Diagnosis and imaging of essential and other tremors

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CHAPTER 1

INTRODUCTION

This is a thesis on tremor, a movement disorder in the category of 'too much movement', which is called hyperkinesia. In this thesis, two aims are addressed: first, to improve on diagnosis of tremor, and second, to investigate the pathophysiology of one tremor disorder, essential tremor, by means of functional neuroimaging.

BACKGROUND: TYPES OF TREMOR

Tremor is the most common movement disorder in adults (1). Most patients presenting with trembling of the upper extremities have either got tremor as a symptom of Parkinson's disease (PT), essential tremor (ET), enhanced physiological tremor (EPT) or functional tremor (FT).

The type of tremor that is best known to the general public is PT, and many tremor patients are initially worried that they may have Parkinson's disease (PD). Typically, PT starts of as a unilateral, 'pill-rolling' rest tremor (2). It is the presenting symptom of 70% of PD patients (3, 4). Clinically, presence of the other cardinal symptoms (rigidity, disturbances in balance and most importantly bradykinesia (5)) increases the likelihood of a diagnosis of PD.

By contrast, ET is a tremor disorder without additional neurological symptoms. It has a worldwide prevalence of 0.9%, increasing to 4.6% in the population older than 65 (1). ET is a bilateral tremor occurring during posturing and movement of the affected limbs (6). Intention tremor, an increase of tremor amplitude towards the end of a goal-directed movement, is described in about half of ET patients (7, 8). Apart from the arms and hands, the head, voice, and less frequently jaw and legs can also be affected. About half of ET patients report a positive family history (9). Moreover, 50% of patients report a beneficial effect of moderate consumption of alcohol on their tremor (10).

Another bilateral tremor is EPT. This tremor closely resembles the tremor every human being experiences from time to time (11, 12), be it after too much coffee, when hungry, after strenuous physical exercise, during a job interview or a PhD defence. EPT is an 'exaggerated', more constant form of physiological tremor. It is usually mild, and distal. A relationship with the circumstances described above may point to the diagnosis. Similar to ET, EPT may be familial.

FT completes the list of tremors that consultation is most commonly sought for. It was recently argued to define FT on the basis of its clinical appearance as a tremor that is significantly altered by distraction or nonphysiological manoeuvres (including a strong placebo response) and which is clinically incongruent with tremor known to be caused by neurological disease (13). FT can be characterized by sudden onset, which is atypical in tremor disorders apart from post-stroke (14). On examination, most patients' tremor has a combined yet fluctuating presence at rest, during posture, and during action, together with positive findings that are described in more detail later on (**Chapter 2**) (15). Apart from the hands and arms, tremor can occur in any body part, including the legs, head or palate (15).

Briefly, other more rare tremor disorders that are encountered are dystonic tremor (of the arms and possibly head, together with dystonic posturing (16)), cerebellar tremor (usually as a consequence of multiple sclerosis (17)) and Holmes tremor (resulting from mid brain stroke (18)).

CLINICAL DIAGNOSIS OF TREMOR

Distinguishing one type of tremor from another is important, because of the consequences for prognosis and treatment. Prognosis can range from generally mild, monosymptomatic and non-progressive in disorders such as EPT, all the way to complicated, progressive and life-shortening in a

disease such as PD. In terms of management, treatment options differ for different tremors, and range from no medication, to dopamine and trihexyfenidyl or beta-blockers and anti-epileptics drugs, to deep brain stimulation (19, 20)(Table 1.1).

In getting to the diagnosis, history taking and clinical examination by a neurologist are of primary importance (21). However, accurate clinical diagnosis can be challenged by the fact that not all patients have a classic presentation. In contrast to the typical presentations described above, action tremor can also occur in PT, ET patients may have rest tremor, EPT may be a serious handicap, FT can be fairly consistent. Finally, stress may exaggerate any neurological disorder. The phenomenology of tremor is complex, involving a broad variety of signs and symptoms. Over the years, large steps have been made in describing the phenomenology of different tremors (22-26), with some tremor disorders presenting with presumably typical signs. However, a lot of the work has described groups in isolation, or either comparing only specific or small groups. In **Chapter 2**, we will describe our work in determining sensitivity and specificity of five 'typical' tremor phenomena in a large and diverse tremor population.

CLINICAL NEUROPHYSIOLOGICAL DIAGNOSIS OF TREMOR

A neurologist can request clinical neurophysiology testing to help establish a diagnosis in more difficult cases. Polymyography, usually combined with accelerometry, assesses tremor frequency and amplitude in a multitude of postures (rest vs action) and during different tasks (for instance, finger-to-nose manoeuvres). The application of clinical neurophysiolocal techniques in tremor diagnosis differs greatly between centres, and is of course dependent on availability but also on a culturally defined attitude towards more (Germany, The Netherlands) or less (United Kingdom) clinical neurophysiology testing. Polymyography objectifies the presence and consistency of tremor characteristics under various circumstances, and is informative of tremor frequency. These tests are usually of great value (27, 28), however, interpretation of results is not always straightforward. For example, tremor frequencies overlap between different tremor disorders (29), and, as mentioned previously, the sensitivity and specificity of certain 'typical' tremor phenomena are generally poorly known. In **Chapter 3**, we describe our work aiming to add to the diagnostic power of routine polymyography, by investigating the potential additional diagnostic value of two advanced EMG measures: intermuscular coherence and cumulant analysis.

ESSENTIAL TREMOR: A MUCH-DEBATED PHENOTYPE

There have been challenges in defining ET. Traditionally, ET has been used and misused as a 'container' diagnosis, gathering together all types of tremor patients that did not fit any particular diagnosis. In 1998, the Movement Disorders Society published their first consensus statement on tremor (30). This was followed, in the year 2000, by the criteria for ET by the Tremor Investigation Group: widely used nowadays, and generally known as the TRIG criteria (6). Core criteria are bilateral tremor of the hands and forearms, with no other neurological signs (except a cogwheel phenomenon and head tremor). Secondary criteria are supportive of a diagnosis of ET, and include duration >3 years, a positive family history and beneficial effect of alcohol. They increase the likelihood of a diagnosis of ET, but are not required. The core criterion of 'no other neurological signs' has evolved over time, with recent reports on gait ataxia (31-33), limb ataxia (34, 35), eye movement abnormalities (36, 37), dystonia

TABLE 1.1 BASIC CHARACTERISTICS AND TREATMENT OPTIONS FOR DIFFERENT TREMOR TYPES

Type of tremor	Frequen -cy (Hz)	Rest	Posture	Goal-directed	Pharmacological treatment options	Stereotactic treatment options
ET	4 to 11	-	++	+	Propranolol, primidone, (level A recommendation), topiramate, atenolol, sotalol, gabapentin, alprazolam (level B)	Thalamotomy and thalamic DBS (VIM, VL, STA) (level C)
PT	5 to 10	++	+-	+-	Pharmacological treatment options for PD effect tremor < bradykinesia and rigidity (level A)	Lesioning or DBS of STN, GPI, VIM, VL (level C)
EPT	7 to 12	-	++	+	Similar to ET (level A-C)	-
FT	4 to 10	+	+	+	Explanation, physiorehabilitation, psychological treatment	-
DT	4 to 10	-	++	+	Trihexyphenidyl, propranolol (level C)	-
CT	2 to 6	-	+	++	Carbamazepine, propranolol, primidone, isoniazid, ondansetron, 4-aminopyride, botulinum toxin (level U)	Lesioning or DBS of VIM (level C)
HT	2 to 5	++	+	++	Levodopa, clonazepam, clozapine, levetiracetam (level U)	Thalamic DBS (level C)

ET: essential tremor, PT: Parkinsonian tremor, EPT: enhanced physiological tremor, FT: functional tremor. DBS: deep brain stimulation, VIM: ventral intermedius (thalamus), VL: ventrolateral (thalamus), STA: subthalamic area, STN: subthalamic nucleus, GPI: globus pallidus interna. Levels refer to the strength of the recommendation based on the quality of the currently published studies. A: established as effective, level B: probably effective, level C: possibly effective, level U: data inadequate or clniflicting, treatment is unproven with current knowledge.

(38), and non-motor symptoms (39) in patients that are otherwise diagnosed as ET.

Application of the TRIG criteria reduces the chance of mislabelling patients as ET significantly. This is important, not only for patients' prognosis and management, but also for research purposes. Being uncritical about including 'ET patients' into any scientific study complicates finding commonalities in such a group, independent of investigating phenomenology, pathology, brain activation or genes. Indeed, lack of a secure diagnosis

has been proposed as a serious limitation for advancement in all four mentioned areas of ET research (40, 41).
Since the publication of the TRIG criteria, it has been suggested to distinguish 'hereditary ET'; patients fulfilling the TRIG criteria and with a positive family history, 'sporadic ET'; fulfilling TRIG criteria, but without a family history, and 'senile ET'; fulfilling TRIG criteria, but with an age-at-onset later than 65 (40). The reason for this distinction is the fact that the penetrance for hereditary ET appears almost complete by age 65, which would make new-onset tremor at old-age more likely to be due to common age-associated neurodegenerative diseases, rather than to specific ET. Although not all currently apply this distinction, we chose to include only hereditary and sporadic ET patients into the ET study that is described in **Chapters 4-7**, resulting in a well-defined group.

ESSENTIAL TREMOR: ASSESSMENT OF TREMOR SEVERITY

ET is often called a benign disorder, but moderate and advanced stages can be physically and socially disabling (42-44). To assess tremor severity, the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) is a well-known and widely used tool in clinical trials (45, 46). The TRS includes both clinician-based ratings in parts A and B, and a patient-based activities-of-daily-life questionnaire in part C. The latter interview takes some time to conduct, and is not always used in clinical trials, nor is it always replaced by another patient-based measure of tremor severity such as subjective visual analogue scale scoring. Intuitively, one would suspect clinician-based and patient-based measures to correlate well; however, because these relations have never been directly investigated. Therefore, the supposition that objective clinical improvement correlates with patients' appraisal of improvement remains unsubstantiated.

ESSENTIAL TREMOR: UNCLEAR PATHOPHYSIOLOGY

Regarding the pathophysiology of ET, three hypotheses exist that are nonexclusive, but may rather work in unison. In all of them, the cerebellum or cerebellothalamocortical circuit plays an important role (see (47) for a review).

The neurodegeneration hypothesis

The hypothesis that has been under debate for the longest time is the hypothesis that ET is a neurodegenerative disease (48). Clinically, the fact that ET is progressive and associated with age supports this hypothesis (49). Moreover, in some studies (50), ET is associated with an increased risk of developing PD or Alzheimer's disease: both neurodegenerative diseases. Three research groups have performed pathology studies, with conflicting results: most of them, but not all, suggesting degeneration of the cerebellum. Currently, the largest pathology study that was done by Louis et al compared 33 ET patients to 21 healthy participants (51). Cerebellar Purkinje cell loss was found in ET patients, with loss of 25% of cells, and 24% of patients had Lewy bodies in the locus coeruleus. Later on, this same research group showed Purkinje axonal swelling (called torpedoes) in ET cerebellums, but not in healthy subjects (52). A second group found evidence of cerebellar degeneration in 29% of patients, but did not replicate the finding of Lewy body disease in the locus coeruleus (53). Finally, a third group reported no Purkinje cell loss nor Lewy bodies in ET, albeit in a smaller sample (54). The controversial results in neuropathology may be explained by patient selection biases and lack of standardization of methods across these studies. Structural brain imaging has also come up with conflicting results: some studies showing decreased cerebellar white-matter integrity and cerebellar atrophy, while others showed no

abnormalities in brain structure (55). Overall, there is heterogeneous evidence mainly for cerebellar neurodegeneration.

The gamma-aminobutyric acid hypothesis

A second hypothesis that has been put forward is that ET is caused by a disturbance of the gamma-aminobutyric acid (GABA) ergic system. In an overall theory to explain ET pathophysiology, the GABA hypothesis contains multiple steps (56). The first step comprises of cerebellar degeneration with Purkinje cell loss. As a consequence, activity of the GABA system decreases in the deep cerebellar neurons. Therefore, the pacemaker activity of the deep cerebellar neurons is disinhibited. As a result, the rhythmic activity of the thalamus and thalamo-cortical circuit increases, ultimately leading to tremor.
Clinically, the notion of abnormal GABA function is supported by the fact that some GABAergic drugs are beneficial in ET, although not all are (19). Secondly, decreased GABA levels have been found in the cerebro-spinal fluid of ET patients (57). Other evidence comes from recent positron-emision topography (PET) studies: it was found that 11C-flumazenil binding to GABA-receptors was increased in ET patients compared to healthy participants (58), and that binding increased with tremor severity (59). Moreover, in a pathology study, decreased levels of GABA receptors were found in the dentate nucleus of the cerebellum in ET patients compared to PD patients and healthy controls (60). On the whole, studies on GABA all point towards decreased cerebellar GABA, however, the hypothesis concerns relatively few studies and not all results have been duplicated.

The oscillating network hypothesis

Historically, a lot of tremor research focused on finding one driving oscillator facilitating tremor based on the fact that some neurons have oscillating properties at an independent frequency, including in the deep cerebellar nuclei (61-64). The idea of a single oscillator has been challenged by several inconsistent findings, for instance that lesions at several locations in the cerebellothalamocortical circuit can relieve tremor (65), and deep brain stimulation of multiple clusters of the ventrolateral and ventral intermediate nucleus of the thalamus and subthalamic area can alleviate ET (35, 66, 67). As a result, current research is focused on identifying a network of oscillators, taking into account the connectivity and interactions between different parts of the cerebellothalamocortical circuit (68). Good examples of this approach are the recent EEG/MEG/thalamic microelectrode-EMG coherence studies, which support involvement of a large part of the physiological central motor circuit in ET (69-71). Moreover, it was found that although both voluntary and pathological tremor arise from the cerebellothalamocortical circuit, bithalamocortical interactions are only found in pathological tremors (72).

Note that while the in the GABA hypothesis cerebellar neurodegeneration is taken as the starting point of its notion (56), in the oscillating network hypothesis it remains open whether the emerging picture of neurodegeneration reflects primary degeneration or secondary changes (68). The strongest advocates of the neurodegeneration hypothesis see the structural changes as primary (73). To add to the clarification of ET pathophysiology, we set up a neuroimaging study in ET patients that is described in **Chapters 4-6**. We felt that functional magnetic resonance imaging (fMRI) had not yet been used to its full potential: therefore, we used the advanced technique of combining fMRI with EMG. I will briefly discuss these techniques in the following section.

TECHNIQUES EMPLOYED IN THIS THESIS: EMG AND FMRI

Two major techniques are used in this thesis. The first one is electromyography (EMG), a technique that is used to measure electrical activity in skeletal muscles: either by placing an electrode intramuscularly (needle EMG) or on the skin above the muscle (surface EMG). The most basic use of EMG is to determine whether a muscle is active. In tremor research, one of the applications of EMG is to quantify the extent of tremor (28), especially fluctuations within one recording. In **Chapter 4**, we employed EMG in this manner: by quantifying the EMG signal, we were able to express changes in tremor intensity over time, which we could then correlate with changes in brain activity over time. This way, we were able to link tremor activity directly to brain activity.

Brain activity was measured with the second major technique used in this thesis, which is fMRI. Clinically, MRI is widely used to investigate human anatomy and pathology in vivo. MRI makes use of the differences in magnetic properties between various types of tissues in the human body to create an anatomical image. Functional MRI adds mapping of regional brain activity to anatomical (structural) MRI, by applying this principle to hemoglobin. When a brain area becomes more active, there is a local increase in blood that is rich in oxyhemoglobin, containing more oxygen than can be used by the brain tissue. This haemodynamic response results in a local increase of the proportion of oxyhemoglobin versus deoxyhemoglobin. The difference in magnetic properties of deoxygenated and oxygenated blood enables the detection of local increases in brain activity. The signal thus obtained is called the Blood Oxygenation Level Dependent (BOLD) signal. Local changes in the BOLD signal can be analysed statically. For example, it is common to compare brain activation in all voxels during a certain task to activation during rest; first for individual participants, then in a group of participants. Finally, statistics can then be used to compare brain activation between different groups.

In this thesis, we employed several fMRI analysis designs and techniques, such as task-related and 'EMG'-related (**Chapter 4**), event-related (**Chapter 5**), and connectivity analysis (**Chapter 6**), all to study changes in brain activations in ET patients.

AIMS

We address two aims in this thesis. In the first part, we aim to improve on the diagnosis of tremor. In **Chapter 2**, we do this by examining the sensitivity and specificity of several presumably 'typical' tremor characteristics. In **Chapter 3**, we examine the potential value of intermuscular coherence and cumulant analysis as additional diagnostic measures in the clinical neurophysiological assessment of tremor. In the second part of the thesis, we aim to investigate the pathophysiology of ET by means of functional neuroimaging. In **Chapter 4**, we take the approach of correlating fluctuations in tremor severity during scanning with brain activity in ET patients performing a postural task. In **Chapter 5**, we perform effective and functional connectivity analysis in the same ET population. In **Chapter 6**, we compare brain activity related to goal-directed movement between ET patients and healthy participants. We investigate to what extent clinician-based and patient-based measurements of tremor severity correlate in **Chapter 7**.

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