Tracing tremor: Neural correlates of essential tremor and its treatment
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Chapter 1

General introduction and aims
Background

Tremor is defined as rhythmic, oscillatory involuntary movements of a body part.\(^1\) It is a common symptom of a wide range of neurological and other disorders, as well as a disease entity in itself.\(^2\) Tremor often originates in the central nervous system.\(^3\) Clinical characteristics, together with correct tremor classification, can help to differentiate between tremor disorders (see Chapter 2 for a review on the diagnostic work-up of a patient with tremor).

Essential tremor (ET) is the most common pathological tremor, with an estimated prevalence around 0.5% in the general population, and a prevalence of up to 4.6% in people over 65 years old.\(^4\) Symmetrical postural and intention tremor between 4 and 12 Hz in the arms without other neurological signs is suggestive for ET (Box 1).\(^2,4,5\) One third of ET patients also suffer from head tremor.\(^6\) Mean age at onset of ET is around 45 years, but tremor can already present itself in early adulthood and even during childhood. A positive family history is often, but not always, present.\(^7\) A causative genetic mutation has not been identified up to now. ET can have a serious impact on patients’ lives. Task-related disability due to tremor, such as difficulties with eating and drinking, functionally impair as many as 60% of patients.\(^8\) Tremor in itself, and the associated functional disability, also causes significant psychosocial impairment, with 39% of patients having had depressive episodes due to tremor.\(^8\) When symptoms progress, they urge patients to seek medical attention.

Treatment

Treatment for ET is often difficult. The first choice of treatment for ET consists of drugs that suppress tremor, including propranolol and anti-epileptic drugs.\(^9,10\) For propranolol and primidone, an improvement in about 50% of patients has been reported.\(^9,10\) Anti-epileptic drugs are hypothesized to improve tremor by affecting the GABA (\(\gamma\)-aminobutyric acid) receptors in the brain.\(^9\) The mechanism of action for propranolol is unexplained. It has been suggested that propranolol might alter properties of the reflexive system, and through this mechanism, dampen tremor.\(^11–13\) Why certain patients only respond to certain types of medication is unknown. Stereotactic surgery in the form of deep brain stimulation and thalamotomy is an option for patients with disabling hand tremor that is not suppressed adequately by drug treatment.\(^14,15\) However, symptoms often seem to progress again over time in a considerable number of patients after deep brain stimulation, contrary to thalamotomy.\(^16\) Up to now, there is no curative treatment for ET available.
Although ET is a common disorder, the exact mechanism of tremor generation in ET remains unknown. Evidence is accumulating that the cerebellum plays a central role in the pathophysiology of ET.\(^{17,18}\) One of the first supportive features raising this hypothesis was the positive effect of alcohol on ET.\(^{19}\) Furthermore, emerging clinical features such as ataxic gait,\(^{20-22}\) eye movement abnormalities,\(^{23-25}\) and intention tremor\(^{26,27}\) all point to cerebellar changes.\(^{20,23,28}\) Currently, there are three mutually non-exclusive hypotheses about the pathophysiology of ET, with cerebellar involvement.\(^{3}\) Reports of alleviation of tremor after thalamic deep brain stimulation and after stroke within the physiological central motor network, or cerebello-thalamo-cortical network, prompted the hypothesis of essential tremor as an ‘oscillating network disorder’.\(^{29}\) Several clues point to the olivocerebellar system and thalamus as key structures within this network.\(^{29}\) Neurons in the thalamus, inferior olive nucleus and dentate nucleus exhibit membrane hyperpolarisations that causes these neurons to oscillate independently.\(^{29-31}\)
still out on whether tremor arises from these single oscillators or from a network of oscillating neurons, dynamically entraining each other. A second hypothesis labels ET as a neurodegenerative disorder. Pathology studies show evidence for structural cerebellar changes, with Purkinje cell loss and axonal swelling, and simultaneous remodelling of the cerebellar cortex.32–37 A third hypothesis is associating ET with abnormal functioning of the inhibitory neurotransmitter GABA. Purkinje cells form the sole output channel from the cerebellar cortex, and lead to the deep cerebellar nuclei, including the dentate nucleus. With their GABAergic synapses, Purkinje cells strongly regulate the intrinsic activity of the dentate nucleus.38 GABAergic neurotransmission dysfunction within the cerebellum has been reported in ET, with increased 11C-flumazenil binding to GABA receptors in the cerebellar cortex, increasing with tremor severity, and in the dentate nucleus, suggesting functional cerebellar changes.39,40 Additionally, a decrease in GABA receptors has been observed in the dentate nucleus in ET.41 This decrease in GABA receptors might result from altered GABA receptor function, and subsequent up-regulation at the level of the dentate nucleus, explaining the increased 11C-flumazenil binding to GABA-receptors.39 How the observed changes within and outside the cerebellum are related to abnormal neuronal oscillations, a neurodegenerative pathological process and/or to (primary) abnormal GABA-related changes remains to be elucidated.42

**Heterogeneity**

ET is a heterogeneous disorder; patients differ in the presence of head tremor, age at onset, family history and response to medication, possibly indicating different underlying disease mechanisms.43 It has even been suggested that ET as a single disease entity does not exist, but belongs to a wide spectrum of ‘essential tremors’.43 Ill-defined subtypes of ET and the clinical overlap with other movement disorders hamper our understanding of the pathophysiology and treatment of ET.
Aim and Outline

The aim of this thesis is to better understand the neural correlates of ET and existing treatments. With respect to the pathophysiology, we hypothesize that the cerebellum plays a crucial role in causing ET. Existing therapies might seize tremor by affecting specific components of the cerebello-thalamo-cortical network. To investigate these hypotheses, we will select a homogeneous group of ET patients to be compared with healthy controls applying several imaging techniques combined with neurophysiological measures. This thesis is organized in 2 parts.

**Part I: neural correlates of essential tremor**

Although the involvement of the cerebello-thalamo-cortical network, and of the cerebellum in particular, often has been suggested in essential tremor, the source of pathological oscillatory activity remains largely unknown. Using a combination of electromyography and functional MRI (EMG-fMRI), we can record the peripheral manifestation of tremor simultaneously with brain activity related to tremor generation. Earlier studies of our group and others have proven that EMG-fMRI allows identification of brain areas involved in the generation of tremor. In Chapter 3 we use EMG-fMRI to identify ET-related brain activations. We hypothesize that tremor is related to widespread activity throughout the cerebello-thalamo-cortical network, but with a clear emphasis on cerebellar activity. Subsequently, to observe how these ET-related brain activations arise and possibly give rise to tremor, we study network dynamics and properties of brain regions within the cerebello-thalamo-cortical network in the context of tremor. This can be achieved by using the same EMG-fMRI recordings, with the help of functional and effective connectivity analyses (Chapter 4). Considering the hypothesized functional changes within the cerebellum, we expect properties of the cerebellum and its outflow tracts and target regions (i.e. the thalamus) to be affected in ET.

Above, we propose that cerebellar changes are present in ET and underlie the emergence of tremor. Consequently, we hypothesize that, because of altered cerebellar activity, normal cerebellar motor output is impaired in ET. It has been reported previously that ET patients show motor timing impairments, which can partially be reversed by repetitive transcranial magnetic stimulation over the cerebellum. In Chapter 5, we use a rhythmic finger tapping task during fMRI scanning to actively engage the cerebellar motor circuitry. We characterize cerebellar and, more specifically, dentate nucleus
function, and neural correlates of cerebellar output in essential tremor during rhythmic finger tapping.

ET has been hypothesized to be a neurodegenerative disease. Several structural imaging studies have been performed and show a diverse and incongruent picture of cortical and cerebellar changes. However, different inclusion criteria and methodological differences between studies raise uncertainty regarding these findings. We expect ET not to be associated with macroscopic structural changes extending age-related atrophy. Here we compare our selected homogeneous group of ET patients with healthy controls and with a group of patients with a clear neurodegenerative disease with Purkinje cell involvement, Familial Cortical Myoclonic Tremor with Epilepsy (Chapter 6). For this study, we will use a technique called voxel-based morphometry (VBM). This allows investigation of focal differences in brain anatomy, in contrast to global atrophy. Additionally we will use diffusion tensor imaging (Chapter 7) to estimate cerebellar white matter tissue composition. We will compare cerebellar fiber density, again between ET patients, healthy controls and patients with Familial Cortical Myoclonic Tremor with Epilepsy. We hypothesize that fiber density in the cerebellum is decreased in Familial Cortical Myoclonic Tremor with Epilepsy, and might show minor changes in ET compared to healthy controls.

**Part II: neural correlates of treatment of essential tremor**

The tremorolytic mechanism of action of propranolol in essential tremor is unknown. It has been postulated that propranolol alleviates tremor by altering the sensitivity of muscle spindles. We hypothesize that if there is a peripheral site of action, for example within muscle spindles, stretch reflex properties would be altered in patients taking propranolol. Alternatively, as suggested in physiological tremor, an effect of propranolol on Renshaw cells, situated in the grey matter of the spinal cord, is a possibility. Considering the positive effect propranolol has on many tremor disorders, we hypothesize that the mechanism of action is not specifically associated with the origin of tremor. We suppose that altering Renshaw cell sensitivity can effectively ‘damp’ tremor, regardless of the underlying origin. We consider a direct effect on the cerebello-thalamo-cortical neuronal loop to be less likely. We will study stretch reflexes in ET patients on and off propranolol medication to investigate these hypotheses (Chapter 8). By applying continuous perturbations, it is possible to characterize motor behaviour and determine the effect of propranolol on the motor system. Using a combination of system identification and
neuromuscular modelling, it is possible to separate muscular and reflexive contributions, and dissociate specific effects of propranolol on different parts of the motor system.\textsuperscript{51,52} Deep brain stimulation and thalamotomy are both used in alleviating tremor. It has been suggested that the effect of treatment of deep brain stimulation decreases in some patients over time, in contrast to patients treated with thalamotomy.\textsuperscript{16} To clarify this apparent difference between these types of surgery, it is interesting to know whether the structural effects of thalamotomy are limited to the thalamus, or are more widespread. In \textbf{Chapter 9}, we look at whether structural changes are present in other parts of the cerebello-thalamo-cortical, or ‘tremor’, network, besides the thalamus, using diffusion tensor imaging. We hypothesize that changes can also be detected in the efferent tracts leading to the lesioned thalamic VIM nucleus, from the cerebellum. Thalamotomy patients provide us with the unique opportunity to compare differences within patients, considering that thalamotomy is only performed unilaterally. This makes comparing differences between the affected (operated) and unaffected (non-operated) side possible. All the imaging and modelling techniques used throughout this thesis to dissociate specific aspects of our aims are clarified in Box 2-6.

\textbf{Patient selection and techniques}

The previously mentioned heterogeneity within the clinical spectrum of ET emphasizes the need for careful selection of patients for scientific studies and to look at specific subtypes when studying ET. For virtually all studies in this thesis, a homogeneous group of ET patients is included, with a positive family history and a positive response to propranolol treatment.
Box 2. Combining electromyography & functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging technique that measures brain activity by detecting changes in the so-called blood-oxygen-level dependent (BOLD) contrast. Neuronal activity causes an increase in local blood flow. Subsequently, oxygen-rich (oxygenated) blood displaces oxygen-depleted (deoxygenated) blood about 2 seconds after, peaking at 4-6 seconds. This is called the hemodynamic BOLD response. The magnetic distortion of deoxygenated blood is different from that of oxygenated blood, which can be captured by the MR scanner. By making a scan every, for example, 2 seconds, it is possible to measure brain activity of specific regions over time. Electromyography, or EMG, is a technique used to record the electrical activity produced by muscles. In essential tremor, rhythmic bursts of activity can be identified over time in muscles exhibiting tremor.

By using advanced, MR-compatible equipment, it is possible to record EMG and fMRI scans concurrently. Subsequently, we can relate tremor intensity with the simultaneously measured brain activity to identify tremor related brain activations. Figure 1 gives an example of the different signals. This technique is used in Chapters 3 and 4.

Figure 1. The upper part of the figure shows a task over time, for example stretch out arm alternated with rest. The second part shows the intensity of tremor during the task recorded with EMG. The lower part shows the associated BOLD signal in the primary motor cortex, a brain region involved in movement (Adapted from Van Rootselaar et al. 2007).
**Box 3. Brain connectivity**

Studying brain connectivity is crucial to understand how neural networks process information. One way to study brain connectivity, is to look at the relation between brain activity, i.e. the BOLD signal (Box 2), of different brain regions, and observe how they are associated. One could simply correlate BOLD signals of separate brain regions, and see which regions are functionally linked to each other. This is termed *functional connectivity*. Another method to study brain connectivity is by estimating *effective connectivity* (Figure 2). This is defined as estimating the influence of one brain region over another, either directly or indirectly, over time. This method therefore implies a causative influence, not merely correlations. Both functional and effective connectivity will be used in Chapter 4.

**Figure 2.** Left side: functional connectivity looks at correlation between BOLD time series of brain regions. Right side: effective connectivity looks at the influence specific brain regions exert over others, over time.
**Box 4. Voxel-based morphometry**

Voxel-based morphometry (VBM) is a neuroimaging analysis that allows studying regional differences in brain anatomy (Figure 3). The technique uses T1-weighted MR images. First, the T1 image is segmented in grey matter, white matter and cerebrospinal fluid. Subsequently, the grey matter image is ‘warped’ to a standard template, to get rid of large differences in brain anatomy. Finally, the image is ‘smoothed’ so that each voxel represents the average of itself and its neighbours, and can be compared across subjects. The typical voxel size used in VBM studies is 1x1x1 mm. VBM is used in Chapter 6.

![VBM preprocessing pipeline](image)

***Figure 3.*** VBM preprocessing pipeline.
**Box 5. Perturbing the reflexive system**

In humans, several mechanisms exist to maintain the limbs in a specific position in the presence of external disturbances. Intrinsic properties of the limbs, such as muscle properties and joint stiffness are contributing mechanisms, and reflex loops, with muscle spindles and Golgi tendon organs providing sensory information about muscle stretch and stretch velocity are involved (Figure 4). One way of quantifying the amount of reflex activity is the H-reflex. A nerve is electrically stimulated, and the direct and indirect (reflex) muscle responses are recorded. However, this technique results in stimulation of many pathways, and is not very specific. Identifying intrinsic and reflexive components of human arm dynamics can be achieved by applying continuous disturbances to the arm, while the test subject is trying to minimize arm movement. Using system identification and neuromuscular modelling, it is possible to separate intrinsic muscular changes from alterations in reflexive contributions. In other words, it is possible to separate intrinsic and reflexive contributions to human arm dynamics. This technique is used in Chapter 8.

**Figure 4.** Schematic overview of the human reflex system. The muscle is excited by the motor neuron, which receives descending input from the cortex, and sensory input from la, lb and II afferent neurons from the tendon and muscle spindles. Renshaw cells, located in the grey matter of the spinal cord, exert inhibitory input on the la afferent neuron and the motor neuron, and receive excitatory feedback from the same motor neuron.
**Box 6. Diffusion tensor imaging**

White matter consists of bundles of axons that connect different parts of the nervous system. Damage to white matter can be quantified using diffusion tensor imaging (DTI). DTI measures the diffusion of water molecules. By applying a magnetic gradient in an MR scanner in many directions, the diffusion of water is quantified in a three-dimensional ellipsoid (Figure 5). Normally, axonal membranes and myelin pose barriers to water displacement, such that water preferentially diffuses along the direction of the axons. In the case of damaged axons, diffusion along the direction of axons is restricted, whereas diffusion tangentially to the axons is increased. DTI is used in Chapters 7 & 9.

**Figure 5.** Diffusion tensor imaging quantifies in which direction water preferentially diffuses. In damaged axons, diffusion along the direction of axons is restricted and diffusion tangentially to the axons is increased.