperative assessment remained the same for three of the subjects as they had been preoperatively. Doses of DOPA were decreased by an average of 75mg/d for subject MG, and by 62.5 mg/d for subject RS. Medication for RS at the six-month evaluation was back to preoperative levels. Subject JL was only tested while off medication.

Despite having withdrawn medication for at least 12 hours, subject MG was not felt to be at "worst off" during her preoperative examination. Appearance of tremor late into the "off" state assessment, or absence of previously-experienced tremor may indicate that RS and BT were not fully "off" during their preoperative or postoperative assessments, respectively.

As this project developed, occasional changes in protocol or errors in sensor placement resulted in uncertainties regarding the reliability of data; such data were discarded, as specified in the following sections.

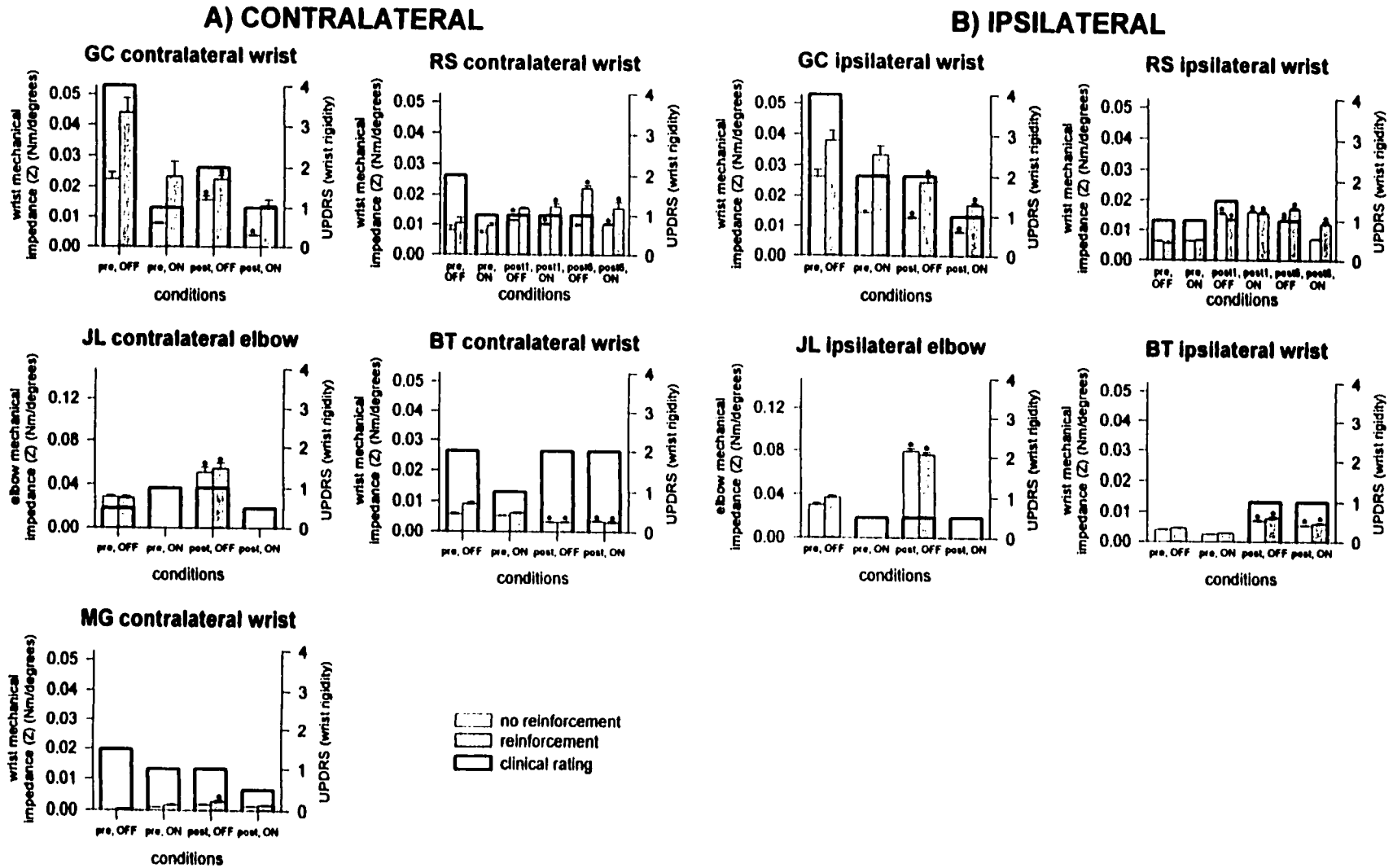
Rigidity

Results of perioperative rigidity quantification and UPDRS ratings are presented in Figure 3-2. Note that impedance measures for subject JL were taken about the elbow, whereas clinical scores are for the wrist.

Contrary to expectations, there was very little improvement in rigidity. This may have been because upper limb rigidity was for the most part quite low preoperatively. Changes in UPDRS measurements agreed with changes in quantified impedance measurements about half of the time.

Contralateral decreases in upper limb mechanical impedance were measured both "on" and "off" medication for two of the four subjects who underwent pallidotomy (GC, BT). One of these subjects (GC) also demonstrated ipsilateral amelioration of rigidity (lower impedance), again in both medication states. Impedance levels remained unchanged or worsened for the other subjects. Clinical ratings agreed with impedance measurements for GC, as well as with some ipsilateral increases in impedance for subjects BT and RS. However, clinical ratings suggested an increase in contralateral wrist rigidity for BT, in contrast to the decrease suggested by the impedance measurements, and showed a reduction in rigidity for two subjects in whom there was an increase or no change in the quantified impedance (MG contralateral, RS contralateral and ipsilateral

Figure 3-2. *Perioperative upper limb rigidity data* Plots show quantified measures of mechanical impedance (mean ± standard error) and independently-obtained UPDRS ratings of upper limb rigidity at one month pre- and one month post-surgery, "on" and "off" medication. Results from six months post-surgery are included for subject RS. Agreement between clinical and quantified measures was strongest for high, and poorest for low, rigidity levels. The y-axes for Z and UPDRS scores are scaled relative to each other (wrist: UPDRS = 76 * Z; elbow: UPDRS = 27 * Z (see Chapter 2)). Notes: Subject JL: Quantified measures were taken at the elbow; UPDRS scores were for the wrist. No quantified measures were obtained while JL was at "best on". Subject MG: Due to negative elastic or viscous stiffness, preoperative sample sizes of non-reinforced mechanical impedance were insufficient for statistical testing against postoperative data (no data while "off", two data points (eight seconds) while "on"). The change in reinforced stiffness while "on" is not statistically significant.


A) CONTRALATERAL
B) IPSILATERAL
GC contralateral wrist
RS contralateral wrist
GC ipsilateral wrist
RS ipsilateral wrist
JL contralateral elbow
BT contralateral wrist
JL ipsilateral elbow
BT ipsilateral wrist
MG contralateral wrist
wrist mechanical impedance (Z) (Nm/degrees)
elbow mechanical impedance (Z) (Nm/degrees)
UPDRS (wrist rigidity)
conditions
pre, OFF
pre, ON
post, OFF
post, ON
no reinforcement
reinforcement
clinical rating

"on"). Impedance and UPDRS rigidity scores for the one subject who underwent thalamotomy increased bilaterally.

Agreement between UPDRS rigidity ratings and the average of reinforced and non-reinforced mechanical impedance values across subjects was greater for the ipsilateral than for the contralateral wrist (Pearson's correlation coefficients (r) =0.82, 0.54 respectively). This difference was largely due to clinical over-rating, relative to quantified impedance values, of the rigidity of the contralateral wrist of BT, and did not appear to be the result of expectation bias. Combining contralateral with ipsilateral scores produced a correlation coefficient of 0.64. The correlation for the subject who demonstrated severe bilateral rigidity preoperatively (subject GC, $r>0.95$), was higher than that for the entire group; agreement was greatest with the highest rigidity levels. Regression coefficients were very similar if reinforced or non-reinforced rigidity levels alone were taken into account.

Quantification of rigidity was performed by someone other than the individual who assigned UPDRS ratings for subject BT, for RS preoperatively and at one month postoperatively, and for JL preoperatively. The wrist was held pronated for all clinical assessments, yet was held supinated for subject RS and possibly BT for the quantified measures; this may affect agreement between findings. There was a change in examiner for the quantification trials between pre- and postoperative assessments for JL, and for the six-month postoperative assessment for RS. Very low impedance levels or patient assistance of the passive movement of the limb resulted in negative elastic or viscous stiffnesses. These segments of the data were omitted. In addition, only one independent sample of impedance could be obtained from every four seconds of data; short periods of reinforcement (or lack of reinforcement) yielded few data points. Consequently, the number of independent samples was low in some patients with few trials. Note that for subject MG there were too few preoperative estimates of non-reinforced wrist impedance for valid comparison with her postoperative findings.

Bradykinesia

Significant improvements in most or all of the quantified parameters of movement (speed, amplitude, frequency, regularity) were observed bilaterally in two subjects and ipsilaterally in one. Improvement in one task was not necessarily accompanied by improvement in the other. Changes in the quantified measurements were usually not reflected in UPDRS scores. Results of bradykinesia tests for the contralateral and ipsilateral limbs are displayed in Tables 3-2 and 3-3, respectively. Note that because only one measure of frequency or normalized harmonicity could be obtained from each trial, there were often too few samples to check for statistical difference from the preoperative state for these parameters. Note also that a higher value of harmonicity corresponds to increased irregularity.

Two of the five subjects demonstrated dramatic, bilateral effects of pallidotomy on hand pronation/supination while "off" medication, such that performance improved to match or surpass preoperative "on" levels. For subject GC, this was manifest as an approximately 150% increase in speed and amplitude, as well as about a 60% improvement in regularity (Figure 3-3); these improvements are reflected in a lowering of the UPDRS ratings for this task. Subject MG showed slightly less impressive improvements in speed (59 - 142%) and frequency (150%), accompanied by reduction in regularity (i.e. increase in normalized harmonicity score) bilaterally and amplitude contralaterally. In the "on" state, no improvement was seen for subject GC, contradicting the UPDRS scores (Figure 3-3). For subject MG, frequency increased bilaterally and speed ipsilaterally. The ipsilateral effects were actually greater than the contralateral for MG, both "on" and "off" medication, contradicting the clinical scores which suggest the opposite. Smaller changes were seen for subject RS, as his performance in this task was among the best of the subjects preoperatively. Due to poor sensor placement, few conclusions can be drawn regarding contralateral speed and amplitude in the "off" state at one month postoperatively. Improvement, if any, was not greater than that observed ipsilaterally. This disagrees with clinical

TABLE 3-2 : *Contralateral hand pronation/ supination and foot taps: results of evaluations before and after surgery*

subject/ test performed	medication	peak-to-peak amplitude (2√2 * RMS) (degrees)				mean speed (mean rectified velocity) (degrees/s)				normalized harmonicity (0 = regular, 1 = random)			
		pre-op	post-op	change	significance	pre-op	post-op	change	significance	pre-op	post-op	change	significance
MG/ hands	off	135 ± 8	87 ± 4	↓	*	181 ± 11	289 ± 14	↑	*	0.017 (n=1)	0.064 (n=2)	↑	
	on	178 ± 9	105 ± 4	↓	*	319 ± 20	312 ± 8	↓	ns	0.033 (n=1)	0.055 (n=2)	↑	
MG/ feet	off	5 ± 1	11 ± 0	↑	*	12 ± 2	68 ± 2	↑	*	0.152 (n=1)	0.112 (n=2)	↓	
	on	13 ± 1	19 ± 0	↑	*	50 ± 3	93 ± 3	↑	*	0.130 (n=1)	0.095 (n=2)	↓	
GC/ hands	off	13 ± 3	32 ± 2	↑	*	70 ± 13	179 ± 16	↑	*	0.321 (n=2)	0.139 (n=2)	↓	
	on	76 ± 3	64 ± 2	↓	*	352 ± 11	313 ± 8	↓	*	0.073 (n=2)	0.076 (n=2)	↑	
GC/ feet	off	9 ± 1	7 ± 1	↓	ns	66 ± 8	62 ± 4	↓	ns	0.384 (n=2)	0.329 (n=1)	↓	
	on	16 ± 0.5	9 ± 0	↓	*	126 ± 4	74 ± 5	↓	*	0.142 (n=2)	0.122 (n=1)	↓	
BT/ hands	off	104 ± 3	67 ± 3	↓	*	163 ± 6	109 ± 7	↓	*	0.026 ± .003	0.041 ± .010	↑	ns
	on	105 ± 2	35 ± 2	↓	*	310 ± 10	130 ± 8	↓	*	0.064 ± .010	0.199 ± .043	↑	*
BT/ feet	off	22 ± 2	28 ± 1	↑	ns	23 ± 2	55 ± 3	↑	*	0.015 (n=2)	0.077 ± .010	↑	
	on	19 ± 1	9 ± 1	↓	*	29 ± 2	22 ± 2	↓	ns	0.027 ± .002	0.067 (n=2)	↑	
RS/ hands	off									0.043 ± .005	0.114 ± .032	↑	ns
	on	100 ± 2	110 ± 2	↑	*	880 ± 12	308 ± 5	↓	*	0.101 ± .018	0.024 ± .003	↓	*
	off (6 mo.)										0.039 (n=1)	↓	
	on (6 mo.)		96 ± 4	↓	ns		506 ± 10	↓	*		0.192 (n=1)	↑	
JL/ hands	off	133 ± 5	82 ± 3	↓	*	416 ± 15	266 ± 12	↓	*	0.040 ± .014	0.044 ± .008	↑	ns

subject/ test performed	medication	main frequency component of displacement signal (Hz)				UPDRS rating for rapid alternating hand movements (contralateral hand) (0 to 4)			UPDRS rating for contralateral heel taps (leg agility) (0 to 4)		
		pre-op	post-op	change	significance	pre-op	post-op	change	pre-op	post-op	change
MG/ hands	off	0.6 (n=1)	1.6 (n=2)	↑	*	1	0.5	↓			
	on	0.9 (n=1)	1.5 (n=2)	↑		1	0.5	↓			
MG/ feet	off	1.3 (n=1)	3.3 (n=2)	↑					2	1	↓
	on	2.1 (n=1)	2.5 (n=2)	↑					1	1	n/c
GC/ hands	off	2.9 (n=2)	3.0 (n=2)	↑		4	3	↓			
	on	2.6 (n=2)	2.6 (n=2)	n/c		2	1	↓			
GC/ feet	off	5.2 (n=2)	5.1 (n=1)	↓					2	1	↓
	on	4.3 (n=2)	4.3 (n=1)	n/c					1	1	n/c
BT/ hands	off	0.8 ± 0.04	0.7 ± 0.05	↓	ns	2	2	n/c			
	on	1.5 ± 0.1	2.0 ± 0.3	↑	ns	1	2	↑			
BT/ feet	off	0.5 (n=2)	0.9 ± 0.1	↑					2	3	↑
	on	0.7 ± 0.04	1.1 (n=2)	↑					1	2	↑
RS/ hands	off	2.3 ± 0.1	2.3 ± 0.1	n/c	ns	1	0	↓			
	on	4.8 ± 0.2	1.5 ± 0.01	↓	*	0	0	n/c			
	off (6 mo.)		1.7 (n=1)	↓			1	n/c			
	on (6 mo.)		2.5 (n=1)	↓			0	n/c			
JL/ hands	off	1.7 ± 0.04	1.7 ± 0.1	n/c	ns	1.5	0.5	↓			

mean ± SEM (if n≥3, otherwise number of trials in parentheses)
n/c = no change, *p<0.05, ns = not significant, significance not tested if n<3

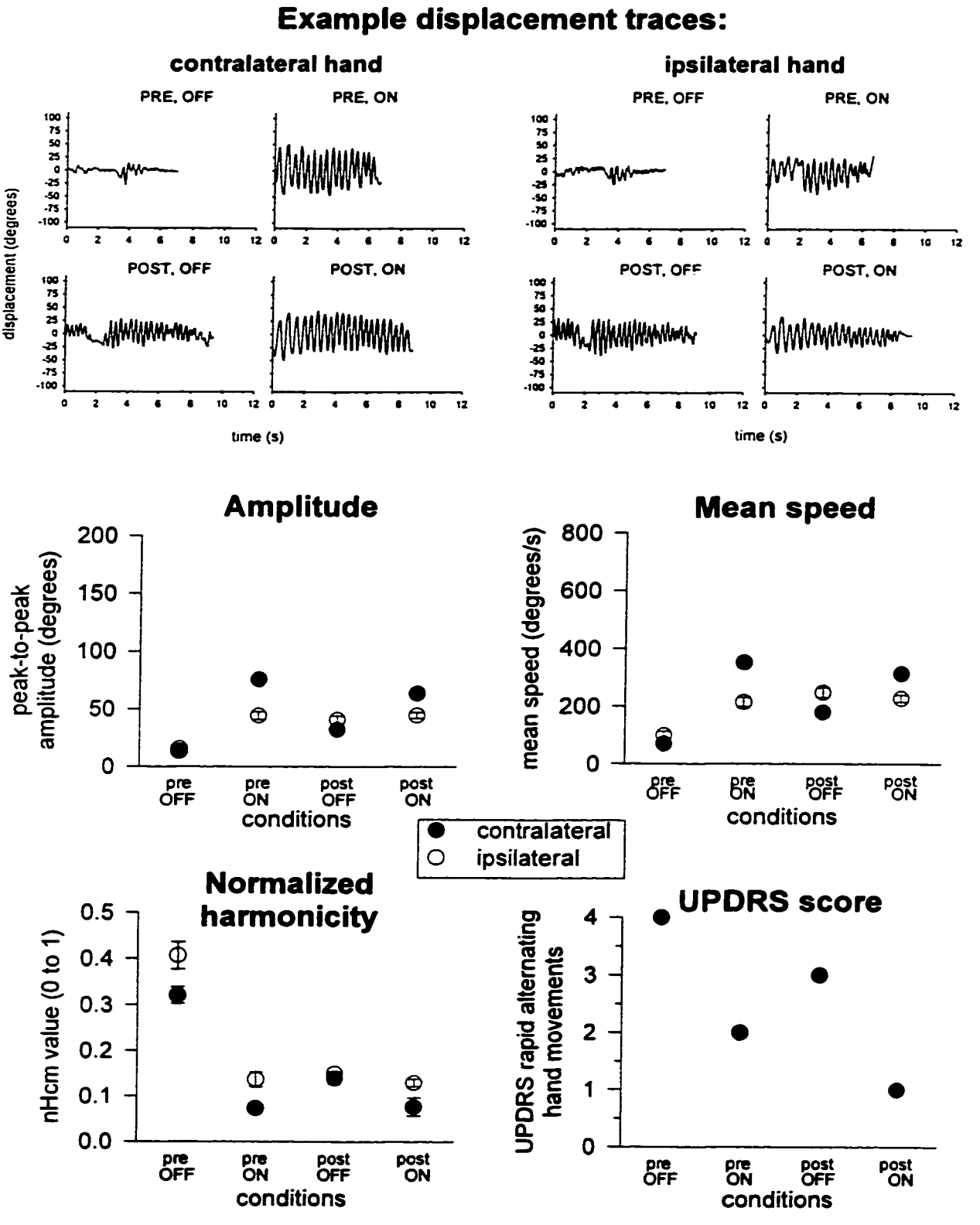
TABLE 3-3 : *Ipsilateral hand pronation/ supination and foot taps: results of evaluations before and after surgery*

subject/ test performed	medication	peak-to-peak amplitude (2√2 * RMS) (degrees)				mean speed (mean rectified velocity) (degrees/s)				normalized harmonicity (0 = regular, 1 = random)			
		pre-op	post-op	change	significance	pre-op	post-op	change	significance	pre-op	post-op	change	significance
MG/ hands	off	109 ± 8	109 ± 4	n/c	ns	146 ± 10	355 ± 10	↑	*	0.017 (n=1)	0.051 (n=2)	↑	
	on	141 ± 8	130 ± 3	↓	ns	255 ± 17	352 ± 9	↑	*	0.029 (n=1)	0.027 (n=2)	↓	
MG/ feet	off	10± 0	13 ± 0	↑	*	49 ± 2	87 ± 2	↑	*	0.125 (n=1)	0.098 (n=2)	↓	
	on	18 ± 1	30 ± 1	↑	*	87 ± 4	148 ± 3	↑	*	0.139 (n=1)	0.095 (n=2)	↓	
GC/ hands	off	15 ± 3	41 ± 3	↑	*	99 ± 14	247 ± 18	↑	*	0.407 (n=2)	0.150 (n=2)	↓	
	on	44 ± 4	45 ± 3	↑	ns	215 ± 16	228 ± 13	↑	ns	0.136 (n=2)	0.129 (n=2)	↓	
GC/ feet	off	8 ± 0	10 ± 0	↑	*	68 ± 4	91 ± 7	↑	ns	0.352 (n=2)	0.251 (n=1)	↓	
	on	11 ± 0	8 ± 0	↓	*	94 ± 6	67 ± 4	↓	*	0.301 (n=2)	0.173 (n=1)	↓	
BT/ hands	off	122 ± 4	75 ± 4	↓	*	195 ± 7	115 ± 7	↓	*	0.027 ± .004	0.036 ± .006	↑	ns
	on	94 ± 3	48 ± 4	↓	*	284 ± 10	161 ± 14	↓	*	0.093 ± .024	0.170 ± .020	↑	ns
BT/ feet	off	2 ± 0	15 ± 1	↑	*	7 ± 0	23 ± 2	↑	*	0.182 (n=2)	0.039 ± .002	↓	
	on	15 ± 1	10 ± 1	↓	*	21 ± 2	17 ± 2	↓	ns	0.028 ± .002	0.051 ± .004	↑	*
RS/ hands	off	108 ± 2	125 ± 3	↑	*	457 ± 14	522 ± 12	↑	*	0.048 ± .004	0.053 ± .008	↑	ns
	on	113 ± 3	158 ± 3	↑	*	1022 ± 26	461 ± 8	↓	*	0.111 ± .011	0.025 ± .004	↓	*
	off (6 mo.)		142 ± 3	↑	*		473 ± 13	↑	ns		0.026 (n=1)	↓	
	on (6 mo.)		96 ± 4	↓	*		506 ± 10	↓	ns		0.192 (n=1)	↑	
JL/ hands	off	112 ± 4	64 ± 3	↓	*	351 ± 12	196 ± 10	↓	*	0.040 ± .014	0.052 ± .008	↑	ns

subject/ test performed	medication	main frequency component of displacement signal (Hz)				UPDRS rating for rapid alternating hand movements (ipsilateral hand) (0 to 4)			UPDRS rating for ipsilateral heel taps (leg agility) (0 to 4)		
		pre-op	post-op	change	significance	pre-op	post-op	change	pre-op	post-op	change
MG/ hands	off	0.6 (n=1)	1.6 (n=2)	↑		1	1	n/c			
	on	0.8 (n=1)	1.5 (n=2)	↑		1	1	n/c			
MG/ feet	off	2.3 (n=1)	3.2 (n=2)	↑					1	1	n/c
	on	2.3 (n=1)	2.3 (n=2)	n/c					1	1	n/c
GC/ hands	off	2.9 (n=2)	3.1 (n=2)	↑		4	3	↓			
	on	2.6 (n=2)	2.5 (n=2)	↓		2	1	↓			
GC/ feet	off	5.5 (n=2)	5.3 (n=1)	↓					1	1	n/c
	on	4.8 (n=2)	5.2 (n=1)	↑					1	0	↓
BT/ hands	off	0.8 ± 0.04	0.7 ± 0.05	↓	ns	2	2	n/c			
	on	1.5 ± 0.10	1.5 ± 0.1	n/c	ns	1	1	n/c			
BT/ feet	off	0.9 (n=2)	0.8 ± 0.03	↓					2	2	n/c
	on	0.6 ± 0.01	0.8 ± 0.1	↑	ns				1	3	↑
RS/ hands	off	2.3 ± 0.1	2.1 ± 0.02	↓	ns	1	0.5	↓			
	on	4.6 ± 0.1	1.5 ± 0.01	↓	*	0	0	n/c			
	off (6 mo.)		1.7 (n=1)	↓			1	n/c			
	on (6 mo.)		2.5 (n=1)	↓			0	n/c			
JL/ hands	off	1.7 ± 0.04	1.7 ± 0.1	n/c	ns	0.5	0	↓			

mean ± SEM (if n≥3, otherwise number of trials in parentheses)
n/c = no change, *p<0.05, ns = not significant, significance not tested if n<3

Figure 3-3. *Perioperative hand pronation/supination data for subject GC* Example displacement traces are shown in the top half of the figure; two trials were performed under each condition. This subject demonstrated bilateral improvement in displacement amplitude, speed, regularity (normalized harmonicity, nHcm), and frequency (not shown) of the repetitive movements while "off" medication, so that postoperative values neared pre- and postoperative "on" values. This improvement is reflected in the UPDRS scores for this task. Note, however, that in the "on" state, these parameters worsened if they presented any substantial change at all, yet UPDRS scores suggest otherwise. Points represent means, error bars (amplitude, speed) represent standard error. (nHcm: 0= completely regular, 1=completely random)


Example displacement traces:
contralateral hand
ipsilateral hand
PRE. OFF
PRE. ON
POST. OFF
POST. ON
displacement (degrees)
time (s)
Amplitude
peak-to-peak amplitude (degrees)
Mean speed
mean speed (degrees/s)
pre OFF
pre ON
post OFF
post ON
conditions
contralateral
ipsilateral
Normalized harmonicity
nHcm value (0 to 1)
UPDRS score
UPDRS rapid alternating hand movements

ratings which describe a larger improvement contralaterally than ipsilaterally. Benefits observed in the "off" state were retained six months after surgery, although this is not evident in the UPDRS ratings. In the "on" state there was a dramatic bilateral reduction in speed and frequency from very high preoperative levels (mean 880 - 1022°/s, 4.6 - 4.8Hz) to near or below preoperative "off" levels. Amplitude and normalized harmonicity showed improvement, more so ipsilaterally. Any benefit while "on" was lost completely at six months; parameters were equal to or worse than they were preoperatively. Clinical ratings for RS while "on" did not change from the preoperative score of 0.

Performance in the hand pronation/supination task deteriorated for subject BT following pallidotomy, and for subject JL following thalamotomy. Amplitude and speed while at "best on" decreased bilaterally to below preoperative "off" levels for BT. This was reflected in the UPDRS scores for the contralateral but not the ipsilateral hand. Subject JL was only tested while off medication; bilateral deterioration in amplitude and speed of the movements detected by our measurements disagreed with UPDRS scores, which in fact suggested an improvement.

Quantified effects of surgery on foot taps were less dramatic than for hand pronation/supination. Subject MG showed the most improvement, demonstrating amelioration of all parameters bilaterally in the "off" state, and of all parameters except frequency in the "on" state. Unlike with hand pronation/supination, ipsilateral effects did not exceed those of the contralateral side. UPDRS ratings for heel tapping, a task distinct from the quantified foot taps, roughly concurred with the quantified findings. For subject GC, apart from an increase in regularity of movement under all conditions, and a deterioration of speed and amplitude while "on", there was little change in foot-tap performance. UPDRS heel tap scores reflected ipsilateral and contralateral "on", but not contralateral "off", changes in normalized harmonicity. BT demonstrated bilateral improvement while "off" (speed, ipsilateral amplitude and normalized harmonicity, contralateral frequency). Aside from a 71% increase in contralateral frequency,

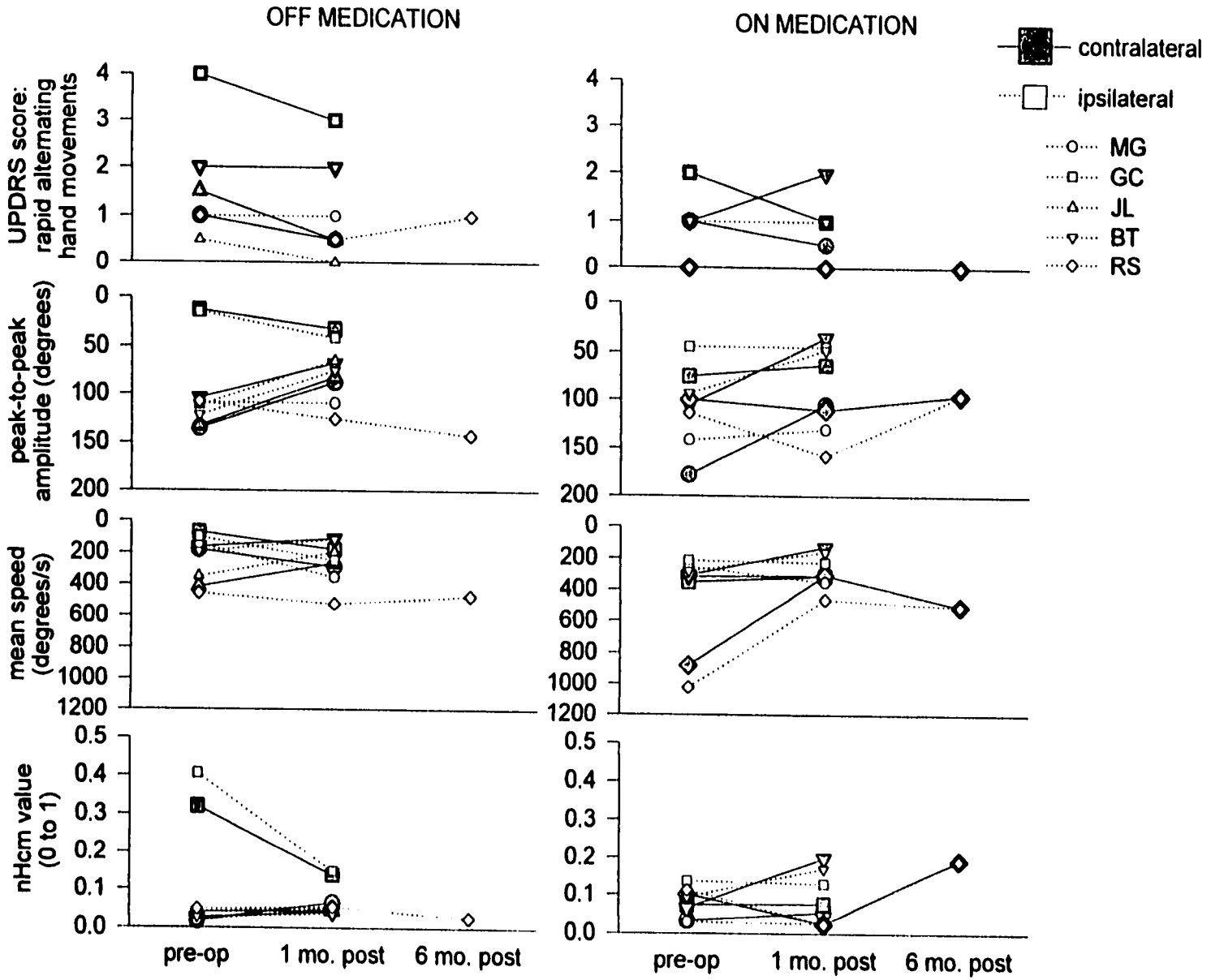
performance while "on" had deteriorated. Clinical ratings for BT suggested an overall worsening of performance of the heel tapping task.

Figure 3-4 demonstrates that changes in the measured parameters were not necessarily reflected in the UPDRS ratings for hand pronation/supination. In the "off" state, measurements of at least three of the parameters disagreed with the change in clinical ratings for one (JL) of the five subjects for both the contralateral and the ipsilateral hands. Agreement between clinical ratings and at least three of the parameters was found for one subject (GC), again bilaterally. The "on" assessments produced agreement between clinical ratings and at least 3 of the parameters for only one (BT) of the four subjects contralaterally, and for no subjects ipsilaterally. Disagreement was observed for two subjects (GC, MG) contralaterally, and for two subjects (GC, RS six-month post) ipsilaterally. The results of foot tap measures cannot be compared in the same way with UPDRS ratings, as these ratings were for a different task than that which was monitored.

Displacement and velocity data for hand pronation/supination in the "off" state preoperatively were discarded for the contralateral hand of subject RS due to incorrect sensor placement. Although the absolute amplitudes and speeds of movement were unavailable, frequency and normalized harmonicity values were unaffected and thus retained, as were all "on" measurements and all ipsilateral and postoperative measurements. Gyroscope placement for subject BT moved from the hand preoperatively to the wrist postoperatively; the data were retained after verification that effects of this change are minimal.

No foot tapping data were obtained for subject JL. Subject RS performed a different tapping task postoperatively than preoperatively, consequently foot tapping data for subject RS were excluded from the analysis.

Figure 3-4. *Perioperative hand pronation/supination data for all subjects* Plots show UPDRS scores, and simultaneously-obtained quantified measurements of amplitude, speed, and regularity (nHcm) of repetitive hand pronation/supination movements for all subjects at one month before and at one month after surgery. Six-month postoperative results are presented for subject RS only. Vertical axes are oriented so that a downward slope on any graph indicates an improvement in the parameter or score. Changes in parameters were not necessarily reflected by change in the clinical rating. No single parameter is affected consistently in all subjects. (nHcm: 0=completely regular, 1=completely random)


OFF MEDICATION
ON MEDICATION
contralateral
ipsilateral
MG
GC
JL
BT
RS
UPDRS score: rapid alternating hand movements
peak-to-peak amplitude (degrees)
mean speed (degrees/s)
nHcm value (0 to 1)
pre-op
1 mo. post
6 mo. post

3.3.2 *Intraoperative impedance evaluation*

Rigidity quantification was not as useful intraoperatively as we had anticipated. Intraoperative changes in impedance were recorded for all subjects and usually occurred following lesioning. The response to macrostimulation was minimal.

Quantitative rigidity testing was performed on four subjects intraoperatively. Impedance was measured contralaterally about the elbow in three subjects, and about the wrist in GC. Ipsilateral measurements were also performed on subject LH, both before the surgery in a waiting area, and intraoperatively immediately following termination of the surgery. Note that LH was seated for pre-surgical measurements, but reclined for intraoperative evaluations. All changes in impedance are expressed as a percent change from intraoperative pre-lesion levels, unless otherwise stated.

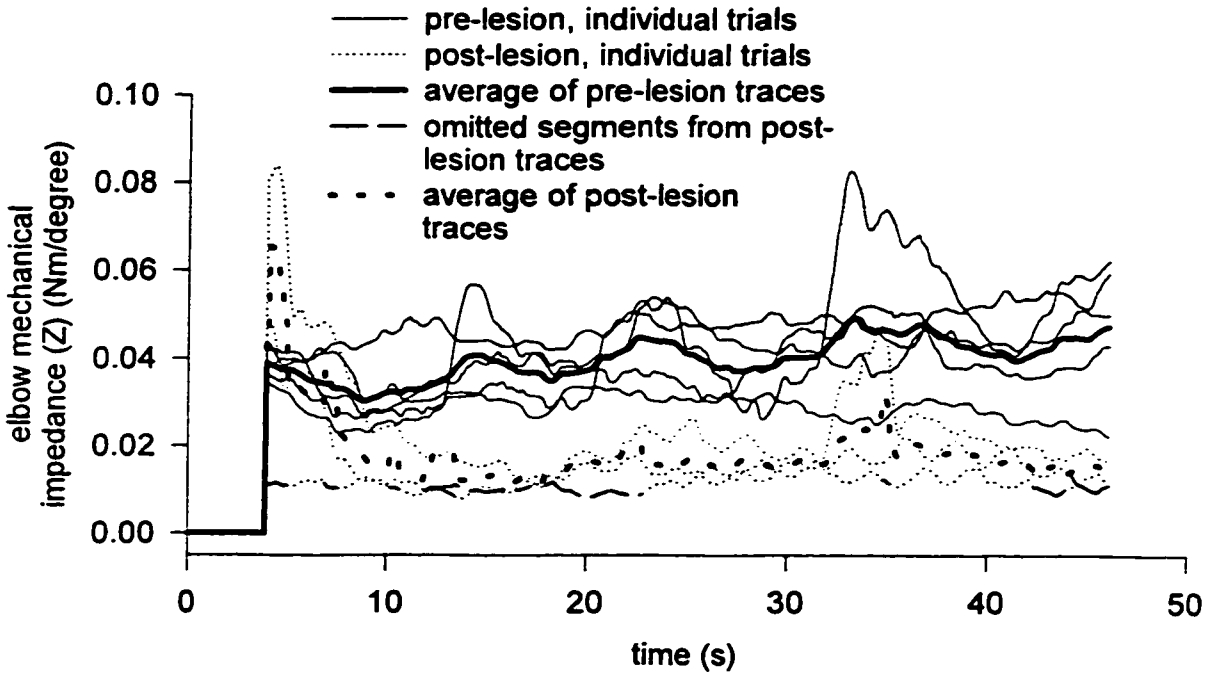
Two of the four patients, LH and AS, exhibited statistically significant decreases in non-reinforced impedance levels following completion of all pallidal lesions, impedance levels dropping 47% and 76%, respectively, from pre-lesion levels. Several plots of the time-course of impedance for subject LH are shown in Figure 3-5A. For this subject, the change was a nearly 54% reduction from pre-surgical values taken in the waiting area. LH also demonstrated a 57% reduction in impedance levels of the ipsilateral elbow compared to pre-surgical levels. Reinforcement manoeuvres were not used for either AS or LH.

Following lesioning, there was a reduction in wrist impedance both with (22%) and without (17%) reinforcement for subject GC, although these differences were not statistically significant. Pre-lesion rigidity levels for GC were surprisingly low intraoperatively, being 70% to 78% lower than observed at his one month preoperative evaluation (Figure 3-5B).

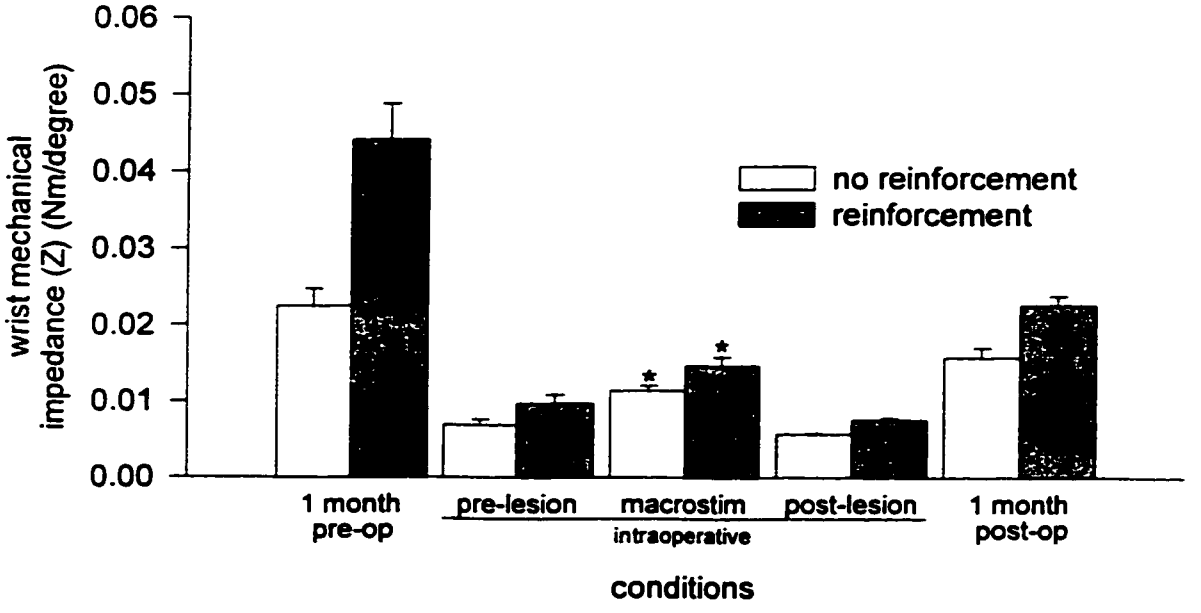
Non-reinforced impedance levels in the fourth subject (HH) had increased 70% after all pallidal lesions had been administered, despite having shown a 38% reduction from pre-lesion levels after only the first lesion. This is in contrast to observations for subject AS where a decrease in impedance seen after the initial lesion was more pronounced following all lesions.

Figure 3-5. *Intraoperative quantified rigidity measurements* **A)** Raw traces of mechanical impedance (Z) measurements taken of the contralateral elbow of subject LH. Impedance levels were significantly higher prior to lesioning (thick solid line: average of individual (thin solid lines) pre-lesion trials) than immediately afterwards (thick broken line: average of individual (thin dotted lines) post-lesion trials). The transient high Z levels at the beginning of one of the post-lesion traces is a record of the "melting away" of elbow rigidity felt by the examiner at the beginning of the first trial performed after completion of lesioning. Thin broken lines within dotted-line traces indicate sections of the trial that contained negative elastic or viscous stiffness values; these sections were omitted from the average. **B)** Contralateral wrist mechanical impedance (means ± standard error) as quantified in the presence and absence of reinforcement manoeuvres, subject GC. Despite the fact that pre-lesion intraoperative impedance levels were 70% to 78% lower than observed one month before surgery, a reduction in impedance was detected post-lesion. Although this reduction was not statistically significant, it was reflective of the postoperative decrease in wrist impedance compared to preoperative levels. For this subject, impedance levels were seen to increase during constant 2 V (0.2 msec pulse width, 185 Hz) macrostimulation, possibly as a result of observed macrostimulation-induced dyskinesias. A statistically insignificant increase in rigidity during macrostimulation (3 V, 200 Hz) was measured for the subject in A) (not shown).

A) SUBJECT LH, CONTRALATERAL ELBOW RIGIDITY



B) SUBJECT GC, CONTRALATERAL WRIST RIGIDITY



There was also a dramatic increase in reinforced rigidity levels for HH following both initial (190% increase) and all lesions (404% increase), although samples were too few to test statistically against pre-lesion levels. Note that performance of the reinforcement manoeuvre, tapping of the hand not being tested, became stronger following the first lesion. As well, the examiner had changed since the pre-lesion trials.

No significant reduction in quantified rigidity was detected during stimulation with the macroelectrode. Subjects AS and LH experienced small (5 - 9%) statistically insignificant changes in impedance with macrostimulation. Both reinforced and non-reinforced impedance increased 51% to 66% over low pre-lesion levels for GC (Figure 3-5B). Rigidity was not quantified during macrostimulation for HH.

For two of the subjects, the examiner administering the rigidity quantification test felt a "melting away", a delayed, sudden diminishing of rigidity, at the beginning of the first trial following the entire lesioning procedure. This abrupt change was recorded for both subjects, and can be seen for LH in Figure 3-5A.

Rigidity testing was begun on subject BT, but as she assisted the movements for the entire trial, further rigidity quantification was abandoned in the interest of time.

3.3.3 Intraoperative movement monitoring

Intraoperative monitoring of movement showed more potential than impedance quantification. Speed and amplitude of repetitive movements most commonly improved. It is interesting to note that amelioration of bradykinesia occurred with macrostimulation, whereas rigidity levels were either unaffected or augmented.

Tests of bradykinesia performed during stereotactic surgery were monitored for five patients. Hand pronation/supination was measured for all five subjects; ipsilateral data are available for three (MG, PM, RS). Foot dorsi/plantarflexion was measured for all subjects except MG;

ipsilateral data are available for all four. Absolute amplitude and speed values are incorrect for the contralateral hand of PM as the sensor was positioned crookedly; regularity, frequency, and relative amplitude and velocity are correct. Intraoperative findings are presented in Table 3-4.

The reality of these surgical cases is that different individuals involved in the surgery have different responsibilities at different stages of the procedure. For example, during the mapping stage, the electrophysiologist is concerned with finding areas of the globus pallidus responsive to active or passive movement. During macrostimulation and lesioning, the neurologist assumes the role of testing of motor performance with the goal of avoiding complications while achieving a clinical effect on motor function. Because of this, in our study there was frequently a change in the administrator of the tests, and consequently a change in instruction or task to be performed during the course of the surgery. For example, unilateral hand pronation/supination became bilateral (RS, AS, BT) or vice versa (PM), and foot plantar/dorsiflexion became tapping the examiner's hand (PM, AS, BT), often with the instructions "tap fast" (PM, AS). In some cases effects of the surgery may therefore have been obscured by a change in instruction.

The intraoperative effect of pallidal lesions was most evident in the speed and amplitude of hand pronation/supination movements. Subsequent to the lesioning procedure, all subjects demonstrated a significant contralateral increase (mean 71%, range 25 - 204%) in movement speed. For subject BT this increase was observed in the unilateral but not the bilateral task. Ipsilateral increases in speed were considerably less (mean 50% range 7 - 103%) and only possibly reached significance for subject PM (although there were not enough samples to test for significance, the average post-lesion speed was in the range of the average speeds recorded during macrostimulation and lesioning, which were significantly faster than pre-lesion speeds). However, during the lesioning process itself all hands monitored at this time, including the ipsilateral hands of RS and PM, moved significantly faster compared to baseline measures acquired during the mapping process (MG's movements were not measured during lesioning). In contrast to the mainly unilateral improvement in movement speed observed at the completion of

TABLE 3-4 : *Results of intraoperative bradykinesia testing*

subject/ test performed	side tested	peak-to-peak amplitude (2√2 * RMS) (degrees) during mapping	during macro stim	during lesioning	post lesions	mean speed (mean rectified velocity) (degrees/s) during mapping	during macro stim	during lesioning	post lesions
MG/ hands	contra	74 ± 4	--	--	107 ± 6*	266 ± 13	--	--	332 ± 14*
	ipsi	65 ± 4	--	--	83 ± 5*	239 ± 14	--	--	257 ± 14
BT/ hands	contra	78 ± 2	73 ± 3	41 ± 2*	37 ± 3*	109 ± 3	215 ± 8*	158 ± 6*	118 ± 12
BT/ feet	contra	32 ± 2	18 ± 2*	28 ± 1	--	45 ± 2	29 ± 2*	45 ± 2	--
	ipsi	13 ± 1	--	17 ± 2*	--	16 ± 1	--	21 ± 2*	--
RS/ hands	contra	51 ± 3	--	71 ± 3*	85 ± 4*	275 ± 12.5	--	390 ± 11*	468 ± 14*
	ipsi	59 ± 1	--	82 ± 2*	77 ± 2*	252 ± 13	--	378 ± 12*	348 ± 13
RS/ feet	contra	8 ± 0	--	18 ± 1*	--	28 ± 1	--	79 ± 3*	--
	ipsi	12 ± 0	--	4 ± 0*	--	45 ± 1	--	15 ± 1*	--
PM/ hands	contra	73 ± 3	97 ± 6*	97 ± 3*	107 ± 8*	167 ± 11	337 ± 21*	643 ± 32*	508 ± 49*
	ipsi	107 ± 4	58 ± 6*	59 ± 3*	63 (n=2)	214 ± 16	347 ± 55*	495 ± 32*	433 (n=2)
PM/ feet	contra	30 ± 1	31 ± 1	32 ± 6	21 ± 1	77 ± 3	154 ± 20*	127 ± 18*	264 ± 13*
	ipsi	33 ± 1	23 ± 0*	50 ± 3*	14 (n=2)	76 ± 4	117 ± 12*	94 ± 11	197 (n=2)
AS/ hands	contra	59 ± 2	--	67 ± 3*	77 ± 3*	294 ± 8	--	353 ± 14*	367 ± 20*
AS/ feet	contra	23 ± 1	--	14 ± 1*	33 ± 2*	40 ± 1	--	44 ± 3	79 ± 2*
	ipsi	23 ± 2	--	15 ± 1	38 ± 1*	43 ± 2	--	37 ± 2	65 ± 2*

subject/ test performed	side tested	normalized harmonicity (0 = regular, 1 = random) during mapping	during macro stim	during lesioning	post lesions	main frequency component of displacement signal (Hz) during mapping	during macro stim	during lesioning	post lesions
MG/ hands	contra	0.047 ± .009	--	--	0.045 (n=2)	2.0 ± 0.1	--	--	1.6 (n=2)
	ipsi	0.048 ± .012	--	--	0.054 (n=2)	2.0 ± 0.1	--	--	1.6 (n=2)
BT/ hands	contra	0.026 ± .003	0.053 (n=2)	0.160 ± .025*	0.109 (n=2)	0.7 ± 0.04	1.5 (n=2)	2.1 ± 0.2*	1.3 (n=2)
BT/ feet	contra	0.036 ± .004	0.103 (n=2)	0.039 ± .005	--	0.5 ± 0.04	0.9 (n=2)	0.8 ± 0.04*	--
	ipsi	0.041 ± .009	--	0.023 ± .003	--	0.5 ± 0.04	--	0.5 ± 0.02	--
RS/ hands	contra	0.172 (n=2)	--	0.163 ± .032	0.210 (n=1)	2.7 (n=2)	--	2.8 ± 0.2	2.3 (n=1)
	ipsi	0.076 (n=2)	--	0.062 ± .006	0.065 (n=1)	2.1 (n=2)	--	2.5 ± 0.1	2.3 (n=1)
RS/ feet	contra	0.135 ± .012	--	0.114 ± .016	--	1.7 ± 0.04	--	2.5 ± 0.1*	--
	ipsi	0.072 ± .008	--	0.190 ± .024*	--	1.9 ± 0.03	--	1.3 ± 0.2*	--
PM/ hands	contra	0.033 ± .006	0.073 (n=1)	0.205 ± .033*	0.253 (n=2)	1.1 ± 0.1	1.8 (n=1)	3.7 ± 0.3*	2.9 (n=2)
	ipsi	0.018 ± .004	0.246 ± .210	0.187 ± .047*	0.033 (n=2)	1.0 ± 0.1	3.4 ± 1.0*	4.9 ± 0.7*	3.9 (n=2)
PM/ feet	contra	0.030 ± .004	0.043 (n=2)	0.242 ± .144*	0.535 (n=1)	1.2 ± 0.1	2.6 (n=2)	2.6 ± 1.1*	5.4 (n=1)
	ipsi	0.015 ± .002	0.027 (n=2)	0.073 (n=1)	0.362 (n=1)	1.3 ± 0.1	2.8 (n=2)	1.3 (n=1)	6.5 (n=1)
AS/ hands	contra	0.140 ± .012	--	0.113 ± .019	0.108 (n=1)	2.5 ± 0.2	--	2.6 ± 0.2	2.4 (n=1)
AS/ feet	contra	0.035 ± .008	--	0.083 ± .032*	0.027 (n=1)	1.2 ± 0.3	--	2.0 ± 0.5	1.3 (n=1)
	ipsi	0.047 ± .015	--	0.019 (n=1)	0.026 (n=1)	1.3 ± 0.4	--	1.2 (n=1)	0.8 (n=1)

mean ± SEM (if n≥3, otherwise number of trials in parentheses)
* $p<0.05$, significance not tested if $n<3$

lesioning, significant increases in amplitude were seen bilaterally in two of the three bilaterally-monitored subjects; again, however, ipsilateral improvement was less than that seen contralaterally. It is interesting to note that PM, who was the only subject to exhibit an ipsilateral increase in movement speed post-lesion, demonstrated a 44° (41%) decrease in amplitude of ipsilateral hand movements. Raw displacement traces of hand pronation/supination recorded immediately before and after pallidal lesioning are shown for subject MG in Figure 3-6.

The movements of only three hands were monitored during macrostimulation (BT contralateral, PM bilateral). Significant increases in speed and increases in frequency were observed during macrostimulation in all three cases. Amplitude was increased contralaterally and reduced ipsilaterally in PM, and remained unchanged in BT. Significant improvement or deterioration of a parameter detected under macrostimulation or during lesioning was never seen to reverse to a significant change in the opposite direction at the completion of the lesioning process. In addition, the response during macrostimulation was always indicative of the post-lesion intraoperative result.

Regularity of hand pronation/supination movements improved intraoperatively only for subject AS and deteriorated for three other subjects. Subject PM, whose post-lesion contralateral hand movements demonstrated the largest (204%) increase in speed and the second-largest increase in amplitude (47%), suffered the greatest decline in regularity (667% increase in nHcm). Frequency increases of 0.6 Hz or greater were detected during lesioning for AS when only the bilateral task was considered, and under all conditions for PM and BT.

All subjects demonstrated increases in speed of foot dorsi/plantarflexion at some point during the surgery. Figure 3-7 shows the intraoperative progression of contralateral improvement and ipsilateral deterioration in foot dorsi/plantarflexion measured for subject RS; improvement occurred with the onset of lesioning. For subjects PM and AS, speed increased bilaterally at the end of lesioning (foot-taps were not tested post-lesion for BT and RS). Improvement was greater on the contralateral side. The increase in speed was accompanied by a significant increase in

Figure 3-6. *Intraoperative changes in performance of the hand pronation/supination task are observable in the raw displacement traces.* Increases in amplitude of the movement were seen both contralaterally (A) and ipsilaterally (B) for this subject (MG) following unilateral pallidal lesion. Changes were also evident in the raw velocity traces (not shown).

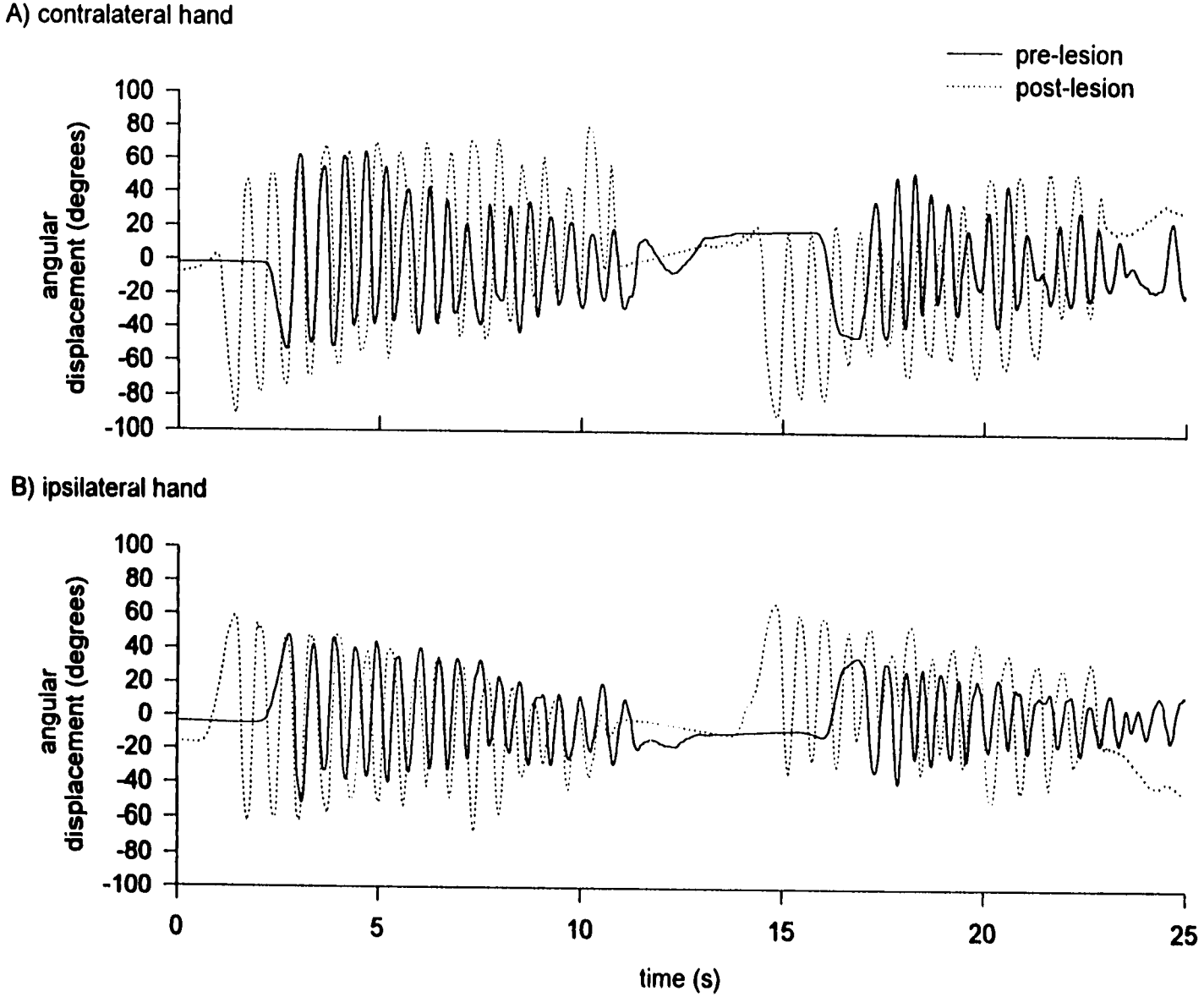
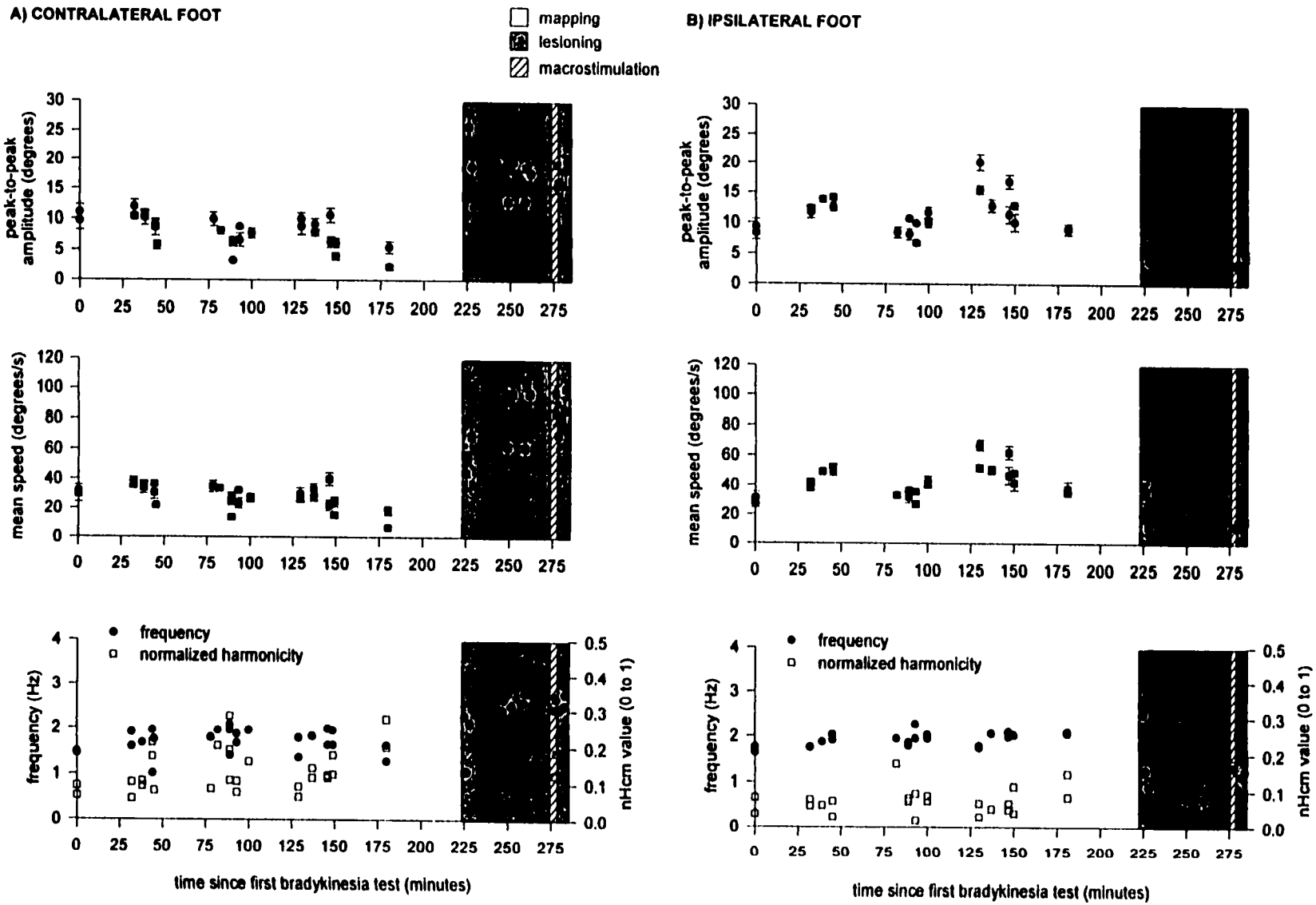

A) contralateral hand
pre-lesion
post-lesion
angular displacement (degrees)
100
80
60
40
20
0
-20
-40
-60
-80
-100
B) ipsilateral hand
angular displacement (degrees)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
5
10
15
20
25
time (s)

Figure 3-7. *Intraoperative progression of contralateral improvement and ipsilateral deterioration in foot dorsi/plantarflexion for subject RS*
Symbols represent the mean value for one trial. Error bars (amplitude and speed only) represent standard error. Only the period of macrostimulation immediately preceding the third lesion is indicated on the plot; macrostimulation was performed prior to generation of the other lesions, but either foot movements were not tested or the tests not recorded at these times. (nHcm: 0= completely regular, 1=completely random)


A) CONTRALATERAL FOOT
B) IPSILATERAL FOOT
mapping
lesioning
macrostimulation
peak-to-peak amplitude (degrees)
mean speed (degrees/s)
frequency
normalized harmonicity
frequency (Hz)
nHcm value (0 to 1)
time since first bradykinesia test (minutes)

amplitude for AS, and by a 360% to 459% increase in frequency for PM. The amplitude of the ipsilateral foot excursions deteriorated for PM.

Foot movements of only one patient were tested during both macrostimulation and post-lesions so no correlation can be made between the observations under these two conditions. Changes in parameters during macrostimulation did not necessarily reflect changes seen during lesioning, which in turn did not necessarily reflect post-lesion results. For example, there was a reduction in the amplitude of movements of the ipsilateral foot of PM during macrostimulation, and a further reduction after lesioning, yet a significant increase *during* lesioning.

One should be cautious in interpreting these results as they may have been in part the result of a change in instruction to the patient once lesioning was underway, as opposed to an effect of the surgery. This may also apply to the bilateral increases in velocity and frequency of foot movements of PM mentioned above. A similar situation, decrease in amplitude during lesioning followed by an increase after lesioning, was recorded for the contralateral foot of AS and this may also have been the result of an instruction change. As discussed above, changes in instruction were an undesirable but probably typical feature of the current approach to intraoperative evaluation.

As with the hand pronation/supination task, regularity of foot dorsi/plantarflexion was either reduced or not affected. The largest deterioration was once again seen to accompany the greatest increase in speed (PM, bilateral).

3.3.4 Correlation of monitored movements with neuronal activity

Neuronal activity was recorded throughout the intraoperative mapping procedure for all patients. In addition to being stored on computer, the output of the gyroscopes used to monitor hand or foot movements was also recorded digitally onto magnetic tape along with the neuronal recordings for subjects RS and AS. Occasionally a response to either passive or active movement

of a joint was accompanied by an alteration of the previously-stable firing pattern of a distinguishable neuron or group of neurons. For example, an increase in the firing frequency of a neuron in the external GPi was observed during volitional dorsi/plantarflexion of either foot of subject RS. This change in firing pattern was also seen with passive movement at the same joints.

3.3.5 Bradykinesia parameters compared to UPDRS ratings

Figures 3-8, 3-9 and 3-10 compare quantified parameters of hand pronation/supination to UPDRS ratings for this task. Data are from perioperative examinations of all subjects, including the three patients who did not complete the study. UPDRS scores correlated best with amplitude (r=0.57) and mean speed (r=0.54) of the movements (Figure 3-8). Normalized harmonicity (r=0.37) appeared to come into play only when movements were severely irregular (UPDRS score of 4), and UPDRS scores were essentially unrelated to the main frequency component of the movements (r=0.12).

In order to describe numerically the approximate combinations of amplitude and velocity that would be associated with each whole-number score in the UPDRS scale, the centroid of the set of points for each score was calculated (Figure 3-9). The same method was also used in Figure 3-10, but this time the normalized harmonicity scores were included in the calculations of the centroids. Scores of 0.5 and 1.5 were taken as scores of 1 in both cases. Control subjects were assigned a rating of 0. The harmonicity score did not appear to be very discriminating with respect to UPDRS scores.

3.3.6 Analysis of bradykinesia tests

During development of the analysis procedure for the bradykinesia tests, the decision was made to divide the raw displacement and velocity signals into one-second intervals to obtain

Figure 3-8. *Correlation between quantified movement parameters and UPDRS clinical scores of repetitive hand pronation/supination*. Data were taken from perioperative trials for all subjects. Amplitude and mean speed of the movements appeared to have the greatest influence on UPDRS scores, as evidenced by the larger regression coefficients. Frequency was essentially unrelated to the clinical rating. Dotted lines represent 95% confidence intervals. (nHcm: 0= completely regular, 1=completely random)

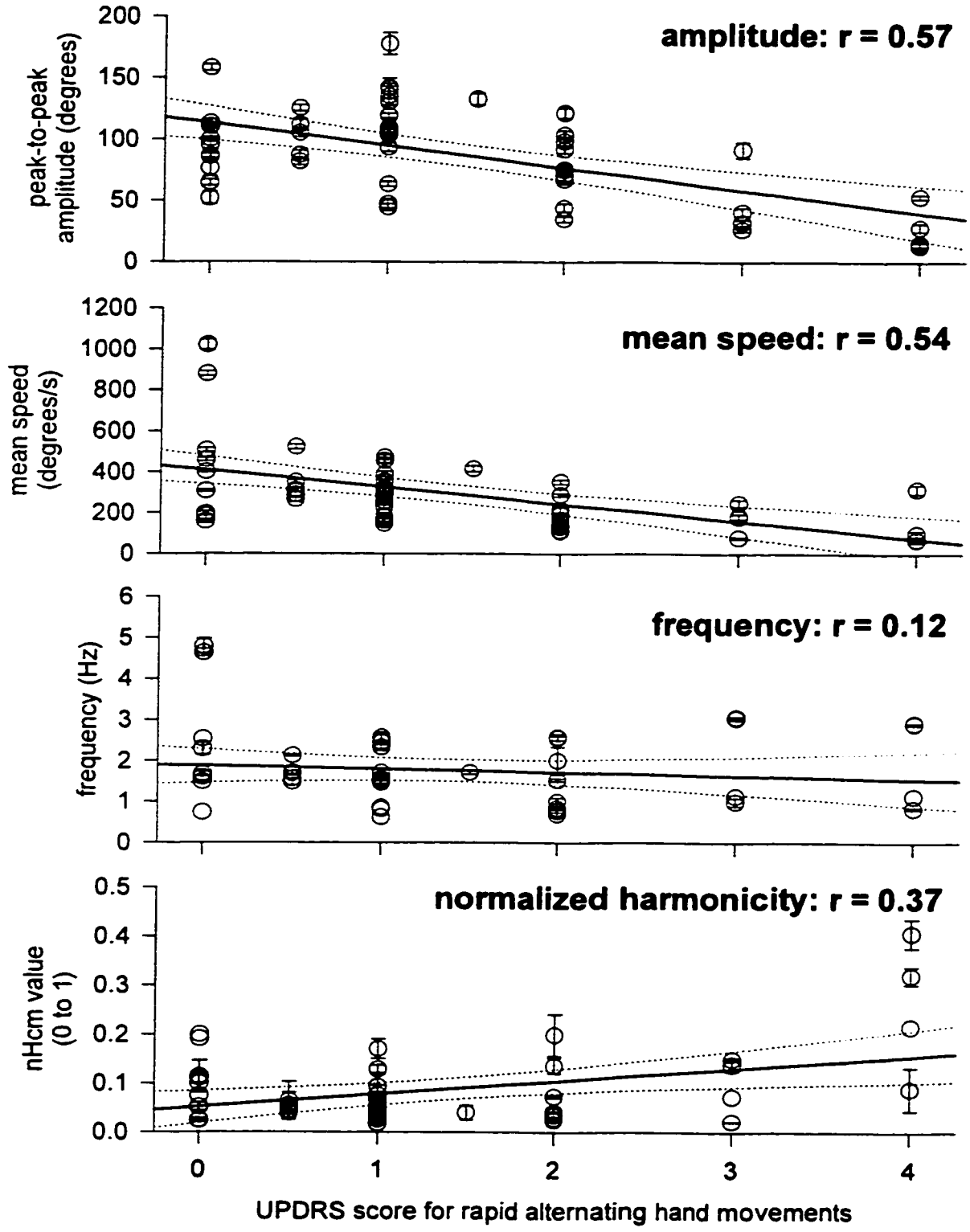

amplitude: r = 0.57
peak-to-peak amplitude (degrees)
200
150
100
50
0
mean speed: r = 0.54
mean speed (degrees/s)
1200
1000
800
600
400
200
0
frequency: r = 0.12
frequency (Hz)
6
5
4
3
2
1
0
normalized harmonicity: r = 0.37
nHcm value (0 to 1)
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
UPDRS score for rapid alternating hand movements

Figure 3-9. *Distribution of UPDRS scores for repetitive hand pronation/supination with respect to simultaneously-obtained measurements of amplitude and mean speed of the movements.* Each large circled number represents the centroid of all data points for that UPDRS score. The score of 0 includes data from control subjects. Scores of 0.5 and 1.5 were considered as scores of 1. Amplitude and mean speed appeared to be the primary factors in determining the clinical rating, and only these parameters are considered in this figure. The graph contains all data obtained from patients during perioperative examinations. Note that the scale on the axis for mean speed is logarithmic.

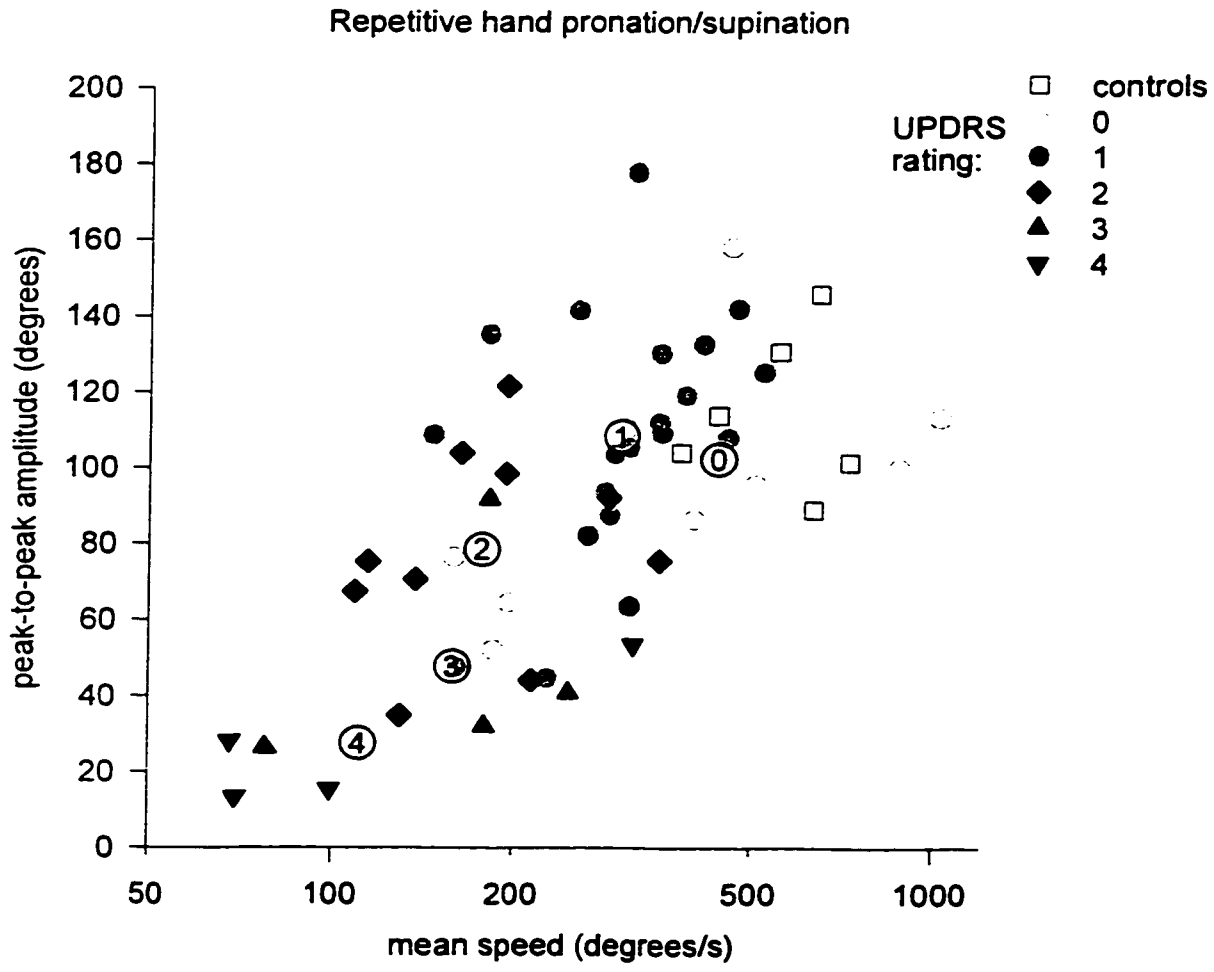
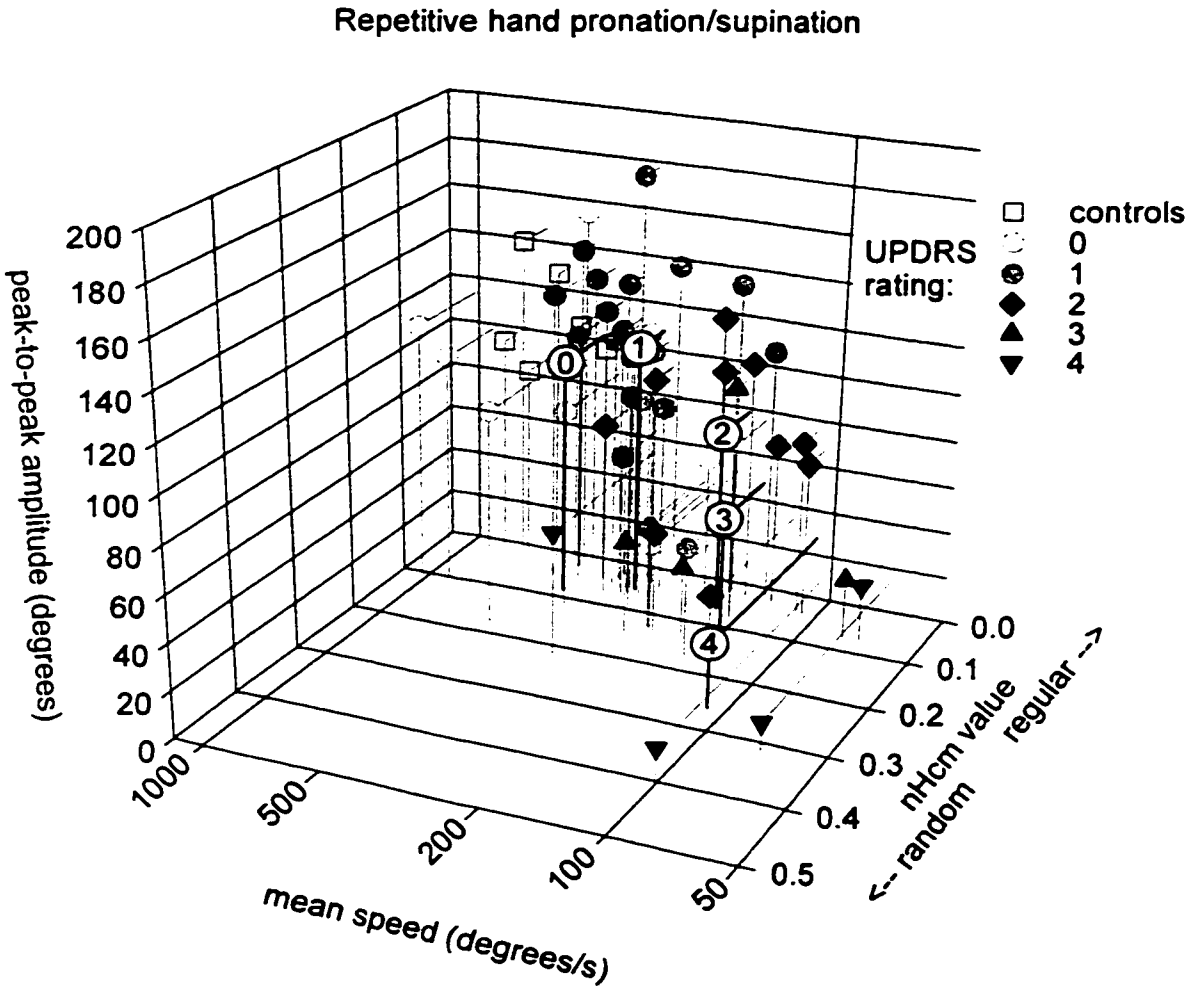

Repetitive hand pronation/supination
peak-to-peak amplitude (degrees)
mean speed (degrees/s)
200
180
160
140
120
100
80
60
40
20
0
50
100
200
500
1000
UPDRS rating:
controls
0
1
2
3
4

Figure 3-10. *Distribution of UPDRS scores for repetitive hand pronation/supination with respect to simultaneously-obtained measurements of amplitude, mean speed, and normalized harmonicity (nHcm) of the movements.* As in Figure 3-9, each large circled number represents the centroid of all data points for that UPDRS score. The score of 0 includes data from control subjects. Scores of 0.5 and 1.5 were considered as scores of 1. The harmonicity score was important only when movements were very irregular (UPDRS score of 4). Note that the scale on the axis for mean speed is logarithmic. (nHcm: 0= completely regular, 1=completely random)


Repetitive hand pronation/supination
peak-to-peak amplitude (degrees)
200
180
160
140
120
100
80
60
40
20
0
1000
500
200
100
50
mean speed (degrees/s)
0.0
0.1
0.2
0.3
0.4
0.5
nHcm value
regular -->
<-- random
UPDRS rating:
controls
0
1
2
3
4

multiple samples. Amplitude and mean speed were obtained from each of the one-second intervals; the mean and variability of these parameters over a trial or set of trials could then be expressed. Calculation of peak-to-peak amplitude was based on the RMS value of the segment. Division of the traces into cycles, as opposed to one-second intervals, would have been more intuitive, and subsequent calculation of peak-to-peak amplitude (Johnson *et al.*, 1994) either directly or based on local maxima and minima possibly more accurate. However, such tasks are difficult to automate, and in attempting to do this we found it necessary to include judgements of the programmer in the analysis procedure when movements were irregular. The analysis procedure applied in this paper worked well in most cases, based on comparisons of results with calculations performed by hand of mean amplitude or speed over a single trial. The peak-to-peak amplitude was overestimated when the displacement signal was more of a square wave than a sinusoid (e.g. MG preoperative "on" assessment of hand pronation/supination), and was underestimated if the movements were under 0.5 Hz (e.g. BT intraoperative pre-lesion assessment of contralateral foot dorsi/plantarflexion).

3.4 DISCUSSION

The debate over the effectiveness of stereotactic surgery in Parkinson's disease is in part the consequence of inconsistencies in or subjectivity of the assessment methods employed (Gross *et al.*, 1997; Hariz, 1997; Ondo *et al.*, 1998). In this paper we examine the use of two novel quantification methods for post- and intraoperative evaluation of the outcome of surgical intervention with respect to limb rigidity and some aspects of bradykinesia contained within the UPDRS. Rigidity about the wrist or elbow was computed as the examiner passively flexed and extended the joint in question, applying the movements through force sensors held on either side of the hand or wrist. Small solid-state gyroscopes were used to monitor repetitive voluntary

movements performed by the subjects in assessments of bradykinesia. Both methods essentially quantify standard clinical tests of the symptoms.

3.4.1 Outcome of surgical intervention

Only data concerning elbow and wrist rigidity, hand pronation/supination, or foot dorsi/plantarflexion were presented here. Effects pertaining to other symptoms and complications, although relevant to an overall evaluation of outcome, are out of the scope of this paper. Too few subjects were involved in this study to permit definitive conclusions regarding the effects of pallidotomy or thalamotomy on symptoms of Parkinson's disease. Rather, the intention of this paper was to introduce simple, quantitative methods of monitoring rigidity and bradykinesia in the clinical and surgical setting and to illustrate some of the advantages and difficulties of applying quantitative techniques in these circumstances.

We have quantified frequently-reported intraoperative changes in symptom levels (Dogali *et al.*, 1996; Laitinen *et al.*, 1992; Lozano *et al.*, 1995; Sutton *et al.*, 1995). In agreement with previous observations, a mixture of responses was observed with macrostimulation. Arm mechanical impedance did not significantly change in two subjects, but worsened slightly in the third. Speed and frequency of repetitive movements were usually found to increase upon macrostimulation at the lesion site, often with a concomitant deterioration of amplitude or regularity. Progressive amelioration of symptoms with successive lesioning (Sutton *et al.*, 1995; Vitek *et al.*, 1998) was also measured.

Clear postoperative improvements in rigidity and/or bradykinesia were observed in some subjects. These effects were seen ipsilaterally as well as contralaterally, and "on" medication as well as "off" medication. Following unilateral pallidotomy, one subject demonstrated bilateral reduction in wrist impedance in both medication states; these findings were corroborated by UPDRS ratings except for contralateral "on" scores which indicated no change. A second subject

showed a decrease in contralateral wrist impedance both "on" and "off" according to quantified values, but not UPDRS scores. Impedance and UPDRS rigidity scores worsened bilaterally for the one subject who underwent thalamotomy.

Following pallidotomy, increases in either speed or amplitude of repetitive voluntary movements were seen either bilaterally or ipsilaterally for four subjects while "off" medication, and for two subjects while "on". Increases in *both* speed *and* amplitude of such movements were measured bilaterally for two subjects while "off" medication (GC hand pronation/supination, MG foot taps), and for one of these while "on" (MG foot taps). Improvement of regularity was more often observed with hand than foot movements, although statistical significance usually could not be tested due to an insufficient number of trials. Quantified measurements showed a deterioration of hand pronation/supination for the one subject who underwent thalamotomy, contrary to the improvement expressed by the clinical scores. UPDRS ratings for hand pronation/supination frequently disagreed with the quantitative findings. This may be partially due to the lower resolution of the UPDRS scale in cases where the clinical scores described "no change". Comparisons of UPDRS scores with quantified parameters of movement showed that the clinical rating was better correlated with mean speed and amplitude of the movements than it was with normalized harmonicity.

Due to the small number of subjects whose rigidity was quantified intraoperatively and the fact that only one of these was also examined perioperatively, it is difficult to make conclusions regarding the predictive power of intraoperative rigidity measurements concerning postoperative outcome. The intraoperative reduction in impedance for GC, although statistically insignificant, was indicative of the reduction in wrist rigidity, compared to preoperative levels, observed one month postoperatively and agreed upon by both quantitative measures and UPDRS ratings (Figures 3-5B and 3-2). The absolute impedance values measured postoperatively for subject AS agreed with those observed intraoperatively following the initial lesion, and with those taken immediately after the surgery while AS was in the recovery room; they were not as low as those

seen intraoperatively at the termination of all lesions. UPDRS rigidity scores for the wrist (not elbow) suggested there had been an increase in rigidity by half of a point (1.5 to 2) since one month before surgery. No quantified measures were taken preoperatively.

Only three of the subjects whose intraoperative tests of hand pronation/supination were monitored also participated in the perioperative measurements. For two of these, bilateral improvements were observed intraoperatively at the completion of lesioning; bilateral improvements were also detected at one month post surgery, although the improvements were not necessarily of the same parameters as during the surgery. Intraoperatively, contralateral hand movements for the other subject (BT) showed a mixture of improvement and deterioration (ipsilateral movements were not recorded); at one month after surgery, bilateral deterioration of the movements compared to preoperative performance was observed. BT was the only subject for whom foot dorsi/plantarflexion was monitored both intra- and perioperatively; in accordance with positive intraoperative findings, bilateral improvements in this task were demonstrated postoperatively (taking into account only those intraoperative trials in which BT was asked to tap the neurologist's hand with her foot: see below).

3.4.2 Enhancement of clinical assessment

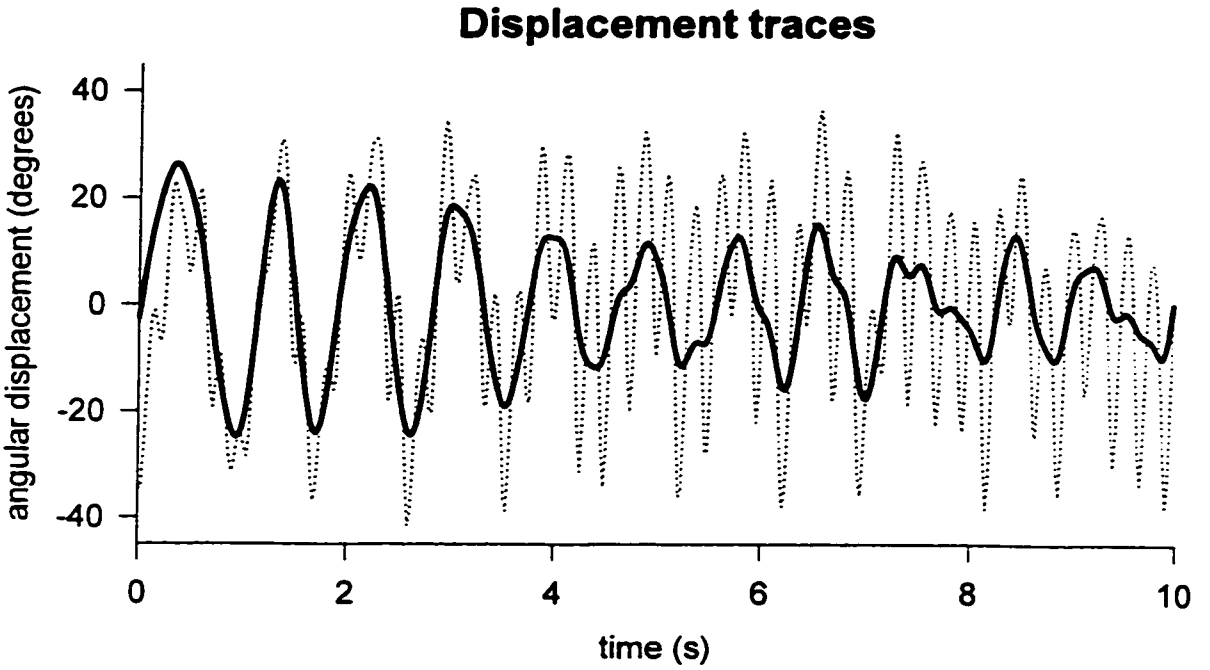
Hariz (Hariz, 1997) recognizes the UPDRS as " currently the best available tool" for evaluation of surgical results, and its acceptance is evidenced by its almost universal application in recent published studies of stereotactic procedures. However, its subjective nature makes it susceptible to examiner bias (Gross *et al.*, 1997) and open to individual interpretation. In employing sensors to monitor tests such as those outlined in the UPDRS, we have complemented the clinical observations by non-subjective measures of stiffness, speed, amplitude, regularity, and frequency. In addition, the resolution of the quantitative measures appears to be greater than

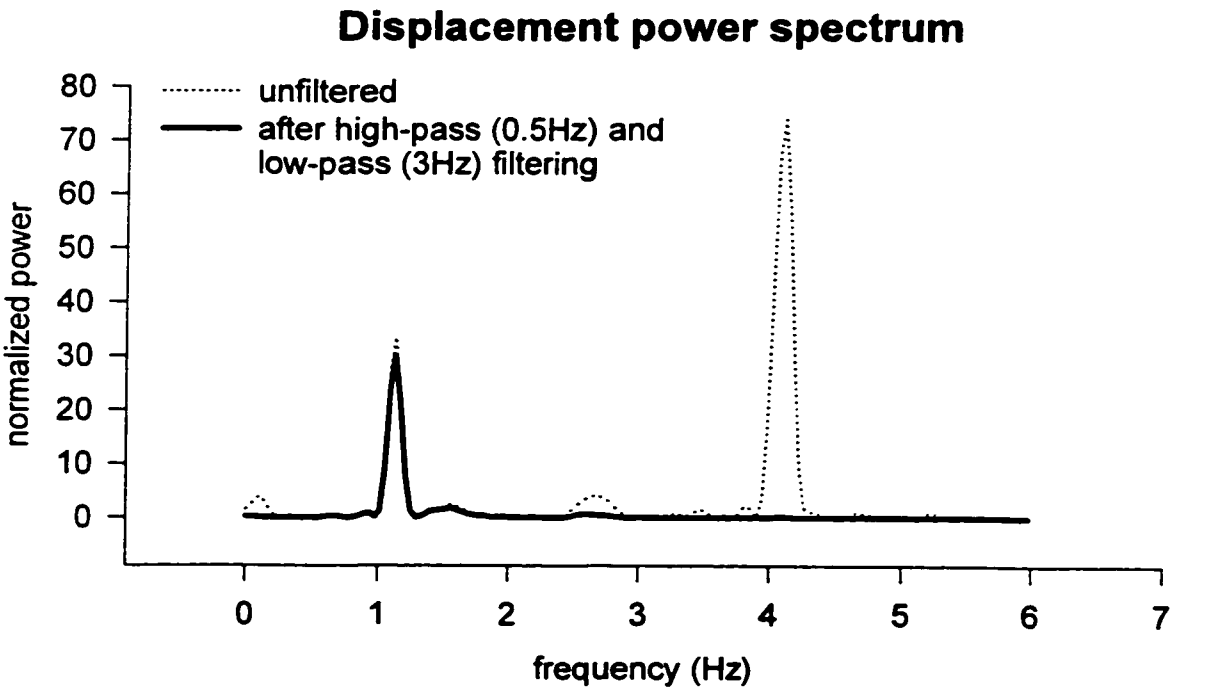
that permitted by the qualitative judgements of the UPDRS scales, potentially revealing more subtle effects of surgical intervention.

Quantifying specific aspects of volitional movements may reveal more than can be observed clinically. One of the subjects who did not complete the study presented a severe pronation/supination tremor of the contralateral hand during the hand pronation/supination task. Off-line filtering of the displacement trace revealed underlying slow voluntary movements of the contralateral hand which had been obscured by the tremor (Figure 3-11). These movements, which went unnoticed clinically and were assigned a rating of 4 ("Can barely perform the task" (Langston *et al.*, 1992)) were actually similar to or better than those of the ipsilateral hand, which had been assigned a rating of 3. On a similar note, Lang and Fahn (Lang and Fahn, 1989) point out that in some cases tremor may be mistaken for volitional movement. A suggestion that would help distinguish volitional movement from tremor in either case would be to instruct the patient to perform the task at a frequency significantly slower than the frequency of the tremor. Simple low-pass filtering would then allow selective observation of underlying voluntary activity. This could distinguish subjects who are *able* to generate voluntary movement, albeit hidden by tremor, from those physically unable to do so.

During stereotactic surgery, the response of a patient's symptoms to lesioning and possibly macrostimulation are important considerations in determining the correct site or extent of the lesion. Observation of symptoms during macrostimulation appears to play a larger role in the final positioning of electrodes in DBS procedures than it does in the finalization of lesion site in pallidotomy procedures (e.g. Limousin *et al.*, 1995; see also Vitek *et al.*, 1998). A dramatic improvement in symptoms may render quantification of rigidity or bradykinesia unnecessary. However, intraoperative effects are not always obvious, as was the situation in this study with GC (wrist rigidity) and MG (hand pronation/supination). From a clinical standpoint, quantification of symptoms during surgery may prove most valuable when the changes in them are subtle. Reduction in akinesia in particular may be difficult to judge (Limousin *et al.*, 1995). Conversely,

Figure 3-11. *Voluntary hand pronation/supination underlying pronation/supination tremor is revealed upon filtering.* Raw traces and normalized power spectra of the displacement signal before (dotted line) and after (solid line) filtering shows the volitional movement underlying the tremor. Filtering completely removes the tremor component with little effect on the volitional-movement component.


Displacement traces
angular displacement (degrees)
40
20
0
-20
-40
0
2
4
6
8
10
time (s)


Displacement power spectrum
unfiltered
after high-pass (0.5Hz) and
low-pass (3Hz) filtering
normalized power
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
frequency (Hz)

Bakay describes "shaping" the lesion as a precise, extensive process relying entirely upon intraoperative observations (Favre *et al.*, 1996 (commentary by Bakay)). Refinement of the lesion subsequent to a dramatic effect would, then, involve detection of these subtle changes; quantified measures would aid in this process.

3.4.3 Appropriateness of devices for clinical setting

In accordance with the demands of the clinical setting (Terävänen *et al.*, 1989), both of the quantification methods proposed in this paper are simple to use, quick, and relatively inexpensive. In addition, their nature permits simultaneous administration of the UPDRS scale by the examiner. For example, in the present study, repetitive hand pronation/supination movements were monitored quantitatively during the clinical evaluation of this task. Rigidity scores were assigned independently, immediately prior to quantification trials. In some instances in which the same examiner administered both types of rigidity assessments, the clinical rating was modified upon completion of the quantification trials but without knowledge of the quantitative findings; in a previous study, ratings were assigned during quantification of impedance (Prochazka *et al.*, 1997). Foot taps do not constitute part of the UPDRS and were consequently not rated. Alternatively, heel taps could have been objectively monitored by placing the gyroscope on the thigh. Thus, tests that are already part of the UPDRS battery may be monitored using the sensors.

The benefit of these quantitative methods of assessment over others that have been introduced is that they provide the flexibility demanded by a clinical environment. The quantified bradykinesia tests offer a more complete description of volitional movements than timed tests, which offer only a simple count of the number of cycles and do not consider the parameters to which the UPDRS scales attend (Lang and Fahn, 1989). Further, the timed tests outlined in the CAPIT protocol (Langston *et al.*, 1992) require specific numbers of repetitions of pronation/supination or finger or hand taps, which may be too difficult for some patients to

achieve (Samuel *et al.*, 1998). The use of gyroscopes to monitor repetitive tasks allows for objective evaluation of the patient's performance over a fixed or flexible duration of trial.

The few methods of objective measurement that are suitable for use during a clinical examination are generally not appropriate for the surgical setting. Exceptions include use of accelerometers (Benabid *et al.*, 1996; Benabid *et al.*, 1993), EMG (Benabid *et al.*, 1994; Iacono *et al.*, 1995a; Lozano *et al.*, 1996), an instrumented glove (Iacono *et al.*, 1995b), and gyroscopes (Felsing, 1996). Timed tapping was found to be too fatiguing for subjects intraoperatively (Limousin *et al.*, 1995). In the present study, small sensors were employed to monitor clinical tests that are normally administered during the course of the surgery. Raw data were immediately available, setup time was minimal, and the time spent in the operating room was prolonged by a few minutes at most. The gyroscopes were usually secured at the beginning of the surgery and remained in place until the end of the procedure. Most tests of volitional movement initiated by a member of the surgical team, regardless of duration, were recorded. Any test over two seconds long could be analyzed. The sensors for rigidity measurement were easily applied before, and removed following, each set of trials. Rigidity tests normally lasted 50 seconds and were usually performed during micro- or macroelectrode repositioning, during macrostimulation at a constant voltage, and following lesioning. Measures of resonant frequency and torque motor displacement amplitude (Walsh, 1992), as well as EMG recordings (Benabid *et al.*, 1994), have been used to document or monitor intraoperative changes in rigidity. However, to our knowledge, this is the first time limb stiffness has been quantified on-line during stereotactic surgery using a method based on the clinical examination.

3.4.4 Application to the research setting

Rating scales, video, and EMG have been used to document symptoms perioperatively and over the course of stereotactic surgery for research, as opposed to clinical, purposes. Studies of

the role of the globus pallidus or thalamus in movement have employed video recording (Lozano *et al.*, 1996) and EMG (Iacono *et al.*, 1995a; Ohye *et al.*, 1976/77; Raeva, 1993) to supplement microelectrode neural recordings. Besides contributing an objective measure, the devices utilized in the present study have an advantage over discrete clinical ratings in that they produce records of joint rigidity or movement *with time*. This enables exploration of the time course of effects of reinforcement manoeuvres, DBS, or intraoperative macrostimulation or lesioning. While videotape provides a visual record (Lang and Fahn, 1989) of movements, the quantification devices additionally provide a numerical measure. EMG permits more precise study of the relation of neuronal firing to initiation of voluntary activity; the use of gyroscopes introduces the ability to monitor passive movements. Accelerometers are ideal for tremor assessment, but information about displacement amplitude of volitional and passive movement is more easily obtained from the output of a gyroscope.

3.4.5 Need for further standardization

For comparison of postoperative results obtained by different examiners or between centres, there is a need for more standardization than currently offered by the UPDRS and CAPIT protocols. Differences in application of CAPIT timed-tasks (Lang *et al.*, 1995) have been acknowledged and efforts have been made to standardize administration of UPDRS tests (Goetz *et al.*, 1995). While the use of "blinded, randomly-evaluated, videotaped examination" as advocated by Gross and co-workers (Gross *et al.*, 1997) may remove expectation bias, it does not standardize the way the scales are interpreted or the way the tests are applied, which certainly vary between centres. For example, "upper limb rigidity" was tested at the wrist at the Foothills Hospital in Calgary, whereas the entire arm (wrist, elbow, shoulder) was assessed simultaneously in perioperative examinations at the Toronto Hospital. It is the experience of two of the authors

(SP, AP) that inter-rater reliability of UPDRS rigidity scores improves with specification of the joint, plane of movement, and by extension of the duration of the trial.

Utilization of objective measures does not of course by itself guarantee reliability of results. It is still necessary to provide as much standardization in the way of application of the methods, conditions of testing, and instruction to the patient as realistically feasible. Fatigue of the subject may be a problem during long sessions of clinical evaluation. Although this cannot be avoided during the surgery itself, the perioperative clinical examinations may prove more accurate if the different conditions (i.e. different medication states) are assessed on different occasions instead of over one lengthy session as is the current practice.

In the present study, instruction of the task to the patient almost always changed over the course of the surgery. This often occurred at the commencement of macrostimulation and lesioning, as it was generally at this time that a new clinician assumed the role of assessment of motor function. If what being sought intraoperatively is "normality" of movement, then comparison of absolute measures of impedance or movement to measures observed in control subjects for that particular task may be more useful, and a different approach should have been taken in this paper. However, if it is a *change* in symptoms that is to be detected, then consistency of instruction between trials becomes more important. If the instruction itself changes enough that the task is no longer the same, then comparison of performance with prior performance becomes meaningless. For example, amplitude and speed of foot dorsi/plantarflexion movements increased slightly (about 30%: 4°, 4.7°/s) and only ipsilaterally during lesioning compared to pre-lesion measures for subject BT. However, the instructions had changed. During the mapping process, the patient was instructed to "move your foot up and down like you're pressing a gas pedal" whereas for the final trial before the commencement of lesioning, she was asked to tap the hand of the neurologist. Comparing trials during lesioning (tap hand) to this one pre-lesion tapping trial shows significant increases in amplitude and speed contralaterally (80% (12.5°), 60% (17°/s)) and ipsilaterally (362% (14°), 197% (14°/s)).

In the early stages of this study, it was suspected that the urgency of the surgical setting might not allow for controlled measurements of motor function. However, it became apparent that there is in fact time for standardized measurements intraoperatively, particularly when these are seen to aid in decision making. Hand pronation/supination was monitored during electrode repositioning for subject MG, and 50-second measurements of impedance were carried out during macrostimulation for three other patients. Monitoring of motor function by necessity takes on a faster pace during the lesioning process; employment of gyroscopes for bradykinesia assessments under these circumstances is still feasible since the method does not require either a long or fixed test period.

3.4.6 Recommendations proposed based on difficulties encountered

The present study served essentially to test the feasibility of quantifying rigidity and bradykinesia during a routine clinical examination and under the demanding conditions of a neurosurgical procedure. Numerous difficulties were encountered which led to improvements in the design and layout of both software and hardware aspects of the measuring devices. Other difficulties stemmed from the nature of the clinical setting and, while demonstrating the flexibility of our methods, encouraged suggestions to help facilitate, standardize, and clarify assessments.

The following are recommendations for investigators wishing to quantify aspects of motor function either peri- or intraoperatively:

1. Apply the same approach to impedance quantification as during clinical assessments of rigidity, that is, use slow, gentle movements (Spillane, 1996). In the present study, we found that experienced clinicians would sometimes change their technique of rigidity assessment when using the quantification device, notably increasing the speed of the imposed movements.

2. Discard and repeat trials of impedance measurement in which the patient assists the examiner in moving the joint. Assistance can be detected either by the experienced clinician, or from the on-line display of viscous stiffness. Failure to repeat the trial may result in insufficient data for statistical analysis.

3. Avoid changes in instruction to the patient between trials. If possible, avoid changes in examiner.

4. When possible, use a fixed duration of trial during perioperative assessments of bradykinesia. While this is not always practical in the clinical setting, it controls one more factor potentially affecting patient performance and consequently test outcome.

3.4.7 Future considerations

In the present study, it is suspected that the patient's behaviour and emotional response to his physical condition or surgical outcome, expectations of both patient and examiner, and the level of other symptoms or their response to surgical intervention may all have influenced UPDRS ratings. It was also noted that motor performance or rigidity on one side of the body was often if not always compared to that on the other side, and the clinical score adjusted accordingly. A longer-term study comparing blinded clinical assessments of repetitive movements with quantified measurements would be desirable, as would the inclusion of a greater number of subjects including control subjects with Parkinson's disease but who had not undergone surgery. Implementation of more of the controls discussed above, and assignment of UPDRS rigidity ratings during impedance measurement would strengthen any future study.

3.4.8 Conclusion

We present in this paper quantified measurements of limb impedance and patient performance of repetitive tasks before and after stereotactic surgery. The methods used were based on the clinical examination, allowing for simultaneous clinical assessment. In addition, we have demonstrated that these methods may be used for intraoperative monitoring of limb rigidity and distal limb voluntary and passive movements.

The consideration here of only limb rigidity and repetitive movements obviously does not permit a complete objective evaluation of the effects of surgical intervention in Parkinson's disease. However, it is an important start in that these methods allow for quantitative measurement of at least four components of the UPDRS.

Our intention is to complement the regular clinical examinations thus retaining their value; the quantitative measures are in no way intended to replace the current clinical evaluation methods. Their use may help standardize methods of evaluating bradykinesia and rigidity, thus increasing the precision and reliability of long-term, multi-centre, or multi-clinician studies.

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CHAPTER 4

Quantified effects of deep brain stimulation on bradykinesia and upper limb rigidity.

4.1 INTRODUCTION

Pallidotomy as treatment for Parkinson's disease, largely abandoned with the introduction of levodopa in 1968, has been recently reintroduced due to limitations of the drug and advances in technology (Laitinen *et al.*, 1992). More recently, based on clinical observations that chronic deep brain stimulation (DBS) of the ventral intermediate (Vim) nucleus of the thalamus can have the same effect as a lesion in reduction of tremor (Benabid *et al.*, 1987; Blond *et al.*, 1992), implantation of DBS electrodes into the globus pallidus (GPi) has been introduced as an alternative surgical treatment (Siegfried and Lippitz, 1994). Results of stimulation and lesioning of the subthalamic nucleus (STN) in animal studies (Benazzouz *et al.*, 1993; Bergman *et al.*, 1990) have inspired the implantation of DBS electrodes into this site as well (Pollak *et al.*, 1993). Despite some disadvantages of DBS, such as risk of infection, cost of the stimulator, and necessity of surgical intervention for replacement of batteries, it is widely (although not universally, or under all circumstances – see Kumar *et al.*, 1998; Merello *et al.*, 1999; Tronnier *et al.*, 1997) agreed that the reversibility of the procedure makes it potentially more attractive than a lesioning approach such as pallidotomy (Benabid *et al.*, 1998; Ghika *et al.*, 1998; Starr *et al.*, 1998; Volkmann *et al.*, 1998).

There are limited published studies on the effects of chronic DBS of the GPi or STN in humans. Despite some reports of positive and even dramatic effects with DBS of the GPi, including enhancement of motor function (Ghika *et al.*, 1998; Gross *et al.*, 1997; Iacono *et al.*, 1995; Siegfried and Lippitz, 1994; Volkmann *et al.*, 1998), one group has found little benefit

accorded to patients by the procedure outside amelioration of levodopa-induced dyksinesias (Tronnier *et al.*, 1997). The effects of stimulation of the GPi on akinesia are in particular variable, and appear to depend on the exact location of the field of stimulation within the GPi (Bejjani *et al.*, 1997; Krack *et al.*, 1998b). Bilateral stimulation of the STN appears to hold more promise (Brock *et al.*, 1998; Krack *et al.*, 1998c; Kumar *et al.*, 1998; Starr *et al.*, 1998; Tronnier and Fogel, 1998). Indications for and advantages of stimulation of either site are still indefinite, and both surgical treatments remain experimental.

Despite concerns regarding the subjective nature of ordinal rating scales such as those of the Unified Parkinson's Disease Rating System (UPDRS) (Obeso *et al.*, 1996; Teräväinen *et al.*, 1989; Ward *et al.*, 1983), and at least in part due to the paucity of quantification methods suitable for the clinical setting, quantified measures are rarely employed in studies assessing the effects of DBS and are largely limited to timed tasks. However, some groups have presented quantified data of the effects of DBS on upper limb function (Brown *et al.*, 1999; Iacono *et al.*, 1995; Volkmann *et al.*, 1998), gait (Volkmann *et al.*, 1998) and axial function (Robertson *et al.*, 1999). Although a reduction of stretch-invoked electromyographic activity has been recorded with chronic stimulation of the STN (Benabid *et al.*, 1994), the effect of DBS on mechanical impedance has never been quantified.

In the present study, we demonstrate quantitative reductions in rigidity in the upper limb, and enhancement of performance of repetitive volitional tasks such as hand pronation/supination and heel tapping with DBS of the GPi or STN.

4.2 METHODS

4.2.1 Subjects

All experiments were performed with the informed consent of the subjects according to the Declaration of Helsinki Guidelines on Human Experimentation, and with local ethical board approval.

Nine subjects (age mean 54 years, range 35 to 72 years) with idiopathic Parkinson's Disease (duration mean 14 years, range 8 to 23 years) agreed to participate in this study. Chronic deep brain stimulator quadripolar electrodes (Medtronic) had been implanted from one month to 3.5 years prior to assessment of effects of stimulation. The surgeries were performed at the Oregon Health Sciences University in Portland (CB, FG, RR, BK, GH, JO), at the Foothills Hospital in Calgary (RC, RH), and at the Toronto Hospital (MH) using microelectrode recording and magnetic resonance imaging; details of the surgical methods have been described elsewhere (Lozano *et al.*, 1996; Taha *et al.*, 1996). Microelectrode recording was not used for one subject (BK). Two patients (RC, RH) received unilateral stimulation of the internal segment of the GPi, three (CB, FG, RR) received bilateral stimulation of the GPi, and four (BK, GH, JO, MH) received bilateral stimulation of the STN. RH had previously undergone a pallidotomy of the contralateral GPi almost two years prior to DBS implantation surgery. Patient characteristics at the time of testing are described in Table 4-1.

Subjects were selected based on the site of DBS electrode implantation (STN, GPi), subject availability, and willingness to participate in the study. All subjects receiving chronic pallidal or STN stimulation and to whom we had access were included in the study. The selection criteria for enrollment in the surgical programme itself varied slightly between centres. The presence of dyskinesias and motor fluctuations was an indication for the procedure in all three centres.

TABLE 4-1 *Subject characteristics*

subject	age	sex	duration of disease (years)	Hoehn and Yahr, preoperative, off med/on med	Hoehn and Yahr, time of testing, off med, off stim/ on med, on stim	levodopa dose* (mg/day)	other anti-parkinson medication* (mg/day)	DBS site	time since stimulator implantation	tests performed**
RC	42	M	9	3 / 2	3 / 2.5	800	0	right GPi	1 mo.	R,H,F
RH	46	M	12	3 / 2.5	3 / 2.5	900	625	left GPi	1 mo.	R,H,F
					3 / 2.5	800	615		6 mo.	R,H,F
CB	35	M	10	4 / (n.a.)	***	1500	300	bilat GPi	1.6 y	R,H,L
FG	50	F	8	***	***	450	0	bilat GPi	3.5 y	R,H,L
RR	69	M	12	***	***	2000	204	bilat GPi	5 mo.	R,H,L
BK	72	F	9	4 / (n.a.)	***	400	0	bilat STN	7 mo.	R
						400	0		1.25y	R,H,L
GH	54	M	22	***	***	1350	50	bilat STN	7 mo.	R,H,L
JO	44	M	19	4 / 3	***	0	0	bilat STN	1.9 y	R
MH	71	F	23	5 / (n.a.)	3 / (n.a.)	800	0	bilat STN	6 mo.	R

n.a. = not available

*medications are from time of testing

**tests performed: R = rigidity, H = hand pronation/supination, L = leg agility (heel taps), F = foot taps

*** information unavailable at time of printing of this thesis: see pending publication

Bradykinesia and rigidity as predominant symptoms were also specified as inclusion criteria in Portland.

4.2.2 Stimulation parameters

Stimulation parameters were controlled using Itrel II implantable pulse generators (Medtronic). The settings were as follows: pulse width ranged from 60 to 180 μs (mean 133 μs), frequency was set at either 130 Hz or at 185 Hz, and amplitude ranged from 1.3 to 5.5 V (mean 3.0 V). Stimulator settings had not been optimized for subject FG for several months.

All subjects with bilateral stimulators were tested with both stimulators off and with both stimulators on. Subjects BK (seven months post-surgery) and JO were also tested with only one of the two stimulators on.

4.2.3 Assessment of effects of DBS

The effects of DBS on elbow or wrist rigidity, and on repetitive hand, leg, or foot movements were assessed during a single session. Three of the subjects (RC, RH, MH) were assessed over the course of a regular post-operative assessment, which included evaluation according to the full UPDRS. The other subjects agreed to come to the research facility exclusively for the purpose of our study (CB, FG, RR, BK, GH) or primarily for another study (JO, BK). Subjects RH and BK were tested with stimulation on two occasions 5 and 8 months apart, respectively.

Subjects were tested with and without stimulation in the practically defined "worst off" condition, i.e. not having taken anti-parkinson medication for at least 12 hours (Langston *et al.*, 1992). All subjects except JO were also tested with and without stimulation at "best on", that is, when subject and examiner agreed that the subject was receiving maximal or near maximal benefit from the medication. Pre-operative assessments "on" and "off" medication were also

performed three months (RC) or one month (RH) prior to surgery for two subjects. Note that times of last medication for subjects GH and RR were 5 and 6.5 hours, respectively, before assessment; they rated their "off" state as 7/10 and 9/10, respectively, with 10 being the worst "off" they experienced. Subject RH did not feel fully "off" for his pre-operative or one-month post-operative assessment. Subject RC did not feel as "on" as usual during his post-operative assessment. Neither RH nor RC was fully "on" for the pre-operative assessment.

Rigidity was assessed at the wrist for subjects RC and RH, and at the elbow for all other subjects, using a device that quantifies resistance (mechanical impedance, Z) of a limb to passive movement (Prochazka *et al.*, 1997) (Figure 4-1A). This device is described in Chapter 3. From one to five 50-second tests were carried out under each condition ("off" medication/off stimulation, "off" medication/on stimulation, "on" medication/off stimulation, "on" medication/on stimulation). Measurements while the subject was "on" medication are not available for three sessions (subjects CB, BK seven months post-surgery, JO). Reinforcement manoeuvres, which served to enhance rigidity levels, consisted of tapping the contralateral knee with the contralateral hand, or waving the contralateral arm in the air; these manoeuvres were performed by the subject for approximately half of at least one trial per condition. Independent samples of Z were obtained from a trial by selecting one data point every four seconds. Only Z values calculated from positive values of K and $B\omega$ were accepted (see Chapter 3).

Bradykinesia was assessed for seven subjects by using solid-state gyroscopes to monitor repetitive movements of the hand and leg or foot. Repetitive pronation/supination of the hands was performed either with the hands held vertically in the air (RC, RH), or by touching the ipsilateral thigh alternately with the palm and dorsum of the hand (CB, FG, RR, BK, GH). The task was performed with both hands simultaneously (RC, RH, FG, RR, GH) or one hand at a time (CB, BK), depending on the preference of the examiner. Subjects were instructed to make the movements fast and large. Leg movements were performed, one leg at a time, according to item #26 ("leg agility") of the UPDRS (Langston *et al.*, 1992); the subject, while seated, repeatedly

Figure 4-1. *Schematic of the methods of quantification of limb rigidity and bradykinesia* **A)** Rigidity about the elbow or wrist (not shown) was assessed using a hand-held device that quantifies resistance (mechanical impedance) of the joint to passive movements imposed by the examiner. **B)** Gyroscopes were used to measure angular displacement, speed, frequency, and regularity of repetitive voluntary movements of the limbs. The tasks monitored were pronation/supination of the hands, leg agility (heel taps), and tapping of the foot (not shown).

B
A

lifted the entire leg at the hip to lift the heel about three inches (7.5 cm) from the floor ("heel taps"). The movements were to be performed as quickly as possible. Foot tapping was measured instead of leg agility for two subjects (RC, RH); the subject tapped the toes of one foot, keeping the heel on the floor, as quickly as possible with as large an amplitude as possible. Gyroscopes were attached to the radial side of the dorsal surface of the wrist, or to the back of the hand to monitor hand pronation/supination. To monitor leg or foot movements, gyroscopes were attached to the thigh just proximal to the knee, or to the dorsum of the foot. Gyroscope placements for hand and leg movements are shown in Figure 4-1B. For subjects RC and RH, from one to five trials lasting three to 13 seconds were obtained under each condition for each task. For all other subjects, two (CB, BK) or three (FG, RR, GH) trials lasting about 15 to 20 seconds were carried out for each task.

Peak-to-peak amplitude, mean speed (mean rectified velocity), regularity, and frequency of the repetitive movements were calculated as described in more detail in Chapter 3. Values reported for amplitude and speed are the mean ± standard error of the mean (SEM) values from all one-second intervals from all tests performed under one condition. At low frequencies of movement these values become inaccurate; therefore, for all trials during which the frequency of movements was less than 0.5 Hz (two subjects "off" medication/off stimulation), peak-to-peak displacement and mean rectified velocity were calculated over the entire trial, instead of from one-second intervals. Tremor during the hand pronation/supination task was filtered out of the velocity signal off-line (4.5 Hz low pass filter) before calculation of mean rectified velocity (two subjects, "off" medication). For all trials, regularity was determined from the displacement signal using a score of "harmonicity" (Edwards and Beuter, 1999) as described in Chapter 3. As in Chapter 3, one measure of normalized harmonicity (nHcm) and one measure of frequency were obtained from each trial performed. Values reported are the mean ± SEM value of all trials for one condition.

UPDRS ratings were obtained for rigidity, and for hand and leg repetitive movements. The examiners were registered nurses or physical therapists local to the clinic or research facility and were usually familiar with the subject. For subjects RC and RH, ratings of rigidity were obtained at the wrist using the examiners' usual clinical method of assessment, immediately prior to quantification of mechanical impedance at the wrist. Clinical ratings for rigidity at the elbow were not available for subject MH. Ratings were assigned and recorded during quantification trials for subjects CB, BK, GH, and JO; the examiner voiced scores during the course of the trial, as the rigidity was felt to change. For the remaining two subjects (FG, RR), rigidity was assessed during the quantification trials, but scores were only given at the end of each trial. Hand pronation/supination and leg agility tests were rated during the quantification trials, scores assigned during each trial (CB, BK), at the end of each trial (FG, RR), or at the end of all trials (RC, RH). Individual trials were scored from video for subject GH. No clinical ratings were obtained for the foot tapping task (RC, RH) since this is not part of the UPDRS.

Subjects and examiners were aware of the medication state and whether the stimulators were on or off for most assessments. However, on one occasion two subjects were tested in a double-blind design (JO, BK seven months post-surgery).

Off-line analysis was performed using Matlab® Version 4.2c.1 (The Math Works, Inc.). Student's t-test and Mann-Whitney Rank Sum test were used to test for significance between measures obtained on- and off stimulation under a given condition. One-way ANOVA (Bonferroni or Dunnett's test post-hoc) and one-way ANOVA on ranks (Dunn's test post-hoc) were used to compare between sessions (subjects RC, RH), or when effects of individual stimulators was tested (both off, both on, just one on, subjects JO, BK 7months post-operative). Statistical analysis was performed using SigmaStat™ Version 1.0 (Jandel Scientific). Alpha was set at 0.05 (95 % confidence interval).

4.3 RESULTS

The effects of chronic DBS on mechanical impedance at the elbow or wrist were quantified in seven subjects receiving bilateral stimulation of the STN or GPi, and in two subjects receiving unilateral stimulation of the GPi. Effects of stimulation on repetitive movements of the hands or legs were also measured in five subjects with bilateral stimulation and in both subjects with unilateral stimulation. Assessments were performed "off" medication for all subjects and "on" medication for seven subjects. Clinical UPDRS ratings were obtained simultaneously with or immediately prior to the quantified measurements for eight subjects.

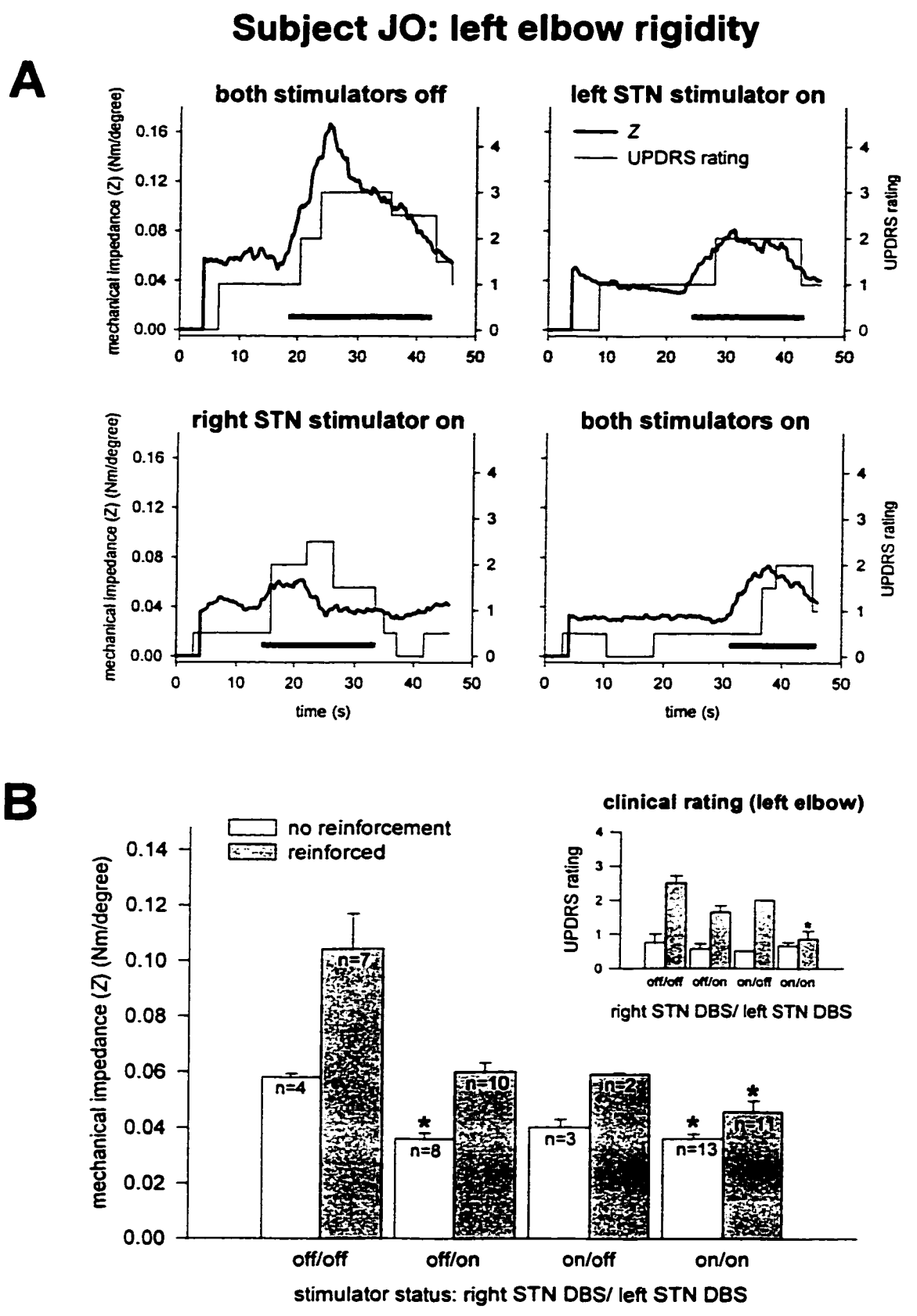
4.3.1 Rigidity

Bilateral stimulation

"OFF" MEDICATION: Resting (non-reinforced) mechanical impedance at the elbow was significantly reduced during bilateral stimulation of the STN or GPi in at least one arm in six of seven subjects examined (10/14 arms tested) while "off" medication. Five of these subjects also showed similar reductions in reinforced mechanical impedance (8/14 arms tested). Statistically significant reductions ranged from 20% to 78%, and were most often in the range 30% to 60% (5 subjects, 8/14 arms tested (no reinforcement) or 6/14 (with reinforcement)). Figure 4-2A shows examples of measurements of mechanical impedance obtained from one subject while off medication. For this subject, non-reinforced and reinforced Z measured about the left elbow decreased by 37% and 51%, respectively, upon bilateral STN stimulation (Figure 4-2B).

The effects of unilateral STN stimulation on rigidity at the elbow were compared to effects of bilateral STN stimulation in two subjects (JO, BK). Both subjects were "off" medication at the time of testing. From Table 4-1, JO was 1.9 years post-operative, and BK was 7 months post-

Figure 4-2. *Effect of stimulation of the STN on rigidity at the elbow, "off" medication*
Mechanical impedance (*Z*) at the elbow was measured with and without stimulation. Part **A** shows example traces of *Z* obtained from the left elbow of subject JO while off medication. Clinical ratings were assigned during the course of each trial (thin solid lines). Large increases in *Z*, accompanied by increases in the clinical rating, were the result of performance of reinforcement manoeuvres by the subject (approximate duration marked by thick bars). A reduction in both non-reinforced and reinforced rigidity during bilateral stimulation of the STN is evident from both traces (**A**, lower right plot). A similar reduction was measured with unilateral stimulation (**A**, upper right and lower left plots), although this was not seen in the other arm for this subject (not shown). Part **B** shows the results from all trials performed; "n' indicates the number of data points obtained under each condition. Note that both non-reinforced (open bars) and reinforced (filled bars) *Z* measures decreased with stimulation. The y-axes for *Z* and UPDRS scores are scaled relative to each other (UPDRS score = 27 * *Z*, Chapter 2). Bars are mean ± SEM. An asterisk indicates significance difference from when both stimulators were off ($p < 0.05$).


Subject JO: left elbow rigidity
A
both stimulators off
left STN stimulator on
right STN stimulator on
both stimulators on
Z
UPDRS rating
mechanical impedance (Z) (Nm/degree)
UPDRS rating
time (s)
B
clinical rating (left elbow)
no reinforcement
reinforced
mechanical impedance (Z) (Nm/degree)
n=4
n=7
n=8
n=10
n=3
n=2
n=13
n=11
off/off
off/on
on/off
on/on
right STN DBS/ left STN DBS
stimulator status: right STN DBS/ left STN DBS

operative. The results from subject JO are represented in Figure 4-2. For both subjects, non-reinforced mechanical impedance was 37% to 47% lower when both stimulators were on compared to when both were off. When only the left STN was stimulated, a reduction equivalent to that observed with bilateral stimulation on was measured in the left arm of subject JO (Figure 4-2) and both arms of subject BK. Smaller reductions were measured when only the right stimulator was turned on. Effects of stimulation on reinforced rigidity were more variable and often there was no significant change for these two subjects.

The 38% to 47% reduction in non-reinforced mechanical impedance with bilateral STN stimulation in subject BK on this occasion was not detected during a second session 9 months later. In fact, a statistically-significant 29% *increase* in Z with stimulation was recorded for one arm. Similar (20-30%) increases in rigidity were measured unilaterally for another subject (FG, 3.5 years post-operative) while "off" medication. Neither of these subjects was considered to have had a good clinical outcome from the surgery.

"ON" MEDICATION: Although rigidity levels were sometimes considerably lower while subjects were "on" medication than when they were "off", statistically significant decreases in non-reinforced Z with bilateral stimulation were measured in four of five subjects tested (5/10 arms tested). The percent reduction was equivalent to or greater than that observed while "off" medication for three subjects. These included the two subjects who showed no reduction in Z with stimulation while "off" medication (BK second session, FG). Reinforced impedance was also reduced, to a somewhat smaller extent, in three of the subjects (5/10 arms tested). The amount of reduction of non-reinforced or reinforced impedance, when significant, ranged from 12% to 56%; as was the case without medication, most reductions were between 30% and 60%.

The response of rigidity to stimulation, either "on" or "off" medication, was remarkably consistent between the left and right arms of a subject in a few cases. Usually, however, there were differences under at least some conditions. These differences generally involved the degree of effect of stimulation on impedance, or lack of effect on one side despite a significant effect on

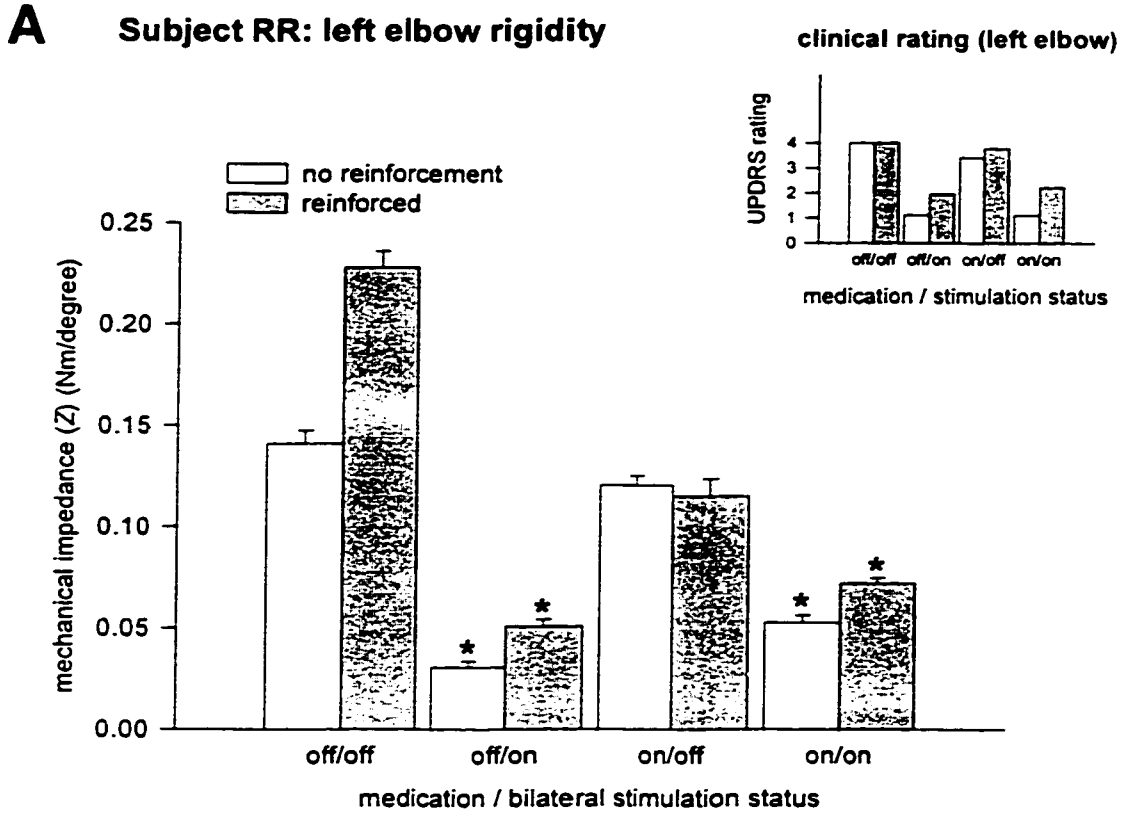
the other. Occasionally, a reduction of or no change in rigidity on one side was accompanied by an increase on the other under some of the testing conditions. Figure 4-3 shows data from a subject in whom a reduction in non-reinforced impedance was demonstrated only in the left elbow, while reinforced impedance decreased bilaterally but to different degrees.

Clinical ratings agreed with the direction of change of the level of impedance, about two-thirds of the time, but not necessarily with the degree of change. A statistically significant change in Z was accompanied by little or no change ($\leq$10%) in clinical scores about a quarter of the time. In less than 10% of cases, there was a change in clinical ratings (always an increase) while Z was either unchanged or showed an opposite change (decrease). The best agreement between clinical and quantified measures occurred when there was a change in a relatively higher level of rigidity; in some cases, UPDRS scores tracked quantified measures very closely (e.g. Figure 4-2A, Figure 4-3A). Z measures and UPDRS rigidity scores for all subjects receiving bilateral stimulation are presented in Figure 4-4.

Unilateral stimulation

Z levels in the wrists of the two subjects (RC, RH) receiving unilateral stimulation of the GPi were quite low both pre- and post-operatively. Nevertheless, small, usually not statistically significant decreases in Z were recorded with stimulation for both subjects about the contralateral wrist. A significant but small decrease in Z for the ipsilateral wrist upon stimulation one month post-surgery became a slightly larger, significant increase at six months for subject RH. There was insufficient data from the ipsilateral wrist of subject RC for statistical analysis.

Figure 4-3. *Effect of bilateral stimulation may differ between sides.* Shown are plots of Z about the left (**A**) and right (**B**) elbows of subject RR both "on" and "off" medication. In the left arm, bilateral GPi stimulation reduced both non-reinforced (open bars) and reinforced (filled bars) Z by 37% to 78%. In the right arm, stimulation had no apparent effect on non-reinforced Z. Reinforced Z was reduced by 24% to 38%. The y-axes for Z and UPDRS scores are scaled relative to each other (UPDRS score = 27 * Z, Chapter 2). Bars are mean ± SEM. An asterisk indicates significance difference with stimulation compared to without stimulation in the same medication state ($p < 0.05$).


A
Subject RR: left elbow rigidity
clinical rating (left elbow)
UPDRS rating
0
1
2
3
4
off/off off/on on/off on/on
medication / stimulation status
no reinforcement
reinforced
mechanical impedance (Z) (Nm/degree)
0.25
0.20
0.15
0.10
0.05
0.00
*
off/off
off/on
on/off
on/on
medication / bilateral stimulation status

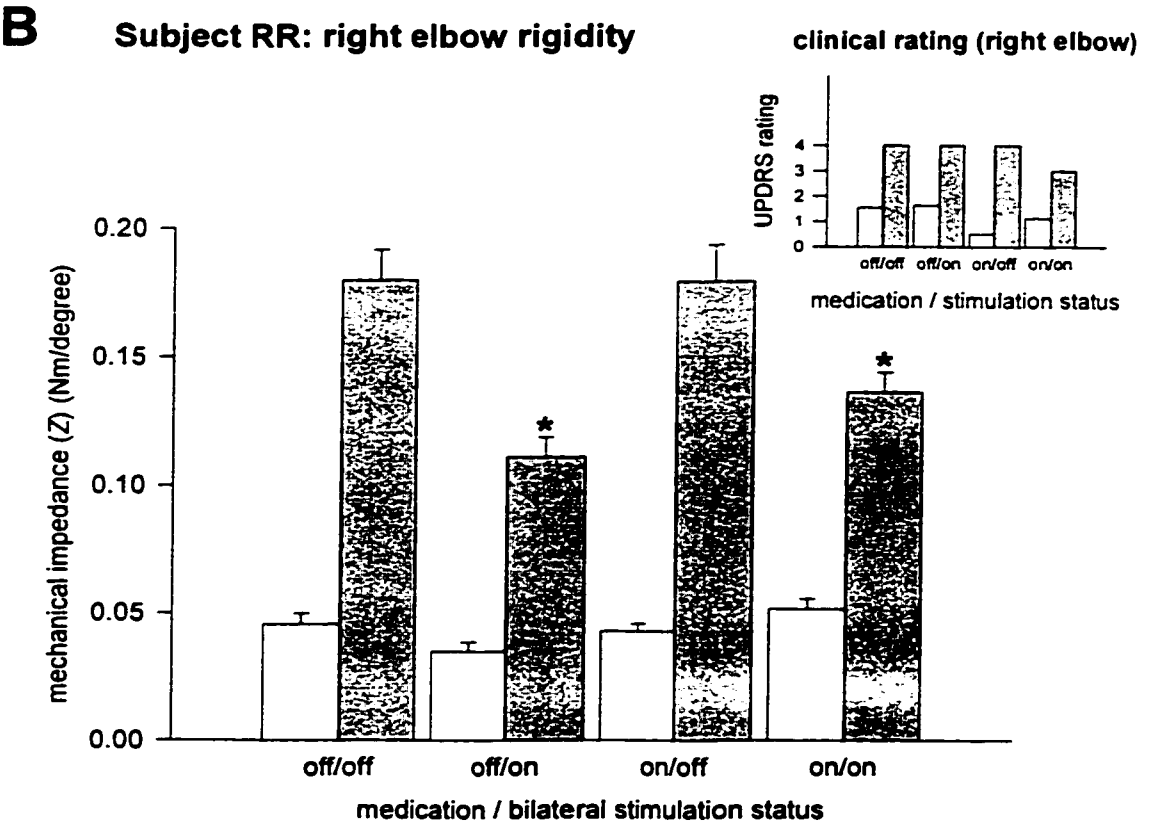
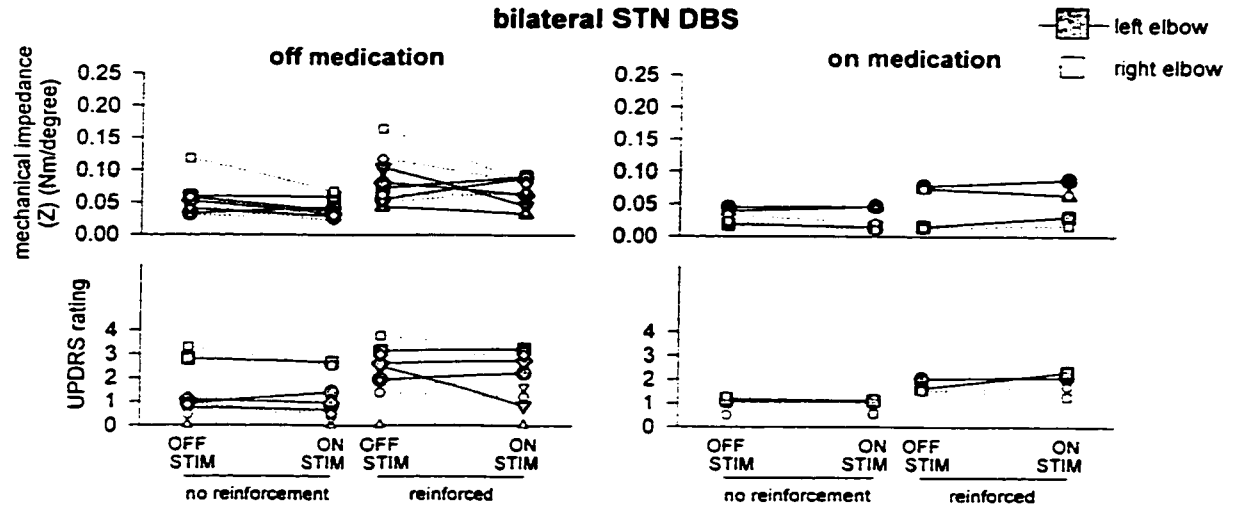
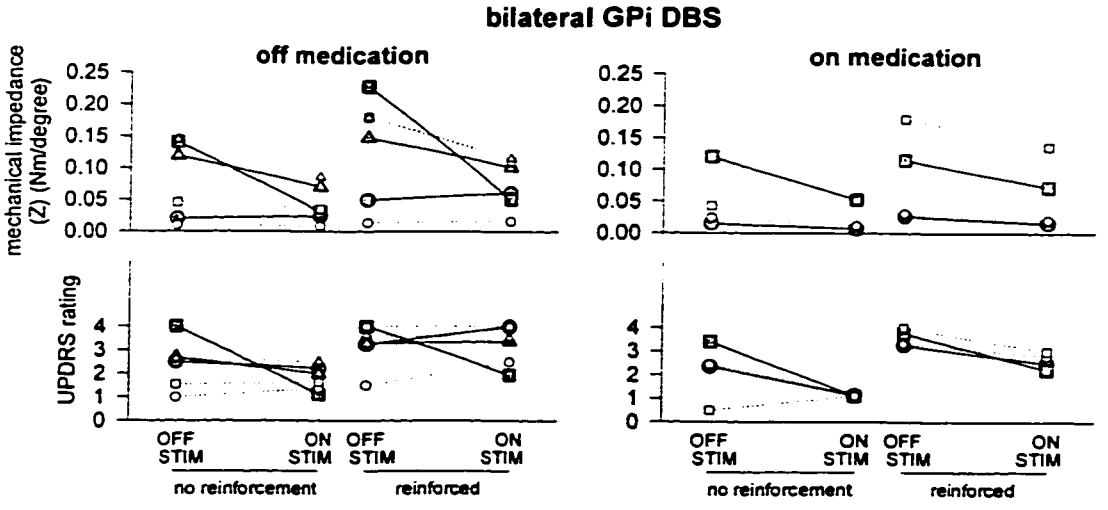

B
Subject RR: right elbow rigidity
clinical rating (right elbow)
UPDRS rating
0
1
2
3
4
off/off off/on on/off on/on
medication / stimulation status
mechanical impedance (Z) (Nm/degree)
0.20
0.15
0.10
0.05
0.00
*
off/off
off/on
on/off
on/on
medication / bilateral stimulation status

Figure 4-4. *Effect of bilateral stimulation of the STN or GPi on elbow rigidity: all subjects* Mean Z about the elbow with and without bilateral stimulation of the STN (top plots) or the GPi (bottom plots) are shown for all subjects. Measurements were taken with the subject "off" or "on" medication, with or without reinforcement. Lines connect estimates of Z obtained with and without stimulation under one condition for each arm (left arm: larger filled symbols, solid lines; right arm: smaller open symbols, dotted lines). A negative (downward) slope of a line indicates reduction in Z (reduced rigidity). Clinical ratings (bottom two plots for each type of stimulation) were obtained during quantification trials. No clinical ratings were available for subject MH (Δ, STN DBS). Error bars were omitted for clarity; SEM ranged from .0005 to 0.0154 Nm/degree for Z measures (all subjects), and from 0 to 0.3 for UPDRS ratings (four subjects). Note that in subsequent Figures 4-7 and 4-8, each symbol for STN or DBS stimulation represents data from the same subject as for STN or DBS stimulation here. In this figure, the diamond (◇) and circle (○) symbols on the bilateral STN DBS plots represent different sessions (seven months and 1.25 years post surgery, respectively) for the same subject (BK).


bilateral STN DBS
left elbow
right elbow
off medication
on medication
mechanical impedance (Z) (Nm/degree)
0.25
0.20
0.15
0.10
0.05
0.00
UPDRS rating
4
3
2
1
0
OFF STIM
ON STIM
OFF STIM
ON STIM
no reinforcement
reinforced


bilateral GPi DBS
off medication
on medication
mechanical impedance (Z) (Nm/degree)
0.25
0.20
0.15
0.10
0.05
0.00
UPDRS rating
4
3
2
1
0
OFF STIM
ON STIM
OFF STIM
ON STIM
no reinforcement
reinforced

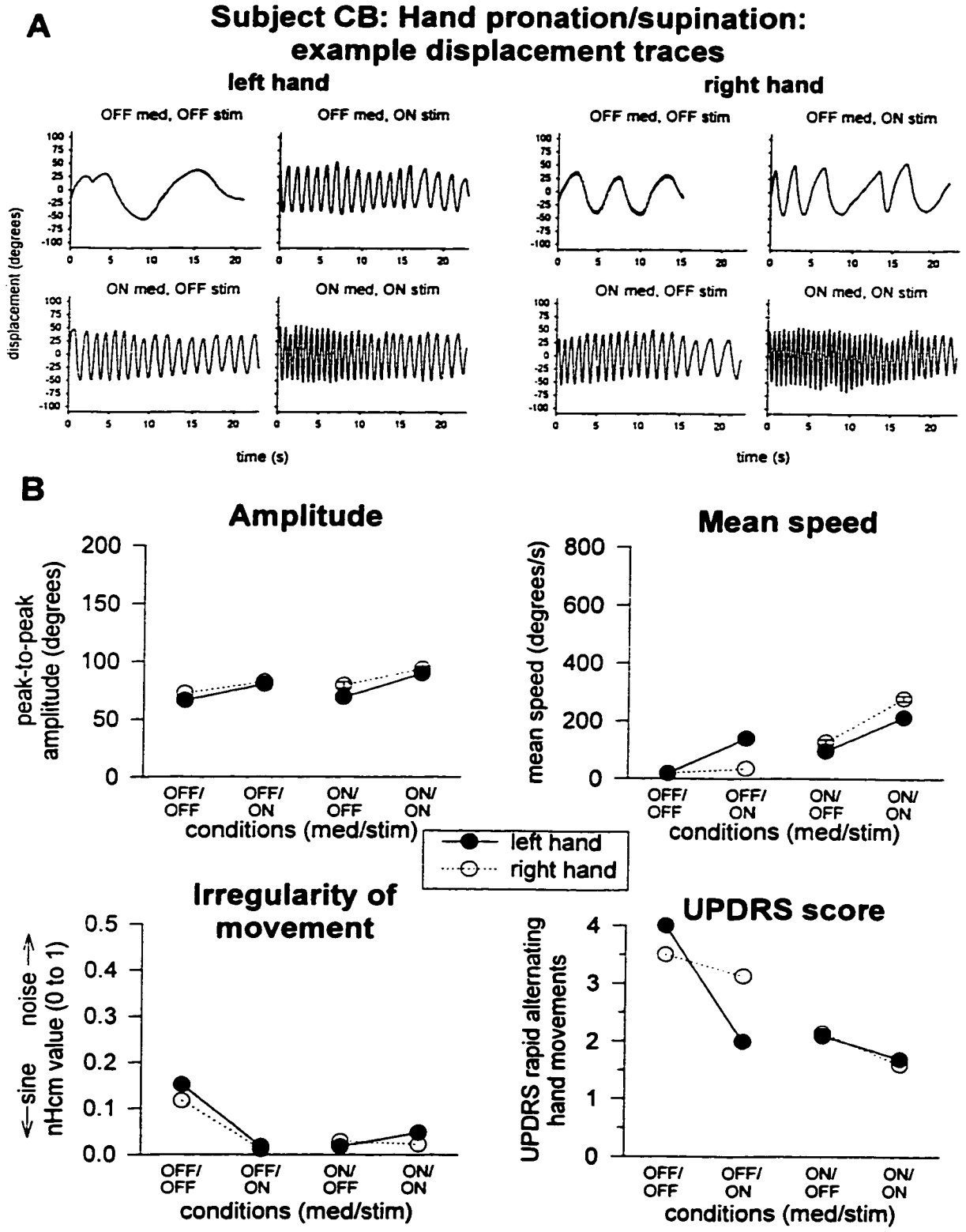
4.3.2 *Repetitive movements*

Bilateral stimulation

"OFF" MEDICATION: All five subjects demonstrated improvement in hand pronation/supination movements in at least one hand with stimulation while "off" medication. Usually this was an increase in mean speed (mean rectified velocity) accompanied by an increase in peak-to-peak displacement of the movements. Statistically significant increases in displacement occurred in three of the five subjects (5/10 hands) and ranged from 11% to 52%, i.e. 10° to 35° increases. Significance could not be tested in two subjects for whom the frequency of the movements was below 0.5 Hz without stimulation (CB, GH, see methods); increases from 14% to 25% (10° to 14°) were recorded for these subjects (3 hands). Significant increases (12% to 46%) in mean speed occurred in two subjects (three hands). Increases in mean speed for subjects CB and GH (4 hands) ranged from 50% to 691% (but again could not be tested for significance). The changes in these four subjects reflect increases in mean speed of 15 to 122°/s. There was a trend towards increasing frequency of movements with stimulation, but this was not significant when tested. The change in regularity of movement was variable across subjects and was also not significant when tested. Results from one subject (CB) in whom stimulation produced some of the most dramatic results seen in our study are presented in Figure 4-5.

Two of the five subjects showed statistically significant bilateral improvement in at least one of speed or displacement while "off" medication. Subjects CB and GH also showed bilateral improvements (but could not be tested for significance). The remaining subject (RR) did not show significant improvement in one hand (the right hand), but the level of impairment in this hand was less than for the other hand or for the other subjects; stimulation improved performance of the right hand so that it matched that of the left.

Figure 4-5. *Improvement in hand pronation/supination with bilateral stimulation of the GPi in subject CB* Shown are example individual traces of displacement data (**A**) and mean values of peak-to-peak displacement amplitude, mean speed, and regularity of movement (**B**). Means include data from both of two trials carried out under each condition of assessment. Mean UPDRS scores, which were assigned during the course of each trial, are also shown. Small (14%-21%, 10°–14°) increases in amplitude of the movements, and dramatic (81%-691%, 15°/s - 122°/s) increases in mean speed were recorded bilaterally with bilateral stimulation of the GPi while the subject was "off" medication (top traces of **A**, and left side of each plot in **B**). Significance could not be tested since only one value could be obtained from each trial for which the frequency of movement was < 0.5 Hz. Tremor in the right hand (top right plots in **A**) was filtered out of the velocity signal before mean speed was calculated. When the subject was "on" medication, statistically significant increases in amplitude (18%-30%, 14°-20°) and mean speed (119%-123%, 118°/s -152°/s) were recorded with stimulation, again bilaterally ($p<0.05$). Error bars (amplitude and mean speed, "on" medication) represent SEM; no error bars are shown for scores of regularity (nHcm values), or for the "off" medication state since only one value could be obtained from either of the two trials performed per condition.

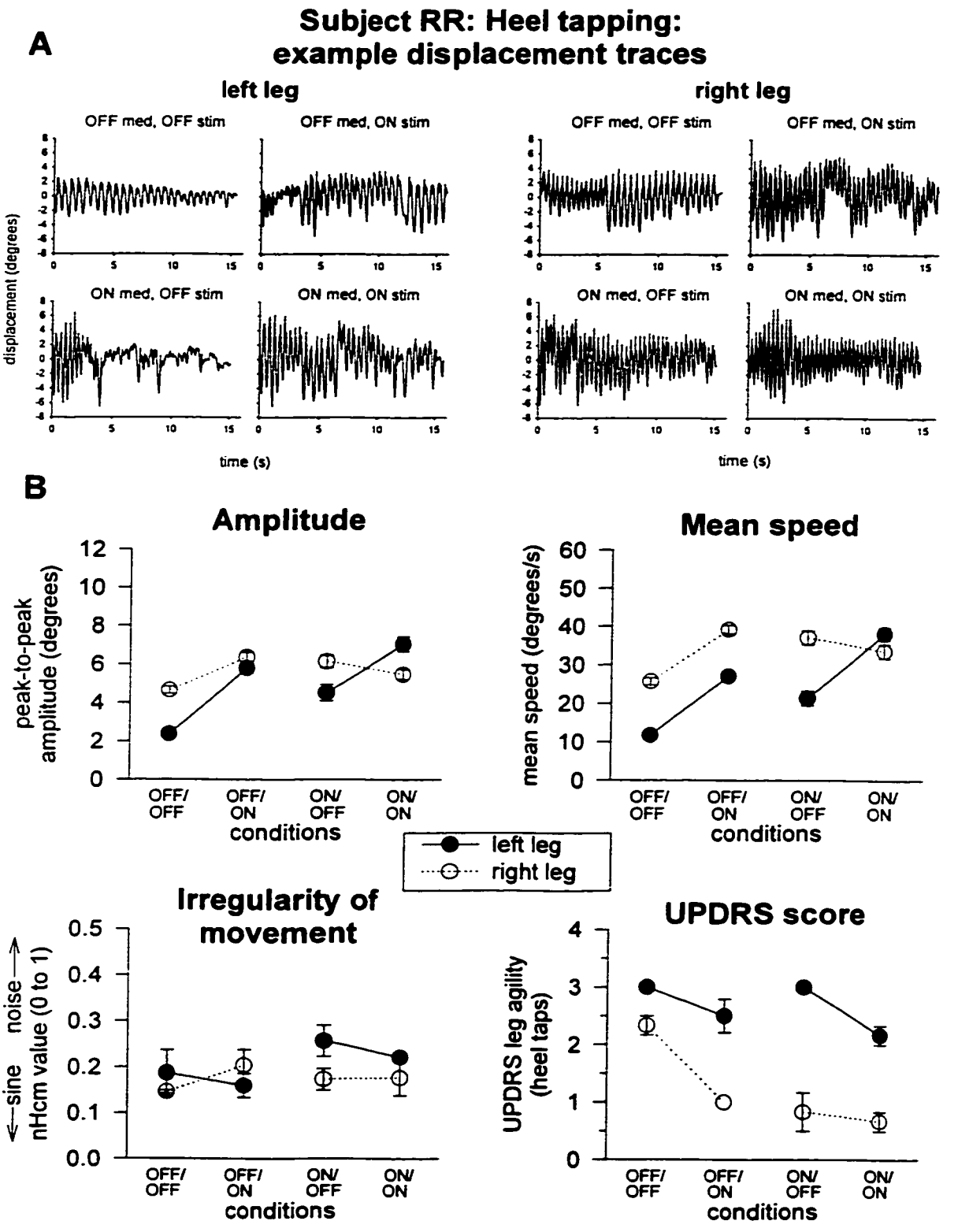

A
Subject CB: Hand pronation/supination:
example displacement traces
left hand
right hand
OFF med, OFF stim
OFF med, ON stim
ON med, OFF stim
ON med, ON stim
displacement (degrees)
time (s)
B
Amplitude
peak-to-peak amplitude (degrees)
Mean speed
mean speed (degrees/s)
OFF/ OFF
OFF/ ON
ON/ OFF
ON/ ON
conditions (med/stim)
left hand
right hand
Irregularity of movement
←sine noise→
nHcm value (0 to 1)
UPDRS score
UPDRS rapid alternating hand movements

Leg agility, as assessed by heel-tapping, improved bilaterally with stimulation in all subjects "off" medication. Displacement amplitude increased significantly in at least four of the five subjects (data from CB could not be tested for significance). The amount of improvement ranged from 23% to over 250%; (corresponding to increases of ~1° to 7°). Mean speed increased from 52% to about 430% (2°/s to 22°/s); this was significant in at least four subjects (7/10 legs tested); data from CB could not be tested. As with hand pronation/supination, there was a trend towards increasing frequency of movement; this was significant, unilaterally, in at least two subjects. The response of regularity of the movements was variable and not always significant. Although the changes in the parameters of movement appear small, with stimulation, displacement and speed measured were in the range of that observed in control subjects for at least two subjects; one of these subjects also demonstrated frequency of movement similar to that seen in controls. Data from this subject are presented in Figure 4-6.

"ON" MEDICATION: In general, improvement in hand pronation/supination task was not as extensive when subjects were "on" medication as when they were "off". Significant improvement in peak-to-peak displacement (range 12% to 30%, i.e. 13° to 24°) and mean speed (range 25% to 152%, i.e. 25°/s to 152°/s) were observed unilaterally in three of the five subjects, and bilaterally in two (one of whom is represented in Figure 4-5). By contrast, significant *decreases* in movement parameters were measured bilaterally in both subjects with bilateral stimulation of the STN, and unilaterally in one subject with bilateral stimulation of the GPi. Statistically significant decreases in displacement and velocity ranged from 7% to 17% (4° to 18° change in displacement and 22°/s to 47°/s change in velocity). Regularity of movement deteriorated significantly, unilaterally, for at least one of these subjects. The effect on frequency was variable across all subjects.

As with hand pronation/supination, improvements in the leg agility task while subjects were "on" medication were not as universal as when subjects were "off" medication. Displacement and

Figure 4-6. *Improvement in leg agility task with bilateral stimulation of the GPi in subject RR* Shown are leg agility (heel tapping) data from same subject from whom rigidity data are presented in Figure 4-3. The format is the same as for the previous figure (Figure 4-5). Symbols represent mean ± SEM; three trials were performed under each condition of assessment. UPDRS scores were rated during but assigned immediately following each trial. Increases in displacement amplitude and mean speed with stimulation were statistically significant for right (open symbols, 52%-37%) and left (filled symbols, 129%-145%) legs while the subject was "off" medication ($p<0.05$). When the subject was "on" medication, the performance of the right leg improved significantly (amplitude 56%, speed 78%, $p<0.05$). Changes in performance of the right leg were not significant. Changes in regularity of movement or frequency (not shown) were not significant.


A
Subject RR: Heel tapping:
example displacement traces
left leg
right leg
OFF med, OFF stim
OFF med, ON stim
ON med, OFF stim
ON med, ON stim
displacement (degrees)
time (s)
B
Amplitude
peak-to-peak amplitude (degrees)
Mean speed
mean speed (degrees/s)
OFF/ OFF
OFF/ ON
ON/ OFF
ON/ ON
conditions
left leg
right leg
Irregularity of movement
sine ← nHcm value (0 to 1) → noise
UPDRS score
UPDRS leg agility (heel taps)

mean speed increased bilaterally in two subjects, and unilaterally in two subjects (one of whom is represented in Figure 4-6). In subject BK, only displacement improved significantly, and only unilaterally; both displacement and speed decreased significantly for the other hand. Frequency tended to decrease in all subjects (8/10 legs), but this never statistically significant when tested. Regularity of movement tended to increase (9/10 legs), and this was significant for at least two subjects (3 legs).

For hand pronation/supination while "off" medication, and for heel tapping while "on" medication, the side that was most affected in the absence of stimulation was also the side that received the most benefit from the stimulation for all subjects. This was not necessarily seen for hand pronation/supination while "on" medication, where improvement was more variable, or for heel tapping while "off" medication, where only two subjects showed much difference between sides without stimulation.

Overall, clinical ratings reflected the direction of change of performance (i.e. improvement or worsening) 73% of the time, but not necessarily the degree of change. A change of clinical rating in the opposite direction than that suggested by the quantified parameters of displacement or velocity occurred about 17% of the time. Results from all subjects are presented in Figures 4-7 and 4-8.

Unilateral stimulation

Increases in displacement amplitude and mean speed of hand pronation/supination were measured under nearly all conditions for the two subjects tested, although this was usually only statistically significant for the contralateral limb. When significant, improvement in these parameters while "off" medication was similar to that observed with the subjects receiving bilateral stimulation (18% to 58% increase in displacement, 53% to 63% increase in mean speed), although it is important to note that the task was not the same as that used for testing bilateral

Figure 4-7. *Effect of bilateral DBS on hand pronation/supination: all subjects* From top to bottom, UPDRS scores, peak-to-peak displacement amplitude, mean speed, and regularity of movement (nHcm) for repetitive hand pronation/supination are shown for all five subjects. Symbols represent means. Lines connect values measured with and without stimulation under one medication state for one hand; axes are oriented so that a downward slope of the line indicates improvement in the measure. Improvements in amplitude and/or mean speed were measured in all subjects, usually bilaterally, with stimulation while the subjects were "off" medication. Frequency tended to increase (not shown). "On" medication, results with stimulation were more variable, some subjects showing improvement and others showing deterioration of movement parameters. The effect of stimulation on regularity of movements was variable and usually not significant in either medication state. Note that for either type of stimulation (GPi or STN), each symbol represents the same subject as in Figures 4-4 and 4-8. Error bars were omitted for clarity, but range from 1.3° to 4.7° for amplitude, 1.9°/s to 9.4°/s for mean speed, and 0.0004 to 0.04 for nHcm values (SEM was not calculated for conditions yielding < 3 data points).

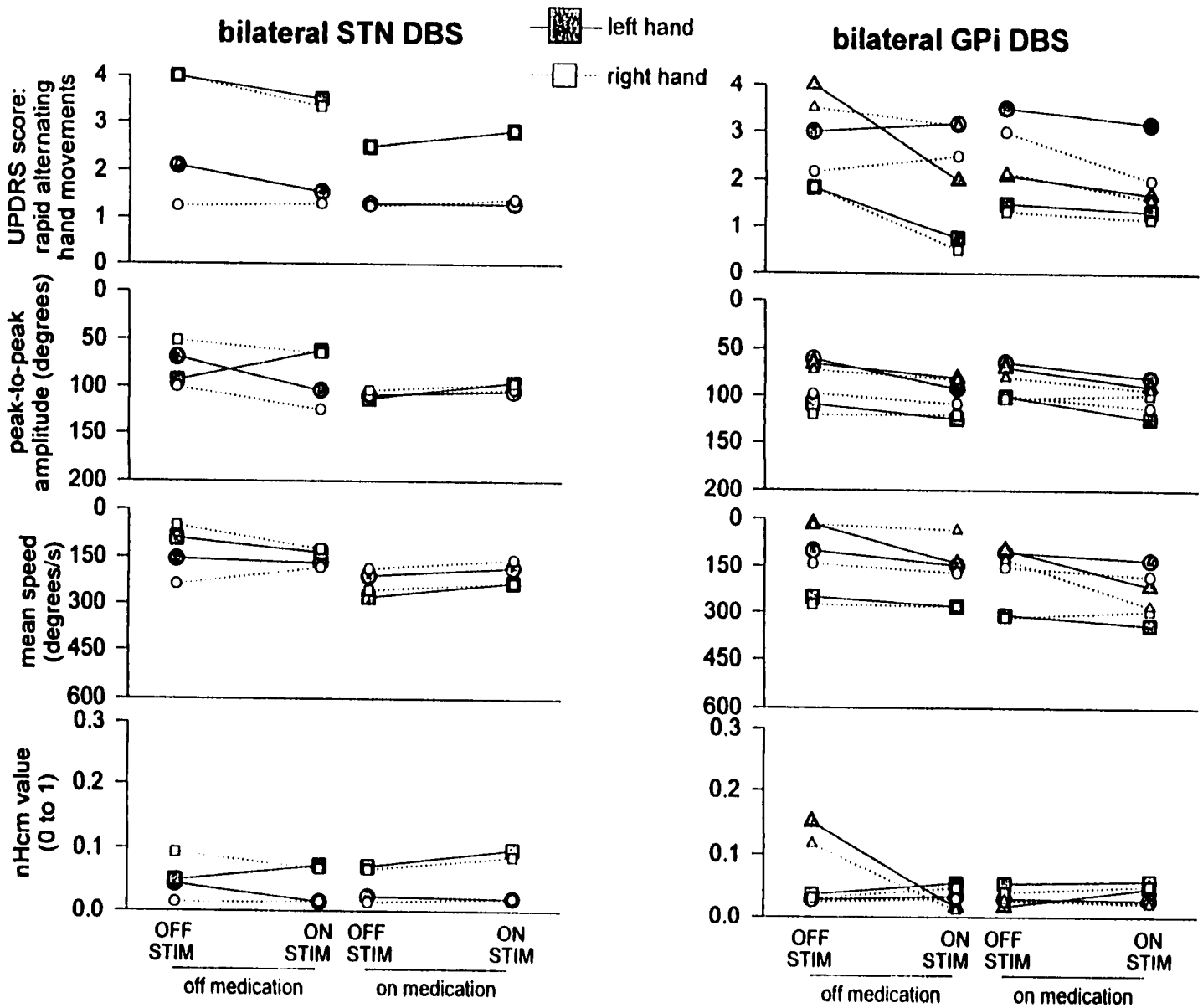
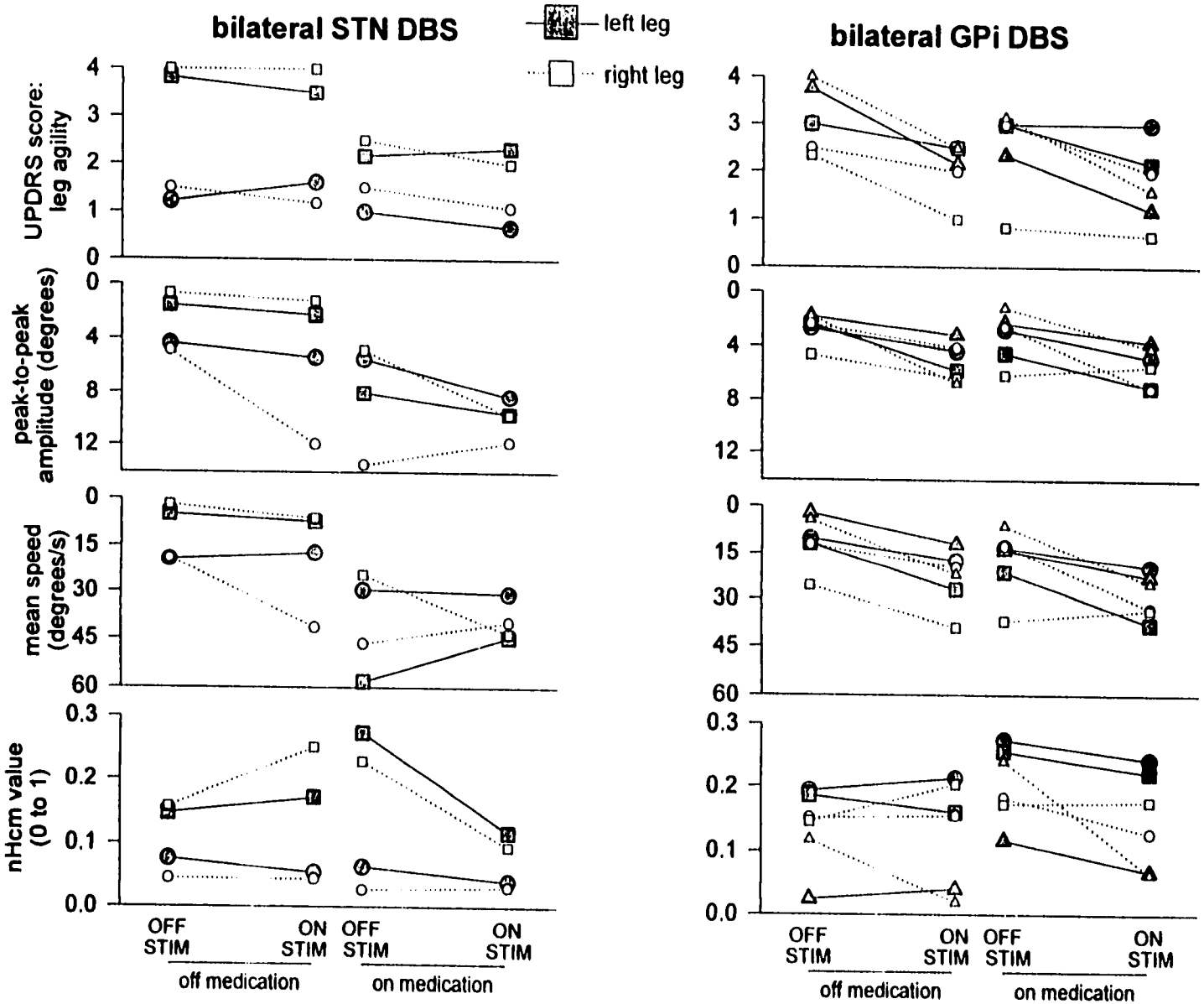

bilateral STN DBS
left hand
right hand
bilateral GPi DBS
UPDRS score: rapid alternating hand movements
peak-to-peak amplitude (degrees)
mean speed (degrees/s)
nHcm value (0 to 1)
OFF STIM
ON STIM
OFF STIM
ON STIM
off medication
on medication
OFF STIM
ON STIM
OFF STIM
ON STIM
off medication
on medication

Figure 4-8. *Effect of bilateral DBS on leg agility: all subjects* The format of this figure is the same as that for Figure 4-7. "Off" medication, most of the five subjects demonstrated significant bilateral increases in amplitude and mean speed of movement with bilateral stimulation ($p<0.05$). Frequency also tended to increase (not shown). Changes in regularity of movement (nHcm) were variable. "On" medication, results were more variable, but most subjects showed at least unilateral increases in amplitude and mean speed ($p<0.05$). Regularity of the movements tended to improve, while frequency tended to decrease (not shown). Note that for either type of stimulation (GPi or STN), each symbol represents the same subject as in Figures 4-4 and 4-7. Error bars were omitted for clarity, but range from 0.07° to 0.60° for amplitude, 0.17°/s to 2.4°/s for mean speed, and 0.001 to 0.05 for nHcm values (SEM was not calculated for conditions yielding < 3 data points).


bilateral STN DBS
left leg
right leg
bilateral GPi DBS
UPDRS score: leg agility
peak-to-peak amplitude (degrees)
mean speed (degrees/s)
nHcm value (0 to 1)
OFF STIM
ON STIM
OFF STIM
ON STIM
off medication
on medication
OFF STIM
ON STIM
OFF STIM
ON STIM
off medication
on medication

stimulation. Improvement measured while "on" medication covered a similar range. Significant improvement with stimulation in speed and displacement of foot tapping occurred only in subject RC, and mainly in the contralateral foot ("off" and "on" medication), although both parameters increased while "on" medication for the ipsilateral foot. Deterioration of task performance was small (15% to 17%) but significant for the ipsilateral foot of this subject while "off" medication. In general, the regularity of movements for both tasks worsened, but significance could usually not be tested. Overall, frequency tended to increase for both tasks while "off" medication, and foot tapping while "on" medication. UPDRS scores for hand pronation/supination usually did not change with stimulation.

4.4 DISCUSSION

Simple quantification methods were used to measure effects of unilateral or bilateral chronic DBS of the GPi or STN on upper limb rigidity (nine subjects) and on repetitive movements of the upper and lower limbs (seven subjects). Measurements made during stimulation were compared to those made in the absence of stimulation in the same medication state and the same examination session. Rigidity, measured as mechanical impedance (Z) to passive movement, decreased significantly either unilaterally or bilaterally in the elbows of six of seven subjects receiving bilateral stimulation of the GPi or STN while "off" medication, and in four of five of these subjects tested while "on" medication. Small, usually insignificant reductions in already low Z levels about the wrist were measured contralaterally in the two subjects receiving unilateral stimulation of the GPi. Significant increases in amplitude and mean speed of hand pronation/supination or heel or foot taps were recorded in all subjects while "off" medication; these increases were usually bilateral in subjects receiving bilateral stimulation, and mainly but not exclusively contralateral in subjects receiving unilateral stimulation. The effects of stimulation on performance of repetitive tasks while "on" medication were more variable across

subjects; although improvement occurred most frequently, some subjects demonstrated unilateral or bilateral deterioration of the movements. In either medication state, the effects of stimulation on frequency and regularity of the movements were in general more variable and usually not significant.

When significant, the amount of reduction in rigidity with bilateral stimulation while "off" medicine in the present study was generally in the range of 30% to 60%. This is comparable to the range of reduction of clinical scores of upper limb or overall rigidity with bilateral or unilateral stimulation, compared either to levels without stimulation or to preoperative levels, reported in several other studies (41 to 71%, Bejjani *et al.*, 1997; Brown *et al.*, 1999; Krack *et al.*, 1998b; Krack *et al.*, 1998c; Kumar *et al.*, 1998; Limousin *et al.*, 1998; Volkmann *et al.*, 1998). However, when results from all subjects with bilateral stimulation were combined, the average decrease in Z in our study was 27% for non-reinforced impedance, and 16.8% for reinforced impedance. (Removing the one subject whose stimulator settings had not been recently optimized increased these figures to 32% and 23%, respectively.)

In general, clinical assessments have determined that unilateral or bilateral stimulation of the STN or GPi is also effective in reducing rigidity in the "best on" medication state, although not necessarily as effective as when the subject is "off" medication (Krack *et al.*, 1998c; Limousin *et al.*, 1998; Volkmann *et al.*, 1998). In contrast, two investigations found no effect of GPi stimulation on rigidity while "on" medication (Bejjani *et al.*, 1997; Kumar *et al.*, 1998). In the current study, percent reduction in Z measures about the elbow with bilateral stimulation while "on" medication, *when significant*, could be as large as those measured with stimulation while "off" medication. Pooling of the results from all subjects with bilateral DBS , however, showed an overall smaller percent reduction with stimulation "on" medication (1% to 25 %) than "off" (17% to 27%). UPDRS ratings for upper limb rigidity both "on" and "off" medication in our study usually showed smaller improvements (4% to 14%, pooled data) than those detected by Z values.

The improvement in bradykinesia reported in many studies with stimulation while "off" medication ranges from about 13% to 38%. In the present study, pooled results from subjects with bilateral DBS showed an overall increase in amplitude and velocity of hand pronation/supination and heel tapping to nearly double values obtained without stimulation.

Improvement of bradykinesia with stimulation while "on" medication has generally been reported as less than that observed while "off" medication. In fact, aggravation of bradykinesia has been reported with stimulation of the GPi (Bejjani *et al.*, 1997; Krack *et al.*, 1998a; Krack *et al.*, 1998b; Tronnier *et al.*, 1997). In the present study, combined results from all subjects with bilateral DBS describe percent increases in amplitude and velocity of repetitive hand pronation/supination and heel taps that were lower "on" than "off" medication. Though most subjects showed improvement, there was deterioration of one or both parameters in three subjects; this deterioration frequently reached significance in the two subjects receiving bilateral stimulation of the STN. Aggravation of bradykinesia with stimulation of the GPi appears to be dependent on task as well as on stimulation parameters and on the precise location of the field of stimulation within the GPi (Bejjani *et al.*, 1997; Krack *et al.*, 1998a; Krack *et al.*, 1998b). Worsening of bradykinesia with STN stimulation, as was measured in two subjects here, has been previously noted, but this conclusion was reversed when the authors studied more subjects with longer follow-up (Kumar *et al.*, 1998).

There is a growing evidence that bilateral stimulation of the STN is more effective in reducing the "off" symptoms of Parkinson's disease than bilateral stimulation of the GPi (Krack *et al.*, 1998c; Kumar *et al.*, 1998; Starr *et al.*, 1998). Although both rigidity and performance of repetitive movements improved more in subjects with bilateral GPi DBS than in those with bilateral STN DBS in the current study, the number of subjects is too small to draw any conclusions. In another study involving a slightly larger number of subjects with similar "off" characteristics, a possible superiority of STN over GPi DBS was suggested by statistically

insignificant trends toward greater improvement of quantified measurements of upper limb function (Brown *et al.*, 1999).

Discrepancies in results between our studies and the findings of other groups pertain mainly to the amounts of amelioration of rigidity and bradykinesia, and are likely due in part to the low numbers of subjects involved in all the studies and differences in subject characteristics. However, the methods of assessment, including parameters measured and problems with subjectivity of the rating scales, may also have contributed to variations in results. There are very few quantified measures of the effects of DBS on symptoms of Parkinson's disease. The most common objective techniques employed measure aspects of bradykinesia, and these are generally composed of timed tests and simple counts of repetitions of movements. While more objective than qualitative rating scales, these measures offer only limited information regarding the subject's performance of the task, describing essentially the frequency of movements (Lang and Fahn, 1989), and in fact for some tasks may themselves be open to the subjective interpretation of the examiner (Lang *et al.*, 1995). Recording of more parameters of volitional activity permits a better picture of motor function, and may reveal more benefits of DBS than suggested by measures of frequency alone (Obeso *et al.*, 1996).

In the present study, effects of DBS on frequency of movement were variable and frequently not statistically significant. By contrast, increases in amplitude and velocity of the movements were much clearer and more consistent. Another study investigating the effects of bilateral stimulation of the STN or GPi on upper limb function determined that improvement in frequency of tapping was small compared to other measures such as rate of force production at the wrist and movement time (Brown *et al.*, 1999). An increase in amplitude of finger taps of over 400% with unilateral stimulation of the GPi in one subject, as recorded using a fibre optic glove (Iacono *et al.*, 1995), certainly falls within the range of improvement in amplitude of hand movements or heel taps encountered in the current study.

4.4.1 Conclusion

Significant decreases in rigidity and limb bradykinesia with bilateral and unilateral STN or GPi DBS were determined using simple quantification techniques. The effects were more consistent in the "worst off" medication state compared to "best on" but were significant under both conditions. The quantification methods employed in this paper offer objective assessments of items contained within the UPDRS; it is projected that, with sufficient numbers of subjects, these methods would allow a more accurate and precise description of the effects of DBS on rigidity and limb bradykinesia than would be possible with subjective ordinal ratings.

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CHAPTER 5

Activity-induced changes in tone of normal and spastic finger flexors

5.1 INTRODUCTION

Spasticity is in part a disorder of muscle tone and is symptomatic of injury to the central nervous system (CNS) and implicating the descending corticospinal tracts (Noth, 1991). Monitoring and understanding spasticity has assumed a considerable importance in both the clinical and research settings (Allison *et al.*, 1996; Pierrot-Deseilligny and Mazieres, 1985), particularly since it is often implicated in impairment of volitional movement (Ashby *et al.*, 1987; Bobath, 1990; Haley and Inacio, 1990).

A measure of the resistance of a joint to passive movement, or of a muscle to passive stretch, is frequently considered to be a reflection of the level of spasticity present. Increases in tone observed in hemiplegia following stroke have been attributed not only to a change in excitability of the stretch reflex (Powers *et al.*, 1988; Thilmann *et al.*, 1991) but also to mechanical changes of the muscle (Dietz *et al.*, 1991). Contracture, a physical shortening of the muscle, also contributes to hypertonia (O'Dwyer *et al.*, 1996). In addition, the level of contraction of the "resting" muscle can be influenced by synergies or associated reactions evoked by volitional movement (Bobath, 1990; Brennan, 1959; Haley and Inacio, 1990). Thus, a measurement of tone is not, strictly speaking, a measure of spasticity by Lance's definition ("disinhibition of the stretch reflex") (Lance and McLeod, 1981). Rather, a measure of tone encompasses all factors contributing to the resistance to stretch (Ashby *et al.*, 1987). It is this measure that is of interest in this paper.

Currently the most commonly accepted method of assessment of muscle tone in spasticity employs the modified Ashworth scale (Ashworth, 1964; Bohannon and Smith, 1987) to grade the

resistance to passive stretch of a muscle as felt by the examiner. However, this is a subjective scale and is thus open to the interpretation of the examiner. Despite some studies reporting good inter- and intra-rater reliability (Bohannon and Smith, 1987; Lee *et al.*, 1989), other groups have yielded less satisfactory results (Allison *et al.*, 1996; Haas *et al.*, 1996). Dissatisfaction with the modified Ashworth scale is exemplified by the numerous other scales and methods developed since its introduction (Worley *et al.*, 1991). The need for a method to evaluate spasticity quantitatively has often been expressed (Allison and Abraham, 1995; Haas *et al.*, 1996; Stefanovska *et al.*, 1988), yet no method of quantification of tone or other, neurophysiological, measure of spasticity has been accepted into common use due to the complexity and expense of the systems that have been developed in the past (Haas *et al.*, 1996; Worley *et al.*, 1991).

In the present study, we quantified tone in the hands of subjects with hemiplegia due to cerebral vascular accident. The method used calculates mechanical impedance during passive movements of the metacarpophanlangeal (MCP) joints imposed by the examiner. The magnitude and time-course of the effects of volitional limb movement and electrical stimulation on mechanical impedance were also measured.

This study emerged from the development of a device that uses FES to stimulate hand opening (Prochazka, 1997). The device had two purposes: it provided exercise to the affected hand, and additionally had the potential to be used for functional tasks. Spasticity in the hand permitted a grasp; hand-opening augmented the utility of the grasp. When the hand was relaxed, the stimulation was able to overcome any resistance to hand opening presented by the antagonist. However, it was noticed that during some attempts to use the FES device for functional purposes, this resistance could be increased to the point where the stimulation became ineffective (Cameron *et al.*, 1999). Flexing the wrist or resting the arm on a supporting surface would help relax the muscles (Cameron *et al.*, 1999). We wished then, to measure the effects of volitional movement on tone in the hand, as well as the time-course of these effects. The eventual aim was to

determine if other strategies could be adopted which would reduce tone enough to allow hand opening, or augment tone enough to allow grasp.

The purposes of this study were threefold: 1) to test the method of quantifying tone in the hand; 2) to determine the effects of volitional movement on the level of tone in the hand in subjects with hemiplegia as well as in neurologically-intact control subjects; and 3) to determine if stimulation itself reduced the level of tone in the hand at rest.

Parts of this paper have been presented elsewhere and have appeared in abstract form (Patrick *et al.*, 1998).

5.2 METHODS

This paper describes two studies. In Study #1, tone in the hands of subjects with hemiplegia was quantified by two examiners, first in subjects at rest, then following a period of volitional activity or FES to produce hand opening. In Study #2, tone was quantified in the hands of subjects with hemiplegia as well as control subjects *during* volitional movement or short trains of FES.

5.2.1 Measurement of tone on the hand

Mechanical impedance was measured about the metacarpophalangeal (MCP) joints of the hand. The device used was originally designed to measure parkinsonian rigidity and has been described in detail elsewhere (Prochazka *et al.*, 1997) and in Chapter 3. Briefly, mechanical impedance of a joint is measured as the joint is repeatedly flexed and extended over a 50-second trial. Two air-filled pads connected to a differential force transducer measure the force used to produce the flexion-extension movements, and a gyroscope mounted on the force pads is used to monitor the resultant displacement. The signals are low-pass filtered at 20 Hz (Sallen-Key),

sampled at 20 s^{-1} by a Motorolla 68HC11 microprocessor, and processed using a laptop computer. Alternatively, filtered analogue signals can be obtained from the hardware of the device. The software calculates elastic (K) and viscous ($B\omega$) stiffnesses from a moving 4-second (Study #1) or 3-second (Study #2) window of force and angular displacement data obtained from the sensors. The result is two 20 s^{-1} traces of K and $B\omega$. Mechanical impedance (Z) is the vectorial sum of K and $B\omega$.

In order to measure mechanical impedance at the MCP joints, the force pads were modified to fit across the first and second interphalangeal joints of all four fingers at once. The pads were strapped around the hand so that one pad was positioned on the palmar side of the fingers and the other on the dorsal side.

For both studies, the subject was seated comfortably during the measurement. The forearm was semi-pronated and resting on the padded armrest of the chair. The hand was not supported by the armrest. A wrist brace held the wrist at an angle of approximately 20° flexion from neutral.

5.2.2 Subjects

All experiments were performed with the informed consent of the subjects according to the Declaration of Helsinki Guidelines on Human Experimentation, and with local ethical board approval.

Tone in the hand was measured in eight subjects with hemiplegia due to stroke, and in eight control subjects with no known neurological disorder. The subjects with hemiplegia consisted of five males and three females, ranging in age from 13 to 58 years (mean 37), who had suffered cerebral vascular accidents (CVA) at least 11 months prior to the beginning of the study (mean 72 months, range 11 to 130 months). Control subjects ranged in age from 18 to 65 years (mean 35),

and consisted of four males and four females. Tone was measured in the affected hand of subjects with hemiplegia, and in the right (dominant) hand of control subjects.

5.2.3 Study # 1

Seven subjects with hemiplegia participated in the first study. Subjects came into the laboratory for two sessions. They were seated comfortably in a quiet room, watching a movie on video. Each session began with a 40-60 minute rest period during which baseline measures of tone were obtained. At this time, mechanical impedance in the hand was measured every 15 minutes in sets of six 50-second trials. It took about seven minutes to perform the six trials, so that there were eight minutes between the end of one set and the beginning of the next. Two examiners each performed three tests per set (one performed the first three, the other the last three), and the examiners kept the same order throughout the study. The force pads of the quantification device remained on the hand for the entire rest period.

In the first session ("movement session"), the baseline measures were followed by two additional sets of measurements each preceded by five minutes of voluntary activity. For this activity, subjects were asked to repeatedly raise their hand to the level of their nose at a comfortable rate; the force pads were usually removed to allow more freedom of movement.

For the second session ("stimulation session"), the baseline measures were followed by a 20-minute period of FES, during which surface electrodes were used to stimulate hand opening for 5-7 seconds alternating with 10-second rest intervals. After these 20 minutes of stimulation, two more sets of measurements were carried out. The wrist brace and force pads were removed for the period of FES, and replaced prior to assessment of tone.

Tone was expressed as the average mechanical impedance over one trial. To compare subjects, Z measures from each trial were normalized to the first trial of the session.

Inter-rater reliability was investigated by comparing raw, unnormalized *Z* measures from the last trial of examiner 1 to the first trial of examiner 2 for every set of trials performed across all subjects (Wilcoxon Signed Rank test). Intra-rater reliability was estimated by comparing unnormalized *Z* measures from the third trial performed by an examiner in each set of trials for a subject (one-way repeated measures ANOVA with Student-Newman-Keuls test post-hoc, or one-way repeated measures ANOVA on ranks with Student-Newman-Keuls test post-hoc). For all statistical tests, alpha was set at 0.05.

5.2.4 Study #2

In Study #2, changes in tone that occurred *during* volitional activity or FES were measured. Seven subjects with hemiplegia, and all eight control subjects participated in the second study. Mechanical impedance was quantified over trials lasting 62 seconds each. For the first 20 seconds of each trial, the subject was instructed to relax so that a baseline measure of tone at rest could be obtained. Following this was a "test interval" during which measurement of tone continued while the subject performed a task, or alternatively, while FES was used to produce hand opening. The subject was then once again instructed to relax for the remainder of the quantification trial ("recovery"). Four to 10 trials were performed for each task or for stimulation.

Each voluntary task was performed for approximately 10 seconds and involved either the contralateral or ipsilateral arm. The subject practised each task before data collection to ensure the instructions were understood. Not all tasks were performed by every subject.

IPSILATERAL BICEPS ISOMETRIC CONTRACTION: (seven subjects with hemiplegia, eight control subjects) The subject was asked to hold 20% maximum voluntary contraction (MVC) of the biceps using a target on an oscilloscope displaying electromyographic (EMG) recordings as a guide. A strap around the arm of the subject and the frame of the chair was used

to minimize movement. A second set of air-filled force pads was strapped around the forearm to measure the force produced by the isometric contraction.

IPSILATERAL BICEPS ISOTONIC CONTRACTION: (five subjects with hemiplegia, eight control subjects) The subject was asked to flex the arm to 20% (or 37% for subject LB) of the active range of motion (ROM) and hold it there, keeping the elbow on the armrest of the chair. A physical target was positioned over the arm such that the subject just needed to lift the forearm to touch the target. The active ROM was measured as the amount of voluntary flexion possible starting with the forearm resting on the armrest of the chair, and keeping the elbow on the armrest.

IPSILATERAL ISOMETRIC CONTRACTION OF EXTENSOR CARPI RADIALIS LONGUS (ECRL): (four subjects with hemiplegia, one control subject) The subject held a 20% MVC contraction of the ECRL against the restraint of the wrist brace. A target on the oscilloscope displaying EMG recordings was used as a guide.

20% CONTRALATERAL PINCH GRIP: (seven subjects with hemiplegia, eight control subjects) The subject held 20% maximum pinch grip of the contralateral hand as measured by a Jamar® pinch grip gauge. The gauge was stabilized with Velcro onto the thigh of the subject. A target was marked on the face of the meter of the gauge.

70% CONTRALATERAL PINCH GRIP: (six subjects with hemiplegia, eight control subjects) The subject held 70% maximum pinch grip of the contralateral hand as measured by a pinch grip gauge. One early control subject (SY) was asked to hold 75% instead of 70%.

For all tasks, a trigger signal produced by pressing a switch was used to indicate the start and end of the task. MVC (isometric) was determined by asking the subject to contract maximally for two seconds. Maximum pinch grip was determined by the amount of deflection on the pinch grip gauge when the subject pinched the gauge as hard as possible.

Effect of stimulation on tone was measured in all seven subjects with hemiplegia and in two control subjects. Stimulation took place over a 20-second test interval following the initial 20-

second baseline period. This test interval was subdivided into two 6-second periods of stimulation separated by 8 seconds without stimulation. Trigger pulses produced by the stimulator marked the beginning and end of each stimulation period.

Bipolar EMG recordings were obtained for all tasks from the ipsilateral biceps (all subjects) and ECRL (six subjects with hemiplegia, four control subjects) muscles using pairs of surface electrodes (Jason Electro Trace, ET001). Inter-electrode spacing was approximately 1cm. The reference electrode was placed on the olecranon process of the ulna. Signals were high-pass filtered at 30 Hz, full-wave rectified, amplified, and low-pass filtered at 3 Hz using a custom-built amplifier unit and displayed on an oscilloscope.

Signals from the force pads and gyroscope of the quantification device were digitized along with all other signals (EMG, trigger, extra force pads (isometric biceps task only), stimulator trigger pulses (stimulation trials only)) at 20 s^{-1} or 25 s^{-1} (Cambridge Electronic Design (CED) 1401 interface with 12 bit resolution, and SIGAVG version 5.42 software). Mechanical impedance was calculated from the gyroscope and force pad signals using the software for the quantification device.

As described above, each value of Z was calculated from a 3-second window of force and angular displacement data; each point was therefore an estimate of the *average* impedance over those three seconds. Because of this averaging, a sudden increase in tone, produced, for example, by movement of the arm, would become a more gradual increase over three seconds of the Z trace. The Z trace was aligned with the other traces of data so that the centre of the gradual increase would coincide with the point in time of the actual sudden increase. The trace was then divided into baseline, test, and recovery segments based on EMG and/or trigger pulses. Taking one point every three seconds produced a number of independent samples of Z. No data points were selected from 1.5 seconds before to 1.5 seconds after each transition period between baseline or recovery and task or stimulation so that impedance measures would be obtained under only one condition (i.e. rest or task), as opposed to a combination of conditions. For control

subjects, negative values of elastic or viscous stiffness indicate that the subject was assisting the movements of the hand imposed by the examiner. Samples falling in a segment of Z that corresponded to negative K or $B\omega$ were therefore discarded and the point following that segment was selected instead. The subjects with hemiplegia had extremely little or no voluntary control of the hand being tested; negative stiffness values were thought to be due to the spasticity assisting the imposed movements. Consequently, for these subjects, all samples were retained.

One-way ANOVA with Dunnett's test post-hoc (or the non-parametric one-way ANOVA on ranks with Dunn's test post-hoc) was used to test for significance between samples of Z obtained from all test and recovery intervals (compared to baseline) from all trials for the same task for one subject. For trials involving FES, the interval between the two 6-second periods of stimulation was used as the test interval since stimulation to produce hand opening inevitably caused an increase in tone that was due to direct activation of muscle and not to an increase in the level of spasticity. To compare the relative effects of the task or stimulation on subjects, samples of Z were normalized to the mean of the samples taken from the resting period for each task. The averages of the normalized samples from each of the baseline, test, and recovery periods were used to compare subjects. One-way repeated measures ANOVA (or one-way repeated measures ANOVA on ranks) with Dunnett's test post-hoc was used to test for significance from baseline measures. For all statistical tests, alpha was set at 0.05.

5.2.5 Stimulation parameters

For both Study #1 and Study #2, cathodic stimulation of the extensor digitorum communis (EDC) was used to produce hand-opening. The indifferent electrode (anode, custom-made sponge electrodes for Study #1, self-adhesive surface electrodes, ConMed Versa-stim for Study #2, 45 × 90 mm) was placed on the skin proximal to the wrist crease on the anterior surface of the forearm.

The stimulating electrode (cathode, 45 × 45 mm) was placed on the skin over the EDC muscle approximately 10 cm distal to the lateral epicondyle of the radius. Stimulation consisted of 25 s^{-1} trains of current-controlled biphasic pulses with 300 μs pulsewidth. Stimulation intensity was always above motor threshold, so that the amplitude of finger extension was approximately 75% of the full available range of extension.

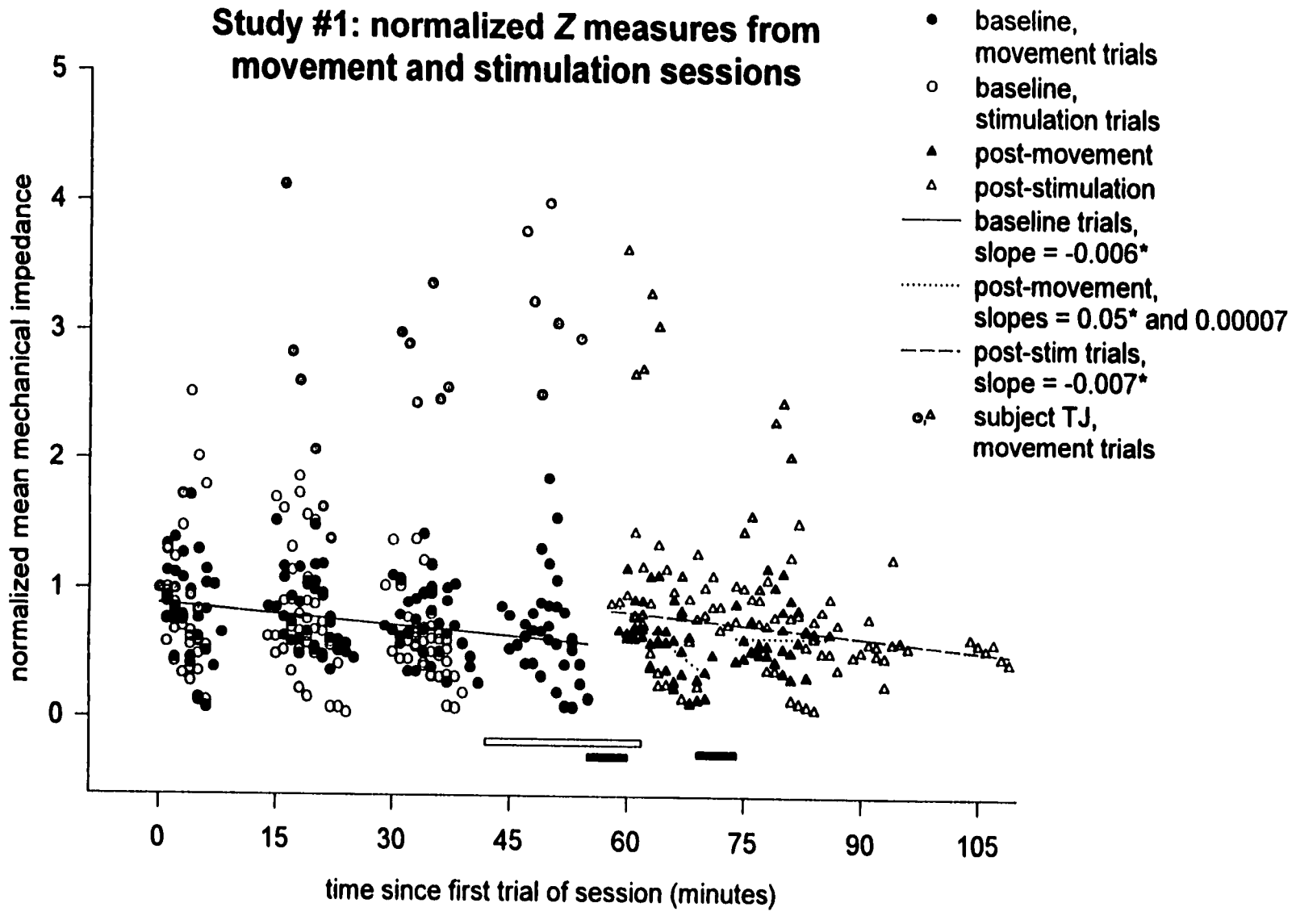
5.3 RESULTS

5.3.1 Study #1

Mechanical impedance in the affected hands of seven subjects with hemiplegia was measured at 15-minute intervals over a period of 40-60 minutes. Tone was assessed again following a 20-minute period of FES-produced hand-opening, or following both of two 5-minute periods of volitional activity involving the ipsilateral arm. Potential effects of stimulation and movement were investigated in two separate sessions.

There was a general, gradual decline of mechanical impedance (Z) measures over the course of a session (Figure 5-1). All subjects demonstrated a general decline in Z over baseline trials of both sessions, as determined from the slope of linear regression lines, with one exception: Z values for subject TJ were very low at the beginning of the session involving the task of volitional movement, but increased four to five times by the second set of measurements and continued to demonstrate a general, milder increase over the remainder of the baseline sets of the session (Figure 5-1, grey filled symbols). The dramatic increase in impedance early in the session obscured the decreasing trend observed in all other subjects; consequently, data from the movement session for subject TJ were omitted from analyses of trends in Z levels.

Figure 5-1. *Study #1: General decline in measures of mechanical impedance over course of a session* Data represented here are from both the movement sessions (filled symbols) and the stimulation sessions (open symbols) for all subjects. Each symbol represents the average Z value obtained from one trial, normalized to the Z value obtained from the first trial of the session. Trials from the movement session of subject TJ (grey filled symbols) were not included in data fitted with linear regression lines (see text for reasons). Altogether 415 trials performed on seven subjects for two different sessions and on one subject for one session were included in the analysis. A gradual overall decline in the level of mechanical impedance measured at the MCP joint of the hand was observed over baseline trials, as well as following a 20-minute period of FES (open bar) or 5-minute period of movement (filled bar). An asterisk indicates significance with alpha set at 0.05.


Study #1: normalized Z measures from movement and stimulation sessions
normalized mean mechanical impedance
time since first trial of session (minutes)
0
15
30
45
60
75
90
105
0
1
2
3
4
5
baseline, movement trials
baseline, stimulation trials
post-movement
post-stimulation
baseline trials, slope = -0.006*
post-movement, slopes = 0.05* and 0.00007
post-stim trials, slope = -0.007*
subject TJ, movement trials

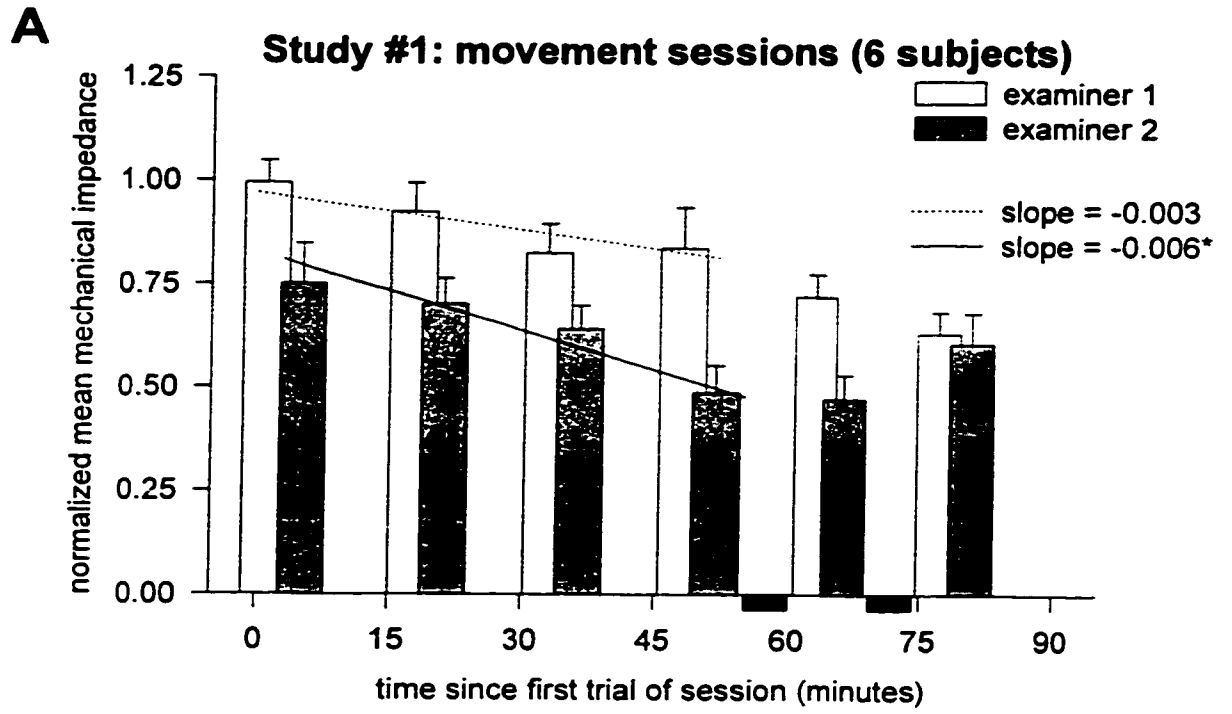
Linear regression lines were fitted to the results from 415 trials; this represents normalized data from all trials from all subjects for both sessions, with the exception mentioned above, and excluding five trials that were omitted due to technical problems. The decrease in Z over baseline trials of both sessions combined was significant (207 trials, linear regression, $p<0.0001$). Based on linear regression lines fitted to data from individual subjects, four subjects showed a significant ($p<0.05$) decline in baseline measures during the movement session, and two showed a significant ($p<0.05$) decline in baseline measures during the stimulation session. Mean ± SD impedance levels for individual subjects during the first set of baseline trials for movement sessions was 0.012 ± 0.011 Nm/degree, and declined 26% to a mean ± SD of 0.009 ± 0.007 Nm/degree during the last (fourth) set of baseline trials. For stimulation sessions, impedance decreased 32% from 0.006 ± 0.004 Nm/degree in the first baseline set to 0.004 ± 0.002 Nm/degree in the last (third) baseline set. Percent changes from the first set to the last set of baseline trials for individual subjects ranged from a 10% increase to a 43% decrease (mean ± SD 22 ± 24% decrease) for movement sessions and from a 9% to 54% (25 ± 16%) decrease for stimulation sessions.

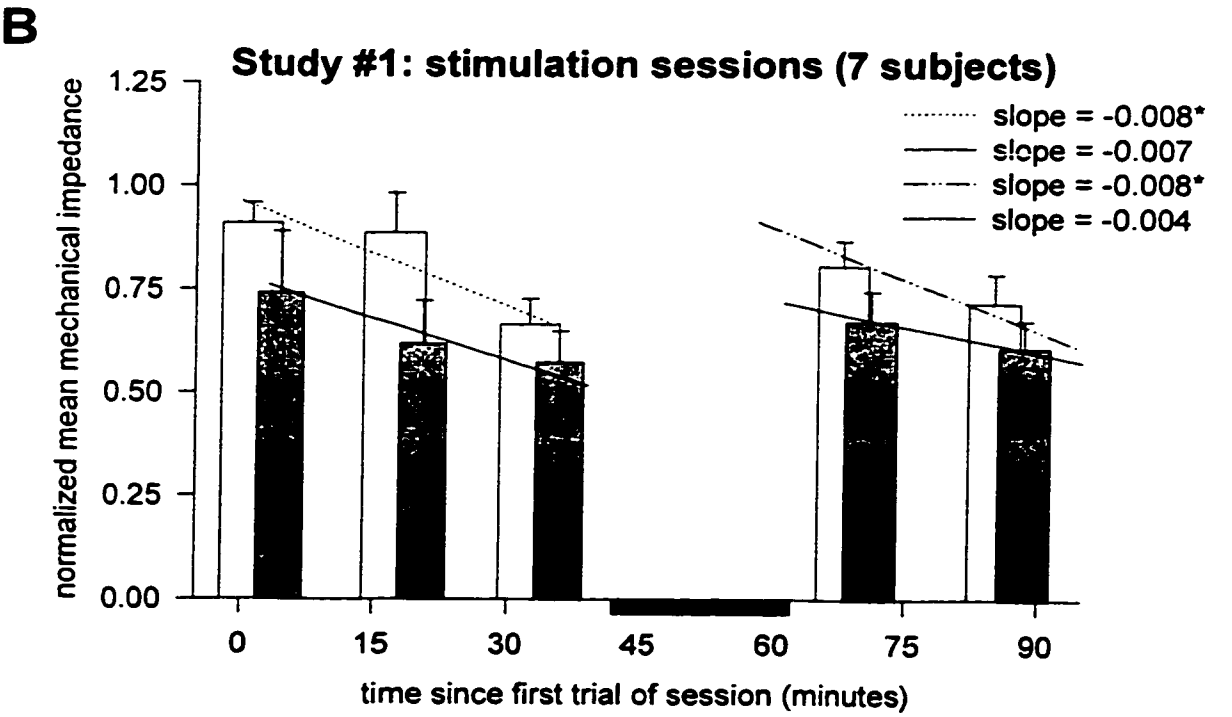
A trend similar to that seen during baseline trials was also observed following stimulation or movement. This decline in Z levels was significant for all subjects combined for the post-stimulation session, as well as for the first post-movement set of trials (Figure 5-1, linear regression, $p<0.05$).

A decline in Z values was evident regardless of examiner or session (Figure 5-2). Measures of mechanical impedance obtained from either examiner during baseline trials before movement or stimulation, or from trials performed after stimulation, showed decreasing trends; this reached significance ($p<0.05$) in three cases.

The general decrease in Z presented an unexpected confounding variable that made detection of effects of volitional movement or stimulation difficult. For movement sessions, since sets of

Figure 5-2. *Study #1: Decline in measures of impedance regardless of examiner* Impedance measures collected during movement sessions (**A**) or stimulation sessions (**B**) were binned according to whether they were obtained during the first (examiner 1, open bars) or last (examiner 2, filled bars) three trials of a set of measurements. Data collected from both examiners demonstrated a similar decline with progression of the session. Regression lines were calculated from the normalized, raw (not binned) averages of individual trials for each examiner. An asterisk indicates significance with alpha set at 0.05. Note that the sharper decline in the level of tone over one set of measurements (one pair of bars) was largely due to an actual decline in impedance levels, and was not a result of inter-examiner differences. Solid black bars along the x-axis denote periods during which the subject performed a task of of voltional movement (**A**) or received FES to produce hand opening (**B**). Effects of movement or stimulation are confounded by the decrease of Z as well as by details of the protocol (see text for details).

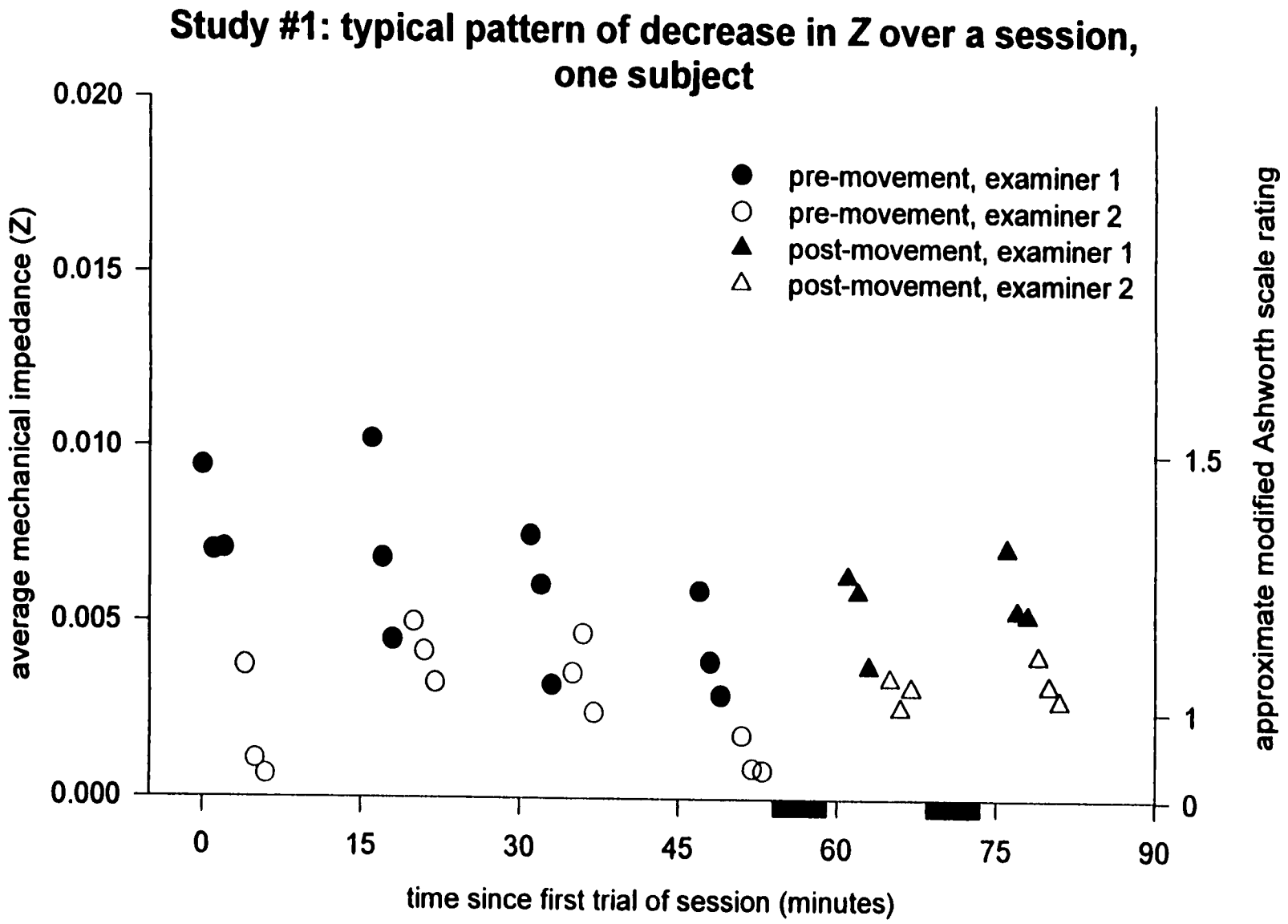

A
Study #1: movement sessions (6 subjects)
examiner 1
examiner 2
slope = -0.003
slope = -0.006*
normalized mean mechanical impedance
1.25
1.00
0.75
0.50
0.25
0.00
0
15
30
45
60
75
90
time since first trial of session (minutes)


B
Study #1: stimulation sessions (7 subjects)
slope = -0.008*
slope = -0.007
slope = -0.008*
slope = -0.004
normalized mean mechanical impedance
1.25
1.00
0.75
0.50
0.25
0.00
0
15
30
45
60
75
90
time since first trial of session (minutes)

measurements were equally spaced at 15-minute intervals throughout the entire session, the difference in average normalized impedance of a subject from one set to the next was compared. A one-way repeated measures ANOVA test showed no statistical difference between impedance measures from successive sets across the six subjects. However, as will be discussed further later, the study design presented additional problems that may have hindered or made impossible detection of effects of movement or stimulation, so these negative results are considered inconclusive. This approach was not applied to stimulation trials since the interval between pre- and post-stimulation sets was longer than any of the other inter-set intervals; these results are also considered inconclusive.

In addition to the gradual decline in Z over the course of a session, subjects typically demonstrated a more pronounced decrease in Z over each set of six trials. Consequently, Z measures obtained by examiner 1, who performed the first three trials of each set, were almost always higher than those obtained by examiner 2, who performed the last three. This is evident in Figure 5-2. Figure 5-3 shows the results of individual trials for one session of one subject. In an attempt to evaluate inter-examiner reliability despite the difficulty presented by this changing level of impedance, the last trial performed by examiner 1 was compared to the first trial performed by examiner 2 for each set of measurements obtained from all subjects (including TJ). No significant difference was found between unnormalized measures obtained by the two examiners (74 pairs of trials). Similarly, in an attempt to estimate intra-examiner reliablity, the third measure performed by an examiner in each set of baseline measures in a session was compared. When data from each examiner were pooled, there was no significant difference between unnormalized measures taken from different sets of baseline trials from movement sessions, but those taken from the first set differed significantly from those taken from the third (last) set of baseline trials for stimulation sessions. When data from the first three sets of both sessions were combined, unnormalized impedance measures from the first set differed significantly from those of the other two sets.

Figure 5-3. *Study #1: Typical progression of Z measures over the course of a session for a single subject* Data plotted here were obtained from one subject during a session in which she was asked to perform a task of volitional movement (solid black bars). In addition to a gradual decline in *Z* values over the course of a session, this and other subjects typically demonstrated a more dramatic decline in *Z* over a set of six trials. To evaluate inter-examiner reliability of the measurements, the third trial performed by the first examiner was compared to the first trial by the second examiner for each set of measurements. Similarly, intra-examiner reliabilty was evaluated by comparing the third trial performed by an examiner across all sets of baseline measures of a session. Modified Ashworth scale ratings are preliminary estimates (rating = $6*Z^{0.3}$, Chapter 2)


Study #1: typical pattern of decrease in Z over a session, one subject
average mechanical impedance (Z)
0.020
0.015
0.010
0.005
0.000
0
15
30
45
60
75
90
time since first trial of session (minutes)
pre-movement, examiner 1
pre-movement, examiner 2
post-movement, examiner 1
post-movement, examiner 2
1.5
1
0
approximate modified Ashworth scale rating

5.3.2 *Study #2*

Because the protocol of the first study was not appropriate for detection of changes in the level of tone in the hand due to volitional movement or FES, a second study was designed to permit recording of such changes as they occurred. Mechanical impedance of the affected hand of seven subjects with hemiplegia and of the dominant hand of eight control subjects was measured while the subject performed a task of volitional movement, or while FES was used to produce hand opening. Mechanical impedances during and after the test period were compared to baseline measures.

IPSILATERAL BICEPS ISOMETRIC CONTRACTION: 20% MVC of the biceps produced a significant increase in mechanical impedance of the MCP joints of the hand in three of seven subjects with hemiplegia, and in five of eight control subjects. Results from two subjects showing potentiation are illustrated in Figure 5-4A. Traces are averages of 4 to 7 trials. Impedance increased by 70% in the control subject (top panel) compared to 291% in the subject with hemiplegia (bottom panel). Although this control subject demonstrated the highest increase in impedance of all control subjects tested for this task, the level of impedance attained was less than that reached by the three subjects with hemiplegia. Results from all subjects tested are shown in Figure 5-4B. The potentiation exhibited by control subjects (8% to 82% increase in impedance) was for the most part smaller than observed in subjects with hemiplegia (26% to 291% increase). Carry-over (an increase in tone extending beyond the duration of the task period) was seen in at least one subject with hemiplegia, but not on every trial. A very small (<6%) but statistically significant increase in tone was measured during the recovery period for one control subject.

IPSILATERAL BICEPS ISOTONIC CONTRACTION: Figure 5-5A shows the results of 4 to 7 trials from the same subjects whose data are shown in Figure 5-4A. Active lifting of the forearm from the armrest of the chair increased mechanical impedance about the ipsilateral MCP joints by

Figure 5-4. *Study #2: Effect of 20% MVC isometric contraction of the ipsilateral biceps on tone in the hand* **A)** Changes in mechanical impedance (thick solid line) with isometric biceps contraction are depicted for two subjects. Traces are averages of 4 to 7 trials; traces from each trial were aligned according to the beginning of the task as indicated by biceps EMG (thin solid line). EMG was also recorded from the ECRL for one subject (dotted line). The top panel shows the response of a control subject who exhibited potentiation. The increase in tone was small relative to that observed in the subject with hemiplegia whose results are shown in the bottom panel. The force trace (broken line) represents the signal from the force pads around the arm of the subject, and indicates the upward force produced by the forearm during the contraction of the biceps. Downward force is due to the weight of the arm resting on the force pads. **B)** Not all subjects demonstrated potentiation, nor was the potentiation uniform across a group of subjects when it did occur. The top panel shows pooled results from all subjects tested; responses of individual subjects are depicted in the bottom panel. Impedance values were normalized to measures obtained during the baseline periods. The asterisk in the top panel denotes significance at $p<0.05$.

Study #2: ipsilateral biceps isometric contraction

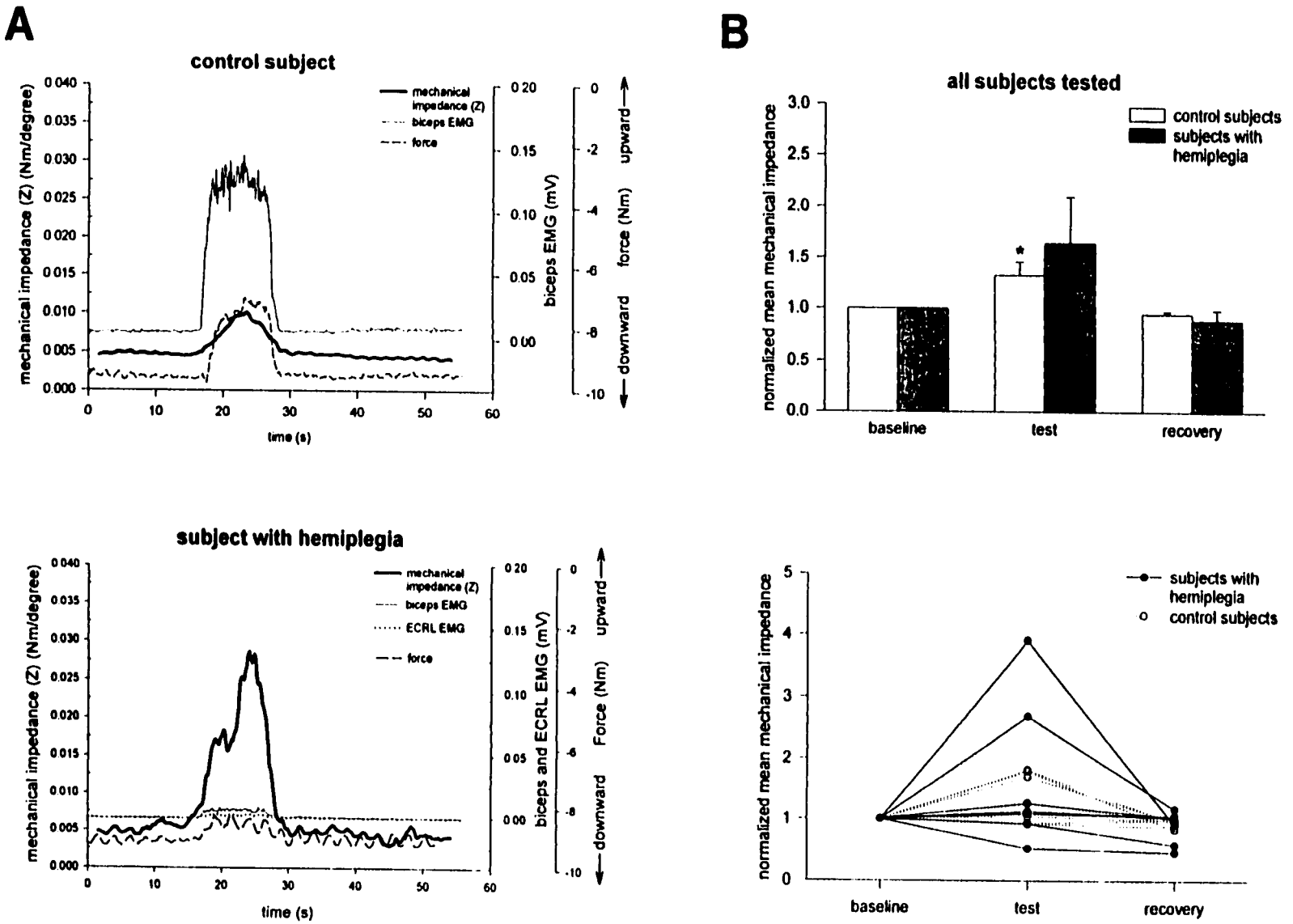
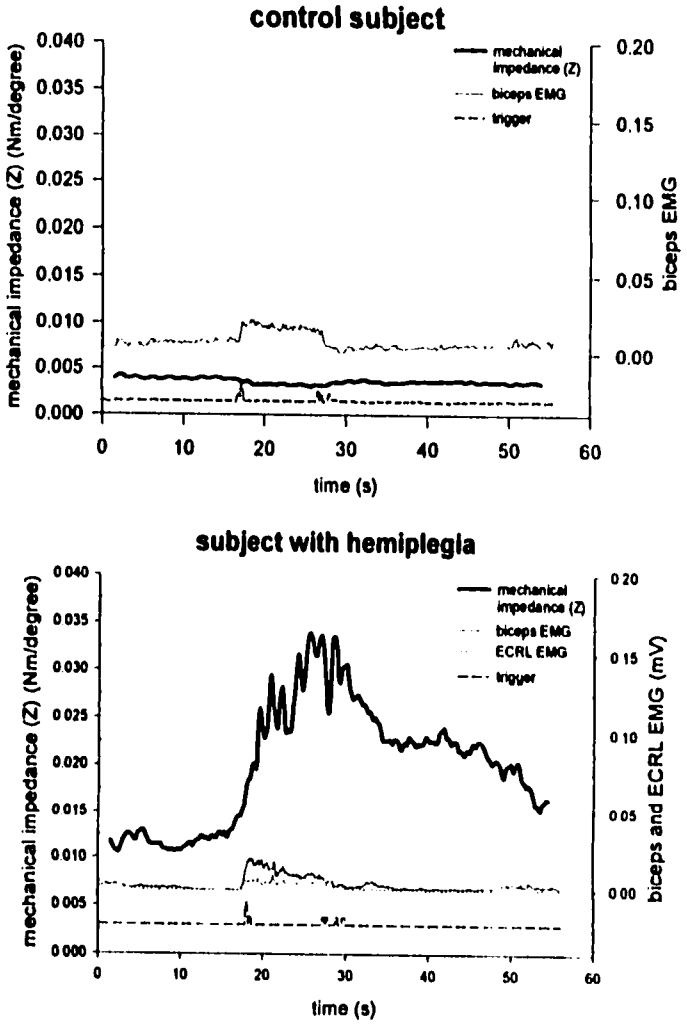


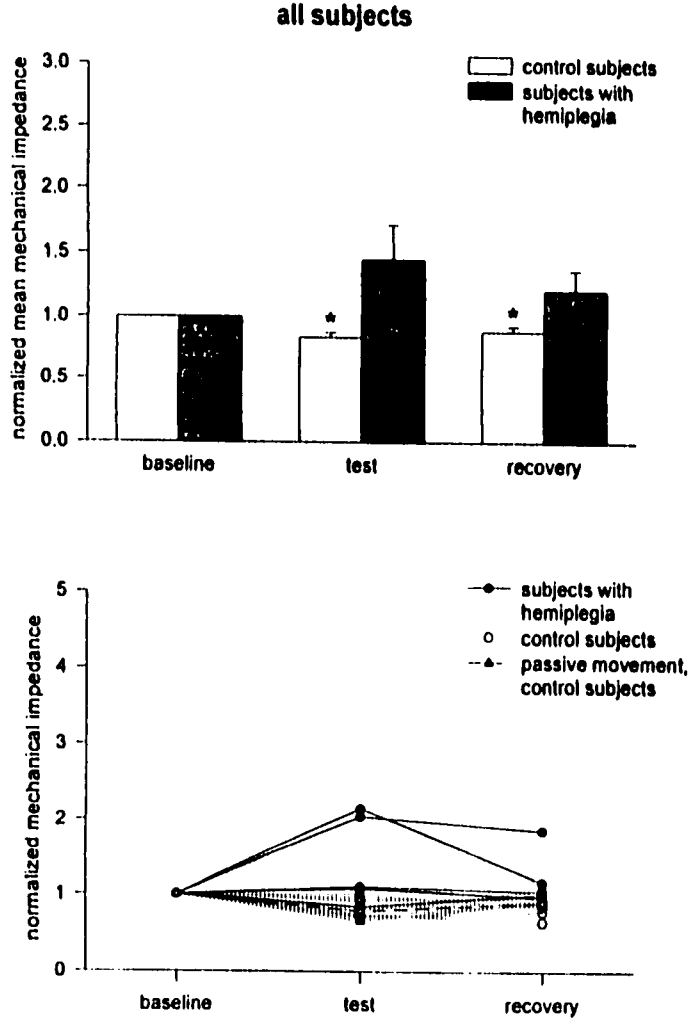
Figure 5-5. *Study #2: Effect of isotonic contraction of the ipsilateral biceps on tone in the hand* **A)** Changes in mechanical impedance (thick solid line) with active lifting of the forearm are shown for the same two subjects from Figure 5-4A. Traces are averages of 4 to 7 trials; traces from each trial were aligned according to the beginning of the task as indicated by EMG (thin solid line) and/or trigger pulses (dashed line). The decrease in tone illustrated in the top panel was typical of control subjects for this task. Most subjects with hemiplegia, by contrast, exhibited an increase in tone during the task. Note the carry-over of the potentiation effect into the recovery period for the response of one such subject shown here (bottom panel). **B)** Pooled data from all subjects are depicted in the top panel; responses from individual subjects are shown in the bottom panel. The decrease in tone observed during the task period in control subjects was thought to be due to mechanical reasons. Passive movement of the forearm in two subjects produced a similar decrease (grey filled triangles, lower panel). Impedance values were normalized to measures obtained during the baseline periods. The asterisk in the top panel denotes significance at $p<0.05$.

Study #2: ipsilateral biceps isotonic contraction

A



B

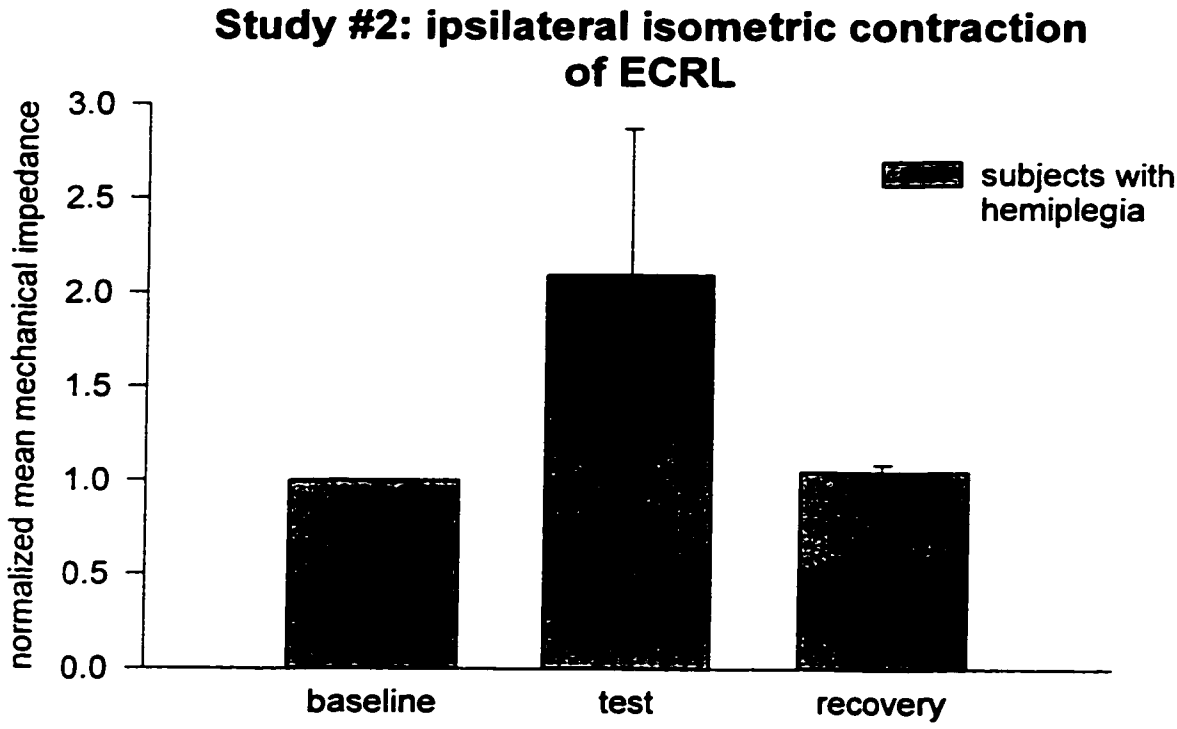


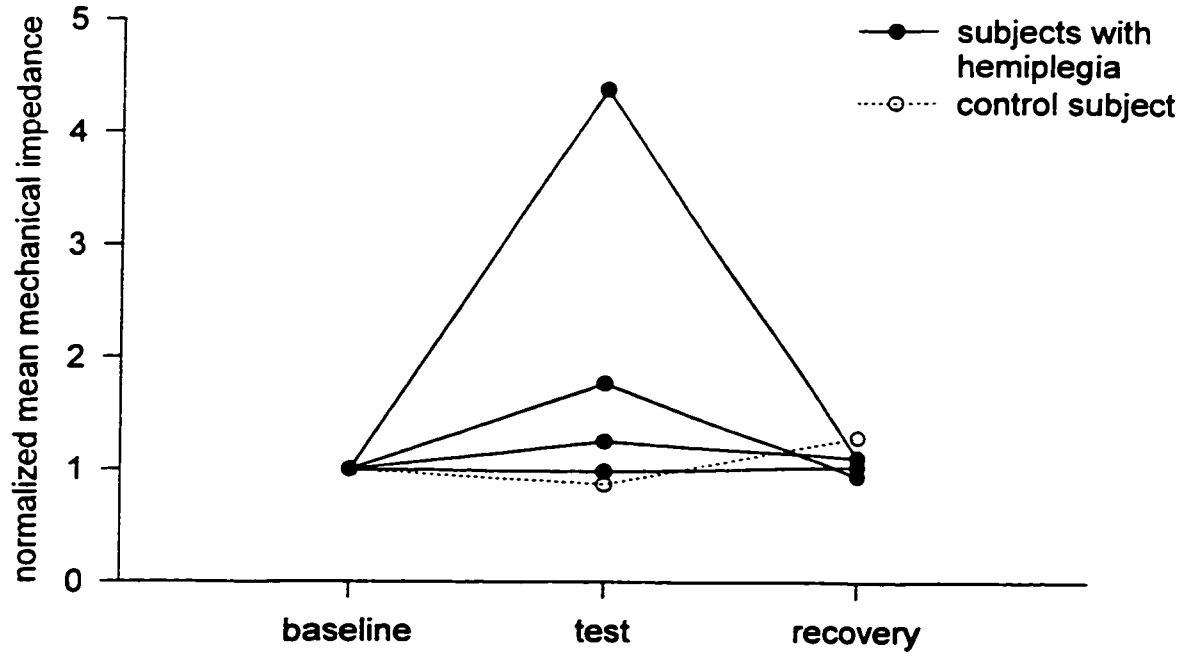
104% in the subject with hemiplegia,[1] and produced a strong carry-over effect. By contrast, the control subject demonstrated a 17% *decrease* in tone during the task, which was typical of control subjects. Results from all subjects are plotted in Figure 5-5B. Mechanical impedance was potentiated by 11% to 116% in three of the five subjects with hemiplegia; this was only statistically significant for one subject. A carry-over effect was evident for two subjects, but only significant for one subject across the set of trials. The significant 9% to 30% decrease in tone observed in five of the eight control subjects, as well as one of the subjects with hemiplegia, was suspected to have a mechanical, rather than a neurological, cause, at least in the control subjects. To test this theory, we passively lifted the arm of two control subjects by the same amount as during the active task (20% ROM: see methods). The results, shown in the lower panel of Figure 5-5B, showed a similar (22 to 34%) decrease in both subjects, including one subject who showed no change in tone with the active task.

IPSILATERAL ISOMETRIC CONTRACTION OF ECRL: Since the effect of ipsilateral biceps contraction was not as dramatic as we had anticipated, we reasoned that perhaps activation of more distal muscles was responsible for the large, sudden increases in tone in the hand that we had observed in subjects attempting functional tasks. Results from all subjects are shown in Figure 5-6. Isometric contraction of the ECRL produced a significant elevation in tone in the ipsilateral hand in three of four subjects with hemiplegia, including one for whom isometric biceps contraction had had no effect (yet who had demonstrated lower levels of activation of the ECRL during the biceps task). Impedance measures during the task were on average 25% to 338% greater than baseline levels for these three subjects, and carry-over was also significant for

1. Although a definite increase in tone was measured in each of the four trials for this subject, and is also evident in the trace in the figure, this increase was statistically insignificant according to a one-way ANOVA on ranks test. It is suspected that this was due to the large variability in tone during the test period. This frequently occurred throughout this study, and it is concluded that ANOVA and ANOVA on ranks may be inappropriate tests for comparing tone during the test interval to baseline tone for individual subjects. Although results of ANOVA tests will continue to be reported for individual subjects, the reader is requested to keep this in mind.

Figure 5-6. *Study #2: Effect of 20% MVC isometric contraction of the ipsilateral ECRL on tone in the hand* Three of four subjects with hemiplegia demonstrated a significant increase in tone at the MCP joints with contraction of the ECRL (filled bars in the top panel, filled symbols in the lower panel). The one control subject tested for this task did not show potentiation (open symbols, lower panel). Impedance values were normalized to measures obtained during the baseline periods.


Study #2: ipsilateral isometric contraction of ECRL
normalized mean mechanical impedance
3.0
2.5
2.0
1.5
1.0
0.5
0.0
subjects with hemiplegia
baseline
test
recovery


normalized mean mechanical impedance
5
4
3
2
1
0
subjects with hemiplegia
control subject
baseline
test
recovery

one. Carry-over was evident in another subject for approximately half of the recovery period, but the increase over the entire recovery period relative to baseline levels (10%) was not statistically significant. The fourth subject, who exhibited a baseline level over three times as high as the other subjects, showed no change in impedance. As this task was added to the protocol part way through the study, only one control subject was tested. If anything, this subject demonstrated a decrease in impedance during this task (Figure 5-6, lower plot).

CONTRALATERAL PINCH GRIP: Performance of a 20% maximum pinch grip with the contralateral hand produced few changes in tone about the MCP joints in either subject group (Figure 5-7A). One control subject demonstrated a small but statistically significant (9%) potentiation, and another a small but statistically significant (4%) decrease. The largest change was a 38% increase in tone exhibited by a control subject during the task, although this was statistically insignificant according to the tests used. The most frequently observed effect was a change in tone during the recovery period; this was either a decrease (two subjects with hemiplegia, two control subjects) or increase (one subject with hemiplegia) in tone. By contrast, a 70-75% pinch grip evoked a significant increase in tone in three of the six subjects with hemiplegia, and in four of the eight control subjects (Figure 5-7B). The *relative* amount of increase was similar for most subjects showing this potentiation, ranging from a 25% to 130% increase. However, mechanical impedance increased to over four times resting level (333% increase) in one subject with hemiplegia (see Figure 5-8). Carry-over effects were statistically significant for two subjects with hemiplegia, impedance during the recovery period averaging 44% to 230% higher than baseline levels. Tone was also higher (14%) during the recovery period relative to baseline for one control subject. Potentiation tended to increase with fatigue as the pinch grip became more difficult to hold. Increases in EMG activity of the ipsilateral biceps and ECRL observed during the 70% task were more common in subjects with hemiplegia than in controls, and reduced or non-existant in the 20% task.

Figure 5-7. *Study #2: Effect of weak and strong pinch grip on tone in the contralateral hand* 20% contralateral pinch grip had little effect on mechanical impedance of the affected hand of subjects with hemiplegia (filled bars and symbols) or the dominant hand of control subjects (open bars and symbols) (**A**). 70% to 75% pinch grip, however, resulted in an increase in tone in subjects in both groups (**B**). Impedance values were normalized to measures obtained during the baseline periods. The asterisk in the top panel of **B** denotes significance at $p<0.05$.

Study #2: contralateral pinch grip

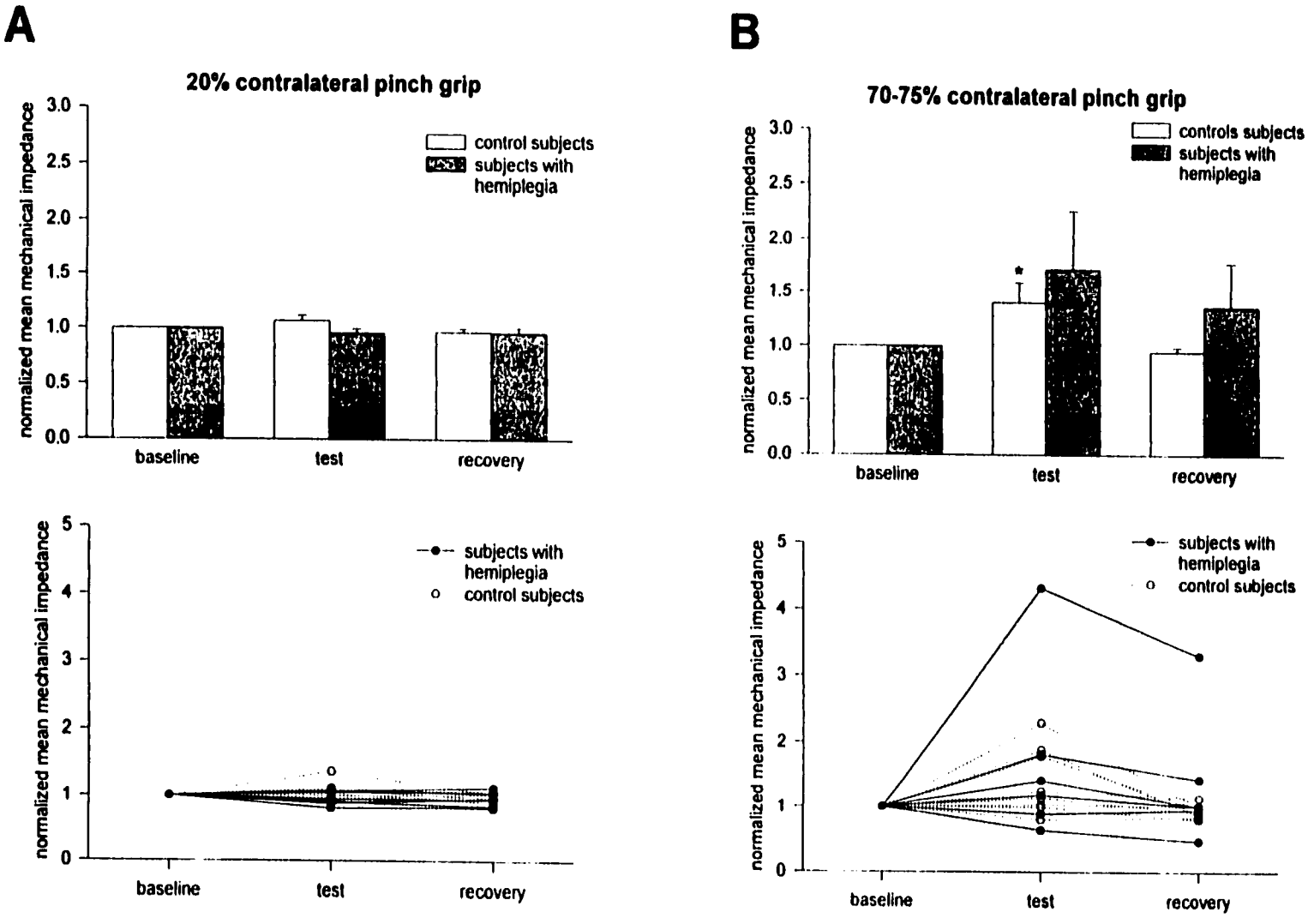
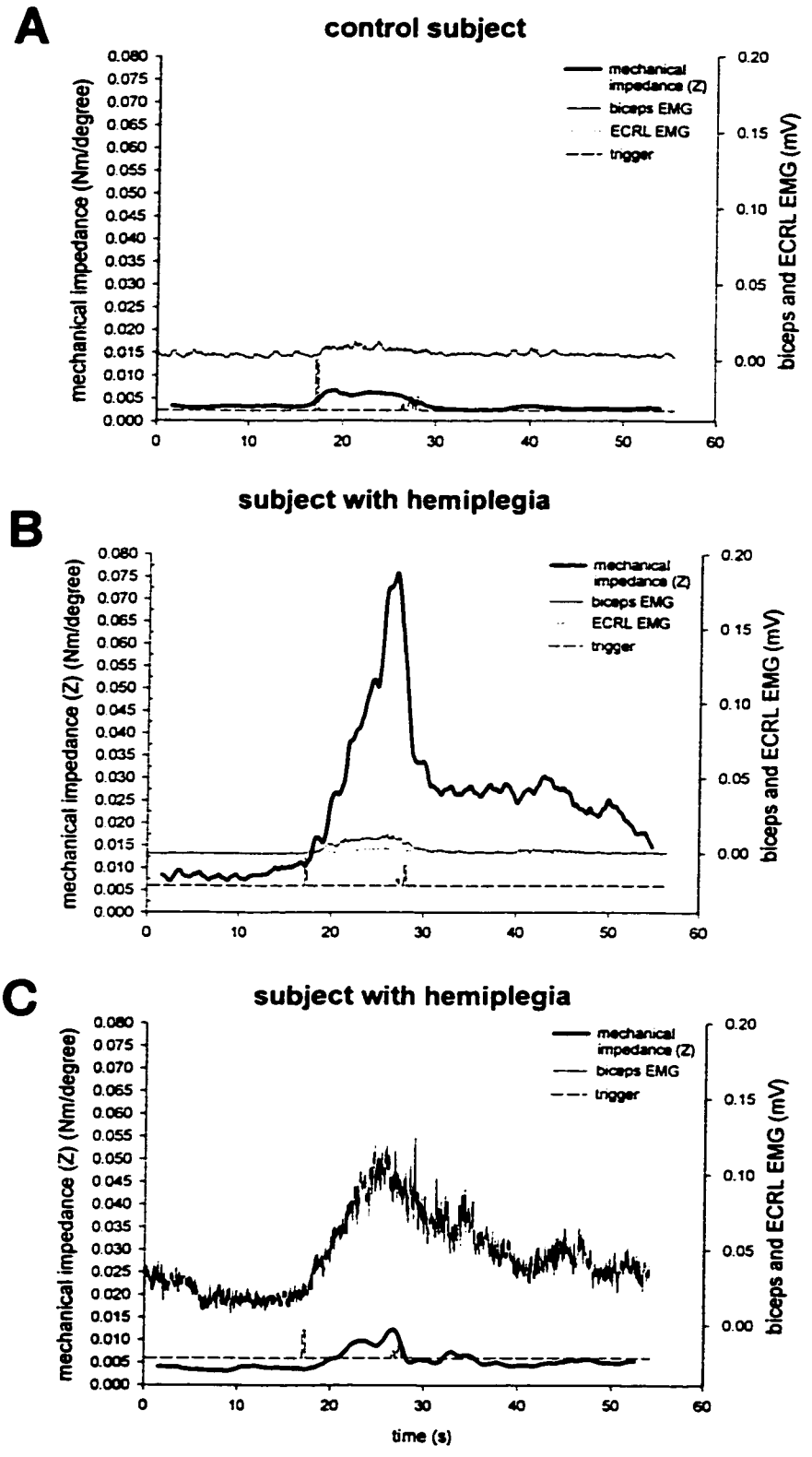


Figure 5-8. *Study #2: Differences in magnitude of response and presence of carry-over in subjects with hemiplegia compared to control subjects* Levels of mechanical impedance attained during performance of a task were usually considerably lower in control subjects than in subjects with hemiplegia, and carry-over was rarely observed. Shown are mechanical impedance at the MCP joints (thick solid line) and EMG of the ipsilateral biceps (thin solid line) for one control subject (**A**) and two subjects with hemiplgegia (**B,C**) during 70% contralateral pinch grip. EMG of the ipsilateral ECRL was also recorded for one of the subjects (dotted line). Traces represent averages of 4 to 7 trials; traces from each trial were aligned according to the beginning of the task as indicated by trigger pulses (dashed lines). The response exhibited by the control subject was among the largest observed for that group. A very dramatic response with large carry-over effect was recorded from the subject in part **B**. A smaller response with a different pattern of carry-over was observed for another subject (**C**). Note the scale change on the ordinate axes compared to previous similar figures.

Study #2: contralateral pinch grip



With the exception of the isotonic biceps (ROM) task, elevation of mechanical impedance during performance of the volitional tasks was *no more frequent* in subjects with hemiplegia thanin control subjects (no conclusion can be made regarding the frequency of effects of isotonic ECRL contractions in control subjects). However, the *relative amount* of increase in impedance was often higher in subjects with hemiplegia than in control subjects. In addition, the average *absolute values* of impedance attained during potentiation were rarely as high for control subjects as subjects with hemiplegia, who often attained impedance values from 1.5 to over four times greater than the highest average response observed for control subjects, 0.008 Nm/degree. Figure 5-8 shows examples of potentiation in one control subject and two subjects with hemiplegia performing a 70% maximal pinch grip with the contralateral hand. Traces are averages of 4 to 7 trials. Figure 5-8A shows one of the larger responses recorded for control subjects. Figure 5-8B shows the largest average response recorded for subjects with hemiplegia; the impedance values reached during the task over the four trials ranged from approximately 0.03 to 0.14 Nm/degree, considerably higher than any response exhibited by a control subject. The subject whose data is shown in Figure 5-8C presents one of the smaller, statistically significant increases in impedance observed in subjects with hemiplegia; together with part B, this demonstrates the range of impedance values recorded with potentiation in subjects with hemiplegia.

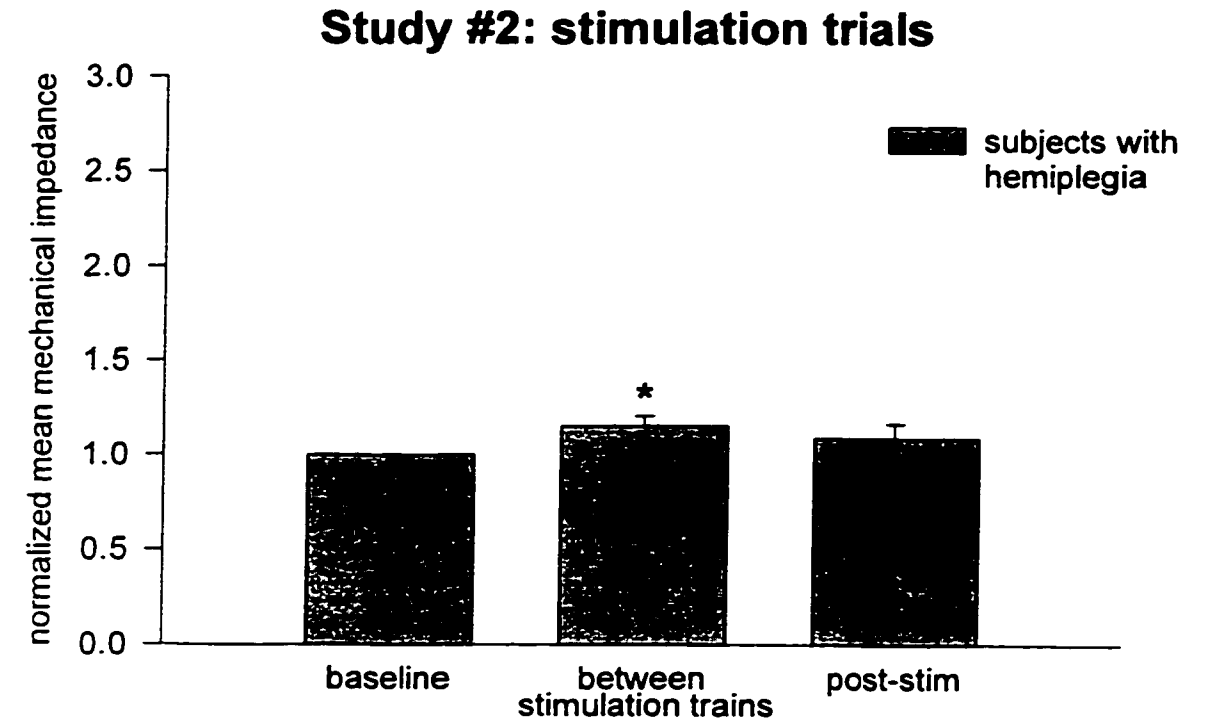
Carry-over was much more frequent, longer lasting, and stronger in subjects with hemiplegia than in controls. Figure 5-8 shows two different patterns of carry-over response in subjects with hemiplegia. The amount of potentiation or carry-over varied not only between subjects, but also between tasks for the same subject. Figures 5-4A and 5-5A show data from the same subject whose results are presented in Figure 5-8B; note the range of impedance values, as well as the complete absence of carry-over effects with isometric contraction of the ipsilateral biceps muscle. Such variability was also observed between trials for the same task and tended to be greater in subjects with hemiplegia.

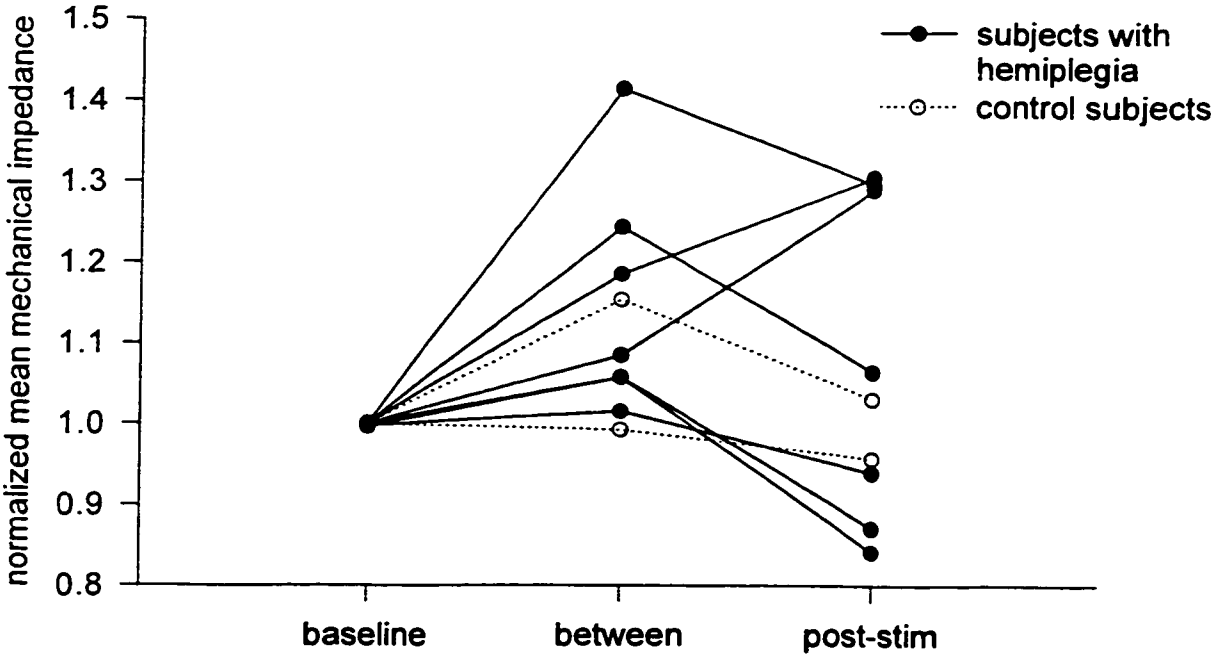
Contraction of the ECRL during volitional tasks involving the biceps was not uncommon for either subject group, but not necessarily accompanied by an increase in tone at the MCP joints. One of the subjects with hemiplegia demonstrated increased EMG activity of the biceps throughout the recovery period following most tasks (e.g. Figure 5-8C), but this did not necessarily correspond to carry-over effects. A different subject exhibited a significant decrease in impedance over test and recovery periods for two of the three tasks he carried out; there were no other apparent effects of the tasks.

There was no apparent relationship between the level of baseline impedance and the amount of potentiation, although one subject with very high baseline levels of tone never showed a statistically significant elevation in tone, due in part to the variability in the tone exhibited. In addition, there was no apparent relation between age and effects of volitional movements in control subjects.

STIMULATION-INDUCED HAND OPENING: Short trains of stimulation of the EDC muscle had little immediate effect on mechanical impedance at the MCP joints for most subjects (Figure 5-9). No statistically significant decreases in tone followed either of the two trains of stimulation for any of the seven subjects with hemiplegia, although two demonstrated insignificant 13% to 16% decreases following the second train. A third subject showed a 42% increase in impedance between stimulation trains. A statistically significant increase in impedance of approximately 30% was measured for this subject as well as another subject following both stimulation trains. The only effect of stimulation on tone for the two control subjects was a 15% increase in Z between stimulation trains for one subject.

Figure 5-9. *Study #2: Effect of FES on tone in the hand* Hand-opening produced by 6-second trains of stimulation of the EDC muscle had little effect on mechanical impedance in the hand for most subjects. Two stimulus trains, separated by an 8-second interval, were delivered per trial. Pooled data for subjects with hemiplegia are displayed in the top graph; individual responses are depicted in the lower graph (filled symbols). Effects of stimulation on two control subjects were also recorded (open symbols, lower graph). Impedance values were normalized to measures obtained during the baseline periods. Note the change in scale of the y-axis on the lower plot compared to previous similar figures.


Study #2: stimulation trials
normalized mean mechanical impedance
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
subjects with hemiplegia
baseline
between stimulation trains
post-stim


normalized mean mechanical impedance
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
subjects with hemiplegia
control subjects
baseline
between
post-stim

5.4 DISCUSSION

Tone about the MCP joints of the hand was measured before, during, and after volitional movement or FES in eight subjects with hemiplegia due to stroke, and in eight control subjects with no known neurological disorder.

In the first study, three or four sets of measurements of baseline resting tone took place over the course of 40 to 60 minutes. All subjects demonstrated a trend of decreasing mechanical impedance during at least one of the two sessions. The dependence of tone on factors such as temperature, effort, and emotion is well known (Brennan, 1959). The decline in tone observed in the present study may have been due to relaxation of the subject and adjustment to the testing environment.

It is also likely that the repeated passive movement of the joint during the quantification process contributed to the decrease in mechanical impedance. Several studies have documented changes in tone with prolonged stretch of the hypertonic muscles, and in fact reduction of spasticity by maintained stretch is the concept behind splinting. Reduction in tone has also been observed after relatively short periods of stretch. A lowering of the Ashworth score for resistance to passive movement of the finger flexors following 10 to 15 minutes of stretch was reported in subjects with hemiplegia due to stroke (Hummelsheim *et al.*, 1994). Improved performance of stroke subjects on a joint-movement tracking task following five minutes of short (maximum 20 seconds) periods of stretch alternating with "several seconds" of rest period was thought to be due to a reduction in the tone of the finger flexors, although tone was not actually assessed (Carey, 1990). In the present study, decrease of mechanical impedance within sets of six quantification trials was more dramatic than the overall decrease observed over the baseline period, and impedance levels at the beginning of one set were higher than at the end of the preceding set (Figure 5-3). This suggests that the stretching of the flexors was the main cause for the measured decline in impedance.

The change in impedance over a test session has important implications for the clinical and research settings, notably for assessment of effects of treatment within a period of a few hours. Whyte and Robinson (1990) caution against the use of multiple evaluations of spasticity in a single session to avoid effects of the assessment procedures. To reduce the effects of other factors, presumably temperature and emotion, it has been suggested that the subject sit alone in a warm, quiet room for half an hour before examination begins (Brennan, 1959).

Dewald and co-workers (1996) measured peak torque during ramp and hold stretches imposed by a torque motor on the elbow flexors of subjects with hemiplegia. Interestingly, they detected no trends in the variability of peak torque measures over sessions lasting from 10 minutes to more than an hour. Differences in observations may be due to differences in parameters measured, techniques of measurement, and muscles examined.

Despite the decrease in levels of tone over the course of the session, inter- and intra-rater reliability of the quantification device was good. Most of the decrease in Z occurring within sets of six trials occurred during the first three trials, which were always performed by the same examiner. Impedance values for examiner 1 were almost always lower than those measured by examiner 2. Alternating the order of examiners would have ruled out examiner effect as the cause of this. However, in several cases the trend observed over the first three trials (examiner 1) often continued through to the fourth and fifth trials (examiner 2). In addition, comparing the last trial performed by examiner 1 with the first trial of examiner 2 for each set of trials showed no significant difference between measures obtained by the two examiners. Because the decline in tone within a set was greater than that seen over an entire session, intra-rater reliability was tested by comparing the third trial performed by an examiner from every set of trials for a session. Any significant difference occurred between sets at either end of the session, and is thought to be due to actual changes in tone.

Negative elastic or viscous stiffness is thought to result from the subject assisting the imposed passive movements, and segments of the data traces containing negative values are thus discarded

from data for control subjects. The subjects with hemiplegia had very little or no volitional control of the muscles controlling finger flexion and extension; negative stiffnesses in these cases may have been due to assistance by involuntary flexor muscle activity. These values were retained and, since impedance is the vectorial sum of K and $B\omega$, resulted in positive values of Z.

The use of pathological levels of tone for functional purposes is not a new concept, the most common example cited being the assistance of a stiff leg in transfer or gait (Haley and Inacio, 1990; Hallett, 1985; Whyte and Robinson, 1990). Fingers locked in flexion allow a grasp, but, as Carey (Carey, 1990) points out, this grasp is of very limited use without a means of opening the hand. FES can be utilised to produce hand opening. For this to be effective, the level of flexor tone in the hand must be low enough to permit hand opening, yet high enough to permit a grasp. It is well known clinically that hypertonus in hemiplegia is enhanced by volitional movement (Bobath, 1990; Brennan, 1959). This phenomenon is attributed to synergies, unmasked reflexes, and associated reactions (Bobath, 1990; Brennan, 1959; Haley and Inacio, 1990). Strategies that reduce these effects are often employed to allow functional, purposeful movements of the affected side following stroke (Bobath, 1990). To our knowledge, the magnitude and time-course of the effects of volitional movement on hypertonus have never before been quantified.

In order to quantify effects of volitional movement on tone in the hand, in the first study we measured mechanical impedance about the MCP joints after five minutes of volitional activity of the affected arm. No apparent effect of the movement on tone was found, but this may be due to the fact that following movement, tone was measured only after a delay during which the force pads were replaced around the fingers. Because it was suspected that this manipulation interfered with the effect of movement on the tone in the hand, or that perhaps the effect of the movement was too transient to be detected after the delay, the second study was carried out during which mechanical impedance was measured during and immediately following volitional activity.

In the second study, tone in the hand was measured during tasks involving the elbow flexors or wrist extensors of the affected (ipsilateral) arm, or the contralateral finger flexors and thumb

adductors. Isometric contraction of the ipsilateral biceps or contralateral pinch grip produced increases in mechanical impedance in similar proportions of both subject groups (subjects with hemiplegia and control subjects). For the ipsilateral task, the relative amount of potentiation was often greater in subjects with hemiplegia. With 70% contralateral pinch grip, the relative amount of potentiation was generally the same between groups, but the absolute values of Z attained were usually much larger in subjects with hemiplegia. In subjects with hemiplegia, isometric contraction of the wrist extensors or isotonic contraction of the elbow flexors was more effective at increasing tone than isometric contraction of the elbow flexors. Carry-over occurred much more frequently in subjects with hemiplegia than in control subjects, and was stronger and lasted longer, in some cases beyond the 25 to 30-second period of recording following the task.

Cernacek (1961) found that EMG activity could be recorded from the finger flexors and extensors of one arm while the opposite hand performed active flexion and extension of the index finger. A significantly higher incidence of this "irradiation" was found in subjects with hemiplegia compared to able-bodied control subjects performing the task with the non-dominant hand. In our study, control subjects always performed the pinch grip task using the non-dominant hand, while subjects with hemiplegia used the unaffected hand. Although we did not perform statistical analysis on individual trials, visual inspection revealed that increases in tone in the hand occurred with the 70% contralateral pinch grip task in about 67% of trials with subjects with hemiplegia; this was slightly higher than the 51-60% observed with control subjects. Cernacek's study reported irradiation in all control subjects; our study showed increases in tone with 70% contralateral pinch grip in at least one trial for six out of eight control subjects, and for four or five of seven subjects with hemiplegia. In general, the results of the studies were in agreement, with variations in results likely due to differences in sensitivity of measurements and task performed.

In the present paper, very little change in tone was measured with the 20% contralateral pinch grip task in either subject group. This is in agreement with other studies reporting larger

irradiation effects, as measured by EMG, with increasing effort on the contralateral side (Cernacek, 1961; Hopf *et al.*, 1974; Mathiowetz *et al.*, 1983). Contrary to the present findings, one study claimed that no increase in tension occurred with irradiation, although the methods and details of observations leading to this conclusion were not reported (Hopf *et al.*, 1974). Again, methods of measurement, and specific task may explain differences in results.

Cernacek hypothesized that the irradiation observed was due to facilitation of the contralateral motor cortex via the corpus callosum (Cernacek, 1961). However, spinal circuits are also likely to be involved in the increase in tone measured in the present study. The tendon jerk, a means of clinical assessment of the monosynaptic reflex, is facilitated by strong contraction of remote muscles in what is known as the Jendrassik manoeuvre. The contraction is believed to produce this effect by increasing excitability of neurons in the central nervous system (Rothwell, 1994). Hyperexcitability of stretch reflexes is often implicated in hypertonus in spasticity (Rothwell, 1994). It follows, then, that hypertonus due to over-excitable stretch reflexes could be enhanced by exertion of remote muscles. It also follows that other central pathways influencing tone may also be affected.

Changes in tone measured in subjects with hemiplegia in the second study presented here may reflect changes in tone that occur during everyday activities. Isometric contraction of muscles of the ipsilateral arm, and production of effort with the contralateral hand may be required, for instance, in stabilization of a jar with the affected hand while opening the jar with the unaffected hand. Tasks involving movement of the affected arm are more likely to represent functional activities during which the FES device would be required to produce hand opening, such as reaching for an object. Although some subjects showed strong potentiation with performance of a task, some showed little or no increase in tone. The test tasks, however, involved relatively simple, isolated muscle contractions; extension of the entire arm as during a reaching task would better reflect a typical functional situation. We would expect to see greater levels of potentiation in a higher percentage of subjects with such an activity. Strategies to reduce such elevations in

tone would further increase the number of functional situations during which the FES device would prove beneficial.

Sometimes a decrease in impedance, relative to baseline levels, was detected during the recovery period. This occurred in both subject groups, although more commonly in control subjects. It is thought that anticipation of instruction to commence the task may have elevated tone in the hand during the baseline period.

In Study #2 of the present paper, two short (six second) trains of stimulation of the EDC via surface electrodes had very little effect on reducing levels of mechanical impedance at the MCP joints of subjects with hemiplegia. The most common change was an approximately 30% increase in tone following both stimulation trains, but most subjects showed no statistically significant difference in Z measures after stimulation compared to before.

Several recent studies have reported a reduction in spasticity of the upper limb after stimulation of the hypertonic muscle itself, with or without stimulation of the antagonist muscles. Ten minutes of surface stimulation over the biceps at intensities below motor threshold was followed by a decrease in peak torque recorded during ramp-and-hold perturbations of the elbow (Daly *et al.*, 1996; Dewald *et al.*, 1996). Increasing the stimulation intensity to above motor threshold, however, increased peak torque (Daly *et al.*, 1996). In contrast, two studies suggest that tone in the hand can be reduced by long-term stimulation of wrist (Hummelsheim *et al.*, 1997) or finger (Weingarden *et al.*, 1998) flexors and extensors at intensities producing muscle contraction; however, both studies used the Ashworth scale and reported decreases in tone of 0.5 or 1 point.

One stimulation protocol used in a long-term study of the effects of stimulation of wrist and finger extensors most closely reflects the protocol used in the current study (Baker *et al.*, 1979). Stimulation was cyclic and at intensities high enough to invoke extension of wrist and fingers as far as possible without causing discomfort to the subject. In that study, a slight decrease in tone of the wrist and finger flexors was detected at the end of four weeks. The authors admit that the

categorical and subjective nature of the rating scale used to assess the tone may have been partially responsible for the lack of more impressive results. It was also mentioned that a "more easily measureable, transient" decline in hypertonus was felt immediately after individual 30-minute periods of stimulation, although no measure of the amount of decline was presented.

In contrast to the results presented by Baker (1979), cyclic stimulation for a period of twenty minutes had no apparent effect on tone in Study #1 of the current paper. However, the gradual decline of impedance measures throughout the period of baseline measures and details of the protocol made the findings inconclusive. The passive movements of the fingers required for quantification of impedance involved cyclical stretching of the finger flexors, and it is likely that this stretching was responsible for the decline in baseline impedance measures (i.e. the measurement caused a change in the measured variable). It is possible that a twenty-minute period without stretch or stimulation would have resulted in a return of impedance measures to the levels recorded at the beginning of the session, but that stimulation prevented a complete return. In addition, Rymer noted that volitional movement reduced, but did not abolish, the effects of 10 minutes of cutaneous stimulation over the biceps in reducing peak torque at the elbow (Daly *et al.*, 1996). Any assistance with replacement of the wrist brace and force sensors attempted by the subjects following stimulation in Study #1 would have counteracted any tone-reducing effects of the stimulation. So it is possible, then, that tone was reduced following stimulation, but that this reduction was not detected with the protocol employed. Studies assessing the magnitude and time-course of effects of therapeutic interventions (e.g. FES) on spastic hypertonus, and which employ measurement protocols that require stretch of the muscle must control for the effect of stretching itself.

5.4.1 Conclusions

The techniques used in this paper appear to provide a reliable, simple method of quantifying tone in the hand. An overall decrease in mechanical impedance was measured in most subjects with hemiplegia over the course of a test session, as well as within sets of six trials. This may have been due to stretching of the hypertonic muscles resulting from the repeated passive flexion and extension at the MCP joints. Changes in tone were measured during performance of volitional tasks involving the ipsi- and contralateral arms of subjects with hemiplegia and control subjects. For most tasks, increases in tone during the task itself were seen in as many control subjects as subjects with hemiplegia, but the impedance values attained in the latter group were almost always higher, and in some cases took longer to subside. Suppression of increases in tone observed with volitional movement would expand the functional potential of FES-produced hand opening. Short-term stimulation had no apparent effect on hypertonus, although this does not necessarily mean that hypertonus would be unchanged after long-term stimulation.

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CHAPTER 6

General Discussion

This thesis describes four studies which together involved the development and application of methods to quantify clinically-established tests of hypertonicity and bradykinesia. All of the studies employed a device to quantify resistance of a joint to passive cyclic extension and flexion. Chapter 2 dealt with technical aspects and clinical testing of the device. In Chapters 3 and 4, the device was used to measure the effect of pallidotomy, thalamotomy, or DBS on rigidity in subjects with Parkinson's disease. Chapters 3 and 4 also measured parameters of movement during performance of simple repetitive tasks. In a preliminary investigation described in Chapter 2, the rigidity quantification device was adapted to allow measurement of tone in the hands of subjects after stroke; this application was explored further in Chapter 5, where it was used to assess the effects of volitional movement and FES on tone in the hands of subjects with hemiplegia and control subjects.

Any method of assessment must be accurate and reliable in order to be useful. In Chapter 2 it was determined that the characteristics of the sensors employed were suitable for monitoring angular displacement and torque under conditions anticipated for clinical assessment of tone. The quantification of elastic stiffness was also validated using a prosthetic arm. The reliability of the device was established both by using the model arm (intra-rater), and during a clinical trial with subjects with Parkinson's disease. Non-linear relationships between quantified measures of impedance and UPDRS ratings were characterized, although a larger study would be useful in refining the proposed conversion formulae.

The quantification techniques described in this thesis were designed for use in the clinical setting. It was hypothesized that these methods could also aid in making accurate and reliable assessments during stereotactic surgery. Chapter 3 determined that both quantification methods

were practical and appropriate for the regular perioperative examination as well as for intraoperative use, in that they essentially quantified components of the clinical evaluation. It was concluded that intraoperatively they may be of particular use in cases where macrostimulation or lesioning produces only subtle effects, but that observed inconsistencies in instruction could obscure results. Perioperatively, these methods offer an objective complement to clinical evaluation of surgical outcome.

Chapters 4 and 5 describe the application of the device to measuring changes in mechanical impedance due to external influences. The goal of Chapter 4 was to quantify effects of GPi and STN chronic DBS on rigidity and volitional movement of the arms and legs. Reduction in mechanical impedance and increases in speed and amplitude of repetitive movements were measured in most subjects, and were statistically significant in both "off" and "on" medication states. In Chapter 5, increases in tone in the hands of subjects with hemiplegia and control subjects were recorded during volitional movement of the ipsi- and contralateral arms. Unexpectedly, gradual decreases in baseline levels of tone were also measured over the course of test sessions in a separate set of experiments involving subjects with hemiplegia. Because of this and other confounding variables, results concerning the effect of 20-minute periods of FES on the level of tone were inconclusive.

6.1 FUTURE DIRECTIONS

The studies described in this thesis deal largely with development of the quantification methods and clinical testing, with some application to clinical investigations. Although further development of the techniques would enhance their utility, these methods have reached a point where they may be applied to investigating physiological and clinical questions.

6.1.1 Further development of quantification methods

Some technical concerns that arose over the course of this work should be addressed. For example, differences in the size of the arm were not taken into account during quantification of mechanical impedance. For the most part, this did not appear to be an issue. However, Z measures were very disproportionate to clinical ratings for two subjects of slighter build compared to findings from other subjects. Although quantification of changes in rigidity would still be accurate, a simple estimate of arm mass may need to be incorporated into the methods in order for absolute measures of rigidity to be scaled according to arm size. Similarly, in Chapter 2 it was noted that small negative values of K are obtained when mechanical impedance is measured about the elbow of a completely relaxed subject without hypertonus. This has been attributed to the varying action of gravitational and inertial forces on the mass of the forearm during its rotation. Our current method of analysis discards negative values of stiffness, and thus does not accommodate such situations. In addition, in Chapter 4, difficulties were encountered with estimating peak-to-peak amplitude and mean speed of repetitive movements in cases of low frequencies of movement. Performing the analysis on intervals of data longer than the 1-second intervals used would reduce the incidence of such difficulties. One alternative may be to analyze the entire trial, although this has the distinct disadvantage that the number of trials required for an adequate power in statistical comparisons might become prohibitive.

Of the four parameters of volitional movement measured during performance of repetitive tasks, peak-to-peak amplitude and mean speed appeared to be the most discriminative. Clinical ratings of hand pronation/supination tasks collected during perioperative assessments in Chapter 3 correlated better with these two parameters than with either frequency or harmonicity. Although not formally analyzed, it is suspected that the same was true for hand pronation/supination and heel taps measured during the DBS study in Chapter 4, as it was these parameters that showed the most consistent effects of stimulation. Better characterization of these relationships may allow

performance of repetitive tasks, as described by the quantified parameters, to be expressed in terms of UPDRS ratings, as was suggested for measures of mechanical impedance in Chapter 2. This would result in a simplified measure, a single score, while still permitting analysis of individual parameters.

6.1.2 Application of quantification methods

Several questions pertaining to the effects of stereotactic surgery remain unanswered. Quantified measures of rigidity and repetitive hand movements provide sensitive and reliable means to aid clinical studies in determining the relative effects of and indications for the different procedures, and in establishing the optimal surgical techniques. In Chapter 4, it was observed in two subjects that unilateral stimulation of the STN could be as effective as bilateral stimulation in reducing rigidity of the contralateral or ipsilateral elbow. Other studies have reported ipsilateral effects of unilateral stimulation of the GPi, but these were either not specifically assessed (Bejjani *et al.*, 1997; Krack *et al.*, 1998), or were limited in scope (Merello *et al.*, 1999; Volkmann *et al.*, 1998). One study reported no ipsilateral effects in any of seven subjects examined (Gross *et al.*, 1997). Reports of effects of unilateral stimulation of the STN are rare. However, in a study by Limousin (Limousin *et al.*, 1995), ipsilateral improvement of rigidity was observed in three subjects with unilateral semi-microelectrode stimulation intraoperatively; postoperative effects were mainly contralateral in the one subject receiving unilateral STN DBS. It would be of clinical and physiological interest to determine if the bilateral effects of STN DBS presented in Chapter 4 are typical, and if other symptoms are similarly affected.

The quantification methods applied in this thesis offer a more sensitive measure than that afforded by clinical ratings, and additionally provide a record of parameters of force and movement with time. Used intraoperatively, they could thus enhance studies aimed at correlating neuronal activity recorded with microelectrodes with imposed and voluntary movements, or with

the severity of or fluctuations in symptoms. Such studies add to our understanding of the physiology and role of the basal ganglia, and may help elucidate the mechanism of motor deficits in Parkinson's disease.

In Chapter 5, mechanical impedance in the hand was quantified during volitional movement. The original motivation for this study stemmed from the introduction of a device that used FES to produce hand opening in subjects with hemiplegia (Prochazka, 1997). Optimal functioning of this device required levels of tone low enough to permit hand opening, yet high enough to produce a functional grasp in the absence of stimulation. Increases in tone during volitional movement could compromise the efficacy of stimulation (Cameron *et al.*, 1999); strategies to modulate the level of tone, such as flexing the wrist or resting the hand on a surface (Cameron *et al.*, 1999), would thus expand the functional potential of the device. It was with the eventual aim of determining other such strategies that the study in Chapter 5 was undertaken. It is evident from the results of the study that the level of tone can vary dramatically with volitional activity. Further, strategies for reduction of hypertonicity have been employed in physical rehabilitation of patients with hemiplegia (Bobath, 1990). Future studies could be directed at finding particular strategies appropriate for use with the FES device.

6.2 CONCLUDING REMARKS

Over the course of the two studies measuring effects of stereotactic surgery, it was noticed that the clinical assessments of rigidity were performed quite differently in each of the three centres in which data were collected, despite a conscientious application of the UPDRS in each of these centres. Similarly, the hand pronation/supination task was also administered in at least two different ways. The need for standardization between centres for the purposes of comparison of results is stated over and over again in the literature pertaining to stereotactic surgery, yet despite recent efforts (Goetz *et al.*, 1995), this has not yet been accomplished through the use of the

UPDRS, and more steps need to be taken. While quantification methods will not aid in standardization unless they are widely adopted, they do offer objective, sensitive measures of surgical outcome, and thus complement the more established clinical evaluations. Precise characterization of the relationships between quantified measures and clinical ratings obtained in a large international study would allow expression of the quantified measures in terms of these scores and, a potentially, comparison of results between centres administering the UPDRS in a similar manner.

The quantification methods employed in this thesis allow objective monitoring of clinically-established tests of motor impairment, including at least four components of the UPDRS (rigidity, hand pronation/supination, hand opening/closing, and leg agility), and allow for simultaneous assignment of clinical ratings. They are not intended to replace the clinical methods, nor are they a substitute for the judgement of experienced clinicians. They do, however, provide an objective complement which would benefit assessments of disease progression and therapeutic intervention.

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