NEURONAL FIRING RATES IN MOTOR THALAMUS OF PARKINSON'S DISEASE (PD) AND ESSENTIAL TREMOR (ET) PATIENTS

By

Gregory F. Molnar

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Abstract

NEURONAL FIRING RATES IN MOTOR THALAMUS OF PARKINSON'S DISEASE (PD) AND ESSENTIAL TREMOR (ET) PATIENTS

Gregory F. Molnar, Master's of Science Degree, 2000
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Current models predict that the motor symptoms of PD result from increased inhibitory outflow from the basal ganglia to thalamic neurons in ventralis oralis posterior (Vop; VLa in monkey). In contrast, ET may result from increased excitatory inputs from cerebellum to the thalamic ventralis intermedius nucleus (Vim; VLp). We examined the firing rates of 122 neurons in motor thalamus in 5 PD, 10 ET and 6 "control" patients (chronic pain; Pain group) during microelectrode guided functional neurosurgery. The mean spontaneous firing rate (MSFR) of neurons responding best to voluntary movements, presumed in Vop, in PD patients (7.4±1.0 Hz, mean ± SEM) was significantly lower ($p < 0.01$) than in the ET (18.1±3.0 Hz) and Pain (19.0±1.9Hz) groups. In contrast, the MSFR of neurons responding best to passive movements, presumed to be in Vim, was significantly greater in ET patients (25.8±3.5 Hz) than in PD (14.3±1.6 Hz) and Pain (16.1±1.5 Hz) groups.

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List of Abbreviations

CR	cerebellar-receiving
DA	dopamine
DBS	deep brain stimulation
EMG	electromyogram
enk	enkephalin
ET	essential tremor
GABA	gamma aminobutyric acid
Glu	glutamate
GPe	globus pallidus external segment
GPi	globus pallidus internal segment
IOC	inferior olivary complex
Ki	kinesthetic-responsive
Lpo	lateral posterior nucleus, oral part
MAO A	monoamine oxidase inhibitor type A
MC	motor cortex
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSFR	mean spontaneous firing rate
PD	Parkinson's disease
PMC	premotor cortex
PPN	pedunculopontine nucleus
PR	pallidal-receiving
rCBF	regional cerebral blood flow
SMA	supplementary motor area
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
Subst P	substance P
VA	ventral anterior
VApc	ventral anterior nucleus, parvocellular portion
Vc	ventralis caudalis
Vim	ventralis intermedius
VL	ventral lateral
VLa	ventral lateral nucleus, anterior part
VLo	ventral lateral nucleus, oral part
VLp	ventral lateral nucleus, posterior part
VPLo	ventral posterior lateral nucleus, oral part
Voa	ventralis oralis anterior
Vol	voluntary-responsive
Vop	ventralis oralis posterior

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Preface

"... the innate intelligence of the body is infinitely more sophisticated than our thinking minds." This quotation from Diamond and Diamond (1985 pg. 21), in their lay person discussion of human biology, provides an indication of the vast detail we have yet to attain about the complex structure and function of the human body. The human brain is indeed the 'head' of this vast sophistication of the body. Research into the human central nervous system (CNS) as it controls behavior is one of the greatest challenges of the scientific community. Many functions of the CNS have been elucidated from the behavioral and pathological symptoms experienced as a result of a particular disorder or disease (i.e. the brain as a dependent variable). The involvement of the basal ganglia-thalamo-cortical loop in the control of movement was discovered in the late 1950s as a result of linking the hypokinetic symptoms (i.e. akinesia, bradykinesia, 4-6Hz rest tremor) of Parkinson's disease (PD) to the degeneration of an area of the basal ganglia (Côté & Crutcher 1991; Mink 1996). Since then various physiological models and theories have been developed to explain how the basal ganglia and other structures such as the cortex and cerebellum work in the control of movement and how the function changes in the presence of a movement disorder pathology. For the purposes of the present thesis two types of movement related pathologies will be discussed, those involved in Parkinson's disease and Essential tremor. Because of the great complexity of the CNS much has yet to be learned and new evidence often contradicts old models and theories. The intent of this thesis is to present data that provide evidence for the involvement of thalamus in both Parkinson's disease and Essential tremor. These data are

proposed to be consistent with current pathological models for these two movement disorders and further our understanding of the control of movement in the human CNS.

Section 1. Introduction

According to the current model of the pathophysiology of Parkinson's disease (PD), the cardinal symptoms (i.e. akinesia/bradykinesia, rigidity, and 3-6Hz rest tremor) are due to hyperactivity of the basal ganglia output nuclei (i.e. globus pallidus internus (GPi), substantia nigra pars reticulata (SNr)) which leads to depression of thalamic neurons and motor cortical areas (Alexander and Crutcher 1991; DeLong 1990). An increase in GPi firing has been observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primates (Filion and Tremblay 1991) and PD patients (Hutchison et al. 1994) and lesions in GPi improve PD symptoms (Lozano et al. 1995).

Essential tremor (ET) is a movement disorder generally characterized by monosymptomatic action or postural tremor with a frequency of 4-12Hz (Findley and Koller 1987). Tremor symptoms have been induced in animal models of ET by means of brainstem lesions (i.e. ventral tegmental area) or harmaline injections, which cause 8-12Hz oscillations in the inferior olive and cerebellar neurons (Lamarre 1984). Functional imaging studies using positron emission tomography have found increased bilateral cerebellar regional cerebral blood flow (rCBF) during rest and involuntary tremor and abnormal red nucleus and thalamic activation during tremor in ET patients (Bucher et al. 1997; Jenkins et al. 1993). Thus the tremor in ET patients may be related to increased activity in cerebello-thalamic pathways.

The tremor of both PD and ET can be effectively treated by thalamotomy or thalamic deep brain stimulation (DBS) in the ventralis intermedius nucleus (Vim) at approximately identical locations (Jankovic et al. 1995; Tasker 1990). Extracellular recordings obtained

during thalamic exploration in human patients reveal characteristic physiological information (i.e. firing rates, firing patterns) about neurons within the various nuclei (Albe-Fessard 1973). Neurons in the ventral thalamus that respond to voluntary movements are located largely within the ventralis oralis subnuclei (Voa/Vop) and neurons that respond to kinesthetic/passive movements about a joint are primarily contained within Vim (Ohye et al. 1976; Raeva 1999; Tasker and Kiss 1995). Voa/Vop areas of motor thalamus and equivalent areas in monkey thalamus (VLo, Olszewski 1952; VLa, Hirai and Jones 1989) primarily receive input from the basal ganglia and project to premotor areas of cortex (Macchi and Jones 1997). Vim and the equivalent area in monkey (VPLo, Olszewski 1952; VLp, Hirai and Jones 1989) motor thalamus primarily receives input from the cerebellum and projects to primary motor cortex (Macchi and Jones 1997).

Current pathophysiologic models of PD predict a decrease in the spontaneous activity in the Voa/Vop subnuclei of thalamus in PD compared to ET and control (pain) groups. The proposed pathology of ET predicts that the neurons in the Vim nucleus exhibit increased firing rates relative to PD and control patients.

Therefore, the primary intent of the present study was to determine whether there are any differences in the spontaneous firing rates of neurons that respond to either voluntary or kinesthetic (i.e. presumed Voa/Vop and Vim neurons, respectively) movements of the hand in PD, ET and control patient groups.

Section 2. Literature Review

2.1.1 Parkinson's Disease

Parkinson's disease (PD) was first described by James Parkinson early in the nineteenth century through analysis of six patient case histories (Parkinson (1917), as reviewed in Capildeo 1984). In his 'An Essay on Shaking Palsy', James Parkinson describes the tremor and gait disturbances associated with PD (Capildeo 1984). Today PD is known as a slowly progressing neurodegenerative disease that results in movement related symptoms including, rest tremor, rigidity, akinesia, bradykinesia, abnormal flexed posture with postural instability, and dementia (for review see Lang and Lozano 1998). Aarsland et al. (1996) reported that 28% of older PD patients had dementia. PD currently affects about one million people in North America with an elderly age onset (mean age is 58 yrs) but in 10 percent of cases there is a young age onset (under 40 yrs) (Bennett et al., 1996; Cote' & Crutcher 1991; Lilienfeld and Pert 1993). These symptoms have a great impact on daily activities of living.

The basal ganglia model (Delong 1990) used to describe the pathophysiology of PD is also the current basis for the understanding of medical and surgical treatment for PD (see section 2.1.2 of this thesis for further detail). Initial medical treatment using Levodopa (dopamine precursor, discovered in the 1960's) is the most effective treatment for PD. However its benefit only lasts five to seven years after such time it is no longer effective or causes motor complication (Cotzias et al. 1967; Lang and Lozano 1998). It had been shown by Cooper (1955) before the discovery of Levodopa that chemical lesions of the pallidum were effective in treating PD symptoms.

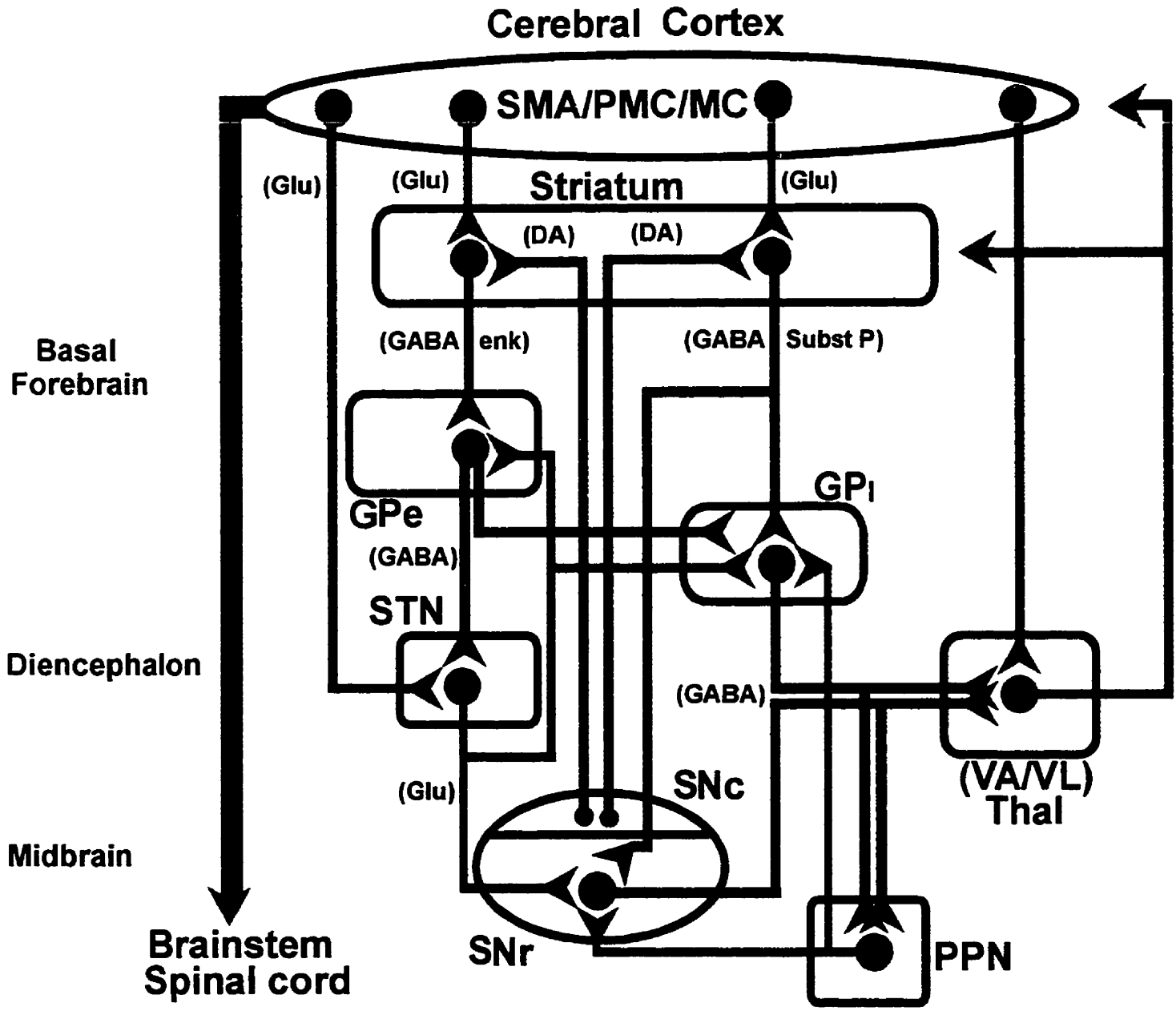
The administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to primates provides an effective model for the study of PD movement symptoms and pathological changes (Burns et al. 1983; Langston et al. 1984; Schultz et al. 1985). The PD pathology and the MPTP-induced parkinsonism involve a degeneration of the nigrostriatal projections due to a substantial loss of (DA) neurons in SNc (Bankiewicz et al. 1986; Burns et al. 1983; Burns et al. 1984; Fearnley and Lees, 1991; Langston and Ballard 1984; Langston et al. 1984, 1990; Marek et al. 1996). The role of this loss of DA neurons in the movement related symptoms will be described in section 2.1.2 of this thesis.

2.1.2 Basal Ganglia model for Parkinson's Disease

The current model of basal ganglia structure and function was originally proposed in the 1980's following observations made from patients who had hypo- or hyperkinetic movement disorders and from animal models of neurodegenerative diseases. (Albin et al. 1989; Alexander and Crutcher 1990a; Alexander et al. 1986; Delong 1990; Marsden and Obeso 1994; Mink 1996; Parent 1990, 1998; Parent and Hazrati 1993). From these mentioned sources a collected summary of the current models for normal function and for PD pathology is as follows (also please refer to **Figure 1** for model summary diagram).

The basal ganglia consist of nuclei of the deep forebrain, the diencephalon and the midbrain. In the deep forebrain the structures involved are the caudate and putamen which comprise the striatum and the external and internal segments of the globus pallidus. The structure involved in the diencephalon is the subthalamic nucleus

Figure 1: Summary basal ganglia model showing neuronal connections between the various nuclei involved, during normal function. Blue arrows represent excitatory connections and red arrows represent inhibitory connections. Abbreviations: DA, dopamine; enk, enkephalin; GABA, gamma-aminobutyric acid; Glu, glutamate; Gpe, external segment of globus pallidus; Gpi, internal segment of globus pallidus; MC, motor cortex; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Subst P, substance P; (VA/VL) Thal, ventral anterior and ventral lateral areas of thalamus.


Cerebral Cortex
SMA/PMC/MC
(Glu)
(Glu)
Striatum
(Glu)
(DA)
(DA)
Basal Forebrain
(GABA enk)
(GABA Subst P)
GPe
(GABA)
GPI
STN
Diencephalon
(GABA)
(VA/VL) Thal
(Glu)
SNc
Midbrain
SNr
PPN
Brainstem Spinal cord

(STN). In the midbrain the two divisions of the substantia nigra (SN) are included in the basal ganglia; substantia nigra pars compacta (SNc) and substantia nigra pars reticulata (SNr). The striatum is the major input stage of the basal ganglia, and the principle inputs are glutamanergic (Glu) excitatory projections from the cerebral cortex and dopaminergic (DA) excitatory and inhibitory projections from SNc. The cortical projections are from areas of motor cortex, premotor cortex, frontal eye fields, supplementary motor area, and prefrontal cortex. The major outputs of the basal ganglia are inhibitory GABAergic projections from the internal segment of the globus pallidus (GPi) and the SNr to ventral anterior (VA) and ventral lateral (VL) nuclei of thalamus and the pedunculopontine nucleus (PPN) of the brainstem. Because of their similarities in histology, physiology and projections the GPi and SNr are considered homologous structures. The basal ganglia consist of two pathways that are thought to be involved in the control of movement, the *Direct Pathway* and the *Indirect Pathway*. The *Direct Pathway* involves direct inhibitory projections (GABA co-localized with substance-P) from the striatum to GPi /SNr. Stimulation of this pathway from either cortical (Glu) input or SNc excitatory (DA) input results in disinhibition of excitatory projection neurons in VA/VL areas of thalamus that project to precentral motor fields. This is considered to facilitate cortically initiated movement. The *Indirect Pathway* involves inhibitory projections (GABA co-localized with enkephalin) from the striatum to the external segment of the globus pallidus (GPe). From the GPe there are inhibitory projections (GABA) to the STN (there are also excitatory Glu projections from cortex to STN). The STN has excitatory projections (Glu) to GPi/SNr and GPe. Activation of the *indirect pathway* from cortical

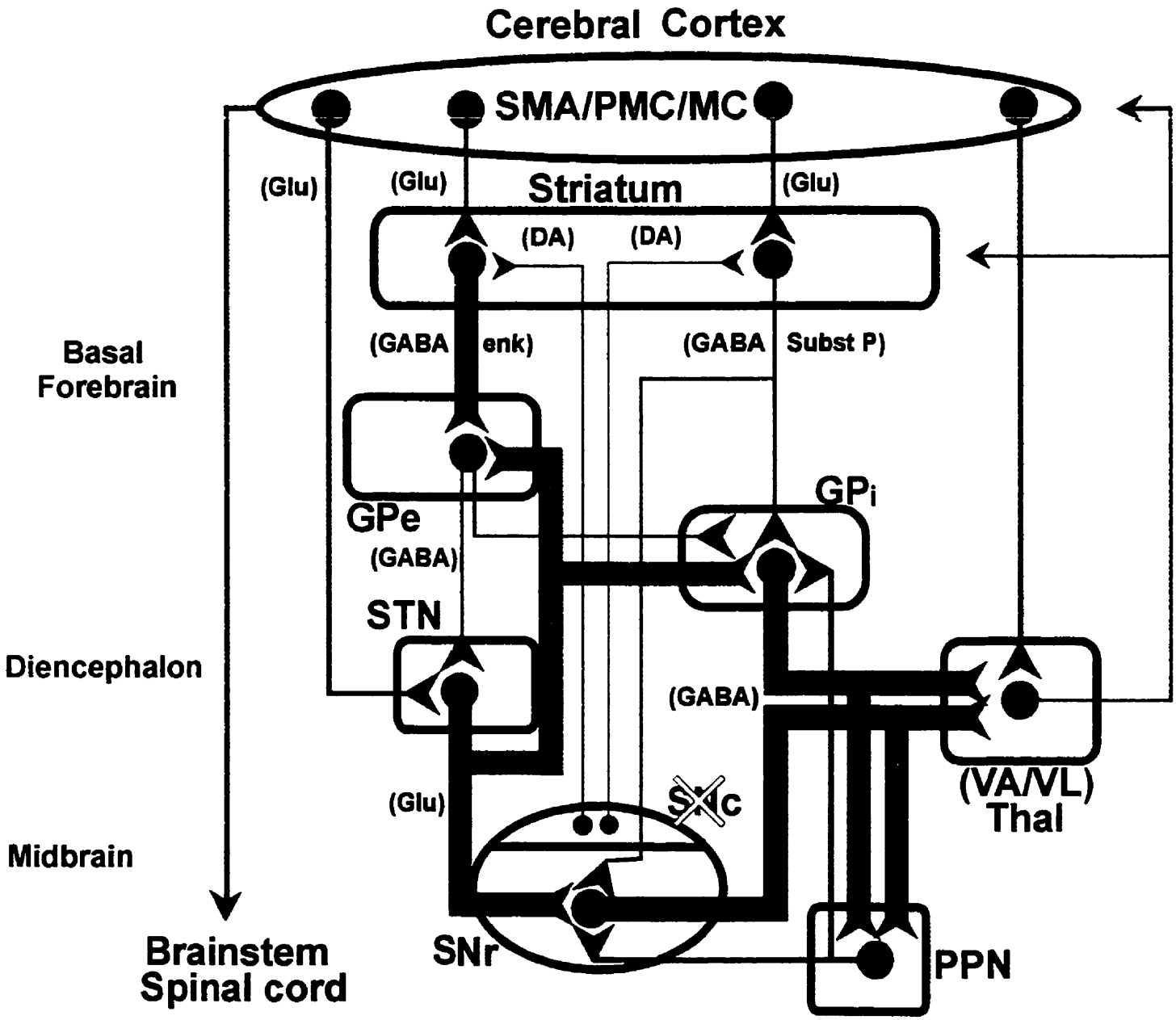
(Glu) input suppresses the activity of GPe neurons thus disinhibiting the STN (Glu) input to GPi/SNr. This leads to increased inhibition from GPi/SNr to VA/VL projection neurons of thalamus resulting in reduced output to precentral motor areas of cortex. DA input from the SNc to the striatum is believed to excite the direct pathway (striatal neurons primarily expressing D1 DA receptors) and inhibit the indirect pathway (striatal neurons primarily expressing D2 DA receptors). Thus, in summary of the current basal ganglia model, the direct pathway provides positive feedback to precentral cortical areas and the indirect pathway provides negative feedback.

The net overall role of the basal ganglia in motor control based on the current model is mediated through interactions between the direct and indirect pathways. Marsden and Obeso (1994) summarize that the direct pathway facilitates appropriate cortically initiated movements, while the indirect pathway suppresses conflicting unwanted motor patterns. The authors used an excerpt from Alexander and Crutcher (1990a) to explain this: 'the motor circuit (in the basal ganglia) might be seen as playing a dual role in the modulation of motor patterns initiated at cortical levels by both reinforcing the currently selected pattern via the direct pathway and suppressing potentially conflicting patterns via the indirect pathway. Overall, this could result in the focussing of neural activity underlying each cortically initiated movement in a fashion analogous to the 'inhibitory surround' seen in various sensory systems.' In addition neural recordings in primates and humans from basal ganglia and output structures provide evidence that the motor circuits of the basal ganglia play a key role in the preparation and execution of normal movements generated in the cerebral cortex (Alexander and Crutcher 1990a; Alexander and Crutcher

1990b; Crutcher and Alexander 1990; Marsden and Obeso 1994; Mink 1996; Raeva et al. 1999).

From the current model it is suggested that the hypokinetic symptoms (i.e. akinesia, bradykinesia, tremor) of PD and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in primates are due to reduced striatal (DA) input and the subsequent effects on the direct and indirect pathways in response to a cortical generated movement (DeLong 1990) (See **Figure 2** for summary). The PD pathology and the MPTP-induced parkinsonism involve a degeneration of the nigrostriatal projections due to a substantial loss of (DA) neurons in SNc (Bankiewicz et al. 1986; Burns et al. 1983; Burns et al. 1984; Fearnley and Lees 1991; Langston et al. 1984; Langston and Ballard 1984; Marek et al. 1996). A loss of (DA) excitation (via D1 receptors) to the direct pathway is thought to reduce striatal inhibitory (GABA/substance P) projections to GPi/SNr leading to increased inhibition in VA/VL of thalamus to support cortically initiated movements. An increase in GPi firing has been observed through microelectrode recordings in PD patients and in MPTP treated primates and lesions in GPi improve PD symptoms (Filion et al. 1991; Filion and Tremblay 1991; Hutchison et al. 1994; Lozano et al. 1995). A loss of (DA) inhibition (via D2 receptors) to the indirect pathway increases the inhibitory drive (GABA/enkephalin) from the striatum to GPe, which reduces inhibitory (GABA) projections to the STN. Reduced inhibitory input to STN increases excitatory (Glu) projections to GPi/SNr again resulting in increased inhibition in VA/VL of thalamus to support cortically initiated movements. There is also increased inhibition to brain stem (i.e. PPN) motor areas to support activity along the reticulospinal

Figure 2: Summary basal ganglia model showing neuronal connections between the various nuclei, during PD pathology. Blue arrows represent excitatory connections and red arrows represent inhibitory connections. An increase or decrease in the thickness of an arrow represents a corresponding increase or decrease in the strength of a connection compared to healthy state. Abbreviations: DA, dopamine; enk, enkephalin; GABA, g-aminobutyric acid; Glu, glutamate; Gpe, external segment of globus pallidus; Gpi, internal segment of globus pallidus; MC, motor cortex; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Subst P, substance P; (VA/VL) Thal, ventral anterior and ventral lateral areas of thalamus. The yellow 'X' over SNc represents the DA neuron degeneration in PD.


Cerebral Cortex
SMA/PMC/MC
(Glu)
(Glu)
Striatum
(Glu)
(DA)
(DA)
Basal Forebrain
(GABA enk)
(GABA Subst P)
GPe
(GABA)
GPi
STN
Diencephalon
(GABA)
(Glu)
SNc
(VA/VL) Thal
Midbrain
SNr
PPN
Brainstem Spinal cord

motor system.

N.B. It is important to note that the thalamic inhibition predicted by the basal ganglia model is based on physiological evidence from structures below and above the level of thalamus. The present thesis is the first known account of changes in the physiology of the human thalamus in PD patients; a preliminary report of thalamic changes in MPTP monkeys has been presented by Vitek et al. (1994) (discussed in section 5 of the present thesis).

Increased STN neuronal activity has been recorded in PD patients and MPTP primates and STN lesions or DBS at sites in STN improves PD symptoms (Bergman et al. 1990; Guridi et al. 1996; Hutchison et al. 1998). Treatment with levodopa (a dopamine precursor) relieves the hypokinetic symptoms of PD, which is believed to be because it restores SNc (DA) function in the striatum (Cote' and Crutcher 1991; Lang and Lozano 1998). Dopamine agonists have been found to decrease the firing rates in GPi in PD patients at doses that relieve bradykinesia (Hutchison et al. 1997). Anderson et al. (1993) (referenced in Mink 1996) recorded the activity of neurons in pallidal receiving areas of thalamus in normal monkeys before and after inactivation of GPi with an injection of muscimol (GABA receptor agonist). They found that the magnitude of phasic movement-related thalamic discharge was increased for some neurons and decreased or unchanged for others. Since the timing of the phasic movement-related thalamic discharge was unchanged with muscimol the authors concluded that GPi exerts a variable tonic inhibitory effect on thalamic neurons (Anderson et al. 1993). Thus, based on the

'dual pathway' current model, the overall effect of PD pathology is a reduction in the (DA) nigral-striatal projection thus resulting in inhibition of thalamo-cortical projections to a depression of cortically initiated movements. This is mediated by changes in both the direct and indirect pathways that effectively increase GPi/SNr inhibitory output.

The current model has been an effective and useful model for understanding the role of the basal ganglia in the control of movement. Many authors credit the model for the generation of further research into the basal ganglia and for the clinical application as seen by the resurgence of stereotaxic ablation surgeries to treat movement disorders (Albanese 1998; Lang and Lozano 1998; Mink 1998).

There are limitations to this model in explaining all the symptoms of PD and the role of many neuronal connections between the various nuclei are unknown and ignored (for reviews see Mink 1996; Parent and Hazrati 1995a,b). The basal ganglia model described above is considered more effective in explaining the akinesia, rigidity and bradykinesia (i.e. by increased inhibition of thalamocortical relays) than in explaining the mechanisms underlying tremor. One hypothesis for explaining PD tremor proposes that tremor is the result of activity of an intrinsic thalamic pacemaker that is activated by the hyperpolarization (i.e. increased inhibition by GPi) of thalamic cells (Pare et al. 1990). This *central* hypothesis is based on evidence that thalamic neurons, when hyperpolarized (i.e. during sleep), have the intrinsic property of oscillating with bursting of the type associated with low threshold calcium spikes at about 9Hz (Pare et al. 1990; Llinás 1984; Llinás and Jahnsen 1982; Steriade et al. 1990; Zirh et al. 1998). Another hypothesis, the *peripheral* hypothesis, suggests that PD tremor results from oscillations of an

unstable/abnormal long-loop transcortical reflex arc (Evarts and Tangi 1974; Mathews 1991; Tatton and Lee 1975). This hypothesis is proposed from evidence showing pyramidal neurons in motor cortex firing in response to muscle stretch and cause contraction of the stretched muscle (Mathews 1991). Tatton and Lee (1975) provide evidence that PD patients have abnormally increased gain in transcortical stretch reflexes and are unable to suppress them in response to instruction. Neuronal modeling studies show that oscillations can result in long-loop transcortical reflexes when they become unstable due to increased gain and thus could be a mechanism of PD tremor (Stein and Oguztoreli 1976). Thalamic phasic bursts due to tremor generation by *peripheral* mechanisms were predicted to have an acceleration-deceleration sinusoidal pattern (Zirh et al. 1998). Zirh et al. (1998) analyzed thalamic tremor cells in PD patients undergoing stereotactic surgery to determine if their neurons had bursting characteristics such that support either the *central* or *peripheral* hypothesis for tremor. The authors determined that the nature of the majority of bursting cells was not consistent with either hypothesis and that some other oscillatory process may be involved in generating PD tremor. Thus much remains to be elucidated as to the exact mechanism(s) involved in PD tremor generation.

2.2.1 Essential Tremor

Essential tremor (ET) is a somewhat prevalent, and often debilitating motor dysfunction, which has been estimated to affect between 0.3-1.7% of the population at large, and 7.2% of those over the age of 50 (Rautakorpi et al. 1984; Salemi et al. 1994).

There is a family history of ET in about half of those affected; ET is presumed inherited as an autosomal dominant trait with variable penetrance (Young 1986). ET is generally characterized by an action or postural tremor with a frequency of 4-12 Hz, which is not present at rest (Gresty and Findley 1984; Hua et al. 1998). Surface EMGs on the tremulous limb in the majority of ET cases reveal synchronous bursts in antagonist muscles whereas for PD tremor the EMG bursts alternate between agonist and antagonist muscles (Marsden 1984; Young 1986). Medical management of ET can be attained with beta-adrenoreceptor blockers (i.e. propranolol), sedatives (i.e. primidone, phenobarbitone), and even ethanol can reduce tremor magnitude (Fahn 1984; Findley and Koller 1987).

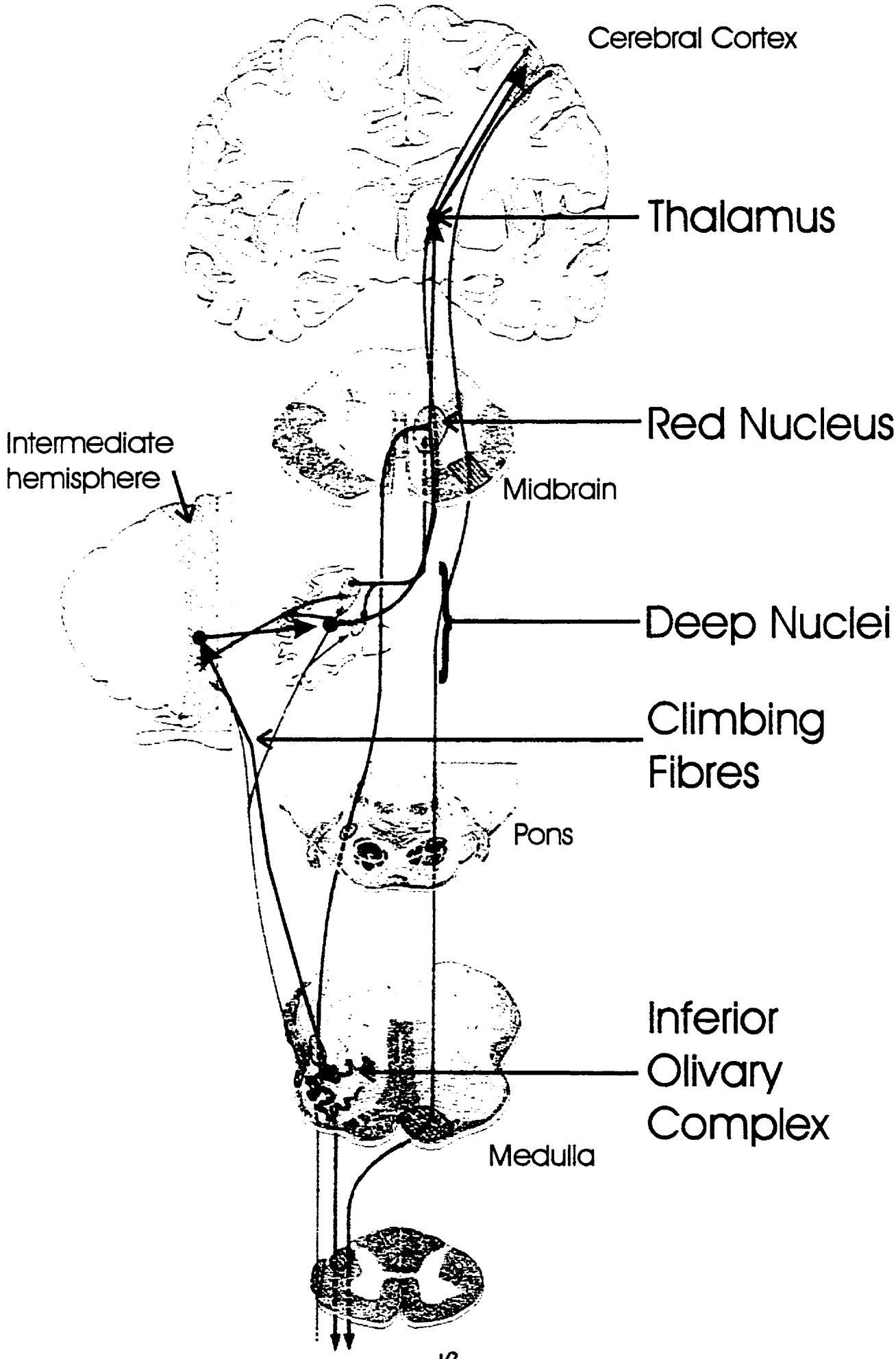
In spite of its pervasiveness, however, relatively little work has been done to elucidate the pathophysiology of ET, and the possible neuronal pathways involved remain poorly understood. What is known is that a lesion or the use of a deep brain stimulator in the ventralis intermedius nucleus (Vim) of the thalamus can arrest or significantly reduce tremor (Goldman et al. 1992; Hirai et al. 1983; Im et al. 1996; Jankovic et al. 1995). Evidence of high frequency tremor cells, which fire synchronously with involuntary tremor, is commonly found during stereotactic thalamic exploration in ET patients (Goldman et al. 1992; Hua et al. 1998; Jankovic et al. 1995). Post-mortem examinations of ET patients have revealed that there are no neuropathologic lesions that might be specific for ET (Rajput et al. 1991). It has also been determined that there are no structural MRI abnormalities in the brains of ET patients (Bucher et al. 1997).

2.2.2 Spinocerebellar model for Essential Tremor

Although it is believed that ET is the result of a central oscillator, the location of that oscillator has not been confirmed, though some studies have suggested the inferior olivary complex (IOC) as a prime candidate (Hallet and Dubinsky 1993; Lamarre 1984). The intermediate zone of the spinocerebellum (see **Figure 3**) is believed to be involved in controlling the execution of movement by monitoring performance and correcting errors based on peripheral afferent input from the IOC (Albus 1971; Ghez 1991). The intermediate zone receives afferent input from the limbs (i.e. spinocerebellar tracts and climbing fibers) and controls the dorsolateral descending systems (i.e. rubrospinal and corticospinal tracts) acting on the ipsilateral limbs (Coté and Crutcher 1991). Based on this theory activity of the climbing fibers from the IOC reduces the mossy fiber input to the Purkinje cells of the cerebellum. This would lead to a decrease in Purkinje cell firing, which would increase the firing of neurons within the deep cerebellar nuclei by means of disinhibition leading to correcting movements.

There is evidence of projections from the deep cerebellar nuclei to the Vim equivalent nucleus in monkeys (VLp, Hirai and Jones 1989; VPLo, Olszewski 1952). In this same nucleus there is also evidence of 'thalamic microexcitable zones' that activate muscles with low stimulation, presumably through rubrospinal tracts (Buford et al. 1996; Vitek et al. 1996). Thus, the activity of the red nucleus and the Vim region of thalamus should also increase with increased IOC activity based on the connections of the intermediate pathway with rubrospinal and corticospinal motor pathways.

Figure 3: Possible pathway linking over-active areas, predicted to be involved in the tremor generating mechanisms of Essential tremor, to the thalamus. The intermediate hemisphere of the spinocerebellum is involved in the execution of movement. Climbing fibers from the inferior olivary complex in the brainstem have projections (excitatory) into the intermediate hemisphere that modulate the activity of purkinjie cells. Output from the intermediate hemisphere project to deep cerebellar nuclei, which then project to thalamus.


Cerebral Cortex
Thalamus
Red Nucleus
Intermediate hemisphere
Midbrain
Deep Nuclei
Climbing Fibres
Pons
Inferior Olivary Complex
Medulla

Functional imaging studies using positron emission tomography have found increased bilateral cerebellar rCBF/activation during rest and involuntary tremor in ET patients and, in addition, abnormal red nucleus activation during involuntary tremor (Jenkins et al. 1993; Wills et al. 1994). A recent study (Bucher et al. 1997) using functional MRI (fMRI) found that during tremor in patients with ET there was significant additional contralateral cerebellar and nucleus dentatus activation and additional ipsilateral red nucleus activation. This study also found increased activation in the thalamus and pallidum during tremor in the ET patients and at the level of the inferior olivary complex (IOC) in the brainstem of two patients. Studies in primates with a harmaline induced tremor, which seems to mimic ET, have indicated an important role for the IOC as part of the olivocerebello-bulbospinal pathway in the mechanism of ET (Lamarre 1984; Hua et al. 1998).

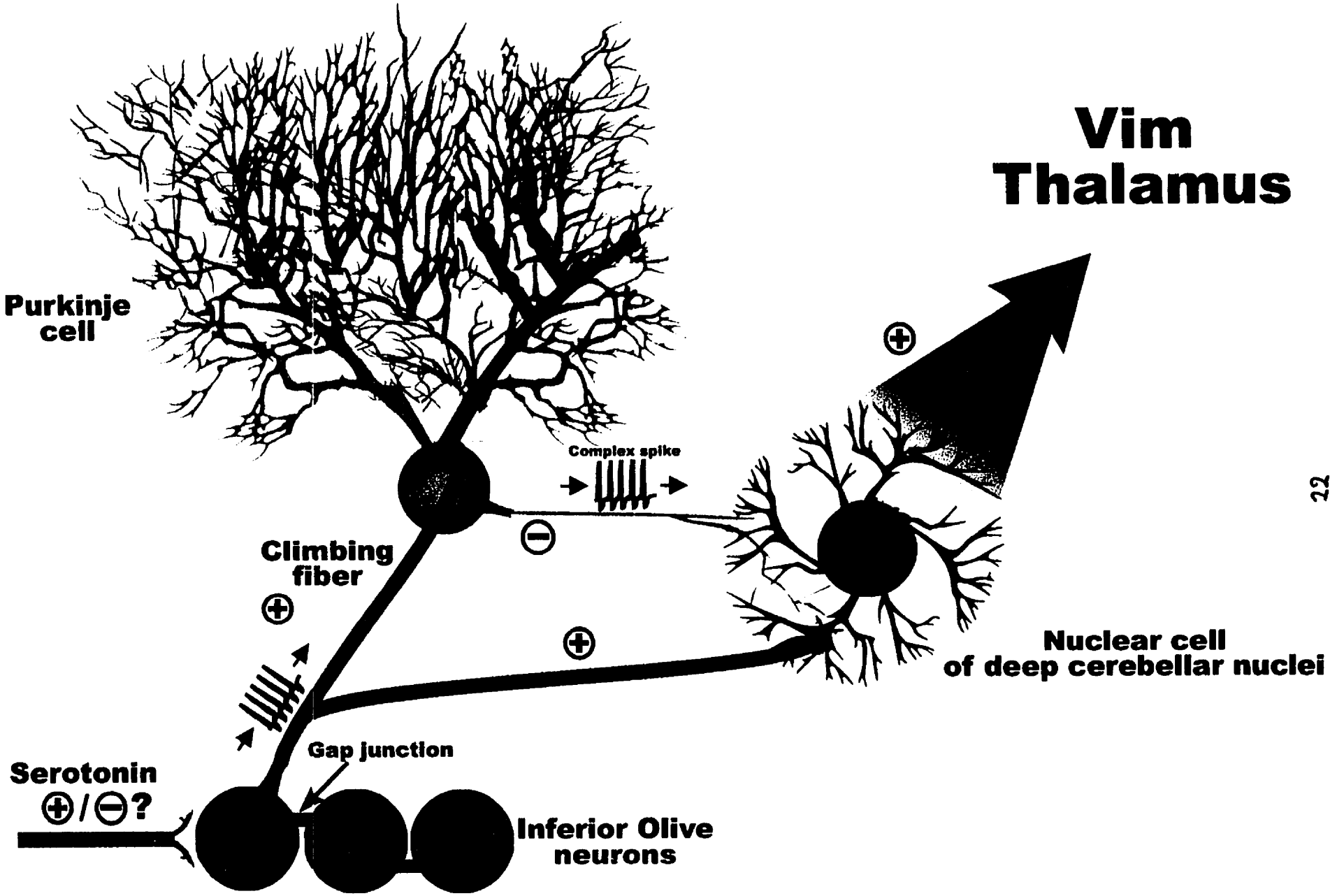
The possible involvement of the IOC in ET is based on evidence from animal models in which it was found that ET like tremor could be induced by the administration of the alkaloid harmaline (Lamarre 1984). Harmaline is a potent reversible competitive inhibitor selective for MAO A that blocks breakdown of serotonin by MAO A (Bergstrom et al. 1997; Callaway et al. 1999; Kim et al. 1997). Harmaline acts as a psychoactive agent in humans and in acute doses causes 8-12Hz oscillations in IOC and cerebellar neurons and tremor in animal experiments (Callaway et al. 1999; Lamarre et al. 1971; Lamarre and Puil 1974; De Montigny and Lamarre 1974; Llinás and Volkind 1973; Yarom and Llinás 1981). Oscillations in the IOC are correlated with animal tremor and have even been shown to oscillate in the absence of tremor (Lamarre 1984).

Harmaline-induced IOC oscillations have been correlated to oscillations in other areas along the olivo-cerebello-bulbar system (i.e. cerebellar Purkinje cells, cerebellar deep nuclei, brainstem neurons) (De Montigny and Lamarre 1974; Lamarre and Puil 1974; Lamarre et al. 1971; Llinás and Volkind 1973). Since the IOC has dense inhibitory serotonergic innervation, the effect of harmaline to induce tremor probably arises from interferences/ upregulation of this innervation (Headly et al. 1976; Sjolund et al. 1977). A 5-10 mV hyperpolarization in IOC neurons can induce calcium-mediated oscillations at 5-8 Hz in animal brainstem slice preparations (Yarom and Llinás 1981). Thus, by upregulating the inhibition of serotonin through MAO A inhibition, harmaline activates the calcium-mediated oscillatory properties through hyperpolarization of IOC neurons. A schematic of a possible neuronal network involved in relaying IOC burst oscillations through the cerebellum and deep nuclei to thalamus is shown in **Figure 4.**

2.3.1 Motor Thalamus

The thalamus is recognized as the primary relay station in the CNS for the incoming peripheral afferent input to the cortex and also plays an extensive role in pathways mediating the control of movement (Buford et al. 1996; Giménez-Amaya and Scarnati 1999; Jasper and Bertrand 1966; Macchi and Jones 1997; Strick 1976; Tasker 1990; Vitek et al. 1994, 1996). This role of the thalamus in the central processing of sensory, motor and higher cognitive function has contributed to its prominence in the pathophysiology of human functional disorders and as a major target for their treatment (Dostrovsky et al. 1993; Jankovic et al. 1995; Jones and Tasker 1990; Lenz et al. 1989;

Figure 4: Possible neuronal pathway relaying oscillatory bursts of IOC neurons through the cerebellum and deep cerebellar nuclei to thalamus. Bursting activity in IOC neurons travel along climbing fibers and evoke complex spikes in Purkinje cells. Purkinje cells have inhibitory projections to nuclear cells of the deep cerebellar nuclei. Projections from the deep cerebellar nuclei project to thalamus (i.e. Vim). Thus increased activity in IOC neurons as a possible mechanism in ET tremor can be relayed to the thalamus. Note that climbing fiber collaterals also project to nuclear cells and that the nature of the serotonergic input to IOC is still not known.


Vim
Thalamus
Purkinje cell
Complex spike
Climbing fiber
Nuclear cell of deep cerebellar nuclei
Gap junction
Serotonin
⊕/⊖?
Inferior Olive neurons

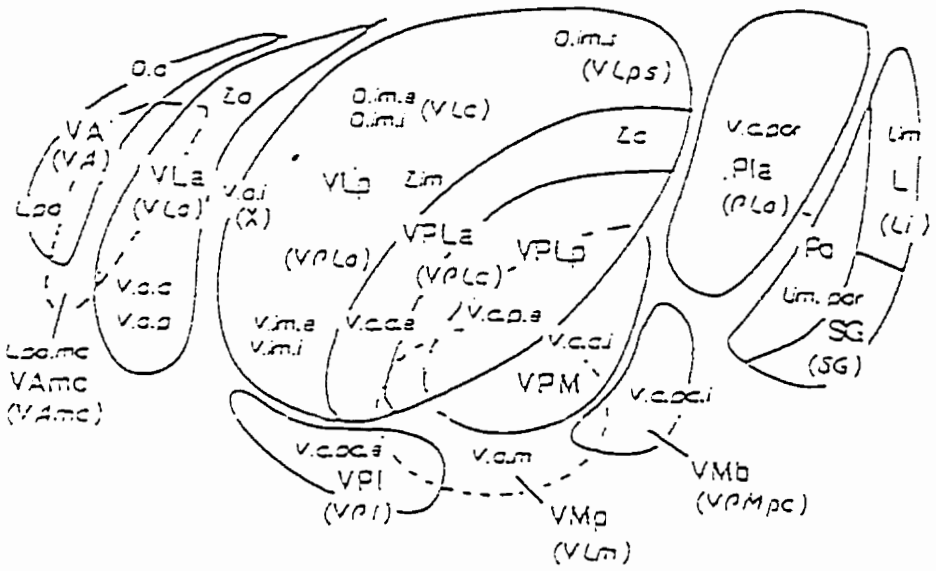
Lozano 1998; Shima et al. 1991; Tasker 1990; Tasker and Kiss 1995). The human thalamus is segregated into numerous histologically distinct nuclei based on neuronal morphology, afferent and efferent neuronal projection, and physiological activity (Albe-Fessard 1973; Hassler 1959; Hirai and Jones 1990; Morel et al. 1997). There are strong similarities between the parcellation of the human and monkey thalamus yet there are several nomenclatures used between the two species (see **Figure 5**). Hassler's (1959) and Hirai and Jones' (1989) nomenclature is from human thalamic studies, and Olszewski's (1952) is based on monkey thalamus. This is to name a few keeping in mind several other nomenclatures exist and that at times heated debate arises as to which one is most accurate and useful (for review see Macchi and Jones 1997a,b; Percheron 1997; Tasker and Kiss 1995). The Hirai and Jones (1989) nomenclature was developed to amalgamate several monkey and human parcellation concepts to simplify comparisons and understanding between species (Macchi and Jones 1997).

> N.B. Please note for the purposes of the present thesis thalamic nuclei will often be discussed in terms of the equivalent Hassler's (1959) nomenclature since is the one most commonly used in human stereotaxis and the one our laboratory uses.

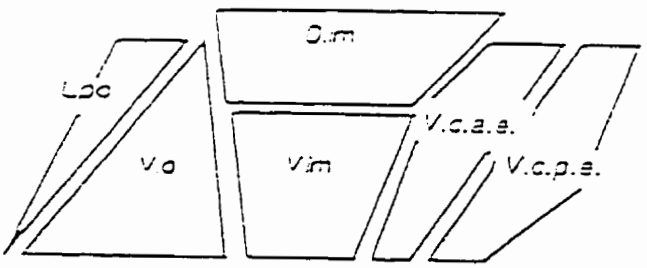
The thalamus contains three main categories of neurons: relay neurons, intrinsic interneurons, and neurons of the reticular nucleus. All relay neurons have a bushy type of morphology, are variably sized (70-400 μm^2), and use excitatory amino acid transmitters (i.e. glutamate) (Steriade et al. 1990). Relay neurons receive several thousand synaptic contacts from ascending afferent fibers (25%), corticothalamic neurons

Figure 5: Schematic sagittal views of the ventral nuclear group in the human thalamus. A; ventral nuclei with nomenclature of Hassler (*italic*) (Hassler 1959), Olszewski (*parentheses*) (Olszewski 1952), and Hirai and Jones (*bold*) (Hirai and Jones 1989). B; parasagittal section of ventral nuclear group by Hassler and by Hirai and Jones (C) with the addition of general input-output connections. (from Macchi and Jones 1997) (see section 'List of Abbreviation' in this thesis for abbreviations used in text).

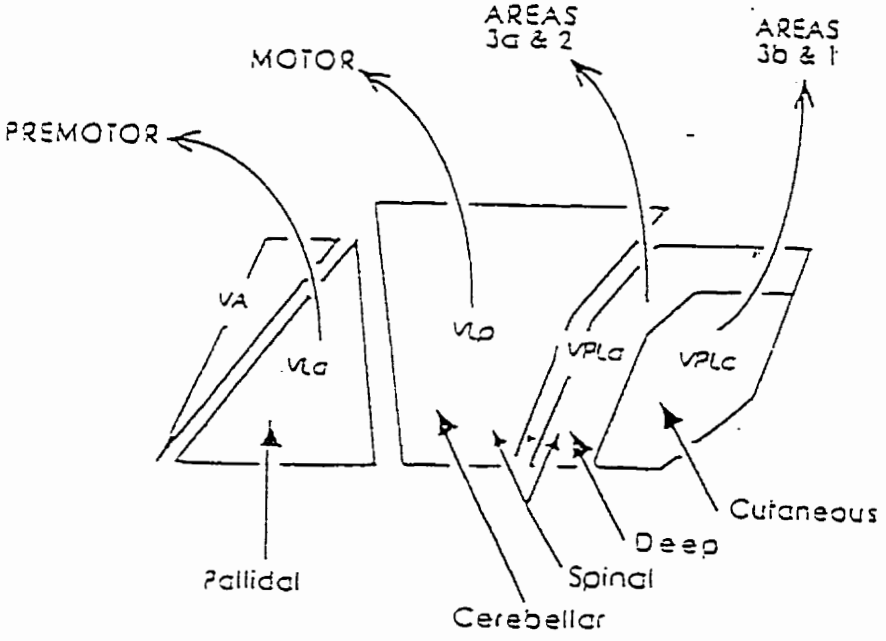
A


O.c
Zo
VA
(VA)
VLa
(VLo)
Loo
Loo.mc
VAmc
(VA.mc)
V.o.c
V.o.p
O.im.a
O.im.i
(VLc)
O.im.s
(VLps)
Zc
Zim
V.o.i
(X)
(VPLo)
VPLa
(VPLc)
VPLp
V.im.a
V.im.i
V.c.a.a
V.c.p.a
V.c.a.i
VPM
V.c.p.i
V.c.p.a
VPI
(VPI)
V.c.m
VMp
(VLm)
VMb
(VPMpc)
V.c.par
Pla
(PLo)
Lm
L
(Li)
Pa
Lim. par
SG
(SG)

B


O.im
Loc
Vo
Vim
V.c.a.a.
V.c.p.a.

C


AREAS
3a & 2
AREAS
3b & 1
MOTOR
PREMOTOR
VA
VLa
VLo
VPLa
VPLc
Pallidal
Cerebellar
Spinal
Deep
Cutaneous

(40-50%), reticular neurons (30%) and interneurons (5-10%) (Steriade et al. 1990). Interneurons and reticular neurons are both GABAergic, interneurons are small cells (65-180 μm^2) with a small number of dendrites and reticular neurons are generally large cells (220-270 μm^2) with disk-shaped dendritic fields (Steriade et al. 1990). Relay and reticular neurons both display two modes of activity: tonic, single-spiked firing when the membrane is depolarized, and rhythmic burst firing when the membrane is hyperpolarized (relay; 0.5-4Hz, reticular; 0.5-12Hz) (Joffroy and Lamarre 1974; Llinás 1984; Steriade et al. 1990)

The main region of interest in the human thalamus as it relates to stereotactic surgery is the ventral thalamus. Intermediate (Vim) and anterior areas (Voa, Vop, Lpo) of the ventral thalamus are considered to be motor thalamus since these regions relay movement-related information from the basal ganglia and cerebellum to motor related areas of cortex (Massion 1977). Page et al. (1993) injected an anterograde tracer (wheatgerm-agglutinin conjugated to horseradish peroxidase) into the medial pallidum (GPi) of *M. fascicularis* and found that the predominate labeled area was the anterior part of the ventrolateral thalamus (i.e Voa/Vop). The cytoarchitecture of the human Vim in its ventral part is characterized by large, deeply stained neurons that are in sharp contrast to the smaller and denser neurons of the adjacent Vop (Morel et al. 1997). It has also been found in the human motor thalamus that there are 'islands' of Vim-similar neurons that extend into Vop (Morel et al. 1997). Continuing more anterior, neurons within the Hassler (1959) equivalent Lpo change from small dense neurons to sparser and larger neurons (Morel et al. 1997).

Extracellular recordings attained from thalamic exploration reveal characteristic physiological information about neurons within the various nuclei (Albe-Fessard 1973; Tasker and Kiss 1995). Neurons in the ventral thalamus that are excited with voluntary movements are generally contained within the ventralis oralis subnuclei (Voa/Vop; VLo, Olszewski 1952; VLa, Hirai and Jones 1989). Vim and the equivalent areas in monkey (VPLo, Olszewski 1952; VLp, Hirai and Jones 1989) generally contain neurons that are excited with passive movements about a joint (Ohye et al. 1976; Raeva 1999a,b; Tasker and Kiss 1995; Vitek et al. 1994a). Evidence of high frequency "tremor cells" which fire synchronously with involuntary tremor are commonly found during stereotactic thalamic exploration in ET patients and lesions made in areas of tremor cells can abolish tremor (Goldman et al. 1992; Hua et al. 1998; Jankovic et al. 1995). This is also the case with PD tremor such that 'tremor cells' are encountered that fire with bursts correlated with EMG activity during tremor (Lenz et al. 1988; Lozano 1998; Zirh et al. 1998). Lpo and the equivalent area in monkey thalamus (VA, Olszewski 1952 and Hirai and Jones 1989) primarily receives input from the basal ganglia (SNr) and has projections to prefrontal areas of cortex (Anderson and Turner 1991; Buford et al. 1996; Macchi and Jones 1997). Voa/Vop areas of motor thalamus and equivalent areas in monkey thalamus primarily receive input from the basal ganglia and project to premotor areas of cortex (Anderson and Turner 1991; Buford et al. 1996; Macchi and Jones 1997; Rouiller et al. 1999; Sakai et al. 1996; Vitek et al. 1994) (**Figure 5**). Vim and the equivalent area in monkey motor thalamus primarily receives input from the cerebellum and projects to primary motor

cortex (Anderson and Turner 1991; Asanuma et al. 1983; Buford et al. 1996; Macchi and Jones 1997; Rouiller et al. 1999; Sakai et al. 1996; Vitek et al. 1994) (**Figure 5**).

Anderson and Turner (1991) recorded neurons in the motor thalamus of monkeys while stimulating in the pallidum or cerebellar deep nuclei to determine the responses and locations of pallidal-receiving (PR) and cerebellar-receiving (CR) neurons. CR neurons were recorded in the Vim equivalent in monkeys and were excited with short latencies from stimulation in the cerebellar deep nuclei. PR neurons were generally located in Voa/Vop equivalent areas and were briefly inhibited after a short latency in response to pallidal stimulation (Anderson and Turner 1991; Inase et al. 1996). Responses to microstimulation can also be used to identify PR and CR neurons. It has been found in monkeys that microstimulation (up to 200 μA) in PR and CR territories can evoke muscle twitches or limb movements though CR territories are characterized by 'microexcitable zones' that have much lower thresholds (5-75 μA) (Buford et al. 1996; Vitek et al. 1996).

Internally generated movement tasks are believed to be processed within parallel loops that go from premotor cortical areas through the basal ganglia then back to cortex via ventral and dorsomedial thalamus (Alexander et al. 1986; Jueptner 1998; Van Donkelaar et al. 1999). The cerebellum has been shown to be activated during movements that are initiated or guided in the presence of sensory cues in functional imaging studies (Jueptner 1997,1998). Van Donkelaar et al. (1999) examined physiological responses in thalamic neurons of monkeys during internally generated and visually triggered movement tasks. The majority of responsive neurons showed increased firing rates at the onset of movement. They found that the largest proportion of neurons that responded exclusively

to internally generated movements were located within PR thalamic areas (i.e.VA, VLo). They also found that the largest proportion of neurons that responded exclusively to visually triggered movements were within CR thalamic areas (i.e. VPLo, area X). There was also some overlap between tasks such that some neurons in PR and CR regions would be excited or burst in relation to both movement tasks (Van Donkelaar et al. 1999).

A study by Vitek et al. (1994a) reported MSFRs for VLo (13 $\pm$ 8Hz) and VPLo (22 $\pm$ 11Hz) in normal monkeys. Another study by this group examined thalamic firing rates in normal and MPTP monkeys and found significant reductions in the mean spontaneous firing rates and increased bursting (i.e. irregularity, short periods of high frequency firing) in the human equivalents of Voa/Vop (i.e.VLo; 16 $\pm$ 8Hz normal to 11.5 $\pm$ 7Hz MPTP, $p < 0.001$) and Vim (i.e. VPLo; 22 $\pm$ 8 Hz normal to 15 $\pm$ 8 Hz MPTP, $p < 0.001$) in the MPTP group (Vitek et al. 1994b). A recent paper by Lenz et al. (1999) reported mean interspike intervals for neurons in presumed Vim (0.076 $\pm$ 0.010 s) and presumed Vop (0.059 $\pm$ 0.012 s) in pain patients at rest that when converted to firing rates (13.2 Hz and 16.9 Hz respectively) are similar to normal monkeys. Since pain patients are presumed to have normal motor thalamic areas (see section 3.6) a comparison between the human data (Lenz et al. 1999) and monkey data (Vitek et al. 1994a,b) shows that MSFR of Vop/VLo and Vim/VPLo are similar except that VPLo neurons had slightly higher MSFR compared to VLo in monkeys whereas this was opposite in humans with Vop being slightly higher than Vim.

Motor thalamus is the common target for stereotactic thalamic lesions and DBS, which are effective in treating tremor symptoms (Benabid et al. 1996; Lozano 1998;

Tasker 1990). Both thalamotomy or thalamic deep brain stimulation (DBS) in the ventral thalamus at approximately identical locations (i.e. commonly within Vim) are effective late-stage procedures used for the treatment of tremor symptoms in patients with PD or ET (Jankovic et al. 1995; Lozano 1998; Tasker 1990). This is interesting since the sources of the pathologies are believed to be quite different as described in above sections. More caudal in the ventral thalamus are the main relays for somatosensory information from the periphery to cortical areas (Dostrovsky et al. 1993; Lenz et al. 1989). This region is of interest for stereotactic surgeries to treat chronic pain-related symptoms (Dostrovsky et al. 1993; Tasker and Kiss 1995).

Section 3. Materials and Methods

3.1 Patient Population

Single-unit neuronal microelectrode recordings from 21 patients with either a movement disorder or chronic pain disorder were studied. These patients all underwent similar stereotactic thalamic exploration to determine a surgical target to effectively treat their symptoms. Surgery was either a thalamic lesion or the insertion of a thalamic deep brain stimulation (DBS) electrode. The study consisted of three patient groups; two movement disorder groups and a chronic pain group. The movement disorder patients consisted of patients with Parkinson's disease (PD, n = 5, aged 67-73) and patients with Essential tremor (ET, n = 10, aged 64-75) that were undergoing thalamic surgery to specifically relieve tremor symptoms. The chronic pain patient group (Pain, n = 6, aged, 45-71) consisted of patients undergoing surgery to treat chronic pain symptoms resulting

mainly from cerebrovascular accidents or deafferentation.

The patients (PD, ET, and Pain) generally stopped their regular medication the night before the surgeries to ensure that the symptoms and signs of their disorder were not suppressed which would prevent the identification of optimal surgical targets. In some cases minimal sedative agents can be administered to help make a patient comfortable during the long procedure, but not at doses that alters their ability to participate in the surgery. Some tremor patients experience 'micro-thalamotomies' such that their tremor symptoms are reduced or arrested completely during microelectrode exploration due to micro neuronal lesions caused by the electrode tips. This affect in addition to the effects of being in the surgical setting can alter a patient's regular tremor symptoms and the number of neurons recorded in the absence of tremor. Thus, because of these effects it was not possible to correlate neuronal rates with symptom severity in patients because symptoms could change quickly during the course of the operation.

This study involved a retrospective analysis of surgical recordings. The purpose of the surgical data collection was directed toward isolating a suitable surgical target with no experimental variables being tested during the procedure. Patients were selected first on the basis of diagnosis (i.e. PD, ET, PAIN). Second, patients in these groups which had electrode trajectories which contained neurons that responded to either voluntary or passive movements about the hand/wrist (see Section 3.7 for details) were selected. Finally, of these patients with selected electrode tracks neurons were recorded that had a clearly defined rest / spontaneous period of firing (for at least 20 seconds) in the absence of movement or stimulation (Section 3.7). This last selection step, though essential for

proper analysis of spontaneous firing, greatly reduced the number of acceptable recorded sites. All procedures were patient consented and conducted in accordance with the Human Experimentation Committee of the University of Toronto and the Toronto Hospital.

3.2 Stereotactic Procedures

Under local anesthesia the patients were fitted with a Leksell stereotactic frame early in the morning of their surgery. The 3-dimensional frame coordinates of two stereotactic landmarks, the anterior commissure (AC) and posterior commissure (PC), were determined in each patient using high-resolution computerized tomography (CT) or magnetic resonance imaging (MRI). A stereotactic surgical target was then calculated from the determined AC-PC coordinates and the distance between them (AC-PC line). A computer program incorporating a set of sagittal thalamic atlas maps based on the Schaltenbrand and Wahren (1977) atlas was used to scale standard anatomical images according to a patient's AC and PC coordinates and draw trajectories to initial surgical targets. Initial targets were directed toward the nucleus of the ventral tier of the thalamus that receives tactile input from the hand. This is a physiologically well-defined region of the ventral thalamus located in the ventral third of the ventrocaudal (Vc) nucleus at about 15 mm lateral from the midline of the brain. An incision was made in the scalp, under local anesthesia, to expose the patient's skull. An access burr or twist drill hole (i.e. for DBS placement or lesion, respectively) was then made in the patient's skull above the area of the target. The dura mater was resected and cauterized to expose the surface of

the brain (i.e. when burr hole was made). A protective surgical gel was injected in the burr hole to seal the opening to minimize fluid loss and entry of air. The Leksell arc car adapter was then attached to the frame and a microelectrode guide tube (1.1 mm outer diameter) was inserted into the brain directed at the initial target but terminating 10 mm short of the target. The initial target was approached in a parasagittal plane from anterior dorsal to posterior ventral at an angle of 50° to 60° from the AC-PC line. A sterile microelectrode in a protective carrier tube was inserted into the guide tube to a level that was flush with the distal tip. The microelectrode was attached to the slave cylinder of a hydraulic microdrive that was carried on the arc car adapter (see **Figure 6**).

From that point in the stereotactic procedure microelectrode recordings and stimulation were made by hydraulically driving microelectrodes beyond the guide tubes into the thalamus. The microelectrodes were driven 10 mm to the target and up to an additional 10 mm beyond the target. Usually three to six electrode trajectories were explored in each patient with placements usually varying by two millimeter increments in anterior-posterior and medial-lateral directions.

3.3 Microelectrodes

The thalamic neuronal recordings were obtained using a microelectrode construction described previously by Lenz et al. (1988a), Lozano et al. (1996), and Dostrovsky (1999). Briefly, the microelectrodes used for the recordings were parylene-C coated tungsten microelectrodes (Microprobe, Inc., Potomoc, MD, WE300), with tip lengths ranging from 15-40 μm. To compensate for the increased depth of exploration required for human

Figure 6: Photograph of the operating room during a functional stereotactic procedure. The patient is awake and co-operative in determining the effective physiological target in the thalamus to alleviate their symptoms. The relevant electrophysiological apparatus are labeled. (refer to sections 3.2 Stereotactic Procedure and 3.4 Equipment of this thesis for details)

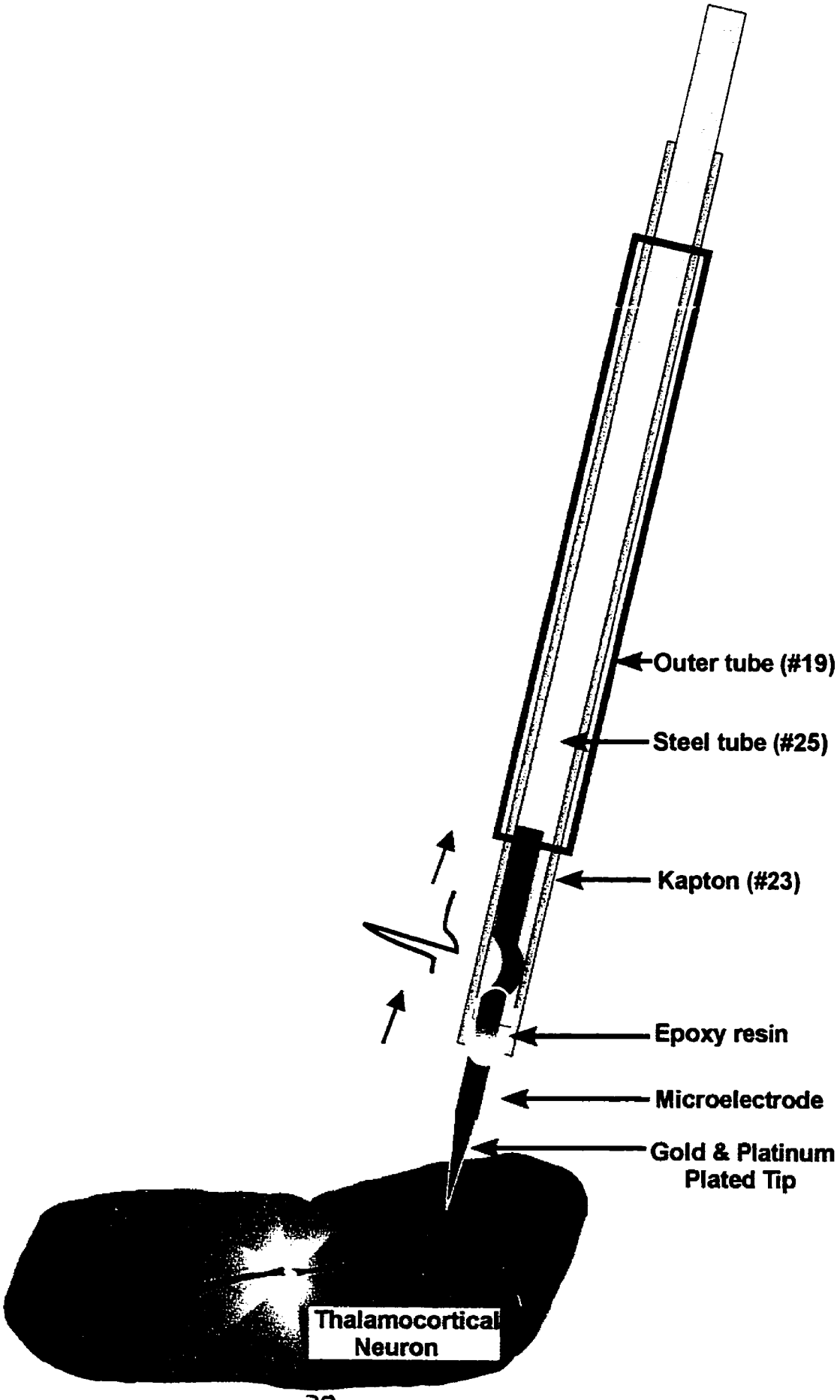
studies compared to that of animal studies, the fine electrodes were adapted to a longer electrode structure. Thus, the microelectrode was combined with a 30cm length of 25-gauge stainless steel tubing (Small Parts Inc., Miami Lakes FL, HTX-25-12) (see **Figure** 7). The microelectrode shank was stripped of insulation beyond 2cm from the tip, slightly bent and inserted into the tube (leaving 2cm from the tip exposed). The tube was insulated with a covering of 23-gauge polyimide Kapton tubing (Micro ML, New York, NY). Using a dissecting microscope the polyimide tubing was extended beyond the stainless steel tube to overlap the insulated region of the microelectrode and was sealed with epoxy resin glue to insulate the junction.

The electrode tips were plated with gold and platinum to reduce the impedance from 1-2 MΩ to a final impedance of a few hundred kΩ. To ensure that there are no breaks in the electrode insulation the electrode is slowly immersed in saline to ensure no significant changes in electrical impedance along the length to just past the junction. In addition, the application of a low DC voltage (3-5 V) to the immersed electrode should result in bubble formation only at the tip if it is properly insulated. The completed electrodes were inserted into a 19-gauge stainless steel tube (Small Parts Inc., Miami Lakes FL, HTX-19-12) for protection.

3.4 Equipment

After gas sterilization the microelectrode was removed from the protective tube and back-loaded into a 19-gauge tube connected to the slave cylinder microdrive assembly. The 19-gauge tube was affixed to the assembly and the tail of the microelectrode was attached

Figure 7: Schematic representation of the microelectrode construction used during the physiological recording and stimulation. (please refer to section 3.3 Microelectrodes of this thesis for details)


Outer tube (#19)
Steel tube (#25)
Kapton (#23)
Epoxy resin
Microelectrode
Gold & Platinum
Plated Tip
Thalamocortical
Neuron

to an arm on the cylinder. The microelectrode, within the 19-gauge tube was inserted into the main stereotactic guide tube attached to the arc. The whole assembly was then attached to the arc car adapter. A calibrated microdrive was connected to the assembly and was used to hydraulically move the cylinder and drive the electrode down out of the guide tubes and into the thalamus (see **Figure 6**). The lead from the microelectrode tail was connected to a Guideline System 3000 (Axon Instruments, Foster City, CA) that amplified, filtered (highpass 100Hz to 5 kHz) and displayed the intraoperative neuronal recordings (see **Figure 6**). This system incorporated a Windows 95-compatible computer with a touch sensitive screen and was capable of discriminating spikes and calculating firing rates. The 19-gauge guide tube of the assembly was connected to ground. The System 3000 amplifier had the capability of allowing stimulating pulses used for microstimulation to be carried along the recording lead. Outputs from the amplifier were led to oscilloscopes, a window discriminator (Winston Electronics, Millbrae, CA), an audio monitor (Grass AM 8; Grass Instruments, Quincy, MA), and a digital recording device (VR-100-B; Instrutech Corp, Great Neck, NY). The oscilloscope display and the audio output were used to combine visual and auditory inspections of neuronal recordings as a means to better identify any changes in neuronal firing rate or pattern or identify responses (i.e. during patient testing of receptive fields). The window discriminator made it possible to discriminate units of interest from background activity.

N.B. In some of the surgeries since 1998 double microelectrodes have been inserted into each trajectory into the thalamus. This made it possible to obtain

dual recordings and to test the effect of stimulating in one and recording in the other or to determine if there was any synchrony between nearby neurons. The effects of stimulation and synchrony between neurons are important physiological aspects to characterize neurons in addition to firing rates but these were not investigated in the present thesis. The two electrodes were either fixed and driven together with tips separated by about 250 μm or driven separately with a customized arc car adapter that housed two independently controlled microdrive cylinders. In either case a double set of amplifiers and output devices were used to monitor and analyze the intraoperative signals.

The digital recording device was combined with a VHS videocassette recorder for storage of up to eight channels of analogue data (1-2 micro recordings, 2-4 electromyographic (EMG) signals, accelerometer output, and other testing equipment) for off-line analysis. A video camera was used to film the patient during surgery. The video images were stored on VHS tape using another videocassette recorder, which also included a recording of the microelectrode signals on one of the two audio channel

3.5 Intra-operative Recording and Stimulation

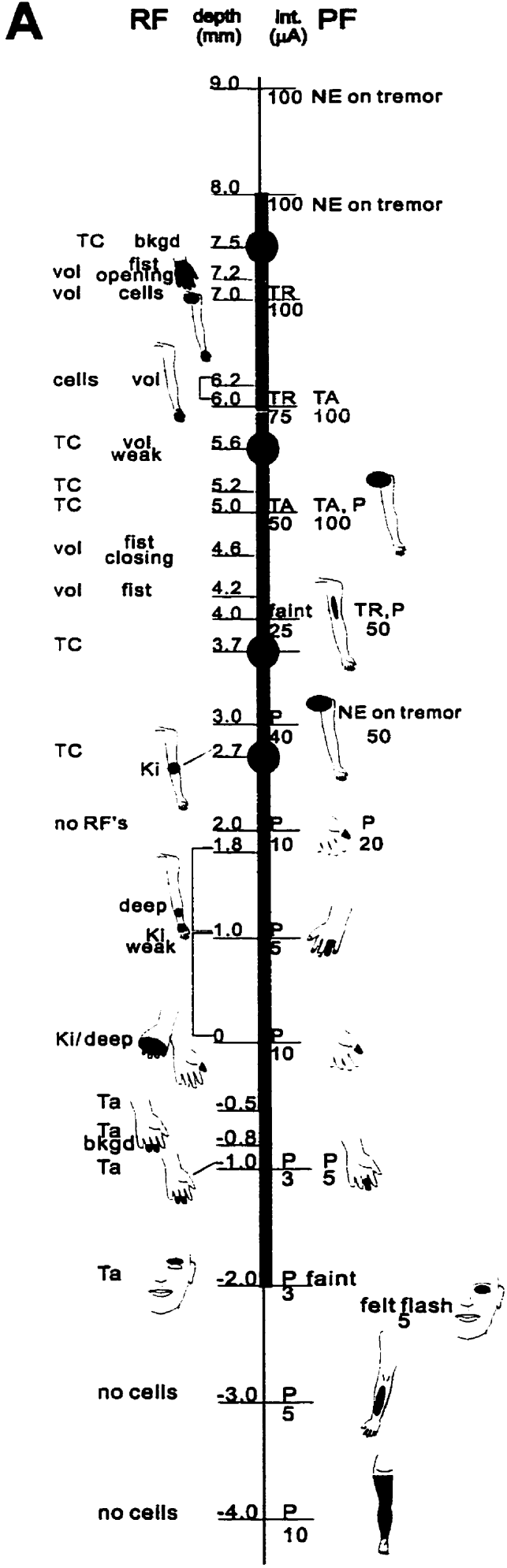
As mentioned in the introduction the ventral thalamus consists of functionally and anatomically distinct nuclei where neurons respond to voluntary movements (i.e. Voa/Vop), passive movements about a joint (i.e. Vim), and to tactile somatosensory input (i.e. Vc). The goal of microelectrode recording was to functionally localize the electrode

position in the thalamus on the basis of the nature of neuronal responses in firing pattern and the effect of microstimulation. **Figure 8B** depicts a map of an initial trajectory directed to the tactile hand area of Vc. The anterior-dorsal to posterior-ventral trajectory to Vc was predicted by the surgical map to cross Vop, Vim and into Vc of the ventral thalamus. For each trajectory the electrode was driven slowly (i.e. fine-scale μm increments) until neural activity was isolated. Thus, at the top of the trajectories receptive field (RF) testing consisted of having the patients perform voluntary movements (or passive, see below) of the upper and lower appendages, jaw, and tongue (i.e. open/close hand, wrist flexion/extension, etc.). Neurons responding optimally to voluntary movements were presumed to be located in Voa/Vop. Further down the trajectory RF testing consisted of the experimenter moving the patient's limbs around various joints and squeezing the joints and tissue. Neurons responding best to these passive/kinesthetic movements were presumed to be of neurons in the Vim nucleus.

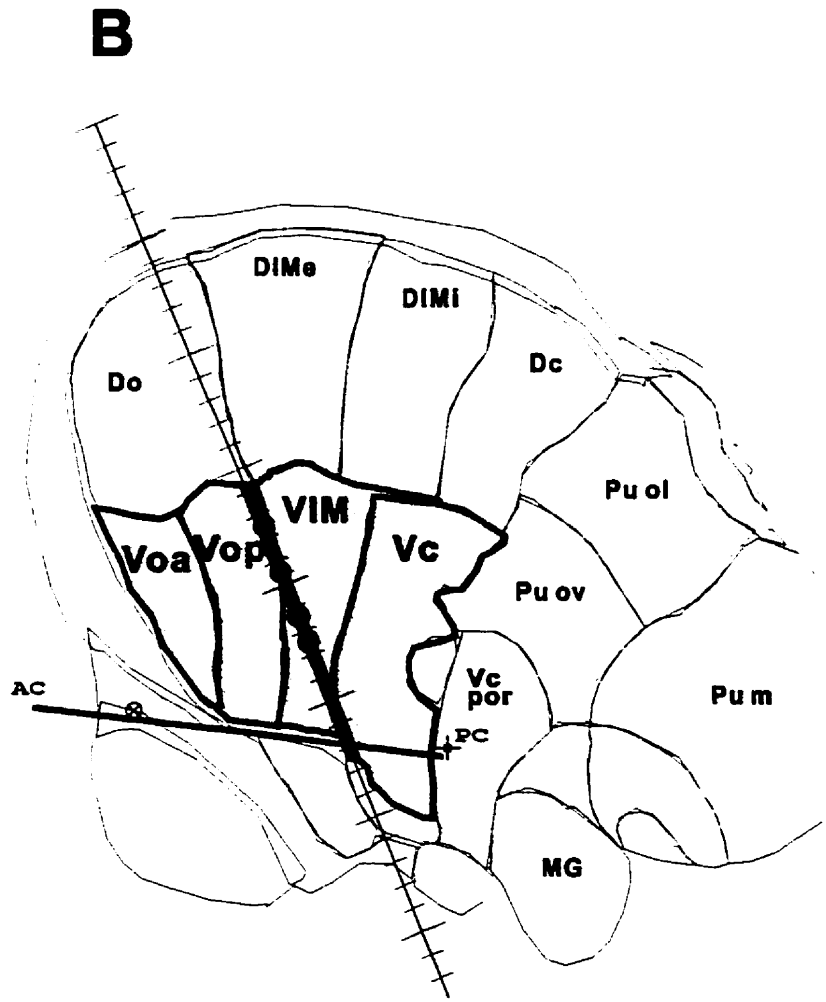
(It is important to note that kinesthetic neurons will also respond during voluntary movement but not as optimally as voluntary neurons for that particular movement, and vice versa. Thus we used optimal changes from the baseline firing rates of neurons in response to a particular type of movement to assign a physiological receptive field, see **Figure 8**)

Continued progression toward the target involved applying tactile stimulation to the patient's skin using a light brush or touch. Neurons responding to the stimulation were assumed to be located within Vc. A sample electrode trajectory based on surgical notes is depicted in **Figure 8A**.

Figure 8: Example thalamic microelectrode trajectory used for the present study (B) and corresponding surgical notes reconstruction (A). A; Reconstruction of surgical records noting the specific receptive fields (RF) and projected fields (PF) of thalamic neurons encountered along the electrode trajectory. This serves as an example of the type of trajectory selected for the present study. The electrode position is measured in millimeters (mm) above the target at '0'. Stimulation intensities are measured in microamperes (μA) and are the numbers listed to the right of the trajectory. (please refer to section 3.5 Intra-operative Recording and Stimulation for details). B; A computer-generated map of the anatomy (based on stereotaxis) corresponding to the location of the electrode is displayed in the background. The map is a parasagittal section at 14.5 mm from the midline of the brain. The ventral lateral tier is yellow-filled. The reconstructions (A & B) include the receptive fields of neurons along the trajectory. The electrode transversed voluntary (green), kinesthetic (blue), and tactile (red) representation of hand (i.e. Vop, Vim, and Vc respectively. Abbreviations (B): AC = anterior commissure; Dc = dorsal caudal; Dim.e = dorsal intermediate external; Dim.i = dorsal intermediate internal; Do = dorsal oral; MG = medial geniculate; PC = posterior commissure; Pu = pulvinar (m = medial; ol = oral lateral; ov = oral ventral); Ret = reticular; Vc = ventral caudal; Vc.por = ventral caudal portae; Vim = ventral intermediate; Voa = ventral oral anterior; Vop = ventral oral posterior. The legend corresponds to A.



BC	bursting cell
D	digit/finger
deep	deep response
Ki	kinesthetic response
NE	no effect on tremor
NR	no response
P	paraesthesia
PF	projected field
RF	receptive field
Ta	tactile response
TA	tremor arrest
TC	tremor cell
TR	tremor reduction
vol	voluntary response



As mentioned in the previous section the electrode recording system was capable of switching between the amplifier and stimulator allowing one to send stimulating electric pulses to the electrode tip. Microstimulation was performed at every millimeter or less along each trajectory to determine the projected fields (PF) or the effect on tremor evoked by stimulation. The patient was required to describe and locate any type of sensation experienced (i.e. tingling, numbness, shock, pain, movement, etc.) when the electrical stimulation was delivered (see **Figure 8A**). In addition to evoking a PF, thalamic stimulation was also used in PD and ET patients to see if there was an effect on tremor (i.e. tremor reduction/arrest). Stimulation consisted of 1-sec. trains of 0.1-0.2 ms monophasic pulses (biphasic for Axon Instruments system) at a frequency of 300 Hz. The current intensity ranged from 1 to 100μA and the threshold of an evoked response was determined.

3.6 Data Collection

In addition to the VHS tapes, which store the electrical recordings and video images, data from the surgery is also recorded in surgical notes describing the main features of the recordings and stimulation effects along the trajectories (see **Figure 8A**). The qualitative surgical notes correspond with the data on the tape and served as a guide to help localize areas of interest in the recordings. Initial data collection involved searching through the surgical notes of PD, ET, and Pain patients for trajectories including recordings of tactile responses to hand stimulation that also traversed voluntary, and kinesthetic areas of the ventral thalamus (see **Figure 8A**). Hand representation was

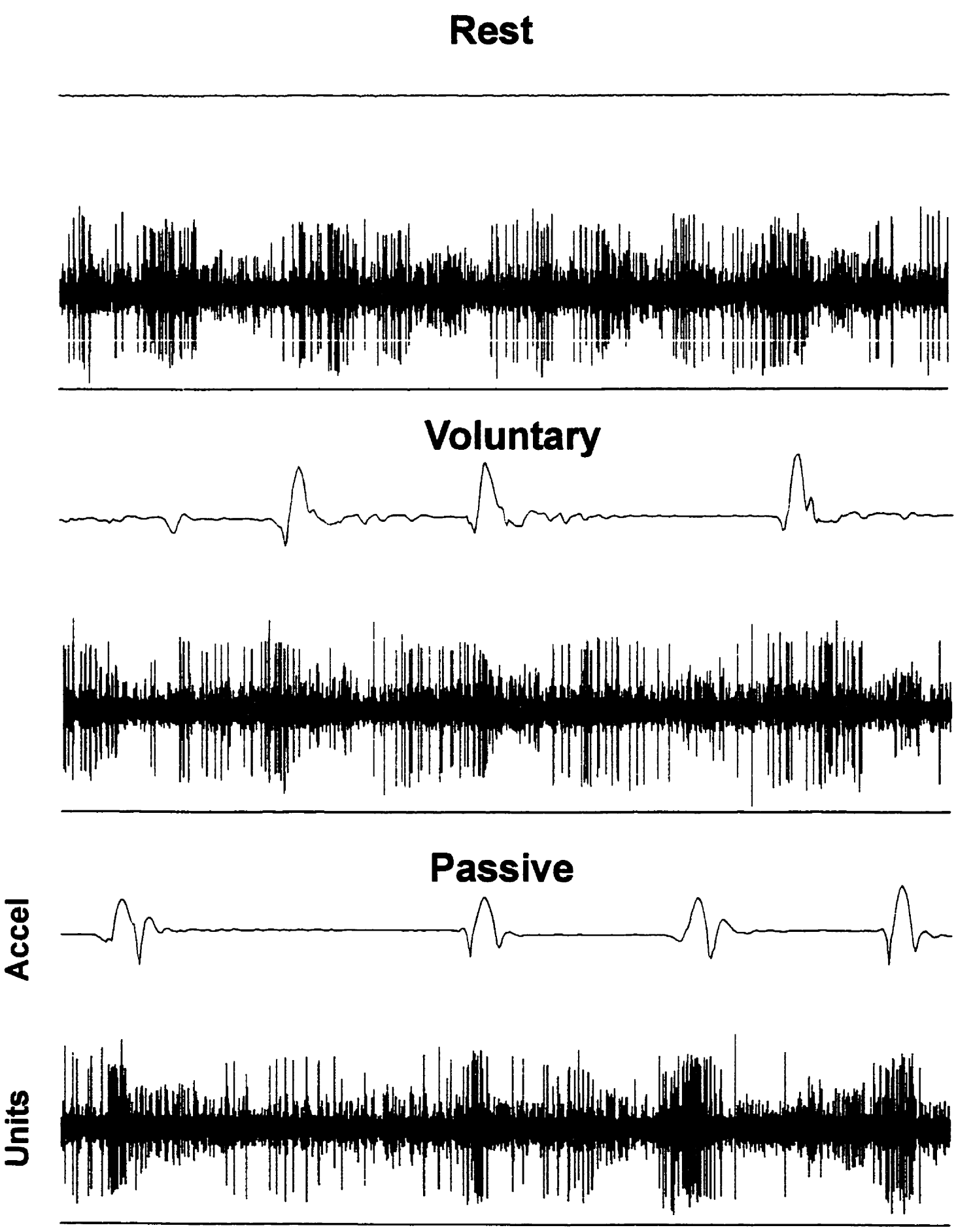
selected for two reasons: 1) the hand has a well-defined representation in the thalamus; 2) areas of hand representation were the most intensively explored areas for the purposes of relieving tremor.

The recordings from the selected trajectories were played back offline through a computerized data acquisition system (CED 1401 with Spike 2, Cambridge Electronic Design Limited, Cambridge, England). Neuronal units of interest were discriminated from other units and digitized using the Spike 2 software. The selected activity was the spontaneous firing of isolated single neurons with predetermined RFs responding optimally to either voluntary or kinesthetic input (i.e. those neurons presumably in either Voa/Vop or Vim respectively). Care was taken to determine periods when there were no passive or active movements of the RF (this spontaneous period was usually 20 to 30 sec in duration). The units selected could be easily discriminated from background activity and had high signal-to-noise ratios. Each digitized neuron was saved in a separate file for subsequent analysis. The depth location of the first neuron along the trajectory with a tactile RF (i.e. presumably a Vc neuron) was also noted for the purpose of trajectory location.

3.7 Data Analysis

The data of interest for the present study were the spontaneous activity of neurons which, when the RF was stimulated, responded best to either voluntary (Vol) (i.e. patient voluntary movement) or passive/kinesthetic (Ki) (i.e. experimenter manipulated) movement of the hand or wrist (see **Figure 9 middle and lower traces**). During this

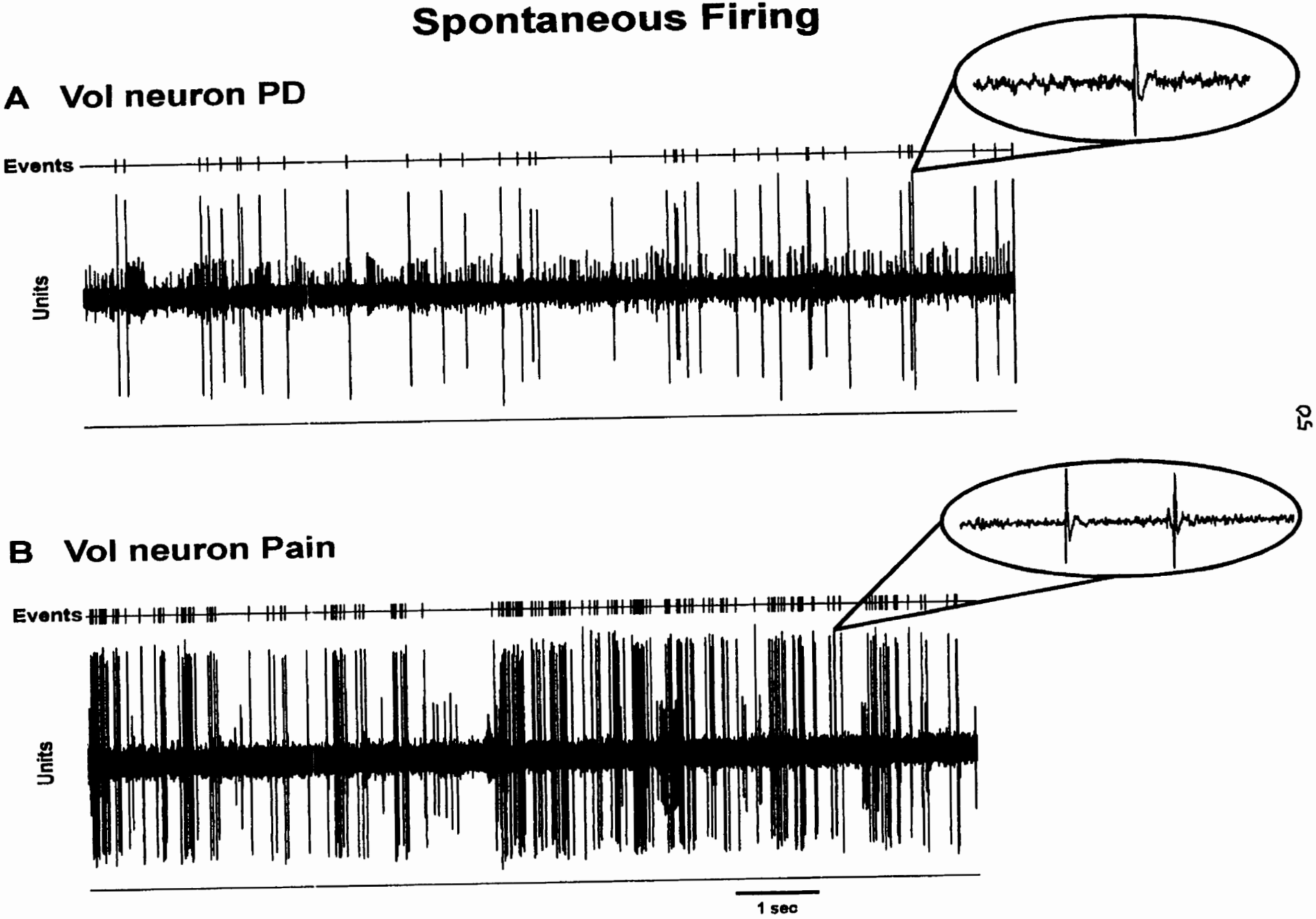
Figure 9: Changes from the baseline firing of a neuron (upper trace) in response to a voluntary (middle trace) and passive (bottom trace) movement of the elbow used to assign a physiological receptive field. The neuron was from an ET patient and was assigned as a passive-responsive (Ki) neuron due to the greater response (increased firing) to the passive movement compared to the voluntary neurons.


Rest
Voluntary
Passive
Accel
Units
1 sec

spontaneous period there was no tremor or activation of the RF or stimulation of the PF. An example of neuronal recordings during the spontaneous firing period of a Vol neuron from both a PD and Pain patient is displayed in **Figure 10** (see also **Figure 9 upper trace** for spontaneous firing of a Ki neuron in an ET patient). The units selected could be easily discriminated from background activity and had high signal-to-noise ratios. As seen in **Figure 10** the unit of interest (in **10A and B**) was easily discriminated from background units with a lower signal-to-noise ratios. For purposes of the present study voluntary-responsive neurons were presumed to be located in the Voa/Vop region and kinesthetic-responsive neurons were presumed to be located in Vim. Firing rates were determined from spontaneous neuronal activity (usually 20 secs), when the patient was at rest performing no task, using Spike 2 (CED 1401, Cambridge Electronic Design Limited, Cambridge, England).

N.B. It is important to note that the reasoning for using the spontaneous period of neuronal firing for our analysis was that it severed as the most effective and consistent controlled condition among the patients in this archival study. To be in a state of no stimulation was ubiquitous for any patient (i.e. rest, no movements, no electrical or peripheral stimulation, same room, etc.). On the contrary stimulation and testing of the patients during the surgery was effective to guide the surgery but for experimental purposes they were uncontrolled conditions. Thus it was difficult to use neuronal responses to particular movements because these movements were uncontrolled and unregulated (i.e. in range, force, direction, etc.)

Figure 10: Spontaneous firing of a voluntary-responsive (Vol) neuron from a PD (A) and a pain (B) patient. The recordings were taken at rest, in the absence of any receptive field activation or movement. In A the PD patient was also without tremor at time of recording. This spontaneous firing period was used for the calculation of mean spontaneous firing rate of a neuron.


Spontaneous Firing
A Vol neuron PD
Events
Units
B Vol neuron Pain
Events
Units
1 sec

within and between patients. In addition most neuronal pathways thought to be involved in PD and ET are predicted to undergo changes in spontaneous activity which leads to symptoms (as outlined in Section 2).

Using a customized Spike 2 script the regularity of firing patterns for neurons were quantified. The script compared the pattern of firing (i.e. digitized action potentials) of a single neuron over a certain sampling period to a pattern that would be generated by a Poisson distribution (i.e. random distribution, mean = 1) over the same period using one millisecond intervals. A value called 'variance' of '1' indicated completely random firing, a value '<1' indicated a pattern with increasing regularity and a value '>1' indicated increased irregularity. The word 'variance' is the name of the script given by it's creator, and though the name implies, it is not calculating statistical variance but simply varying degrees of firing regularity.

The frequency and variance values for each neuron were pooled in either one of two groups in each of the three patient groups; 'Vol' for voluntary-responsive neurons and 'Ki' for kinesthetic-responsive neurons. The frequency and variance pooled values were statistically analyzed within and between patient groups using a one-way ANOVA and Newman-Keuls Multiple Comparison post-hoc test, with a level of significance of $\alpha = 0.05$.

3.8 Neuron Location

The stereotactic locations of the recorded were displayed on an average sagittal plane of 14.5 mm from the midline. The locations were plotted relative to the AC- PC line

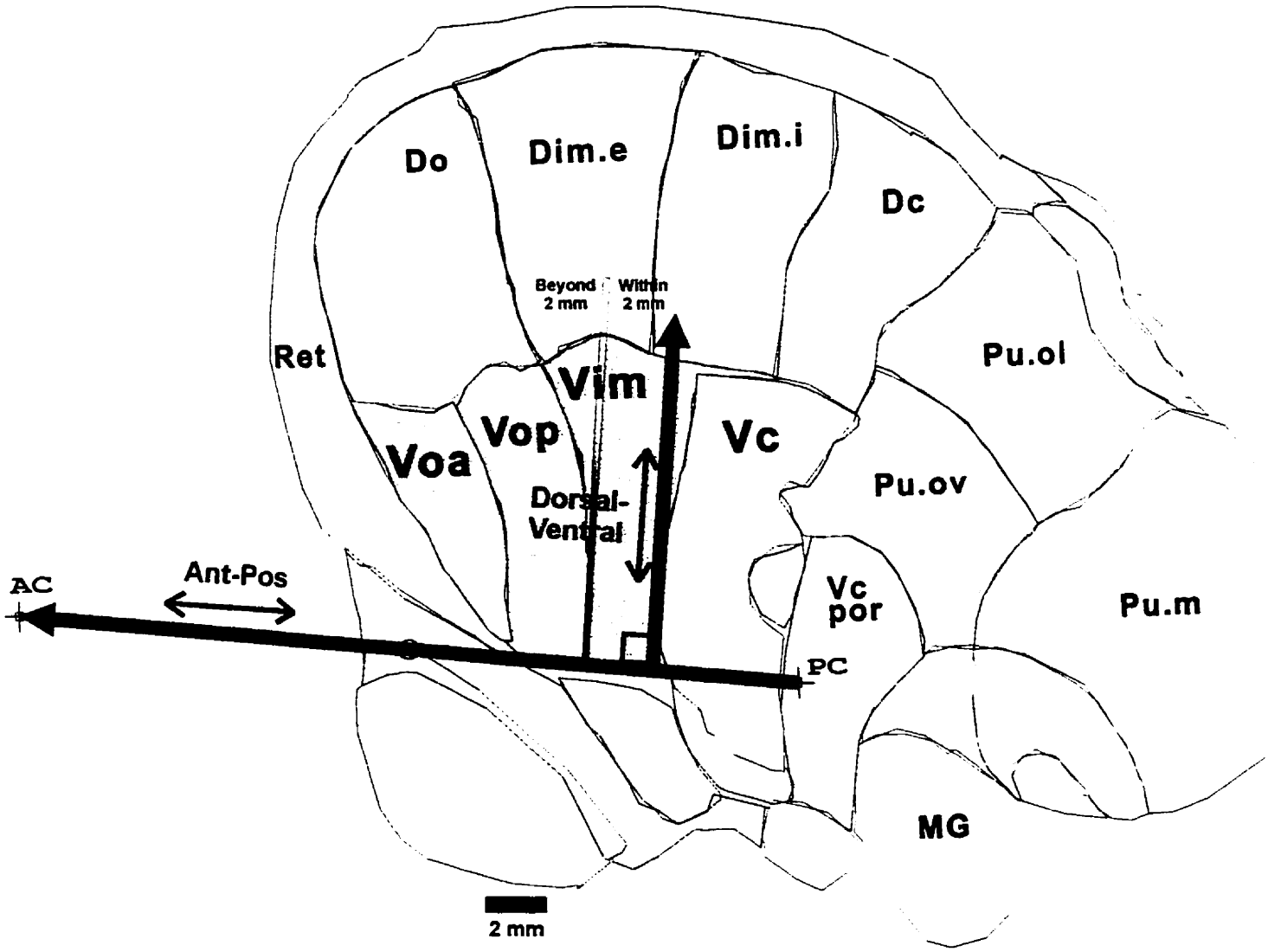
(abscissa) and a line perpendicular to the AC-PC line at the location of the first tactile neuron in that same trajectory (ordinate) (i.e. anterior Vc border) (see **Figure 11**). This was done because the Vc border is considered a well-defined physiological landmark. The difference in mean anterior-posterior locations of Vol and Ki neurons was compared for each patient group (one-way ANOVA with Newman-Keuls Multiple Comparison Post-hoc test ($\alpha = 0.05$). To try and establish a relationship between the physiology and location of the recorded neurons the mean spontaneous firing rates of neurons within or beyond 2mm of the Vc border were also compared for each patient group. The choice of 2mm as a separation distance was used because it is the approximate width of the Vim in its ventral aspect and it presumably did not include any Vop neurons. The ventral aspect of Vim is also the most frequently explored part during surgeries. Similarity of neurons between a presumed anatomic location and a specific receptive field may serve to strengthen assumptions made in the present thesis. Standardized maps of the anatomy (Schaltenbrand & Wahren, 1977) were laid behind the coordinate locations to show relative anatomic locations. Thus, this served as an effective means to verify that the group analysis of neurons based on similar physiology corresponded to similar anatomic location.

Section 4. Results

4.1 Spontaneous Firing Rates:

The results of the one-way ANOVA indicated that the means were significantly different ($p < 0.001$) and the post-hoc test results are as follows. The mean spontaneous

Figure 11: Axes used to plot the stereotactic location of recorded neurons. The abscissa is part of the AC-PC line which is approximately in the anterior (Ant) to posterior (Pos) plane. The ordinate axis is the anterior border of the ventral caudal nucleus (Vc) for each trajectory and lies approximately in the dorsal to ventral plane. The axes are placed in the 14.5mm sagittal section of the thalamus, which is the general location for hand representation. The line perpendicular to AC-PC at 2 mm anterior to Vc is the separation used to categorize neurons as being 'within 2mm' or 'beyond 2mm' from the Vc border (see section 4.1). Abbreviations: AC = anterior commissure; Dc = dorsal caudal; Dim.e = dorsal intermediate external; Dim.i = dorsal intermediate internal; Do = dorsal oral; MG = medial geniculate; PC = posterior commissure; Pu = pulvinar (m = medial; ol = oral lateral; ov = oral ventral); Ret = reticular; Vc.por = ventral caudal portae; Vim = ventral intermediate; Voa = ventral oral anterior; Vop = ventral oral posterior. The grayed areas represent motor thalamus.


Do
Dim.e
Dim.i
Dc
Beyond 2 mm
Within 2 mm
Ret
Vim
Pu.ol
Vop
Voa
Vc
Dorsal-Ventral
Pu.ov
AC
Ant-Pos
Vc por
Pu.m
PC
MG
2 mm

firing rate (MSFR) of Vol neurons (7.4 ± 1.0Hz) in PD (n=5) patients was significantly lower than in the pain (n=6) ($p < 0.01$) and ET (n=10) patients ($p < 0.01$) (**see Figure 12 A**). Furthermore the MSFR of Ki neurons in ET patients (25.8 ± 3.5Hz) was significantly greater than in pain patients ($p < 0.05$), and in PD patients ($p < 0.01$) (see **Figure 12 A**). The neurons from each patient group were also subdivided into two groups based on the calculated stereotactic locations of the recorded neurons (see below for description and **Figure 12 B**). The neurons were divided into 'within 2mm' or 'beyond 2mm' from the Vc border groups, and the MSFR were calculated. In each patient group the MSFR of the 'within 2mm' and 'beyond 2 mm' groups showed differences in means that had a pattern visually similar to the Ki and Vol groups respectively and shared the same p-values between the patient groups (**Figure 12 B**).

4.2 Firing Pattern

Analysis of firing pattern of Vol and Ki neurons in the three patient groups is shown in **Figure 13**. The results of the one-way ANOVA indicated that the means were significantly different ($p < 0.001$) and the post-hoc test results are as follows. The main finding from this analysis was a significantly ($p < 0.01$) greater mean variance value (i.e. increased irregularity) for Vol cells (1.3 ± 0.05) in the PD group compared to Vol cells in the Pain patient group (0.77 ± 1.1). No other significant differences were found. Autocorrelations were performed as a screening tactic on half of the Vol and Ki neurons from PD and ET patients to determined the possible involvement of any residual tremor on neuronal firing. This was performed using Spike 2 in which the neuron's firing was

Figure 12: Bar graphs of mean spontaneous firing rates. A, comparison of firing rates of voluntary (Vol) and kinesthetic (Ki) responsive neurons in Parkinson's disease (PD), essential tremor (ET), and Pain patient groups. B, comparison of firing rates of neurons < 2mm and ≥ 2mm anterior to the Vim/Vc border for each of the patient groups. Horizontal brackets link differences in means that are statistically significant. Error bars represent the standard error of the mean, "n" equals the number of neurons sampled.

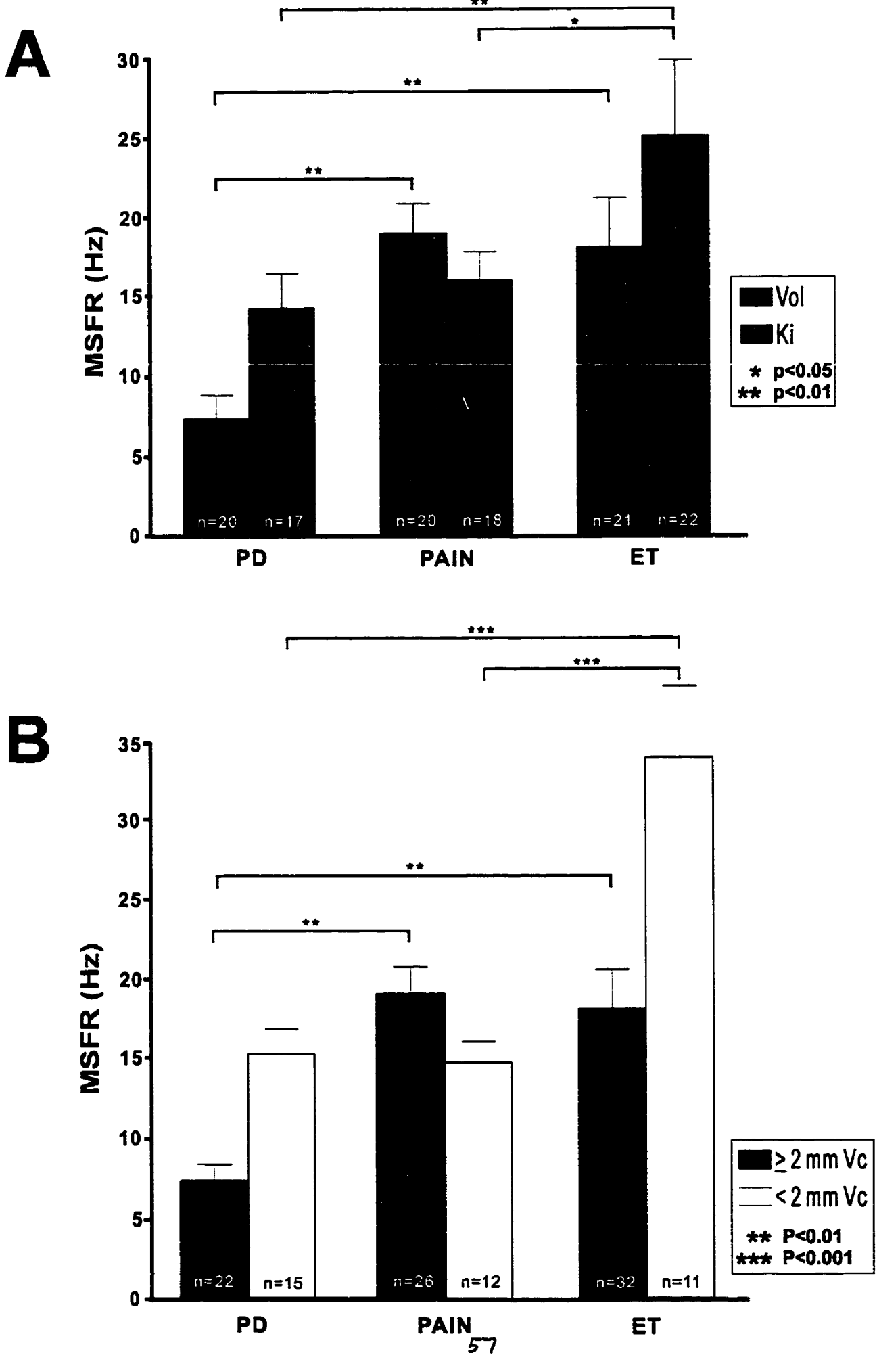

A
MSFR (Hz)
30
25
20
15
10
5
0
**
*
**
**
n=20
n=17
n=20
n=18
n=21
n=22
PD
PAIN
ET
Vol
Ki
* p<0.05
** p<0.01
B
***
***
MSFR (Hz)
35
30
25
20
15
10
5
0
**
**
n=22
n=15
n=26
n=12
n=32
n=11
PD
PAIN
ET
≥ 2 mm Vc
< 2 mm Vc
** P<0.01
*** P<0.001

Figure 13: Bar graphs of regularity of firing (variance value) for voluntary (Vol) and kinesthetic (Ki) responsive neurons in Parkinson's disease (PD), essential tremor (ET), and Pain patient groups. Comparison of average variance value of Vol and Ki neurons between patient groups. Horizontal brackets link significant differences. '**' equals '$p < 0.01$'.

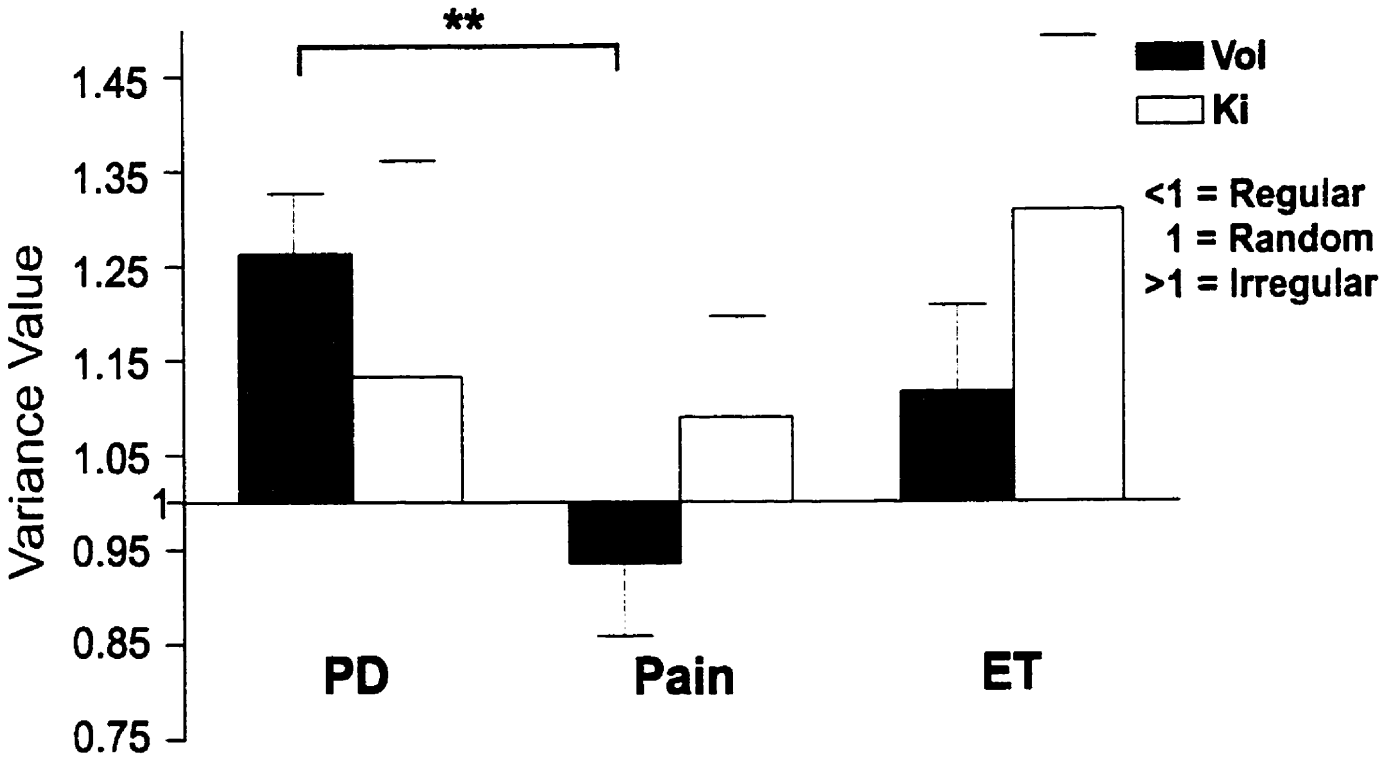

**
Vol
Ki
<1 = Regular
1 = Random
>1 = Irregular
Variance Value
1.45
1.35
1.25
1.15
1.05
1
0.95
0.85
0.75
PD
Pain
ET

Figure 14: Reconstruction of recording sites of voluntary and kinesthetic responsive neurons in each of the three patient groups. A) Parkinson's disease (PD), B) Pain, C) Essential Tremor (ET). The overlaid image is of the motor subnuclei of the thalamus scaled to the dimensions of the graph to show relative anatomic location of the recorded neurons. The vertical line at 2 mm was used to separate the neurons into the 'within 2mm' and 'beyond 2mm' groups discussed in results and shown in figure 1B. Abbreviations: AC/PC, anterior commissure/posterior commissure line; Vc, ventralis caudalis; Vim, ventralis intermedius; Voa, ventralis oralis anterior; Vop, ventralis oralis posterior.

triggered by itself. There was no evidence of any oscillatory activity in the correlograms which would indicate tremor components within the units (not shown).

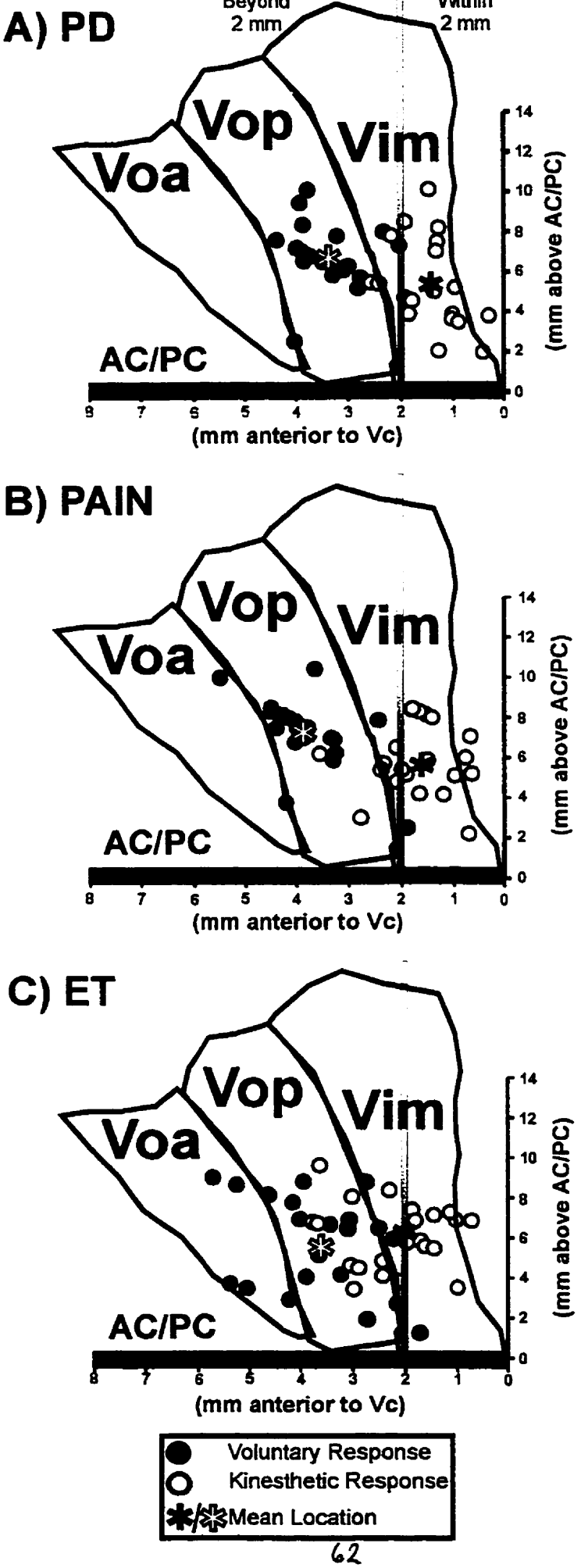
4.3 Neuron Location

The stereotactic locations of the neurons are displayed in **Figure 14**. The location of these neurons in the anterior-posterior axis (i.e. one dimension) was analyzed. The results of the one-way ANOVA indicated that the means were significantly different ($p < 0.001$) and the post-hoc test results are as follows. For all three patient groups the mean location of Vol neurons was significantly more anterior than the mean anterior-posterior location of Ki neurons ($p < 0.001$) (PD, **Figure 14 A; ET, B; Pain, C**). Based on the predicted thalamic anatomy, the mean location of Vol neurons for all three patient groups was within Voa/Vop and the mean location of Ki neurons was within Vim.

Figure 14 A shows the results from the PD group. The average location of voluntary response neurons was central in the ventral third of the Vop nucleus. The average location of neurons with kinesthetic receptive fields (RF) was central in the ventral third of the Vim nucleus.

In **Figure 14 B** the locations of the recorded neurons from Pain patients are displayed. The mean location of neurons with responses to voluntary movements was anterior in the central third of the Vop nucleus. The average location for kinesthetic response neurons was anterior in the ventral third of Vim.

The results from ET patients is displayed in **Figure 14 C**. The mean location of voluntary response neurons was anterior in the ventral third of Vop. The kinesthetic


A) PD
Beyond 2 mm
Within 2 mm
Vop
Vim
Voa
AC/PC
(mm above AC/PC)
(mm anterior to Vc)
B) PAIN
Vop
Vim
Voa
AC/PC
(mm above AC/PC)
(mm anterior to Vc)
C) ET
Vop
Vim
Voa
AC/PC
(mm above AC/PC)
(mm anterior to Vc)
Voluntary Response
Kinesthetic Response
Mean Location

neurons had a mean location near the anterior border of the central third of Vim.

Section 5. Discussion

In this study the mean spontaneous firing rates of neurons within motor thalamus of PD, ET, and Pain (control) patients were analyzed. The MSFR of Vol neurons in PD patients was significantly lower than for Vol neurons in the pain and ET patients (see **Figure 12**). Further the MSFR of Ki neurons in ET patients was significantly greater than that of Ki neurons in pain patients, and PD patients (see **Figure 12**). The results of the present study supported our predictions. It was predicted that there would be a decrease in the spontaneous activity of neurons in the presumed Voa/Vop subnuclei of thalamus (i.e. Vol neurons) in PD patients and an increase in the spontaneous activity of neurons in the presumed Vim (i.e. Ki neurons) of patients with ET.

A previous study which examined thalamic firing rates in normal and MPTP monkeys found significant reductions in the mean spontaneous firing rates and increased bursting (i.e. irregularity, short periods of high frequency firing) in the human equivalents of Voa/Vop (i.e.VLo; 16 ± 8Hz to 11.5 ± 7Hz, $p < 0.001$) and Vim (i.e. VPLo; 22 ± 8 Hz to 15 ± 8 Hz, $p < 0.001$) in the MPTP group (Vitek et al. 1994b). These results are consistent with the Vol findings between the PD and pain group from the present study (**Figures 12-13**) but we found no significant differences in the Ki neurons of PD patients compared to the pain group. Our control group, though free of symptoms of a movement disorder, have pain related pathologies. This could possibly have effects, although unknown, on many areas of thalamus such as Vim which relays 'sensory' input related to

movement. Although an earlier study by Vitek et al. (1994a) reported MSFRs from normal monkeys that are similar to our control group. They found that the MSFR of VLo neurons was 13 ± 8Hz and for VPLo neurons was 22 ± 11Hz in normal monkeys which are also similar with our findings for the MSFR of Vol (19 ± 8.5Hz, SD) and Ki neurons (16 ± 6.2Hz) of our pain (control) group. A recent paper by Lenz et al. (1999) reported mean interspike intervals for neurons in presumed Vim (0.076 ± 0.010 s) and presumed Vop (0.059 ± 0.012 s) in pain patients at rest that when converted to firing rates (13.2 ± 1.7Hz and 16.9 ± 3.4Hz respectively) are also consistent with our findings in our Pain group (see above). The findings in our study and in Lenz et al. (1999) both of which used human subjects seem to have observably lower standard deviations around calculated means. The most likely reason for this could be that human patients are probably more cooperative than trained monkeys during surgery. Even though human subjects would be understandably uncomfortable during the procedure their ability to understand instructions and willingness to participate could make for more stable recordings (less nervousness, tightening of muscles, startle, etc.). The effect of MPTP on the general activity of thalamic neurons could also be factor in the instability of neuronal firing patterns.

According to the model of the basal ganglia, dopamine loss in the striatum results in increased inhibitory outflow from GPi/SNr to thalamocortical relay neurons (Albin et al. 1989; Alexander and Crutcher 1991; Delong 1990). Output from GPi/SNr projects primarily to Voa/Vop regions of thalamus (Macchi and Jones 1997). Recordings from ventroposterior GPi in PD patients reveals increased firing in the off (medication)-state

(Hutchison et al. 1997) which could account for our finding of reduced firing of Vol cells in PD patients since GPi has inhibitory projections to Voa/Vop. When these patients were given apomorphine (i.e. dopamine agonist) and experiencing improvement in akinetic symptoms there was a reduction in firing rates in GPi which could account for firing rates of Vol neurons in our control group being greater than the PD group due to less inhibitory outflow from GPi (Hutchison et al. 1997). Basal ganglia loops through Voa/Vop of thalamus have large inputs to the supplementary motor area (SMA) of the cortex (Macchi and Jones 1997). Functional imaging studies employing positron emission tomography (PET) have demonstrated reduced rCBF in the SMA of PD patients in off-treatment states (drugs/DBS) during a motor task, which was reversed when the patients were in on-treatment states with apomorphine/DBS (Jenkins et al. 1992/ Limousin et al. 1997). Thus the reduced spontaneous firing of Vol neurons in PD patients found in the present study could also be a factor underlying the reduction of the rCBF in SMA.

At the level of the subthalamic nucleus (STN), which drives the GPi, an improvement of PD symptoms in humans and MPTP monkeys is attained with chronic stimulation or lesions which presumably decreases the excitatory input to GPi which would reduce the overactive inhibitory drive to Voa/Vop (Bergman et al. 1990; Guridi et al. 1996; Krack et al. 1998; Limousin et al. 1995).

Irregularity of firing of the Vol neurons in our PD patients (**Figure 13**) might be due to a low threshold, calcium-channel-mediated, rebound excitation of thalamic neurons due over-hyperpolarization by increased GPi output (Llinás 1984; Llinás and Jahnsen

1982; Pare et al. 1990; Steriade et al. 1990). As described in section 2.1.2 of the present thesis increased GPi firing in PD could hyperpolarize thalamic neurons and induce 9Hz bursting oscillations. To investigate this further we used an other analysis (bursting cell script in Spike 2 with parameters set to detect low threshold calcium bursts) but found no evidence of significant calcium spike-like bursting in Vol neurons of our PD patients nor any increased incidence of bursting cells in the vicinity of these Vol neurons (unpublished observation). Thus the irregularity of the PD Vol neurons could not be accounted for by low threshold calcium channel bursting.

Our findings from patients with ET (**Figure 12**) are consistent with some of the evidence and proposed pathologies involved in ET. Animal studies suggest that the olivocerebellar circuit may be a good candidate for tremor generation and perhaps ET. Injections of the alkaloid harmaline into monkeys resulted in the development of an ET-like tremor that is associated with rhythmic firing of neurons in the inferior olivary complex (IOC) (Battista et al. 1970; Callaway et al. 1999; Lamarre et al. 1971; Lamarre and Puil 1974; De Montigny and Lamarre 1974; Llinás and Volkind 1973; Yarom and Llinás 1981). This rhythmic firing was also recorded in climbing fibers in the cerebellum (Lamarre et al. 1971; Lamarre 1984). The IOC receives afferent input from the periphery and has projections to the cerebellum via climbing fibers capable of inhibiting Purkinje cells disinhibiting the efferent pathways of the deep cerebellar nuclei as part of the spinocerebellum (Côté and Crutcher 1991; Lamarre 1971). The spinocerebellum is involved in regulating the execution of movement and has connections to the red nucleus, thalamus, and cortex, which in turn project to the IOC and back to the cerebellum (Côté

and Crutcher 1991). Recent evidence from human studies suggests that the cerebellothalamocortical pathway is involved in ET. Functional imaging data from ET patients during involuntary tremor has shown increased bilateral cerebellar activation and deep cerebellar nuclei activation (Bucher et al. 1997; Jenkins et al. 1993). Since cerebellar input to the human motor thalamus is mainly in Vim and is excitatory in nature, then overactivity from the cerebellum in ET should increase the activity in Vim (Macchi and Jones 1997). Bucher et al. (1997) using Functional Magnetic Resonance Imaging (fMRI) found overactivation (increased rCBF) in the contralateral thalamus in ET patients during tremor but this was not detected at rest. No previous physiological study was found that evaluated the spontaneous firing of thalamic neurons in Vim of ET patients during non-tremor states. However evidence of high frequency tremor cells which fire during involuntary tremor are commonly found during stereotactic thalamic exploration in ET patients and lesions made in areas of tremor cells can abolish tremor (Goldman et al. 1992; Jankovic et al. 1995). In the present study we did however find increased activity of Ki neurons in patients with ET without tremor compared to controls (see **Figure 12**). Perhaps the current imaging techniques are not sensitive enough to detect the magnitude of increased activity we have found. It was found using imaging that there was increased rCBF in the cerebellum in patients with ET also at rest without tremor (Jenkins et al. 1993; Wills et al. 1994). Thus it is possible that this cerebellar over activation at rest could increase the firing of Vim neurons detectable by microelectrode recording. During tremor there would presumably be increased activity in the Vim region of thalamus due to proprioceptive neurons being activated from the arm

movement. This Vim activity could be unrelated to the undetectable increases in spontaneous activity that could be part of the 'loop' involved in ET generation. We propose that the increase in MSFR of Ki neurons found in our ET patients is pathological and predisposes the system to oscillation along the olivocerebellothalamocortical pathway. Thus, these oscillations are only elicited upon activation of the motor system (i.e. analogous to sabotaging a car by disrupting the braking system, the effects only noticed upon an attempt to stop). How this increased activity along the olivocerebellothalamocortical pathway could predispose for oscillations is unknown. To speculate, overactivity of a system that controls the execution of movement might alter its sensitivity (i.e. increased sensitivity) to perturbations and result in over-corrective movements.

The results of the neuron location part of the present study (**Figure 14**) supported an association between the physiological differences and anatomic location of thalamic neurons. As outlined earlier, histological and microelectrode evidence indicates that neurons responding to voluntary movements are contained within Voa/Vop (pallidal input) and neurons that respond to passive joint movements are contained within Vim (cerebellar input) of the thalamus (Macchi and Jones 1997; Ohye et al. 1976; Raeva 1999a,b; Tasker and Kiss 1995). For all three of our patient groups the mean location of Vol neurons was significantly more anterior than the mean anterior-posterior location of Ki neurons ($p < 0.001$) (PD, figure 3A; ET, 3B; Pain, 3C). Based on the predicted thalamic anatomy, the mean location of Vol neurons for all three patient groups was within Voa/Vop and the mean location of Ki neurons was within Vim. The recorded

neurons for each patient group were divided into 'within 2mm' or 'beyond 2mm' from the Vc border groups, and the MSFR were calculated (2 mm being the approximate width of Vim ventral aspect). For all three patient groups the MSFR of the 'within 2mm' and 'beyond 2 mm' groups were statistically similar to the Ki and Vol groups respectively and shared the same significant differences between the patient groups (**Figure 12 B**). Thus categorizing 'voluntary-responsive' neurons as presumed Voa/Vop neurons and 'kinesthetic-responsive' neurons as presumed Vim neurons were not unreasonable assumptions since the mean locations of the two groups were in the appropriate boundaries. Also the differences in firing rates in presumed Voa/Vop and Vim neurons between the patient groups were similar when comparing the neurons on the basis of physiology (i.e. receptive field) and as distance from the anterior Vc border (i.e. anatomy).

According to Morel et al. (1997) from their multiarchitectonic parcellation of the human thalamus there are 'islands' of Vim cell groups within the boundaries of Voa/Vop (i.e. based on the equivalent terminology of the present study). This could prove as a possible confound if one was to only consider gross anatomic location as a means of finding certain neurons. Though there seems to be some overlap between nuclei the general understanding (as described in earlier sections) is that neurons with similar physiological roles are confined within specific nuclei. This also strengthens the argument for the use of microelectrode exploration during functional surgery since anatomic location alone could lead to errors in the location of surgical targets. Other possible limitations of this work include the nature of the data collection and inherent

sampling bias. The recordings were collected from human patients undergoing surgery to treat their symptoms and not solely for the intentions of research. The majority of the recordings were obtained from archived surgical data that varied in experimenters involved and patient testing. Time and patient comfort controlled the length of recordings. Spontaneous firing periods are often varied or interrupted which may have had an effect on calculated values and definitely had an effect on the number of neurons useful for analysis. If certain neuron or tasks were of interest to a particular researcher during a surgery then there were tendencies to have proportionally more time spent on them then other neurons. Trajectories were generally made from an anterior-dorsal to posterior-ventral direction in the area of surgical interest thus there is a bias for more sampling dorsal aspects of Voa/Vop and ventral aspects of Vim and Vc (see **Figure 8)**. This limits statements about these nuclei in their entirety. Also the possibility of experimenter bias has to be mentioned as a possible limitation since prior information may influence interpretation of data. The methods of the surgery were useful in revealing aspects of thalamic physiology, which have not been previously explored in humans. A similar paradigm in primates (i.e. Vitek et al. 1994a; 1994b) could be used to further explore nuclear physiology through a more systematic and thorough approach to examine entire areas and using postmortem histology to localize individual neurons. Experiments with monkeys or surgeries in patients that involve controlled movement paradigms could provide a sound basis to compare physiological changes in movement-related responses of neurons in motor thalamus between different clinical disorders.

In summary this study has shown that physiological changes in PD patients at the level of the motor thalamus include a reduction in the mean spontaneous firing rate of presumed Voa/Vop neurons probably as a result of increased inhibitory output from the basal ganglia. Increased activity of neurons in the presumed Vim of patients with ET suggest that the changes may be related to the pathology as supported by some animal studies or provide a possible explanation for the effectiveness of Vim lesion in treating ET.

Section 6. Future Directions

The most interesting research question I have from my research experience is regarding the paradox of thalamic lesions or DBS being an effective treatment for movement disorder symptoms. The basal ganglia model for PD suggests that increased thalamic inhibition is the cause of hypokinetic symptoms yet making lesions in thalamus to relieve tremor does not exacerbate akinesia, bradykinesia, or rigidity. A future research direction would be to use specific movement tests to see if any deficits arise after lesions or DBS in the thalamus. A study by Canavan et al. (1989) found that large lesions in motor thalamus left monkeys impaired in performing visual conditional tasks yet they were behaviorally normal after a recovery period. Thus this type of paradigm could be applied to movement disorder patients before and after surgical treatment with a lesion or DBS in the thalamus.

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