Neuroimaging in tremor and functional motor disorders

Broersma, Marja

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 27-01-2020
Chapter 1

Introduction
1.1 INTRODUCTION

This thesis is about two disorders with motor symptoms, with different origins and manifestations. Tremor is a common type of movement disorder in the category of too much movement, whereas functional neurological paresis is a functional motor disorder in the category of lack of movement. Both disorders are frequently seen in the neurological setting. Disorders with motor symptoms classified as organic have a known and established underlying structural or neurochemical origin, whereas disorders with motor symptoms classified as functional cannot be attributed to a neurological disorder. What all disorders with motor symptoms have in common is that there is a deficit in the movement system, often caused by altered brain functioning. The aim of our research was to gain more insight in changes in brain functioning in both patient groups and to apply this knowledge by investigating a potential therapeutic option for functional paresis. For this reason, a short introduction of the brain network involved in movement is given first.

1.2 THE BRAIN MOTOR NETWORK

Voluntary movements are initiated to accomplish a specific goal, they are triggered by external stimuli and improve with practice. The four key components of the central nervous system that form the motor system to execute and control voluntary movements are: 1) the descending motor pathways with their associated origins in the cerebral cortex and brain stem, 2) the spinal motor circuits, 3) the basal ganglia and 4) the cerebellum. Distinct areas of the cerebral cortex are involved in the motor system: the posterior parietal cortex, the premotor areas of the frontal cortex, and the primary motor cortex. These motor areas receive input from three sources. First, input from the periphery is transmitted directly from the thalamus and the primary somatosensory cortex to the primary motor cortex or indirectly via the sensory association areas to the premotor areas. Second, input is transmitted by the cerebellum. This input finds its way from the cerebellum through the thalamus to the primary and premotor cortices. The third source is input from the globus pallidus, also through the thalamus to the primary and premotor cortices. The motor areas in the brain have different functions in this motor network. In the cerebral cortex the primary motor area is responsible for the execution of the movement and encodes the direction of force. The premotor areas prepare and plan the movement, whereas the posterior parietal lobe and sensory association areas provide (integrated) visual and sensory information for the targeted movements. The basal ganglia provide information for the adjustment in execution of ongoing motor signals directly or indirectly by increasing inhibition through the thalamus whereas the cerebellum is known to compute signals to correct for differences in intent and actions, or errors.
In the brain motor network two mechanisms to adjust and correct for movement can be active. The feed-back mechanism is a reactive mechanism, which responds to the current state of affairs. The feed-forward mechanism is an anticipatory mechanism, which depends on experience and is essential for rapid action. The feed-forward mechanism can modify the operation of the feed-back mechanism. Together, the feed-back and feed-forward mechanisms are important for providing information to the motor network of the brain.

1.3 DEFICITS IN THE BRAIN MOTOR NETWORK IN ESSENTIAL TREMOR AND FUNCTIONAL PARESIS

The brain motor network is a complicated system and abnormalities in different parts of this network can cause different symptoms, leading to different disorders with motor symptoms that are characterized by variable abnormal involuntary movements. In this section, we specifically focus on the known abnormalities in the brain motor network for essential tremor and functional paresis.

The cause of functional disorders has long been thought to be psychological; a trauma has often been suggested to proceed the symptoms. This line of thought is controversial nowadays, as the presumed psychological factors in functional movement disorders are not apparent in many patients. Below, essential tremor and functional paresis will be introduced in more detail and we present hypotheses about their pathophysiology.

1.3.1 ESSENTIAL TREMOR

Tremor is the most common movement disorder in adults with essential tremor (ET) being among the more prevalent. Estimations about its prevalence worldwide run from 0.9% in all ages up to 4.6% in the population of 65 years and older. ET is characterized by a bilateral action tremor, occurring during posture and movement, of the hands and forearms and by the absence of other neurological symptoms. An intention tremor, a tremor that worsens when performing a goal directed movement, has been estimated to occur in a third to a half of ET patients. Apart from a tremor in the forearms and hand, tremor can occur in the head and voice and less frequently in the jaw and legs. A positive family history is reported in half of the ET patients.

1.3.1.1 DIAGNOSIS AND ET AS A FAMILY OF DISORDERS

Diagnosing ET can be challenging, because not every patient has the classic presentation and symptoms of ET can also occur in other disorders. History and clinical examination by an experienced movement disorders neurologist are in most patients sufficient to establish a correct diagnosis. Further clinical neurophysiological testing such as polymyography can be useful. ET was already described in the late 19th century, but only in 1998 the movement disorders society published a first consensus statement on tremor. In the intermediate years,
ET was used as a diagnosis for tremor not otherwise specified, making it a diffuse diagnosis with a broad spectrum of types of tremor. The most recent and widely used criteria for the diagnosis of ET were published in 2000 by the Tremor Investigation Group (TRIG). In this publication, apart from the core criteria of bilateral action tremor of the hands and forearms and absence of other neurological signs, secondary criteria to support the diagnosis are given. These secondary criteria entail: disease duration >3 years, a positive family history and beneficial response to alcohol. More recent studies show a shift in the idea that no other neurological signs are present in ET. The clinical presentation of ET includes a broad range of other motor features and involuntary movements (gait ataxia, dystonia, eye movement abnormalities), as well as non-motor features (cognitive problems, psychiatric problems). Furthermore, variation in response to pharmacological treatment, variable findings in postmortem studies and variable age-at-onset are discriminating factors. These insights suggest to distinguish different subtypes of ET fulfilling different criteria.

1.3.1.2 PATHOPHYSIOLOGY OF ET

Similar to the heterogeneity in criteria, a diversity in findings and hypotheses about the pathophysiology of ET exists. Three leading hypotheses have been formulated that reflect the clinical heterogeneity of ET: the neurodegeneration hypothesis, the GABA hypothesis and the oscillating network hypothesis. Details about each of these hypotheses are presented in Box 1.1.

In these three nonexclusive hypotheses, the cerebellum, and the more extended cerebello-thalamo-cortical network, are suggested to play an important role in ET. Knowing that the cerebellum computes signals to correct for differences in intent and actions, it is not surprising that when there is a deviation in this process an action tremor may emerge.

1.3.2 FUNCTIONAL NEUROLOGICAL PARESIS

Functional neurological paresis (FNP) is a functional neurological symptom disorder with loss of muscle strength as its core symptom. Functional neurological symptom disorders are commonly seen in neurological practice, with prevalence estimates ranging from 16% up till 27%. Functional neurological symptom disorders occupy a grey area between neurology and psychiatry, making it difficult to agree on a unified terminology to describe these disorders. Historically, functional symptoms were explained to be triggered by emotional trauma. This is reflected in terms used to describe functional neurological symptom disorder, such as hysteria, conversion disorder or psychogenic. An important change in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in comparison to previous editions is that the essential importance of the neurological examination is emphasized, and in recognizing that relevant psychological factors may not be demonstrable at the time of diagnosis. In the DSM-5, published in 2013, the term functional neurological symptom disorder was introduced. The criteria as set out in the DSM-5 are: one or more symptoms of altered voluntary motor or sensory function, clinical findings that provide evidence of incompatibility between the...
BOX 1.1 PATHOPHYSIOLOGICAL HYPOTHESES ABOUT ET

1. The Neurodegeneration Hypothesis
ET has often been compared to neurodegenerative diseases.\textsuperscript{35,36} Its progressive nature and its prevalence in the aging population support the hypothesis that ET is a neurodegenerative disease clinically. Furthermore, ET is associated with neuronal loss and postmortem changes. However, post-mortem studies have provided conflicting results, with cerebellar degeneration reported in some\textsuperscript{37-39} but not all studies.\textsuperscript{40} Structural neuroimaging has also shown conflicting results, since decreased cerebellar white-matter integrity and cerebellar atrophy has been found in some studies,\textsuperscript{41-43} while others found no abnormalities.\textsuperscript{44,45}

2. The GABA Hypothesis
That ET is associated with abnormal functioning of the gamma-aminobutyric acid (GABA)ergic system, is supported by several studies. GABA is an inhibitory neurotransmitter and pharmacological treatment with drugs that increase GABAergic transmission can be beneficial in patients with ET, although its effect is not present in all patients.\textsuperscript{46,47} In addition, reduced levels of GABA in the cerebrospinal fluid of ET patients have been found.\textsuperscript{48} Evidence from positron-emission topography (PET) studies indicates a significant increase in binding of (11)C-flumazenil to GABA(A) receptors in the cerebellum, the ventrolateral thalamus, and the lateral premotor cortex in ET patients compared to healthy controls,\textsuperscript{49} increasing with tremor severity.\textsuperscript{50} In addition, in a post-mortem study, reduction of GABA receptors was found in the dentate nucleus of the cerebellum in ET patients, but not in patients with Parkinson’s disease or healthy controls.\textsuperscript{51}

3. The Oscillating Network Hypothesis
Tremor studies of abnormal brain functioning in ET have mostly concentrated on finding a single oscillator, inspired by the finding that some neurons in the thalamus, inferior olive and cerebellar nuclei have oscillating characteristics at an independent frequency.\textsuperscript{52,53} There is neurophysiological evidence that the cerebello-thalamo-cortical loop is abnormally oscillating in ET; coherence studies that combined EEG and EMG measurements found that groups of neurons are intermittently coherent with muscle activity during tremor.\textsuperscript{54-56} More recent insights also suggest that there is not a single oscillator, but an oscillatory network involved in ET.\textsuperscript{57} This oscillating network hypothesis is supported by the fact that lesions in several locations of the cerebello-thalamo-cortical network can relieve ET\textsuperscript{58} and by results of studies with deep brain stimulation showing that stimulation in several separated clusters of the ventrolateral and ventral intermediate nuclei of the thalamus and subthalamic area can reduce ET.\textsuperscript{59-61}
symptom and recognized neurological or medical conditions, the symptom or deficit is not better explained by another medical or mental disorder and the symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.\textsuperscript{23} In case of FNP the type of symptom or deficit is muscle weakness.

1.3.2.1 DIAGNOSIS AND TREATMENT
Diagnosing FNP has been puzzling. Traditionally, the diagnosis was one of exclusion, the absence of any organic sign or known neurological disorder. More recently, this attitude towards functional neurological symptom disorder has changed and the diagnosis is now rather based upon positive clinical signs and evidence of internal inconsistency. In FNP, the most studied and useful test with good sensitivity and specificity for functional weakness is Hoover’s sign.\textsuperscript{24,25} This test is characterized by an involuntary extension of the weak limb when the contralateral limb is forced to flex against resistance. Other signs that are commonly found in functional weakness include collapsing weakness (the phenomenon in which a limb collapses from an instructed position with a light touch), co-contraction (the contraction of an antagonist muscle), arm-drop (an unusually slow and jerky descent of the arm from an outstretched position onto the lap) or the arms remaining inexplicably elevated, the so called ‘pseudo waxy flexibility’.\textsuperscript{26}

Making a (positive) diagnose of FNP is important because of the consequences for treatment and subsequently the prognosis. In a recommended three-stage approach for the treatment of functional motor disorder, this is part of the first stage. This stage exist of providing an unambiguous positive diagnosis, together with an explanation to help understand the patients that they have a genuine disorder, with the potential for reversibility.\textsuperscript{27} The second stage consists of further exploration of the diagnosis, treating comorbidity, and, in the context of a multidisciplinary team, experimenting with altered movements and behaviors. The third stage is required in some patients and consists of a combination of physical rehabilitation and psychological treatments. Hypnosis, sedation, and transcranial magnetic stimulation (TMS) may have a role in selected patients.

However, many patients do not respond to treatment and their prognosis appears unfavourable. Long duration of symptoms is the most distinct negative predictor, while early diagnosis and young age seem to predict better outcome.\textsuperscript{28} It may be that better understanding of FNP at the level of brain functioning may lead to more effective treatments by specifically targeting the involved brain networks.

1.3.2.2 PATHOPHYSIOLOGY OF FNP
The pathophysiology of FNP has been studied with neurophysiology, serum biomarkers, cognitive tasks, and especially with functional and anatomical neuroimaging. Reviews include both FNP\textsuperscript{29} or a more broader spectrum of functional motor disorders,\textsuperscript{30} in which negative symptoms (weakness) and positive symptoms (e.g. tremor or dystonia) are combined. Two
prominent hypotheses were put forward; the inhibition hypothesis and the conceptualization and initiation hypothesis. Both are discussed in more detail in Box 1.2.

The results from studies of pathophysiology are diverse and therefore complicated, also because different criteria were used to define FNP. Patients were either investigated as a separate patient group or as part of a larger functional motor disorders patient group. In addition, the studies are often limited to small sample sizes and differ in the applied methodology or task. However, the involved brain areas and hypotheses described in this section seem to point more to a disturbance in motor initiation and planning, and not so much to a deficit in the actual movement itself.

1.4 INVESTIGATIVE TECHNIQUES

Different types of functional neuroimaging are available nowadays to study functional brain networks. With functional magnetic resonance imaging (fMRI) brain activity is measured by detecting changes associated with blood flow. fMRI has an excellent spatial resolution, but a poor temporal resolution. Therefore, a recent development in functional neuroimaging has been to add techniques that have better temporal resolution and perform simultaneous recordings. Examples are simultaneous measurement of electrical brain activity with electroencephalography (EEG), stimulation of brain areas with transcranial magnetic stimulation (TMS) or measurement of electrical muscle activity with electromyography (EMG). For movement disorders in particular, the addition of EMG to measure muscle activity related to (abnormal) movement allows to directly link abnormal or involuntary movements to brain activity.

In the studies described in this thesis, the main technique to measure brain activity is fMRI. fMRI is widely used to study the operational organization of the human brain.\textsuperscript{31,32} It is an indirect measurement of brain activity and relies on the fact that cerebral blood flow and neuronal activation are coupled. When a brain area becomes more active, the blood flow to that region also increases. This blood is rich in oxyhemoglobin, and contains more oxygen than the brain tissue can use. This results in a local increase of the proportion of oxygenated versus deoxygenated blood, which is referred to as the hemodynamic response. This relative increase in oxygenated blood can be detected on the basis of its differential magnetic properties compared to deoxygenated blood and enables the detection of local increases in brain activity. The obtained signal is called the blood-oxygen-level dependent (BOLD) signal. Changes in the BOLD signal can be analyzed statistically, for instance by comparing brain activity between different task conditions or between different groups. To investigate ET, we added EMG to the fMRI measurement. EMG is a technique to record the electrical activity produced by skeletal muscles. In our study, we placed electrodes on the skin above the muscle, which is called surface EMG.\textsuperscript{33} EMG can be used to quantify the magnitude of the tremor and thereby express changes
BOX 1.2 PATHOPHYSIOLOGICAL HYPOTHESES ABOUT FNP

1. The Inhibition Hypothesis
The inhibition hypothesis is based on the first functional neuroimaging study of FNP in which intact activation of motor areas was shown when preparing to move the paralyzed limb, while attempts to move failed to activate the primary motor cortex and instead activated prefrontal areas. The hypothesis drawn from this result is that the execution of a movement is inhibited by prefrontal regions in FNP. In recent years, the brain areas involved in this inhibition were extended with other areas that were thought to inhibit the motor areas: putamen, lingual gyrus, insula, basal ganglia and thalamus. Studies that measured motor evoked potentials showed a larger variability in cortical excitability in patients with FNP than in healthy controls and a decreased corticospinal excitability when comparing an affected limb with an unaffected limb. These studies suggested that the changed excitability is also the consequence of an inhibitory process. However, an fMRI study using a motor inhibitory go/no-go task did not find abnormalities in inhibition. Thus, some but not all evidence is in favour of the inhibition hypothesis. Furthermore, most studies did not control for abnormal neural activity as a consequence of abnormal movement by the affected limb, which makes an etiological conclusion complicated.

2. The Conceptualization and Initiation Hypothesis
The concept of impaired movement conceptualization – the inability to actively move the affected limb – is an upcoming hypothesis that has mostly been investigated with neuroimaging. In a PET study, hypoactivity of the left dorsolateral prefrontal cortex (DLPFC) irrespective of the affected side was found in patients with FNP when asked to attempt movement. Because the left DLPFC is linked to the internal generation of action, the authors suggested that there is possible impairment of higher-order internal generation or conceptualization of action. Other studies with a similar design did not replicate these findings, but pointed towards other areas involved in initiation and cognitive planning of a movement. These areas included in particular parietal areas. Several studies have focused on separating motor execution from motor conceptualization and initiation with the use of motor imagery tasks and mental rotation tasks. They showed a slower reaction time in patients with FNP for explicit mental rotation and attributed this to impaired explicit intentional processes of movement. Neuroimaging showed decreased activity in motor regions but no differences in activity in motor inhibitory areas as well as increased activation in the ventromedial prefrontal cortex and superior temporal cortex. Functional connectivity of the left DLPFC and supplementary motor areas (SMA)/primary motor cortex (M1) was found to be increased in FNP when comparing the affected limb with the unaffected limb. In a study focusing on the motor intention phase of movement, decreased activity in the SMA and increased activity in limbic regions (amygdala, anterior insula) were found. These findings, although ambiguous, support the hypothesis of an impairment in motor conceptualization or intention in FNP, involving a DLPFC-SMA network.
in tremor severity over time. By recording EMG and fMRI simultaneously, we were able to link tremor activity directly to brain activity. Because brain abnormalities have been found in FNP, we also used fMRI to investigate rTMS as a possible treatment for FNP. The basic principle of transcranial magnetic stimulation (TMS) is that a magnetic field that changes over time induces an electric field and thereby an electric current in the nearby conducting brain tissue. By applying these magnetic pulses repeatedly at a certain rhythm or frequency, the effect of stimulation that is generated can last longer. This makes this technique interesting for therapeutic application.34

1.5 OUTLINE OF THE THESIS

The overall aim of the first part of this thesis was to increase the knowledge on the pathophysiology of ET. With this aim in mind we conducted fMRI studies in which we added EMG as an index of tremor severity. We also tried to improve upon previous approaches by including a well-defined group of patients with hereditary or sporadic ET, but not senile ET. By employing different tasks and analysis methods, we focused on different objectives for each of these studies. In the second part of this thesis, we examined the potential value of rTMS as a therapeutic tool in FNP. Previous studies reported that there may be a deficit in the brain function of patients with FNP when they attempt to move.

In Chapter 2, we measured tremor severity over time during a postural task that provoked an action tremor and correlated this with brain activity as measured with fMRI. With this approach we expected to improve upon the localization of cerebellar abnormalities found in earlier studies of ET.

In Chapter 3, we took the same approach and correlated fluctuations in tremor severity with brain activity as measured with fMRI in ET patients performing a pointing task that evoked intention tremor. As it is thought that there may be different phenotypes in ET, the objective of this study was to find out whether different brain areas are involved in intention tremor compared to action tremor in ET.

In Chapter 4, we performed effective and functional connectivity analyses in the same ET patients and during the same task as used in chapter two. With this method, we investigated whether there are disruptions in the cerebello-thalamo-cortical network in ET patients, a network that has often been found to be involved in ET.

In chapter 5 we evaluated a two week treatment of rTMS in patients with FNP of the hand with fMRI being one of the outcome measures. We did not only study the effect of rTMS on neural activity, but in addition, we studied changes in muscle strength due to the rTMS intervention in the affected hand, both objectively with dynamometry and subjectively with a questionnaire.

Finally, in chapter 6, a general discussion and future perspectives are provided.
REFERENCES


