Voluntary Tremor Suppression in Parkinson’s Disease

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Abstract

Parkinson’s disease (PD) is a common degenerative neurological disorder, and resting tremor is one of the main symptoms of this disease. It has been observed that some patients with Parkinsonian rest tremor are able to suppress their tremor voluntarily with mental concentration or by focusing attention on the affected limb. This process is not well understood and this study aims to describe and assess voluntary tremor suppression in patients with PD, as well as to identify the critical cortical or subcortical regions activated during this process.

Methods: Nine participants with tremor-dominant PD were recruited for this study. These patients had unilateral rest tremors of the upper limb and were able to consciously stop their tremor for a period of time. Each patient was assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS), movement tracking and functional imaging. Physical characteristics of the tremor such as amplitude and frequency were measured using a 3-D Polhemus Liberty electromagnetic movement tracking in the MoVELab. Functional imaging was undertaken using functional magnetic resonance imaging (fMRI) in a 3.0 Tesla scanner, with functional data collected with a standard T2 weighted MRI sequence along with T1 weighted 3-D anatomical data.

Results: The extent of voluntary tremor suppression differed between the participants with some being able to suppress reliably for long periods of time, and others unable to do so consistently. Participants had slight to moderate tremors according to the UPDRS. The majority of participants described their method of suppression as concentrating on the affected limb and/or focusing on relaxing the limb. Movement tracking confirmed what was observed, with variation in tremor amplitude, and the extent of suppression. FMRI showed differing areas of activation involved in tremor suppression amongst the participants. Activated areas were generally contralateral to the tremor, and were widespread, including parts of the primary motor cortex, superior parietal lobule, supramarginal gyrus and middle frontal gyrus.

Conclusion: This study was the first attempt at describing the process of voluntary tremor suppression in PD. The differing methods the participants used to suppress
their tremor were recorded and described, and objective measures of the suppression taken. Functional imaging revealed a number of areas involved in tremor suppression.
Preface

This thesis is the result of an eventful period of research and study and is submitted for consideration for a Bachelor of Medical Science with Honours. Beginning in 2010, this has been an intensive undertaking and I have found myself gathering skills in many areas I never thought I would have in the past. With the help of many at the Van der Veer Institute (now the New Zealand Brain Research Institute), I have learnt how to independently manage participants, perform focused clinical histories and examinations, apply Parkinson’s disease rating scales, gather three dimensional movement data, and explore functional magnetic resonance imaging. Aspects of this research project have been presented at NZBRI discussion groups and at the Australasian Winter Conference on Brain Research in 2010. Feedback at such meetings has been invaluable in improving this project.
Acknowledgements

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Aims

• To describe and assess voluntary tremor suppression in patients with Parkinson’s disease.

• To identify the critical cortical or subcortical regions responsible for voluntary (i.e. by mental effort or concentration) tremor suppression in Parkinson’s disease.
1. Introduction

This project investigates the process of voluntary tremor suppression in Parkinson’s disease. Parkinson’s disease (PD) is a common neurodegenerative disorder with the majority of patients affected by tremor as a major symptom (Alves et al., 2008). Clinically, it has been observed that some patients are able to voluntarily suppress or stop their tremor by using mental concentration or by focusing attention on the limb affected with tremor.

1.1 Parkinson’s Disease

Parkinson’s disease is a common degenerative movement disorder of the central nervous system (Tanner & Aston, 2000). After Alzheimer’s disease, it is the second most common neurodegenerative disorder, affecting 1-2% of the population aged over 65 years, with prevalence rising to 3-5% of those aged 85 years and older (Fahn, 2003).

Pathologically, Parkinson’s disease is characterized by dopamine producing neuron loss in the substantia nigra and the presence of Lewy bodies- an alpha-synuclein protein aggregate (Braak et al., 2003; Nussbaum & Ellis, 2003). These changes lead to a disruption of neural pathways within the basal ganglia and motor cortex resulting in a variety of motor disturbances.

The definitive cause of these pathological changes is unknown and the majority of patients have sporadic Parkinson’s disease, with a significantly smaller proportion of patients with genetically determined Parkinson’s disease. The present hypotheses on the etiology of Parkinson’s disease suggest complex, multi-factorial causes involving genetic, environmental, gender and age-related risk factors (Allam et al., 2005).

Genetic risk factors have been implicated in a variety of studies. People with a family history of Parkinson’s disease are three to four times as likely to develop the disease than the general population (Kurz et al., 2003). In known cases of familial Parkinson’s
disease, a number of genetic mutations have been identified. These mutations affect several key molecular pathways causing mitochondrial dysfunction, disruption of cellular protein recycling, and increased oxidative stress (Eriksen et al., 2005).

Several studies have also found gender differences in the incidence of Parkinson’s disease (Shulman, 2007; Taylor et al., 2007). In age groups 60 years and above, there is a consistently higher incidence in males (Shulman, 2007). Overall, the incidence of Parkinson’s disease in males is 1.46 times higher than in females (Taylor, et al., 2007). It has been speculated that female steroid hormones such as progesterone may have a neuroprotective effect in preventing Parkinson’s disease (Shulman, 2007).

Environmental causes of Parkinson’s disease have long been a subject of interest and many environmental risk factors such as heavy metals, factory toxins and pesticides have been suggested as having an etiological role (Elbaz & Tranchant, 2007). Pesticides in particular, have a well established role in the degeneration of dopaminergic neurons in areas of the substantia nigra (McCormack et al., 2002). Interestingly, cigarette smoking and caffeine have been found to have a possible protective effect in Parkinson’s disease (Checkoway et al., 2002).

Clinically, Parkinson’s disease is primarily described as a movement disorder, and as such is characterised by its variety of motor symptoms. A significant number of non-motor symptoms are also relevant in Parkinson’s disease (Alves, et al., 2008).

Motor problems in Parkinson’s disease include the four cardinal signs and symptoms that characterize the disease: tremor, rigidity, bradykinesia and postural instability (Fahn, 2003). Tremor is a rhythmical, involuntary oscillation of a part of the body. In PD, the tremor is typically a rest tremor, which in the upper limb is typified by pill-rolling finger movements and/or supination/pronation movements of the forearm. This aspect of Parkinson’s disease will be expanded upon later in the introduction. Rigidity is an increase in muscle tone causing resistance to passive movement of the limbs. Bradykinesia in Parkinson’s disease is a slowness of movement, typically manifesting as difficulty in starting or maintaining movement of the limbs. Postural instability describes a loss of balance and ability to maintain a steady upright posture. Together, these four symptoms combine to give the classical clinical picture of Parkinson’s disease.
Outside of the motor signs and symptoms outlined above, there are also a number of non-motor problems which affect people with Parkinson’s disease (Shulman et al., 2001). These symptoms include cognitive impairment (including dementia), depression, hallucinations, fatigue, sleep disturbances, autonomic dysfunction and olfactory problems (Shulman, et al., 2001). Of these symptoms, cognitive impairment is perhaps the most significant. Cognitive impairment is a decline in mental performance beyond that expected for the person’s age. This may first be noticed as degrading memory, lapses in attention, and visuospatial deficits (Dubois & Pillon, 1997). In Parkinson’s disease, cognitive function declines as the disease advances with an increase in severity and scope of cognitive problems. Hallucinatory symptoms are common in PD, being reported in 40-50% of patients (de Maindreville et al., 2005). Depression is also a significant co-morbidity with up to 35% suffering depressive symptoms (Reijnders et al., 2008). Sleep disturbances include insomnia, excessive daytime sleepiness, parasomnias such as REM sleep behaviour disorder, and limb movement during sleep (Tandberg et al., 1998). This is thought to be due to both pathological changes to the areas of the brain that regulate sleep, and a side effect of the PD patient’s drug regimen (Tandberg, et al., 1998). Over the course of the disease, it is expected that the majority of patients with PD will be affected by at least some of these problems.

1.2 Tremor

As stated earlier, tremor is a rhythmical, involuntary oscillatory movement of a body part. There are a wide variety of tremors, ranging from the pathological to the physiological. Combined with the large range of causes, clinical presentations and confounding symptoms, the classification of tremor has been an ongoing and difficult task. In 1998, the Movement Disorder Society released a Consensus Statement for the clinical classification of tremors (Deuschl et al., 1998). According to this classification system, tremor can be differentiated based on the “activation conditions during which tremor occurs.” A second classification style is based on tremor syndromes, where by
different types of tremor can be combined with information on etiology and medical history into a clinical syndrome. The definitions that follow have been drawn from this consensus statement.

The two main types of tremor, according to the conditions in which they occur, are rest and action tremor. Rest tremor is defined as a tremor that occurs in a body part that is not voluntarily activated, whilst completely supported against gravity. It is most commonly a feature of tremor in Parkinson’s disease—this will be expanded on later.

In contrast, action tremor is defined as a tremor that is produced by voluntary contraction of muscle. Action tremors can be further separated into postural, isometric and kinetic (intention) tremor. Postural tremor is a tremor that is present when the affected body part voluntarily maintains a position against gravity. An isometric tremor is a tremor occurring as a result of muscle contraction against a rigid stationary object, i.e. tremor during voluntary contraction without movement. An example of this is tremor while gripping an object. A kinetic tremor is one that occurs during any voluntary movement. The most significant kinetic tremor is the intention tremor—tremor when moving towards a target.

The above tremor types can be combined with further information from the patient’s medical history and clinical examination to allow classification into distinct tremor syndromes. Elements such as etiology, abnormal movements, neurological or muscular signs and symptoms, and accompanying pathologies form the basis for this classification. Many different tremor syndromes exist including physiologic tremor, essential tremor, parkinsonian tremor, cerebellar tremor, Holmes’ tremor, palatal tremor, drug-induced tremor, psychogenic tremor and dystonic tremor.

Of the many varieties of tremor syndromes listed above, some tremors are more common than others. Physiologic tremor is an example of a non-pathological tremor that occurs in every normal individual. It is present in all skeletal muscle groups but typically unobservable without movement assessment tools. This tremor is usually of very minute severity with low amplitudes but can be modulated under certain conditions (termed enhanced physiologic tremor). Factors such as stress, fatigue, anxiety, hypoglycemia and alcohol withdrawal, can cause physiologic tremor to become apparent.
Essential tremor (ET) is the most common pathological tremor syndrome (Deuschl, et al., 1998). Typically, it has been described as a postural tremor of the hands and forearms, sometimes affecting the head. However, many variations of ET exist and as such, it has substantially varied clinical presentation and indeterminate etiology. ET also encompasses a range of different task/position specific tremors.

Other less common pathological tremor syndromes include cerebellar tremor and dystonic tremor. Cerebellar tremor is a tremor caused by damage to the cerebellum or cerebellar pathways in the brain stem (from pathologies such as stroke, multiple sclerosis) leading to a low frequency intention tremor. Dystonic tremor is a tremor resulting from dystonia, a movement disorder characterized by prolonged muscle contractions causing abnormal postures and twisting of various parts of the body.

The tremor syndrome of focus for this project however, is Parkinsonian rest tremor. This will be covered in the forthcoming sections of this introduction.

1.3 Tremor in Parkinson’s Disease

Of the four cardinal symptoms of Parkinson’s disease, tremor is the most common presenting symptom at the onset of the disease and over the course of the illness, a significant majority of sufferers will develop a tremor (Alves, et al., 2008). Clinically, Parkinsonian tremor usually presents unilaterally in the hand but as PD progresses, the tremor can spread first to other parts of the limb, unilaterally to bilaterally, and then to other parts of the body, including the foot, leg and jaw (Lyons & Pahwa, 2005).

The Movement Disorder Society’s Consensus Statement provides this formal definition of tremor in Parkinson’s disease: “Tremor in PD is assumed if the patient has any form of pathologic tremor and the patient has PD according to the Brain Bank criteria-bradykinesia must be present. As a result of the variability of tremor in PD, this definition of tremor in PD is based around the general diagnosis of PD rather than the specific features of the tremors (Deuschl, et al., 1998).” However within the general
range of tremor in PD, there are different types of parkinsonian tremor that are defined according to tremor features.

Type I: Classic parkinsonian tremor. This is a rest tremor with the possible presence of kinetic and postural tremor components which have a similar frequency to the rest tremor component (Deuschl, et al., 1998). This type of tremor in PD is the most common and considered one of the cardinal symptoms of PD. It is described as a pill-rolling finger movement with pronation/supination of the forearm. Typically, the frequency of the rest tremor ranges from 4-6 Hz with frequencies within 1.5 Hz of the rest tremor for the kinetic and postural components. However, high frequency tremors do exist, and tremor frequencies up to 9 Hz have been found (Deuschl, et al., 1998).

Type II: Rest tremor and kinetic/postural tremors of different frequencies. In this type of PD tremor, the kinetic and postural components have a frequency that is higher and non-harmonically related to the rest tremor component (Deuschl, et al., 1998). An uncommon form of this type of tremor is the postural dominant parkinsonian tremor. It is hypothesized that this form of tremor is a possible combination of essential tremor and Parkinson’s disease.

Type III: Pure postural/kinetic tremor. This group includes all instances of isolated postural and kinetic tremors in PD (Deuschl, et al., 1998). Typical frequencies run from 4-9 Hz. This type of tremor in PD is thought to possibly involve other types of tremor unrelated to Parkinson’s disease such as essential tremor or physiologic tremor. Pure postural or kinetic tremors in PD have proven hard to separate from these other tremor syndromes based on clinical observation alone.

Treatment of tremor in Parkinson’s disease has proven to be difficult. Clinical therapy options are limited as there are no drugs which have been shown to be consistently effective against parkinsonian tremor and side effects often limit the use of pharmacological therapy (Wasielewski et al., 1998). Levodopa is the most widely used drug in patients with PD, as it is effective against a wide range of PD symptoms. It can be effective in treating tremor in some patients; however other patients have tremors which are resistant to levodopa therapy. Other commonly used pharmacological agents in Parkinson’s disease are anticholinergic drugs (such as benztropine). Anticholinergics frequently have significant side-effects, including confusion, constipation, visual impairment and urinary retention. They also interact with other drugs by affecting
intestinal absorption- this is a significant issue in patients with Parkinson’s disease as many are on an extensive drug regimen and therefore therapy for tremor can often affect therapy for other symptoms.

There is also a limited range of surgical options for tremor therapy. Although more widely used in the past, surgery is now limited to patients with advanced cases of Parkinson’s disease with severe symptoms not treatable by conventional pharmacologic therapy or with uncontrolled levodopa-induced dyskinesia. Currently, the most widely used surgical intervention for tremor in PD is deep brain stimulation (DBS). DBS involves the implantation of a lead into the brain which is connected to an implanted pulse generator which sends electrical signals to target sites in the brain. These electrical pulses modulate neural activity in the targeted brain region, reducing symptoms that arise from pathological changes in these areas of the brain. The most common locations for DBS in PD are the subthalamic nucleus and the globus pallidus interna. Another surgical intervention that has been successfully trialled is the lesioning of the above brain regions. Again, use of these surgical interventions is limited and only used in the most severe cases of Parkinson’s disease.

1.4 Tremor Assessment

The great diversity of tremor types and syndromes has lead to the development and use of many methods of assessing tremor. These techniques range from simple observation to more complex and objective limb motion tracking systems. With regards to tremor in Parkinson’s disease, the most commonly used methods have been rating scales in clinical settings, and accelerometry in the laboratory.

Clinical evaluation of tremor in patients with Parkinson’s disease is predominantly based on the use of rating scales which combine observation and medical examination with the patient’s own reporting of their tremor symptoms to assign a score to the patient. The most widely used rating scale is the Unified Parkinson’s Disease Rating Scale (UPDRS) "The Unified Parkinson's Disease Rating Scale (UPDRS): status and
recommendations," 2003). Other rating systems for PD include the Tremor Rating Scale.

The UPDRS is an assessment system developed in 1987 and later revised by the Movement Disorder Society in 2008 (Goetz et al., 2008). Both clinicians and researchers have adopted it extensively. Because of its universality, ease of use and comprehensiveness (especially in regards to the motor symptoms of Parkinson’s disease), the UPDRS allows for an easily communicable score which can be readily used to follow the longitudinal progression of a patient’s Parkinson’s disease. In this rating scale, the patient is asked to answer a set of questions or undergo specific examinations. For each question/examination, the patient is assigned a score ranging from zero to four, zero generally being not affected or normal, and four being severely affected. For example, multiple items in the UPDRS address tremor. A score of zero would indicate the patient had no tremor. A score of one would indicate a tremor was present but did not interfere with any activities. A score of two would indicate a tremor was present and interferes with a few daily activities. A score of three would indicate a tremor was present and interferes with many daily activities. A score of four would indicate the tremor causes problems with most or all activities.

The original UPDRS comprised six parts: firstly, assessment of “Mentation, behaviour and mood,” rating aspects such as intellectual impairment, thought disorders, depression and motivation by self-report. The second part comprised of questions which allowed for self-evaluation of the patient’s “Activities of daily living,” particularly if they were having any problems with things such as speech, handwriting, dressing, falling, walking and tremor, amongst other things. The third part of the UPDRS is a motor examination in which the clinician/researcher would evaluate the patient’s motor symptoms. This exam focuses on problems with speech, facial expression, tremor at rest, action or postural tremor of the hands, rigidity, ability to perform finger taps, hand movements, rapid alternating movements of the hands, leg agility, standing from a chair, posture, gait, postural stability and body bradykinesia and hypokinesia. The fourth part concerned the patient’s complications of therapy, i.e. how they were affected by their treatment. The fifth section incorporates the Hoehn and Yahr Staging system, a measure of disability in Parkinson’s disease. The Hoehn and Yahr scale is a five stage rating scale ranging from stage 1: unilateral symptoms only; stage 2: bilateral symptoms; stage 3: balance impairment, mild to moderate disease,
physically independent; stage 4: severe disability, but still able to walk or stand unassisted; stage 5: severe disability resulting in the loss of physical independence. Finally the sixth part is the Schwab and England Activities of Daily Living Scale- a rating scale that assesses the patient's dependency and ability to carry out normal daily activities.

In 2003, the Movement Disorder Society established a taskforce to address the shortcomings of the UPDRS "The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations," 2003). The MDS sponsored UPDRS (MDS-UPDRS) clarified items in the scale to reduce ambiguities and improve ease of use of the scale by both patients and clinicians. It was also modified to address inadequacies in the non-motor symptoms sections of the scale. The motor symptom related sections of the UPDRS have been largely unchanged, as the original scale was already very complete in this area. Like the original scale, the MDS-UPDRS is made up of multiple sections. The four sections are: non-motor experiences of daily living, motor experiences of daily living, motor examination and motor complications.

The comprehensive assessment of the motor symptoms of Parkinson’s disease in both the original UPDRS and updated MDS-UPDRS make it an ideal rating scale for use in Parkinson’s disease research and as a key measure in tremor specific research. In scientifically-focused research projects it is often used as an adjunct to more objective tremor assessment tools such as accelerometry and electromyography. The present project used the updated MDS-UPDRS because of its more comprehensive set of instructions for the examiner, ensuring more consistency across multiple subjects.

Accelerometry is the measurement of acceleration of a limb caused by tremor. This is generally achieved by measuring relative changes in limb velocity with respect to time. Accelerometry can be performed by a variety of tools but the most commonly employed device is the piezoresistive accelerometer. Piezoresistive accelerometers are lightweight devices which contain crystals sensitive to acceleration (Hallett et al., 1994). Placed on the limb of interest, they are able to quantify tremor movements easily and effectively. Both unidirectional and multidirectional accelerometers have been used widely in tremor research.

A more recently developed technique which measures tremor movement is electromagnetic movement tracking. In this method, sensors are placed on the affected
A small magnetic field is generated by an external device and as the sensors on the limb move inside the magnetic field, the movement of the limb is able to be tracked. Such systems are able to measure absolute displacements of a limb (with an accuracy in the millimeter range), and from these measurements, the frequency and amplitude of the tremor can be found (Myall et al., 2008).

### 1.5 Functional Imaging

Functional imaging encompasses a number of imaging techniques that serve to measure the physiological activity of a body system. This is contrasted with structural imaging which details the physical structure of a body part. Functional imaging has uses throughout the body, but a field in which it has had a large impact is in the imaging of the brain (neuroimaging). The use of imaging techniques to view the brain has allowed the elucidation of not only the structural elements that make up the brain but also the function of these structures and their role in controlling the various human body systems.

There are a number of functional neuroimaging techniques. These include functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT).

PET scanning involves injection of radioactively labeled chemicals (radiotracers) into the patients’ bloodstream. As the radiotracer makes its way through the brain, it emits positrons and gamma rays which are detected by the scanner. Various metabolites such as water, glucose and ammonia can be radioactively labeled. The use of labeled glucose for example (the most commonly used clinical PET radiotracer) allows investigators to visualize which parts of the brain are metabolizing the most glucose and thus gives an indication of activity in different regions of the brain. PET scanning has found uses in the diagnosis of Alzheimer’s disease where brain metabolism of glucose and oxygen is greatly reduced. It has also been used in the functional imaging of tremor (this will be explored later).
SPECT scanning operates in a similar way to PET. A gamma-emitting radiotracer is injected into the bloodstream and is taken up by the brain. Sensors detect the emitted gamma rays and thus allow visualization of the areas of the brain which take up the radiotracer.

Magnetic resonance imaging (MRI) is the imaging technique of interest in this project. MRI involves the placing the person into strong magnetic field. This causes changes in spin states of protons within water molecules in the body. When the magnetic field is turned off, the spin of the protons revert, releasing energy, which is detected by the scanner to image the area of interest. Functional MRI uses an MRI contrast called blood-oxygen-level dependence (BOLD). This uses differences in MRI signal between oxyhemoglobin and deoxyhemoglobin to measure brain activity. Neurons that are more active require more oxygen and this increases the concentration of oxyhaemoglobin in the blood. This gives a higher BOLD signal. FMRI has been used successfully to map complex human movements (Rao et al.) as well as other tremor movements such as essential tremor (Bucher et al.).

Functional imaging in Parkinson’s disease tremor research has mainly focused on the metabolic biochemical aspects of Parkinsonian tremor (Grafton). PET and deep brain stimulation have been used to identify metabolic brain networks associated with Parkinsonian tremor and other symptoms (Ceballos-Baumann). This includes many areas of the brain, particularly the primary motor cortex, the supplementary motor area, the premotor cortex, sensorimotor cortex, cerebellum and thalamus (Antonini et al., 1998; Deiber et al., 1993), with the thalamus thought to be of particular importance.

1.6 Significance of the Project

Rest tremor is one of the main symptoms of PD and is present in the majority of PD cases (Alves, et al., 2008). In some patients, tremor is difficult to treat and can be resistant to drug therapy. Currently the only non-pharmacologic therapy for PD tremor is with deep brain stimulation of the subcortical structures in the brain such as the sub-
thalamic nucleus and globus pallidus. Thus, other therapeutic avenues need to be explored.

Voluntary tremor suppression is a process that has been observed clinically but one that has not been defined or described in the scientific literature. There is an abundance of information of the characteristics of Parkinsonian rest tremor, but none on the characteristics associated with people who are able to voluntarily suppress their tremor. The method by which they do so also remains a mystery. Furthermore, there is a lack of objective measurements on the process of voluntary tremor suppression, with key measures such as the amount of reduction in the amplitude of tremor not known. Finally, there have been no studies which look at the brain regions active during this process. This study aims to address these gaps in the literature.

By investigating the process of voluntary tremor suppression, this project hopes to identify other regions of the brain that are active in tremor suppression and open up the possibility of these regions being used as targets for future tremor therapy. For example, if we could identify a specific cortical region recruited by patients in tremor suppression, then repetitive transcranial magnetic stimulation could be used to target these areas. Alternatively, if a new subcortical region was identified, this might suggest an alternative target for deep brain stimulation.

Furthermore, the conscious behavioural strategies employed by the participants may be as simple as focused relaxation or co-contracting all the muscles in the forearm to prevent muscle movement. In these cases, these techniques may be able to be taught to other patients with parkinsonian tremor to temporarily reduce tremor at certain times where it is particularly inconvenient.
2. Methodology

The two aims of this study—assessment of voluntary tremor suppression and identifying the brain regions involved—were investigated using a number of methods. Clinical histories and examinations were used to get an overall picture of the participants and their tremors. The clinical rating scale “Unified Parkinson’s Disease Rating Scale” (UPDRS) was used to assign a current score of the status/severity of the participants’ Parkinson’s disease. Of particular interest were the components of the UPDRS which assessed the participants’ tremors. Electromagnetic movement tracking was used to measure and evaluate objectively the physical characteristics of tremor such as frequency and amplitude. Functional magnetic resonance imaging (fMRI) was used to identify the brain regions active during tremor suppression. Furthermore, video recording of the tremor and tremor suppression was undertaken to allow for descriptive characterisations of the process, as well as cross-referencing of each method of tremor assessment. Surface electromyography of the tremor and tremor suppression was measured but is not presented here due to problems with data collection and analysis. I undertook the clinical histories, examinations, UPDRS and data collection for the movement tracking independently while functional imaging acquisition was done at Hagley Radiology with additional expertise from the New Zealand Brain Research Institute (NZBRI). I carried out the analysis of all the data collected, with key assistance from other researchers at the NZBRI.

2.1 Subjects

A total of nine participants were recruited from the Christchurch and greater Canterbury region. Participants ranged from 50 years old to 76 years old with a mean
age of 68 years of age; all except one were aged above 60. Six participants had tremors primarily in their left upper limbs, while three participants had tremors primarily in their right upper limbs. In the majority of the participants, the tremor of the upper limb was the only location of the tremor and most had no other major motor symptoms caused by their Parkinson’s disease. Of these nine participants, two were unable to suppress their tremor consistently enough to undergo tests of movement tracking and MRI scanning. An additional two participants elected not to undergo the MRI. Two participants did not undergo movement tracking due to technical issues with the equipment at the time of the experiment. The female/male split was five females and four males. The participants’ duration of disease ranged from 3 months to 8 years. In regard to medications, participants were not asked to make any changes to their normal drug regimen.

2.2 Participant Selection

Participants for this study were primarily identified by Professor Tim Anderson as they visited his Parkinson’s disease clinic throughout the year of 2010. A minority of participants were also identified by other researchers at the Van der Veer Institute as they underwent assessments for other ongoing Parkinson’s disease research projects.

Inclusion criteria were that the participant must have been diagnosed with Parkinson’s disease, have a typical Parkinsonian rest tremor, and be able to voluntarily suppress their tremor reliably and reproducibly without the use of external aids. Ideally, the participant would have a tremor that affected predominantly one limb on one side of the body and also have been of consistent, observable severity.

Participants were excluded if they had a history of other central nervous system disorders such as stroke or head injury, major medical illness, major psychiatric disorders, were unable to undergo or tolerate MRI, took psychoactive medication or were unable to speak and read English.
2.3 Tremor-Focused Clinical History and Clinical Rating Scales

For each participant, details such as date of birth, gender and which limb the tremor occurred in were collected before a brief medical history was conducted to decide whether or not the participant was in breach of any of the exclusion criteria. This covered the participants’ past medical history, any potentially relevant family and social medical history, and the participants’ current medications.

Once it had been determined that the patient satisfied the inclusion and exclusion criteria, a more focused clinical history regarding their Parkinson’s disease and tremor was undertaken. This focused on details such as the date of onset of Parkinson’s disease symptoms, the duration of the illness, self-reported advancement in the progression of the participants’ PD, major and minor motor symptoms and non-motor symptoms. Regarding the tremor, participants were asked about the location of the tremor, the involvement of proximal parts of the affected limb, severity and duration of the tremor, onset and progression of the tremor, minor involvement in any of the other limbs, the conditions and times of the day that modulated the tremor, difficulties in daily activities caused by the tremor and any other signs and symptoms associated with the tremor.

Each participant’s individual process of tremor suppression was also documented. Each participant was asked to describe the thought processes they invoked to stop their tremor and based on their replies and follow-up questions were used to further elucidate what they were doing to suppress their tremor. For example, if a participant described their process of tremor suppression as relaxing the affected limb, the participant would be asked about the perceived tension of the associated muscles in the limb. During this, observation of the process would take place, noting significant aspects of the tremor suppression such as changes in body or limb position, duration of the suppression,
whether the suppression was absolute or a relative reduction in severity and differences in suppression of each component of the limb (such as fingers, thumb, hand, forearm).

A clinical rating scale, the Unified Parkinson’s Disease Rating Scale (UPDRS) was also used to assess the participants’ Parkinson’s disease and tremor. Particular attention was paid to the tremor components of this rating scale: self-reported impact of tremor on the participants’ daily activities, a motor examination looking for postural and kinetic tremors of the upper limb, a motor examination of any tremors present at rest in the upper and lower limbs and the lip/jaw.

2.4 Movement Assessment

Objective assessment of the participants’ tremor and tremor suppression was employed using electromagnetic movement tracking. Surface electromyography was attempted however that data is not presented here due to difficulties in collection and analysis. Video recordings of the tremor and tremor suppression were also taken.

Electromagnetic movement tracking was used using a 3-D Polhemus (Colchester, Vermont) Liberty electromagnetic tracking system in the MoVELab (Myall, et al., 2008) at the Van der Veer Institute (now known as the New Zealand Brain Research Institute). This system allowed movement to be quantified with 6 degrees-of-freedom (three translational and three rotational) with a sampling rate of 240 Hz. Four electromagnetic sensors were placed on the participants’ affected limb- one on each of the posterior surface of the forearm, hand, index finger and thumb. These sensors moved with the limb inside a small magnetic field generated by the Polhemus Liberty tracking system, allowing data to be collected regarding the position of the sensors and thus the limb.

The MoVeLab gathered spatial position data in a Cartesian xyz coordinate frame related to the room (one coordinate representing the vertical direction and the other two being parallel to the room walls). This coordinate system was an arbitrary one when
applied to tremor movements. A tremor consisting purely of wrist flexion/extension could result in movement occurring in any two or all three of the x, y or z axes, depending purely on the posture of the hand. For example, simple wrist flexion extension could be along a direction which was primarily vertical, horizontal, or oblique with respect to the room, depending on the hand posture. When plotted as amplitude in each of the three xyz directions, the total amplitude would not be immediately apparent as it would be spread into smaller components across all three axes, even if it was primarily a unidirectional movement. Accordingly, principal components analysis was used to select a new axis which contained most of the variability in sensor position. In essence, a new coordinate system was chosen such that the primary axis went through the direction in space in which the tremor was primarily directed, with two other coordinates at mutually orthogonal directions. This coordinate system would generally be rotated relative to the original room-centred coordinates, and was recalculated for each 30 s block to account for the subject repositioning or changing posture during the recording. The plots in the results section show the amplitude of movement along the primary axis of tremor and are close to representing the total tremor amplitude (as much less movement occurred in the other orthogonal axes).

During each 30 s block, the participants could sometimes make large voluntary movements or posture changes which made it difficult to present the smaller magnitude of tremor on appropriate scales. Hence a rolling mean, sampled over 1 s, was subtracted from the data to remove the appearance of these contaminating large movements in the plots. Hence the plots appear to show that the participants kept almost perfectly still apart from their tremor: this is an artefact of this correction process, but it allows us to view the tremor on consistent and convenient scales.

The following procedure was used. Once the sensors and electrodes were in the correct position and confirmed to be performing satisfactorily, the experiment would begin. Participants were instructed to relax and let their tremor appear with the verbal instruction of “tremor” for a 30-second block, followed by an instruction to suppress their tremor with the verbal instruction of “suppress” for a 30-second block. The movement tracking system would emit one beep to indicate the initiation of each “tremor” block (accompanied by a verbal cue) and after the 30-second duration of that block, two beeps were sounded to indicate a “suppression” block (again, also
accompanied by a verbal instruction). This pair of blocks was repeated in sequence, ten times for a total experiment time of ten minutes. This procedure was identical to our fMRI experimental protocol.

**2.5 Functional Magnetic Resonance Imaging**

Magnetic resonance imaging was performed on a 3.0 Tesla General Electric HDx MR scanner equipped with an 8-channel brain radiofrequency coil at Hagley Radiology, Christchurch. Each participant was positioned lying supine with his or her head in the MRI coil. Padding was arranged for the participants’ comfort and to allow free movement of the limb with the tremor. The participants’ movements, tremor and tremor suppressions were monitored and recorded using video.

Structural images were acquired using a T1 weighted, 3D spoiled gradient echo recalled (SPGR) sequence with interleaved slice acquisition (echo time (TE) = 2.81 ms, time to repetition (TR) = 6.56 ms, flip angle= 15°, acquisition matrix = 256x256 mm, reconstruction matrix = 512x512x170 mm, field of view (FOV) = 250 mm, slice thickness = 1 mm, spacing = 1 mm, voxel size = 0.49 x 0.49 x 1 mm³)

Following this, each participant undertook three T2 weighted functional MRI runs (TE = 35 ms, TR = 3000 ms, flip angle = 90°, acquisition matrix = 64x64x40 mm, reconstruction matrix = 64x64 mm, FOV= 240 mm, slice thickness = 4mm, spacing = 4 mm, voxel size = 3.75 x 3.75 x 4mm³).

An fMRI block design was used in this study. An fMRI block design consists of a block of predefined time (such as 30 seconds or one minute), in which the participant is undergoing one condition, followed by another block in which the participant is undergoing another condition, repeated a number of times. The two conditions are then contrasted.

The first fMRI run comprised of a block design with tremor and tremor suppression as conditions. During the tremor condition, participants were instructed verbally via
headphones to relax and let their tremor occur as normal. During the suppression condition, participants were instructed verbally via headphones to suppress their tremor. Each block lasted 30 seconds and was repeated ten times each for a total scan time of ten minutes.

After a brief rest period, the second functional run was undertaken. The conditions in this run were tremor and voluntary movement. During the tremor condition, participants were instructed to relax and let their tremor occur as normal. During the voluntary movement condition, participants were instructed to perform a predefined finger tapping routine. This involved a sequence in which participants repetitively moved each of their fingers in sequence to oppose the thumb using the limb affected by tremor. Each block lasted 30 seconds and the pair of blocks was repeated five times each for a total scan time of five minutes. This second paradigm was to provide a control condition.

The third functional run was a repeat of the first.

MRI data was analysed using Statistical Parametric Mapping 5 (SPM5) (Wellcome Department of Cognitive Neurology, University College London, UK) in Matlab 7.6.0 (R2008a, Mathworks, Massachusetts, USA). A number of steps were taken to preprocess the data prior to statistical analysis. Firstly the T1-weighted SPGR image was reorientated to the anterior commissure. This image was then segmented (Ashburner & Friston, 2005) using tissue priors from a probabilistic elderly brain template (Lemaitre et al., 2005). Tissue images were concurrently normalised. Functional images were reoriented to the anterior commissure using co-ordinates determined from the structural image and then co-registered to the structural image. Functional images were then realigned to the first volume. The motion regressors generated from this were included in the design matrix to remove motion artefacts (see Figure 1). Normalisation parameters produced during segmentation of the structural image were used to warp functional images into the standard space of the elderly template. Finally, normalised functional images were smoothed with a 8 x 8 x 8 mm Gaussian kernel.

Statistical analysis of the functional data based on the General Linear Model (GLM) was carried out to identify areas of brain activity during each condition of each paradigm.
From the above two functional imaging paradigms, three contrasts were defined for statistical analysis. From the first paradigm, the tremor suppression condition was contrasted with the tremor condition. The opposite contrast was also applied, with the tremor condition contrasted with the tremor suppression condition. From the second paradigm, the voluntary movement condition was contrasted with the tremor condition. Significance was set at $P<0.05$ with familywise error correction.

Figure 1: An example of a design matrix used in the statistical analysis. The first column shows the suppression condition. The second column shows the tremor condition. The rest of the columns show motion regressors generated to remove motion artefacts.
Participant results are presented individually due to the small number and variability in results.

3.1 Participant 1

Participant 1 was a 60-year-old female who first began to notice symptoms of Parkinson’s disease six years previously. This was predominantly an intermittent minute rest tremor of her left hand. Since then, she had noticed a progressive worsening of her tremor in her left hand, and the beginnings of a postural tremor in her right hand. She reported that certain situations (such as when she is stressed or under pressure) tend to make her tremor worse. She reported minor difficulties using the hand in her daily activities, particularly when typing.

On examination, a mild to moderate resting tremor of the participant’s left hand was evident. A smaller postural tremor of her upper limbs was seen bilaterally. Slight rigidity and bradykinesia of the left upper limb was also noticed. Power in all limbs was normal.

The UPDRS showed findings which corresponded with the above findings in the history and examination. Her total UPDRS score was thirteen, with the following tremor related components: slight postural tremor of the hands bilaterally (score of 1), mild rest tremor of left hand (2), tremor was present all the time (4). Rest tremor was not present in her other limbs. No action tremor was present.

Participant 1 was able to consistently visibly suppress her tremor. She described her thought process as “concentrating on relaxing” her affected hand. When employing this
method, she was able to quickly reduce the severity of her tremor. This suppression occurred for the entirety of the periods she is concentrating.

Movement data using the MoVELab was taken from participant 1’s thumb, fingers, hand and forearm. Her thumb showed the most consistent and obvious tremor movement but measure was noisy so finger sensor data was used instead. This data showed smaller a smaller amplitude tremor but one that was still clearly suppressed. The amplitude of the tremor in her finger was an estimated 1-2mm. This was compared to an estimated movement of 0 mm when suppressing her tremor (see Figure 2). In a frequency analysis, participant 1’s finger movements consistently showed peaks at 4.4 and 4.8 Hz both during tremor and tremor suppression (see Figure 3).
Figure 2: Plot of movement (in mm) of a sensor placed on Participant 1’s fingers showing blocks in which she was instructed to “tremor” and blocks in which she was instructed to “suppress” her tremor. To make the contrast between the tremor and suppression conditions more easily apparent, we plot the tremor and suppression blocks grouped together rather than alternating in sequence. Only the first 15 s of each 30 s block is depicted in order to allow the tremor waveform to be seen clearly without being overly compressed. In this participant, a tremor of 1-2 mm is suppressed to 0 mm.
Figure 3: Frequency analysis of movement data from a sensor placed on participant 1’s finger during a 30-second block in which she was instructed to “tremor.” This shows frequency peaks at 4.4 and 4.8 Hz. Frequency peaks during a block in which she was suppressing her tremor were similar.

From the functional scanning, three fMRI contrasts are presented here, two from the first scanning paradigm of tremor and tremor suppression and one from the second scanning paradigm of tremor and voluntary movement.

The first contrast of the tremor suppression condition versus the tremor condition, significant activation was found in the medial parts of the pre and postcentral gyrus on the right side of the brain during the suppression block (see Figure 4). This was consistent across two trials. The second trial showed stronger activation and also activation in parts of the superior parietal lobule (see Figure 5). These areas were mainly on the right side of the brain, contralateral to her left sided tremor.

The second contrast is the opposite of the first, with tremor contrasted with tremor suppression. In this contrast, artefacts are evident artefacts are evident in the first trial
(see Figure 6) and there are isolated areas of activation in the cortex and cerebellum in the second trial (see Figure 7).

The last contrast of voluntary movement versus tremor showed activation of the primary motor cortex and other motor areas (see Figure 8).
Figure 4: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the first trial for participant 1. Here small parts of the medial pre and post central gyrus on the right side of the brain are activated. This was contralateral to the tremor.
Figure 5: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the second trial for participant 1. Here there is activation of medial parts of the pre and post central gyrus on both sides, and also parts of the superior parietal lobule.
Figure 6: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the first trial for participant 1. Here major artefacts can be seen.
Figure 7: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the second trial for participant 1. Isolated areas of activation are seen.
Figure 8: FMRI data showing areas more active during voluntary movement than during tremor for participant 1. Here widespread activation of the primary motor cortex bilaterally can be seen as well as in the cerebellum.
### 3.2 Participant 2

Participant 2 was a 76 year old male who was first diagnosed with Parkinson’s disease two years previously. He was primarily troubled by a persistent tremor of his right hand, but also reported some periods of confusion and memory difficulties. He reported the tremor of his right hand caused him difficulty using the hand in his daily activities and felt his general dexterity had gotten worse.

On examination, participant 2 exhibited a persistent mild/moderate rest tremor of the right hand. There was also evidence of a slight rigidity and bradykinesia of the right upper limb. Other motor impairments were not seen and gait appeared functional but with a lack of right arm swing.

His total UPDRS score was twenty with the following tremor related components: mild rest tremor amplitude right hand (2) constant rest tremor (4). Rest tremor was not present in any other limb. No other types of tremor were present.

Participant 2’s tremor was a typical Parkinsonian rest tremor with obvious movements at the wrist and fingers, and to a lesser extent the forearm. He described suppressing his tremor by concentrating on the hand and focusing on stopping the tremor. He reported having difficulty sustaining suppression for longer than a few seconds at a time. This was evident when participant 2 demonstrated attempting to suppress his tremor. He was able to stop wrist and forearm movements for around 10 seconds before the tremor reasserted itself. Finger tremors continued despite effort to suppress.

Movement data using the MoVElab was taken from participant 2’s thumb, fingers, hand and forearm. His fingers showed the most consistent and obvious tremor movement so that data is highlighted here. In a frequency analysis, Participant 2’s fingers showed peaks varying from 4.5 Hz to 5.5 Hz. The amplitude of the tremor in his fingers varied from an estimated 3 to 5 mm. He was able to suppress this tremor to an estimated 1mm for 10 seconds before the tremor with its original amplitude of 3-5 mm would reappear.
Figure 9: Plot of movement (in mm) of a sensor placed on Participant 2’s fingers showing blocks in which he was instructed to “tremor” and blocks in which he was instructed to “suppress” his tremor. To make the contrast between the tremor and suppression conditions more easily apparent, we plot the tremor and suppression blocks grouped together rather than alternating in sequence. Only the first 15 s of each 30 s block is depicted in order to allow the tremor waveform to be seen clearly without being overly compressed. In this participant a tremor of 3-5 mm was suppressed to 1mm. This suppression lasted for approximately 10 seconds in each block before the tremor would reappear.
Figure 10: Frequency analysis of movement data from a sensor placed on participant 2’s finger during a 30-second block in which he was instructed to “tremor.” This shows a frequency peak between 4.5 Hz and 5 Hz. Other blocks were of similar frequency with peaks ranging between 4.5 Hz and 5.5 Hz.

From the functional scanning, three fMRI contrasts are presented here, two from the first scanning paradigm of tremor and tremor suppression and one from the second scanning paradigm of tremor and voluntary movement.

The first contrast of the tremor suppression condition versus the tremor condition, significant activation was found in a part of the left middle frontal gyrus (contralateral from tremor). This was consistent across two trials.

The second contrast of tremor versus tremor suppression showed inconsistent widespread areas of activation.

The last contrast of voluntary movement versus tremor movement showed no areas of activation which were different between the two tasks.
Figure 11: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the first trial for participant 2. Here activation is seen in small parts of the left middle frontal gyrus (contralateral to the side of the tremor).
Figure 12: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the second trial for participant 2. Here activation is seen in small parts of the left middle frontal gyrus (contralateral to the side of the tremor). This is consistent with the first trial.
Figure 13: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the first trial for participant 2. Here a number of discrete areas of activation can be seen.
Figure 14: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the second trial for participant 2. Here widespread activation of many areas can be seen.
Figure 15: FMRI data showing areas more active during voluntary movement than during tremor for participant 2. Here, no activation is observed.
3.3 Participant 3

Participant 3 was a 66 year old female with Parkinson’s disease. She first began experiencing symptoms eight years earlier, noticing her handwriting deteriorating and becoming smaller. Since her diagnosis, her symptoms had got progressively worse with the notable development of a rest tremor first in her right hand and subsequently in her right leg. She reported that her tremor was mild, constant and worsens when she is stressed. She reported that she was generally slower to move and would often find her balance impaired. Her tremor caused significant distress as it interfered with many activities of daily living, in particular food preparation and dressing.

On exam, participant 3 exhibited a constant mild rest tremor of her right hand and right foot. Rigidity was evident in her right and left legs, and most pronounced in her right arm. Gait was slow with decreased arm movements. Power and reflexes were normal across all limbs.

Her total UPDRS score was twenty seven with tremor related components as follows: mild rest tremor of right hand (score of 2), slight rest tremor right and left leg (1), tremor is constant (4). No other types of tremor were present.

Participant 3 was able to consistently suppress the tremor in her right hand. She described her process as thinking “stop.” She does not believe she is tensing up her arm in order to stop her tremor. Upon close observation, it was noticeable that she was able to stop her tremor of her hand but after a period of 10-15 seconds, a very small tremor returns distally, particularly in her right thumb.

Movement data using the MoVElab was taken from participant 3’s thumb, fingers, hand and forearm. Her hand showed the most consistent tremor movement so that data was used in the analysis. In a frequency analysis, participant 3’s movements did not show any consistent frequency peaks. This was applicable to both tremor and suppression blocks. The amplitude of her tremor was difficult to measure because it was very small at the time of the experiment. However, her tremor movements were an estimated 0.5-1 mm in amplitude when not suppressing and 0 mm when suppressing (see Figure 16).
Figure 16: Plot of movement (in mm) of a sensor placed on Participant 3’s fingers showing blocks in which she was instructed to “tremor” and blocks in which she was instructed to “suppress” her tremor. To make the contrast between the tremor and suppression conditions more easily apparent, we plot the tremor and suppression blocks grouped together rather than alternating in sequence. Only the first 15 s of each 30 s block is depicted in order to allow the tremor waveform to be seen clearly without being overly compressed. In this participant a tremor of 0.5-1 mm is suppressed to 0 mm.

From our functional scanning, three fMRI contrasts are presented here, two from the first scanning paradigm of tremor and tremor suppression and one from the second scanning paradigm of tremor and voluntary movement.
The first contrast was the tremor suppression condition versus the tremor condition. Inconsistent areas of activation were found, with the first trial showing activation in parts of the lateral aspects of the superior parietal lobule on the left (contralateral to her right sided tremor) (see Figure 17). The second trial showed activation of in parts of the medial aspects of the superior parietal lobule on the left, along with activation in the supramarginal gyrus (see Figure 18).

The second contrast is the opposite of the first, with tremor contrasted with tremor suppression. In this contrast, widespread areas of activation were seen (see Figure 19 and Figure 20).

The contrast of voluntary movement versus tremor showed no activation (see Figure 21).
Figure 17: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the first trial for participant 3. Here there is activation in parts of the lateral aspects of the superior parietal lobule on the left side of her brain (contralateral to her right sided tremor).
Figure 18: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the second trial for participant 3. Here there is activation of in parts of the medial aspects of the superior parietal lobule on the left, along with activation in the supramarginal gyrus.
Figure 19: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the first trial for participant 3. Here there is widespread activation in many areas.
Figure 20: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the second trial for participant 3. Here there is widespread activation in many areas.
Figure 21: FMRI data showing areas more active during voluntary movement than during tremor for participant 3. Here there is no activation.
3.4 Participant 4

Participant 4 was a 50 year old male with a two year history of Parkinson’s disease. His first symptom was a tremor of his left upper limb and since then has noticed an additional general loss of coordination, especially handling things such as eating utensils.

On examination, a mild resting tremor of the left arm was present. No other motor signs were evident.

His total UPDRS score was twelve with the tremor related components as follows: mild rest tremor amplitude in left hand (2), rest tremor present for most of the time (3). Rest tremor was not present in the other limbs. No other types of tremor were present.

Participant 4’s tremor was a typical rest tremor of mild severity. It tended to affect not only the left hand but also the arm and forearm. Throughout the session, the tremor fluctuated in severity, going from completely absent to mild severity. Participant 4 describes his process of tremor suppression as an act of relaxation, “actively relaxing muscles” proximally to distally in the limb. He is able to reliably completely stop his tremor with regular ease and is able to hold this suppression for minutes at a time. He reports that anxiety and stress makes the tremor worse and negatively affects his ability to stop his tremor.

No movement data was collected for this participant due to technical difficulties at the time.

From our functional scanning, three fMRI contrasts are presented here, two from the first scanning paradigm of tremor and tremor suppression and one from the second scanning paradigm of tremor and voluntary movement.

The first contrast was the tremor suppression condition versus the tremor condition. Significant activation was found in the lateral aspects of the precentral gyrus on the right side of the brain (contralateral to tremor). This was consistent across two trials. However additional areas of activation was found in the second trial- parts of the
superior parietal lobule on the right, and parts of the medial frontal gyrus on both the right and the left.

The second contrast is the opposite of the first, with tremor contrasted with tremor suppression. In this contrast, many areas are activated particularly on the left side of the brain.

The contrast of voluntary movement versus tremor movement showed widespread activation of the pre/post central gyrus on both sides of the brain.
Figure 22: FMRI data showing the first contrast—areas more active during suppression than during tremor. This is the first trial for participant 4. Here activation was found in the lateral aspects of the precentral gyrus on the right side of the brain (contralateral to tremor).
Figure 23: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the second trial for participant 4. Here activation was found in the lateral aspects of the precentral gyrus on the right side (contralateral to tremor) with additional areas of activation in parts of the superior parietal lobule on the right, and parts of the medial frontal gyrus on both the right and the left.
Figure 24: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the first trial for participant 4. Here many areas are activated particularly on the left side of the brain.
Figure 25: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the second trial for participant 4. Here many areas are activated particularly on the left side of the brain.
Figure 26: FMRI data showing areas more active during voluntary movement than during tremor for participant 4. Here widespread activation pre and post central gyrus.
3.5 Participant 5

Participant 5 was a 75 year old female who was only very recently (less than three months at time of meeting) diagnosed with Parkinson’s disease. She first noticed a tremor in her left hand which had slowly gotten worse over the past year. She also reported a general increase in fatigue and apathy. Her activities of daily living were unaffected by her symptoms.

On examination a very mild tremor of her left hand was present. No other motor signs were found.

Her total UPDRS score was fifteen with the tremor related components as follows: slight rest tremor amplitude in left hand (1), constant rest tremor (4). Rest tremor was not present in her other limbs. No other types of tremor were evident.

Participant 5’s tremor was a small rest tremor of her left hand. The tremor was more evident distally, rather than proximally particularly in the thumb. She reported that fatigue, stress and anxiety tend to make the tremor worse and had also noticed that it was worse during the evenings. Distractions and focusing on other things tend to bring on the tremor, and it was observed during the session that distracting the participant by talking about unrelated topics would make the tremor worse. Participant 5 was able to stop her tremor completely for minutes at a time. She describes her process of suppression as “thinking about releasing tension in her wrist” and relaxing.

No movement data was collected for this participant due to technical difficulties at the time.

From our functional scanning, three fMRI contrasts are presented here, two from the first scanning paradigm of tremor and tremor suppression and one from the second scanning paradigm of tremor and voluntary movement.

The first contrast was the tremor suppression condition versus the tremor condition. Areas of activation were inconsistent between the two trials. In the first trial, a part of the medial frontal gyrus on the left side of the brain was more activated in the suppression task (see Figure 27). In the second trial, activation was seen the a small part
of the precentral gyrus on the left, a lateral part of the left supramarginal gyrus, a small part of the left superior frontal gyrus, and a small part of the superior parietal lobule on the right (see Figure 28).

The second contrast is the opposite of the first, with tremor contrasted with tremor suppression. In this contrast, widespread activation was observed on both sides of the brain (see Figure 29 and Figure 30).

The contrast of voluntary movement versus tremor showed activation of many areas, particularly of the pre and post central gyrus (see Figure 31).
Figure 27: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the first trial for participant 5. Here there is activation in a part of the medial frontal gyrus on the left side.
Figure 28: FMRI data showing the first contrast- areas more active during suppression than during tremor. This is the second trial for participant 5. Here there is activation in a small part of the precentral gyrus on the left, a lateral part of the left supramarginal gyrus, a small part of the left superior frontal gyrus, and a small part of the superior parietal lobule on the right.
Figure 29: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the first trial for participant 5. Here there is widespread activation in many areas.
Figure 30: FMRI data showing the second contrast- areas more active during tremor than during tremor suppression. This is the second trial for participant 5. Here there is widespread activation in many areas.
Figure 31: FMRI data showing areas more active during voluntary movement than during tremor for participant 5. Here there is activation of many areas, particularly of the pre and post central gyrus.
3.6 Participant 6

Participant 6 was a 73 year old female with a 4 year history of Parkinson’s disease. She first presented with a significant tremor in her right hand, which has progressed to being now severe and persistent. Tremor had also spread to affect her other limbs at times. In addition to her tremor, she also reported slowness and difficulty using her hands, stating it takes her much longer to do normal daily tasks.

On examination, participant 6 had a moderate rest tremor affecting the right arm, and a mild tremor in her other limbs. Mild rigidity and bradykinesia was also evident in all her limbs.

Her total UPDRS score was 48 with the tremor related components as follows: moderate rest tremor amplitude of her right upper limb (3), mild rest tremor in right leg (2), slight rest tremor in left limbs (1), constant rest tremor (4). No other types of tremor were evident.

Participant 6’s tremor was a moderate rest tremor of her right arm with coarse flexion-extension movements at her wrist. She was able to achieve suppression of her tremor by spreading her fingers and “locking” her hand in that position. Her tremor would stop immediately. As she grew fatigued, the duration of participant 6’s suppression got progressively shorter. Interestingly, suppression of her tremor in her right hand also brought about a reduction in the severity of the tremor in her right foot, though this effect was variable.

Movement data using the MoVELab was taken from participant 6’s thumb, fingers, hand and forearm. Her fingers showed the most consistent tremor movement and suppression so that data is highlighted here. In a frequency analysis, participant 6’s finger movements varied in peaks from 4.3 to 5.3 Hz with no consistent patterns in during both tremor and tremor suppression (see Figure 33). The amplitude of the tremor in her fingers was an estimated 10 mm, reducing to 1mm when suppressing her tremor. (Note that these estimates were drawn from the raw data and do not quite match the amplitudes seen in Figure 32).
Figure 32: Plot of movement (in mm) of a sensor placed on Participant 6’s fingers showing blocks in which she was instructed to “tremor” and blocks in which she was instructed to “suppress” her tremor. To make the contrast between the tremor and suppression conditions more easily apparent, we plot the tremor and suppression blocks grouped together rather than alternating in sequence. Only the first 15 s of each 30 s block is depicted in order to allow the tremor waveform to be seen clearly without being overly compressed. In this participant there is a clear reduction in the amplitude of the tremor.
Figure 33: Frequency analysis of movement data from a sensor placed on participant 6’s finger during a 30-second block in which she was instructed to “tremor.” This shows frequency peaks around 4.7 Hz. In general for this participant, peaks varied between 4.3 to 5.3 Hz during both tremor and tremor suppression.

No MRI data was collected from this participant as she was uncomfortable undergoing MRI.

3.7 Participant 7

Participant 7 was a 71 year old male with a four year history of Parkinson’s disease. He first noticed a loss of smell and the beginnings of a tremor in his left hand, which had not progressed significantly over the last four years. He maintained that he had good
mobility due to a vigorous exercise regime. Despite this, daily tasks such as handwriting prove difficult. He also reported feeling muddled at times.

On examination, a mild resting tremor of the left hand was present, accompanied with mild rigidity bradykinesia in that limb also. Slight rigidity was noticed in the right arm.

His total UPDRS score was twenty seven with the tremor related components as follows: mild rest tremor amplitude in left hand (2), constant rest tremor (4). Rest tremor was not present in any other limb. No other tremor types were observed.

Participant 7’s tremor was a mild typical Parkinsonian rest tremor of his left hand. Tremor movements were most noticeable in the thumb and fingers. Notably, when the participant was thinking about his tremor, or paying any attention to it, it would stop. Distracting him from his tremor by talking about other things would bring the tremor back after a period of around 10 seconds. His tremor tended to be inconsistent in persistency and would appear and reappear frequently. He also reported the tremor being more severe when he is nervous or stressed.

Movement data using the MoVElab was taken from participant 7’s thumb, fingers, hand and forearm. Participant 7’s tremor was inconsistent so collecting data proved difficult. No discernable frequency peaks were found in a frequency analysis. The amplitude of the tremor (when present) was very small, estimated around 1-2 mm, reduced to 0 mm when actively suppressing (see Figure 34).
Figure 34: Plot of movement (in mm) of a sensor placed on Participant 7’s fingers showing blocks in which he was instructed to “tremor” and blocks in which he was instructed to “suppress” his tremor. To make the contrast between the tremor and suppression conditions more easily apparent, we plot the tremor and suppression blocks grouped together rather than alternating in sequence. Only the first 15 s of each 30 s block is depicted in order to allow the tremor waveform to be seen clearly without being overly compressed. In this participant the tremor was very inconsistent. When present, the amplitude of the tremor was very small, estimated around 1-2 mm, reduced to 0 mm when actively suppressing.

No MRI data was collected from this participant as he was uncomfortable undergoing MRI.
3.8 Participant 8

Participant 8 was a 62 year old female with Parkinson’s disease. She first began to experience symptoms five years previously with difficulties with her gait, and developed a tremor of her left hand three years ago. Her tremor had gotten progressively worse over the 3 years, becoming more persistent, especially during the evenings when she is fatigued. She noticed it had gotten particularly more troublesome since the September 2010 Christchurch earthquake.

On examination, participant 8 showed a mild rest tremor of her left hand. In addition, she had slight rigidity and bradykinesia of the left arm and leg.

Her total UPDRS score was twenty five, with the tremor related components as follows: mild rest tremor of left hand (2), constant rest tremor (4). Rest tremor was not present in any of her other limbs. No other types of tremor were present.

Participant 8 had tried a number of ways to control her tremor. She reported having some success using meditation and relaxation techniques and had found that changing limb positions helped stop tremor movement. Meditation with a focus on “releasing the tension and relaxing muscles” had worked to suppress her tremor at home. Unfortunately during our time, she was unable to suppress her tremor noticeably. She speculated she had difficulties relaxing in the test environment. As a result no movement or MRI data was able to be collected for this participant.

3.9 Participant 9

Participant 9 was a 67 year old male with a 2 year history of Parkinson’s disease. His initial symptom was a very slight tremor of his left hand which had not gotten worse over the previous 2 years. Other than his tremor, he had noticed being slow to move and having slower and softer speech. He also was troubled with fatigue.
A rest tremor of his left hand was present very intermittently. Concentrating on his tremor would cause it to stop and not return until some time after he had taken his mind off the affected limb. Distractions, such as talking about unrelated subjects, would lead to the tremor returning. Because of the nature of participant 9’s tremor, movement data and imaging was unable to be completed as a consistent tremor and suppression were not evident.
4. Discussion

This project set out with two aims: firstly, to describe and assess the process of voluntary tremor suppression in patients with Parkinson’s disease and secondly, to identify key areas in the brain responsible for this voluntary tremor suppression. I believe significant steps have been taken to achieve both aims of this project.

Before this project, the process of voluntary tremor suppression had been observed clinically, but the process itself remained undefined in scientific literature. I offer the following definition for voluntary tremor suppression: the process by which a person with a tremor is able to stop their tremor by mental will or concentration, without the assistance of any external aid.

To achieve the above aims, this study used a number of different modalities. Firstly, a clinical history and examination was employed to get a general idea of the participants’ Parkinson’s disease. The Unified Parkinson’s Disease Rating Scale (UPDRS) was then applied to assign score to the participant’s PD. 3D electromagnetic movement tracking was used to objectively measure the physical characteristics of tremor and tremor suppression. Finally, functional magnetic resonance imaging (fMRI) was used to identify brain regions active in this process.

The main findings of this study are summarised in Table 1.
Table 1: Summary of the main findings

<table>
<thead>
<tr>
<th>Participant</th>
<th>Tremor Characteristics</th>
<th>Amplitude (tremor and suppression in mm)</th>
<th>Frequency</th>
<th>FMRI- areas more active during suppression Trial 1</th>
<th>FMRI- areas more active during suppression Trial 2</th>
<th>FMRI- areas more active during voluntary movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild rest tremor left hand</td>
<td>5/6mm to 3mm when suppressed</td>
<td>2 bands at 4.4Hz and 4.8Hz</td>
<td>Medial parts of pre and post central gyrus on the right</td>
<td>Medial parts of pre and post central gyrus bilaterally + part of the superior parietal lobule</td>
<td>Widespread activation of primary motor cortex</td>
</tr>
<tr>
<td>2</td>
<td>Mild/moderate rest tremor of right hand</td>
<td>3-5mm to 1mm when suppressed</td>
<td>Peaks varying between 4.5 to 5.5Hz</td>
<td>Left middle frontal gyrus</td>
<td>Left middle frontal gyrus</td>
<td>No areas more active during voluntary movement</td>
</tr>
<tr>
<td>3</td>
<td>Mild rest tremor of right hand</td>
<td>1mm to &lt;1mm when suppressed</td>
<td>No consistent peaks</td>
<td>Lateral aspects of the superior parietal lobule on the left</td>
<td>Medial aspects of the superior parietal lobule on the left + part of the supramarginal gyrus on the right</td>
<td>No areas more active during voluntary movement</td>
</tr>
<tr>
<td>4</td>
<td>Mild rest tremor of left hand</td>
<td>-</td>
<td>-</td>
<td>Lateral aspects of the precentral gyrus on the right</td>
<td>Lateral aspects of precentral gyrus on the right + parts of superior parietal lobule on the right + parts of medial frontal gyrus bilaterally</td>
<td>Widespread activation of pre/post central gyrus</td>
</tr>
<tr>
<td>5</td>
<td>Slight rest tremor of left hand</td>
<td>-</td>
<td>-</td>
<td>Medial frontal gyrus on the left</td>
<td>Part of precentral gyrus on the left, lateral part of supra marginal gyrus, small part of superior frontal gyrus on the left, small part of superior parietal lobule on the right</td>
<td>Widespread activation</td>
</tr>
<tr>
<td>6</td>
<td>Moderate rest tremor of right upper limb</td>
<td>10mm to 1mm when suppressed</td>
<td>Peaks varying between 4.3 to 5.3 Hz</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Mild resting tremor of left hand</td>
<td>1-2mm to 0mm when suppressed</td>
<td>No consistent peaks</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Mild rest tremor of left hand</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Slight rest tremor of left hand</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
From the focused clinical histories and examinations, we can see that our nine participants feature a range of characteristics but one common thread is that all of our participants were in the relatively early stages of their Parkinson’s disease. The longest history of Parkinson’s disease (from time of first symptoms) was eight years, with the shortest being just three months. This observation is evident, not only in the length of the history but also in the symptoms the participants’ described. As expected, tremor significantly troubled the participants, and most were affected by other motor complications such as bradykinesia and rigidity as well. Despite this, the impact of these motor symptoms on their lives was not marked with most able to continue with work or hobbies. Non-motor symptoms such as cognitive impairment or depression were generally not evident or very slight in our participants.

The UPDRS also showed findings which lends support to the observation that these participants were in the early stages of their Parkinson’s disease. Three participants had total scores in the early tens, four participants had total scores in the twenties, and one participant had a score of 48. Participants generally reported being not affected or only mildly affected in their experiences of daily living. The motor examination and tremor related components of the UPDRS proved to be the section where our participants scored the highest. None of the participants scored in the section relating to motor complications of dyskinesias or motor fluctuations.

The characteristics shown by the clinical histories, examinations and UPDRS may be noteworthy because it may be related to the ability to suppress tremor. It is perhaps significant that this study only managed to recruit people with mild symptoms and tremor who could suppress their tremor. No patients with severe Parkinson’s disease who could suppress their tremor were recruited. Future research needs to expand the population of participants, and identify whether or not there are patients with severe symptoms who can voluntarily suppress their tremor.

This study also went on to describe the techniques people use to suppress their tremor. The majority of participants described concentrating on the affected limb as a key step in suppressing their tremor. Relaxing the muscles of the limb rather than increasing the tension in the arm seemed to be a common focus of concentration, although one participant did “lock up” the muscles in the arm to stop her tremor. For
one participant, relaxation was taken one step further, with meditation said to be her method of suppressing her tremor.

Stress and anxiety have been shown to make tremor significantly worse (Raethjen et al., 2008), and this was indeed reported by many of the participants in this study. This is able to be contrasted with the above observation- that relaxation and focusing on reducing tremor facilitates improvement (i.e. reduction in the tremor). The role stressors play in tremor and tremor suppression presents an interesting dilemma in that it may be a potential limitation to the study but also a possible avenue of exploration for future research. The research environment itself may have been a potential stressor, possibly exaggerating the participants’ tremor and minimising their ability to suppress their tremor. This was minimised in this study by making the participants comfortable and building a rapport with the participant. Most participants responded well and were able to carry out their suppression though one participant was unable to relax enough to suppress their tremor. Future studies may explore the role of stressors on tremor suppression. Mental arithmetic (such as subtracting from 100), is a simple mental stressor that has been shown to modulate tremor in Parkinson’s disease (Raethjen, et al., 2008). The effect this has on tremor suppression will be an interesting point to explore in the future.

Objective measures of tremor and tremor suppression were also undertaken in this study in the form of 3D electromagnetic movement tracking. The severity of tremor varied from very mild to moderate, with a range of one to ten millimetres in amplitude. The extent or amount of suppression also varied from individual with some able to reduce their tremor to be barely visible and others unable to do so consistently. Tremor was often not able to be completely suppressed.

Movement data collection using the MoVElab proved to be robust. Most had a tremor and tremor suppression technique that could be tracked in three dimensions by our electromagnetic movement tracking systems. In some cases however, significant physical limitations of the equipment used was observed. The wired electromagnetic sensors placed on the different parts of the limb were small but the collective weight of the sensors and their wires may have been cumbersome and had some impact on the movement of the limb. This was minimized as much as possible by the use of structures to suspend the wires, avoiding the problem of them dragging
down the limb. However it was seen that the sensors prevented natural movement in some people, and in these participants, movement tracking had to be abandoned.

Although the length of suppression was not formally measured in our movement tracking study paradigm, it was observed that this varied between participants. When collecting movement data, participants in this study were instructed to tremor for a 30 second block, and then suppress their tremor for a 30 second block. This structure was adopted with the aim of using a common test amongst our participants, as well as being a paradigm that could also work well for functional imaging. It was observed that some participants were able to suppress their tremor for the full 30 second block with no reoccurrence of the tremor. Other participants were only able to suppress their tremor for a partial section of that 30 second block. For example, participant 3 was able to significantly suppress her tremor for 10 seconds but after that the tremor would re-emerge.

Consistency and reliability of tremor suppression also varied between participants. Again our movement assessment design was a limiting factor in that the paradigm was troublesome for participants who did not have a consistent tremor, or those who were unable to consistently suppress their tremor on cue. Participants for example, who may have been able to suppress their tremor but took more than 30 seconds to do so, were unsuitable for our methodology. Recording continuously over a much longer period of time and letting the person suppress and tremor on their own cues would capture data for these groups of people.

These variations in extent, length and consistency of voluntary tremor suppression may be due to a number of reasons. Firstly, the tremors themselves were not uniform with some participants more troubled by their tremor and others not less affected. Secondly, the technique of tremor suppression itself differs amongst participants—each participant is employing their own thought processes and methods to reduce their tremor. Some participant may be more practised at using their technique to suppress their tremor. In future studies it will be interesting to see if participants are able improve their tremor suppression with practice, or if people are able to adopt other suppression techniques.

Frequency analysis showed frequency peaks varying, with some participants exhibiting the classic 4-6 Hz pattern typically found in rest tremors (Deuschl, et al.,
There didn’t appear to be significant differences in frequency during tremor suppression compared with tremor. That is, although the amplitude of tremor could be markedly reduced, a tiny underlying oscillation remained at the original frequency.

Additional techniques are needed to further assess movement in tremor suppression. Tools such as electromyography can assess the underlying muscle activity in tremor and (hopefully) tremor suppression, allowing us to determine if there is a change in the muscles used during suppression. With this we may be able to determine if the process of suppression is truly a process of relaxation, or if indeed there is some sort of tensing or co-contracting of the muscles as described by participant 6. Surface electromyography was attempted in this study, but methodological difficulties in the collection and analysis of sEMG data precluded its inclusion in this study.

Functional imaging in this study was undertaken using fMRI. Five participants underwent fMRI scanning and the results are presented individually to allow for the expected variation in a range of factors such as the subjects’ tremor, tremor suppression ability and tremor suppression technique. The fMRI scanning protocol in this study was a standard fMRI block design. In the first paradigm, participants were instructed to tremor for thirty seconds, and then suppress their tremor for thirty seconds. In the second paradigm participants were instructed to tremor for thirty seconds and then carry out a finger tapping voluntary movements for thirty seconds. The block design allowed us to contrast the two conditions. Therefore the results gathered in this study are reflections of the areas of the brain which are more active in one condition when contrasted with the other condition. Three contrasts were presented in this study- tremor suppression contrasted with tremor, tremor contrasted with tremor suppression, and voluntary movement contrasted with tremor.

In the first contrast, that of tremor suppression versus tremor, the areas which are seen are areas which are more active during tremor suppression than during tremor. Participant 1 showed the pre and post central gyrus were more active during the suppression condition than during the tremor condition. This was consistent across two trials. In the second trial, a part of the superior parietal lobule was also more active. These areas were seen on both sides of the brain, but more activation was seen on the right side, contralateral to the side of the tremor. Participant 2 showed
consistent activation in the left middle frontal gyrus, again contralateral to the side of the tremor. Participant 3 showed differing activation in the superior parietal lobule and parts of the supramarginal gyrus. These areas were on the left side of the brain, and contralateral to the side of the tremor. Participant 4 showed consistent activation of the precentral gyrus on the right side, with additional activation of the superior parietal lobule on the right, and the medial frontal gyrus on both the left and the right in the second trial. Again we can see the main areas of activation being mainly on the contralateral side to the tremor. Participant 5 showed inconsistent active brain areas with the small parts of the medial frontal gyrus on the left more active in one trial, and small parts of the left precentral gyrus, the left supramarginal gyrus, the left superior frontal gyrus and the right superior parietal lobule more active in the second trial. This was the one participant where the main areas of activation were on the ipsilateral side rather than the contralateral side.

The second contrast was a reverse of the first contrast; tremor was contrasted with tremor suppression. In this contrast, widespread areas of activation were seen. These areas were inconsistent and in the first subject, the data was affected by artifacts with signal seen outside normal brain areas. I am unsure how to interpret these results but speculate that changing the thresholds for this contrast could reduce the noise of the data.

In the third contrast, voluntary movement was contrasted with tremor. Three of the five participants in which MRI was done showed widespread activation, particularly of areas associated with motor functions such as the primary motor cortex and the premotor cortex. This was expected as it had been found in fMRI previous studies on human movements (Rao, et al., 1993). The other two participants showed no areas more active with this contrast. This may have occurred if the voluntary movement tasks were not carried out effectively and the actual movements were similar to the tremor movements.

The significance of the areas activated in tremor suppression is difficult to determine as the actual role these areas play in suppression is unknown. I can speculate that these areas may have a role in providing direct inhibitory input to brain networks which are involved in tremor. Alternatively, they may have a role in relaxing the muscle groups involved in the tremor. It may also be that they are involved in
activating muscle groups which act in direct opposition to the tremor. It is also possible that these areas do not have a direct role in producing tremor suppression at all; rather they are areas which are activated as a consequence of the reduction in tremor. For example, it has been suggested that the superior parietal lobule has a role in integrating information about limb position with sensory input (Wolpert et al., 1998). The parts of the superior parietal lobule activated in this study may represent areas which are processing information about changes to the tremor during tremor suppression, rather than causing the suppression itself.

The limitations presented for the paradigm used in the movement data collection also applies to our functional imaging paradigm as they were structured in the same way. That is, the paradigm we used composed of the 30 second blocks, is not suitable for people who have inconsistent tremor suppression, are unable suppress on cue, or are unable to suppress for the appropriate length of time. In fMRI block designs (such as the one used in this study), the blocks are contrasted to reveal the areas of activation. If the participant is unable to carry out the task in one block (such as suppress their tremor), the contrast with the other block is not as strong and it therefore more likely to result in no detectable activation. An alternative to block design is an event-related design where the fMRI data is recorded simultaneously with the event or stimulus. An event-related design would require the simultaneous recording of movement and fMRI data, something not possible with our current electromagnetic movement tracking system. External optical motion tracking systems have been used to track head movements during MRI (Dold et al., 2006) and it may be possible to adapt such a system to track tremor movements.

In addition to exploring other fMRI designs, future research should also attempt to find alternative contrast conditions for use in the standard fMRI block design. With fMRI block designs, activation in areas which are equally active in each of the contrasting condition is lost, as only areas more active in one condition are presented. Contrasting tremor suppression with tremor presents a problem as many of the same areas may be involved. Thus a more optimal contrast condition could be found for suppression.

Clinical or practical applications of this research are a long way down the line, but it is hoped that if the process of voluntary tremor can be further elucidated, new
information may form the basis for therapy. For example, certain techniques for tremor suppression may be able to be taught to other people troubled with tremor. This may allow them to consciously reduce their tremor at certain times or in certain situations where tremor is particularly unwanted. Another potential application may be the identification of new targets for deep brain stimulation or transcranial magnetic stimulation if specific cortical or sub cortical brain areas directly responsible for tremor suppression can be identified.
References


