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## Diagnosis and imaging of essential and other tremors

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## CHAPTER 8

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## DISCUSSION

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In this thesis, we addressed two aims: to improve on diagnosis of tremor, and to investigate the pathophysiology of essential tremor by means of functional neuroimaging. In the following paragraphs, important findings related to these aims will be discussed. Next, I will share some general considerations connected to this work. Moreover, I will indicate future directions for follow-up research, and provide general conclusions.

## DIAGNOSING TREMOR CORRECTLY

### DISTINGUISHING TREMOR DISORDERS BY TYPICAL TREMOR PHENOMENA

It was a valuable endeavour to determine the sensitivity and specificity of tremor characteristics that are thought to be typical for a certain tremor disorder, as we did in Chapter 2. We demonstrated that the five phenomena that we investigated were indeed specific: a decrease in tremor frequency upon loading of the arm does point to enhanced physiological tremor (EPT), while signs of distraction, entrainment or an increase in tremor amplitude upon loading indicate a diagnosis of functional tremor (FT), and intention tremor suggests essential tremor (ET). Contrarily, it should be noted that not all characteristics were sensitive measures to identify their corresponding tremor disorder. This was the case for the measures related to changes in tremor appearance as a result of loading in both EPT and FT, and intention tremor in ET. Therefore, absence of these phenomena is not informative, and clinicians need to be aware of this fact when looking for these characteristics in the examination room. We would also like to point out that although specificity of all characteristics was high (85-95%) it never reached a hundred percent. An absolute one-to-one translation from phenomenon to tremor diagnosis is thus impossible. This is particularly important regarding FT: the reality is that 'functional' characteristics can occur in tremor

that is ultimately diagnosed as 'organic'. This has been reported before (3-6), and illustrates that functional symptoms can occur in organic tremor (or other neurological disease (10)). Although the tremor phenomena have been discussed in separate studies (1-9), we are the first group to establish the prevalence of these phenomena in such a large and diverse tremor population, and we believe the information we presented in Chapter 2 will help clinicians to better distinguish different types of tremor.

### CLINICAL NEUROPHYSIOLOGY TESTING FOR TREMOR DIAGNOSIS

The frequency-based phenomena that are mentioned in Chapter 2 and in the previous paragraph are best assessed by means of clinical neurophysiology testing. These tests are generally of great value (11, 12), as we also confirmed in Chapter 2. In Chapter 3, we explored the potential value of intermuscular coherence and cumulant analysis as additional diagnostic measures in the poly-myographic assessment of postural tremor. This proved a valuable first exploration: coherence values differed between groups, and we were able to distinguish EPT patients by their low coherence, and we found characteristic muscle activity patterns in ET and PD. Apart from contributing to diagnosis, our results are also input to the discourse on pathophysiology in terms of contributions of central oscillators to tremor in ET, PT and FT, versus a larger role for a peripheral origin of tremor in EPT (13-15). Overall, our results do not directly translate to medical practice as of yet, as this was a retrospective study performed in 4 groups of 20 strictly selected patients. However, our investigation does provide indications for potentially fruitful follow-up studies, for instance in distinguishing ET and EPT.

## PATHOPHYSIOLOGY OF ESSENTIAL TREMOR

### FUNCTIONAL CEREBELLAR ABNORMALITIES IN ET

In our functional MRI studies, we found increased cerebellar activations in ET patients compared to healthy participants. Firstly, in Chapter 4, we demonstrated that increases in tremor severity over the course of an fMRI session correlate with increases in cerebellar activation in ET patients. We were able to identify specific bilateral areas in the cerebellum: in the left lobules V and VI, and right lobules V, VI, VIIIa and b. An early fMRI study, without simultaneous EMG recording, has reported bilateral cerebellar activation before (16), and our findings reinforce the results in this report as well as go beyond. Rather than diffuse bilateral activations (16), our tremor-related activations are specifically located in the somatomotor regions of the cerebellum (17, 18). It should be noted that these activations were specifically tremor-related, rather than movement related, as we correlated the brain activation in these areas with fluctuations in tremor severity over time independently of the movement task of holding the arm at a raised posture. This demonstrates the additional value of simultaneously recorded EMG, when it is mathematically manipulated to represent fluctuations in tremor independent from the task.

In Chapter 6, we again demonstrated increased cerebellar activations in ET patients compared to healthy participants while performing goal-directed movements. We added this task to investigate the brain activations in relation to the intentional component of essential tremor, in addition to the postural component studied in Chapter 4, to examine whether abnormal brain activation may be found in similar areas. Together, the results from these two complementary fMRI studies lend further support to the notion of underlying cerebellar pathology in ET, fitting with some of the evidence from

neuropathology studies (19-22), as well PET imaging (23-25), and early MRI studies (16, 26).

At first, the fact that we found increased rather than decreased cerebellar activations may seem counter-intuitive in the light of the neurodegeneration hypothesis, because signs of neurodegeneration such as Purkinje cell loss and axonal swellings (torpedoes) have been reported in the cerebellar cortex in ET by some groups (19, 20), which seems more compatible with decreased than increased activation. However, we can explain our consistent finding of increased activation in ET by hypothesizing that the affected cells are deficient and disorganized, making them less efficient, and that this inefficiency leads to increased activations.

The idea of cerebellar pathology is further advanced by the results from our connectivity analyses. Regarding effective connectivity, tremor variation during the motor task has an excitatory effect on both the extrinsic connection from cerebellar lobule V to the thalamus, and the intrinsic activity of cerebellar lobule V and the thalamus. In addition, we found that functional connectivity between the cortical and cerebellar motor regions. This decrease in functional connectivity correlates with an increase in clinical tremor severity.

Overall, in this thesis, we report evidence of increased cerebellar activations related to fluctuations in postural tremor, increased cerebellar activations during goal-directed movement, excitatory intrinsic cerebellar activity when incorporating tremor variation during the motor task as modulator of intrinsic activity, and decreased functional connectivity between primary motor cortex and cerebellum, which is partly correlated with clinically assessed tremor severity. Combined, these results impart a major role of the cerebellum in ET.

A strength of the imaging studies is that we

measured aspects of task performance during scanning. In Chapter 4, we used EMG to derive tremor severity fluctuations over time, and used this measure in Chapter 5 as well. In Chapter 6, we used kinematic data to determine how participants performed goal-directed movement while being scanned. This way, we could directly correlate behavioural performance to cerebral (or cerebellar) activations, and were able to compare functioning of our patients and healthy participants. This matters for the interpretation of results: differences in brain function may be attributed to difference in performance, rather than interpreted as cerebral changes 'in itself'. In Chapter 6, we found that our patients did not perform different during the goal-directed movement task from their healthy counterparts. We expected a different performance based on current essential tremor studies where mild ataxia has been described. The lack of ataxia in our patients might be due to the limited duration and severity of their disease, although it can also be speculated that our method was not sensitive enough. In previous studies, more advanced patients were included (27, 28)). The fact that we found a difference in brain activation despite these similarities in behaviour makes the cerebellar difference even more interesting. This suggests that this change in brain function may even precede related disease features such as ataxia, and that it may be inherent to ET as a disorder.

## GENERAL CONSIDERATIONS

### SELECTING THE 'RIGHT' PATIENTS

In this thesis, we have used several different methods for patient inclusion, because to best answer our research questions, different inclusion methods were called for. In Chapter 2, we wanted to test sensitivity and specificity of tremor phenomena in 'the real world', which we felt meant in a varied tremor population, not only in the text book

cases where there is zero doubt about diagnosis. Therefore, we put no constraints on inclusion, other than that patients had to have had a tremor-specific polymyography, and based our selection on the final clinical diagnosis made by the neurologist. Contrarily, in Chapter 3, we wanted to explore whether we could differentiate different types of tremor using coherence and cumulant analysis. Because of the explorative nature of this study we ascertained that diagnosis in all patients was maximally reliable, using clinical, neurophysiological and imaging inclusion criteria: ideal for an initial study. In the second part of this thesis, we aimed to select definite ET patients to study pathophysiology with functional imaging. All our patients met the core TRIG criteria (29) and additionally they met at least two supportive criteria: disease duration >5 years, and a positive family history and/or alcohol responsiveness. Moreover, we decided that age at onset had to be <65 years, thereby excluding 'senile' ET, which some consider to have a different pathophysiology (30).

Despite the fact that ET is supposed to be such a common movement disorder (31, 32) it was difficult to include definite ET patients. Despite several methods used to find patients, most patients who contacted us did not meet clinical criteria for ET. This illustrates the fact that, traditionally, the label 'ET' has been used and misused as a 'container' diagnosis for all types of tremor that did not fit any particular diagnosis. This situation has improved over the last two decades with the establishment of successive clinical criteria (29, 33), but has not dissolved entirely.

### LIMITATIONS OF FMRI ANALYSIS

It is necessary to consider limitations of fMRI analysis to appreciate fMRI results. Here, I focus on interpretation issues concerning group analysis, because this applies to the work on ET presented in this thesis. An (im-

plicit) assumption in the analysis of groups of participants is the assumption of universality: the idea that spatio-temporal dynamics of brain functions have a high degree of uniformity within a population (34). The most commonly used group-analysis methods treat the overlapping activations shared across subjects within the group as true activation (35). Activations that are not shared, and occur only in one participant or a subset of participants are thus considered as noise. Therefore, the significant supra-threshold results depicted in figures and tables may be incomplete, missing activations that occur in a subset of the group, i.e.: may represent false negatives. Contrarily, it has been shown that if only a part of the population shares a certain activation, but with a very strong effect size, such activation may reach a significant level, and is therefore ascribed to the entire group. As such, this method of group-level inference generates false positive findings, as well (34). In the fMRI studies described in this thesis, we were much aware of these issues. The chance of underlying differences in brain activation between ET patients is even more likely than in a group of healthy participants, given the heterogeneity of the disorder (discussed in more detail later on). As a consequence, we paid ample attention to the single-subject (first level) results in our ET patients, particularly in Chapter 4. Macroscopically, we did not find different patterns of activations in our ET patients, although we did see that the effect sizes of the described activations differed between subjects. Conjunction analysis may be of additional value in future analyses (36), as it allows the description of activation on group level while at the same time providing information about how frequently the activations occurred within the group.

## FUTURE DIRECTIONS

### FUTURE DIRECTIONS IN RESEARCH AIMED AT TREMOR DIAGNOSIS & PHENOMENOLOGY

In terms of continuing our own research, the retrospective study we describe in Chapter 2 should be repeated in a prospective and blind study. A complication in organizing such a study is that this is not how everyday clinical practice works: the clinical neurophysiologists are not blind to the request that was sent in, and this helps them focus their polymyography report. To achieve a prospective blind study, we would need to change our clinical practice for approximately five years to get to the same number of patients. A multi-centre approach would reduce this period.

A prospective, blinded follow-up coherence and cumulant study should be conducted. Such a prospective study is useful; interesting questions to answer are whether the cut-off values for coherence remain sensitive and specific, particularly in distinguishing EPT, and whether the cumulant density functions we found in ET and PD remain typical.

Related to this topic of tremor diagnosis is the definition of ET that remains problematic. Over the past years, a debate has evolved whether it is possible to define ET as a single disease entity (37, 38), or whether ET is better understood as a family of diseases (39-41). The variation and complexity of signs and symptoms present in ET appears to be larger than was previously believed, with recent attention for age at onset (42), rate of progression (43, 44), alcohol responsiveness (45), head tremor (44, 46), resting tremor (47, 48), intention tremor (7-9), gait ataxia (49-51), limb ataxia (27, 52), eye movement abnormalities (53, 54), dystonia (55), and non-motor symptoms (56). It has been hypothesized that the heterogeneity in ET phenomenology has led to heterogeneous findings, and that the lack of adequately defined ET subtypes detains scientific advancements regarding

disease mechanism(s) and treatment.

As a follow-up to our imaging study, we have recently started to map phenomenology in families related to the patients who participated previously. The aim is to investigate the level of diversity within families, to examine which phenomena are familial, and whether patterns of disease progression can be found within families that may differ between families. Ultimately, such phenotypical characterization could lead to a better definition of disease subtypes, and a potential gateway to improved, more powerful neuroimaging and particularly genetic studies.

#### FUTURE DIRECTIONS IN NEUROIMAGING RESEARCH OF ESSENTIAL TREMOR

Apart from the suggestions regarding the definition and comparison of ET subtypes, functional neuroimaging will benefit from investigation of different tasks. In relation to our own work, a logical next step is to investigate a task where ET patients raise their left arm instead of their right arm, to investigate lateralisation effects in such a bilateral tremor disorder. Moreover, we are currently investigating a different postural task that may maximize postural tremor. Another suggestion, regarding the investigation of ataxia, is to see what abnormalities in brain activations can be found in more advanced ET patients, during goal-directed movement or other ataxia-related tasks such as diadochokinesis.

#### CONCLUSIONS

To conclude, we advanced the proper diagnosis of tremor in the clinical and clinical neurophysiological setting, by establishing sensitivity and specificity for typical tremor phenomena and exploring the additional value of intermuscular coherence and cumulant analysis. Secondly, we added to the debate on the pathophysiology of ET, with our results of increased cerebellar activations related to

tremor and goal-directed movement, and changes in cerebellar connectivity, which lend important new support to the notion of underlying cerebellar abnormalities in ET.

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