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General Introduction
CHAPTER 1. GENERAL INTRODUCTION

1.1 Introduction

A 63 years old woman started to have a strange muscle jerking at the age of two. The jerks began in her legs, and during adolescence they worsened and spread to her body, neck and arms. In addition to the jerks, she also developed continued twitching of the muscles in her neck and right leg. Eating, writing and stressful situations worsened these movements and during her life, these symptoms did not recede. The use of alcohol alleviated the jerking and twitching. She was able to do the housekeeping independently, but would avoid eating in public and never drove a car. During clinical examination, brain imaging revealed no abnormalities. Genetic screening revealed a genetic mutation that runs in the family that was specific for these movements. Medications were largely ineffective.

1.1.1 Myoclonus-Dystonia

Myoclonus-Dystonia (M-D) is a movement disorder that is denoted with the names of its symptoms, i.e., myoclonus and dystonia. These symptoms are not specific for M-D, but occur (separately) in other movement disorders as well. In general, myoclonus consists of jerks caused by sudden muscular contractions, which can occur anywhere in the body. Its prevalence has been estimated to be 86 cases per million. In general, dystonia is characterized by more prolonged twitching movement of muscles, causing abnormal postures. Dystonia can occur in any part of the body and its name changes depending on the location; some examples are ‘writer’s cramp’ (dystonia in the fingers), ‘torticollis’ (dystonia in the neck) or ‘generalized’ (more severe dystonia in the legs and also in the arms, trunk or neck). The prevalence estimates range from 111 to 3000 per million. Myoclonus-dystonia (M-D) is a more rare movement disorder characterized by a combination of these myoclonic jerks and dystonic postures, but there are also cases in which myoclonus is isolated. In M-D, the myoclonus predominantly occurs in the arms, neck or trunk, and the dystonia is usually mild and occurs in the neck or hands. If an M-D patient has both myoclonus and dystonia, myoclonus weighs heavier and is usually designated as the ‘presenting symptom’. No prevalence estimates have been published for M-D, but families of various origins have been reported including from Europe, South America, North America and Asia. In M-D, a major culprit gene, the e-sarcoglycan gene (SGCE), is located in chromosome region 7q21. This is the 11th dystonia locus, hence M-D with the SGCE mutation is also commonly denoted as ‘DYT-11’. Mutations in this gene have been detected in about half of all diagnosed M-D patients. Other clinical aspects specific for M-D include a high frequency of psychiatric co-morbidity, especially anxiety and depression.

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1 The above is taken from a case report, and even though only a single patient is described, this case is representative for a larger group of people that have been diagnosed with Myoclonus-Dystonia (M-D). All contributing factors for this diagnosis are present in this case, since the diagnosis criteria for M-D are 1) an early age-of-onset of the symptoms (< 26 years), 2) myoclonus (jerking) predominating in the upper body, isolated or accompanied by dystonia (twitching), 3) family members that are also affected, 4) no other neurological disorders, and 5) normal brain scans.

2 Since symptoms start so early in life, it is likely that genetic factors are more important than environmental variables. Consequently, other genes could likely also underlie the symptoms in M-D. Variability in genetic background of M-D has been indeed been reported. In this thesis, the focus is on those patients with mutations in the SGCE gene.
1.2. PATHOPHYSIOLOGY OF M-D

1.1.2 Pathophysiology of M-D and multimodal methods

Dystonia and myoclonus occur in a range of movement disorders, of which M-D is only one specific type. These movement disorders are associated with disorders in the central nervous system; more specifically to abnormal functioning in the brain, in those regions that control for movements and posture\[211;29;189\]. In contrast to other dystonias, where abnormalities have been identified with transcranial magnetic stimulation (TMS) and magnetic resonance imaging (MRI)\[89;158;189\], research in M-D with these methods typically reveal no abnormalities\[103\]. Therefore, in contrast to other dystonias, the pathophysiology of M-D is largely unknown. One possible reason is that the current methods are limited in their sensitivity in detecting functional brain changes\[189\]. More specifically, most methods focus on cortical abnormalities, while sub-cortical abnormalities are harder to detect. The use of multiple imaging methods simultaneously (for example EEG with functional MRI,) is currently referred to as ‘Multimodal research methods’\[134;109;38;203\]. It is a new and promising field that has been used only sparsely in the field of movement disorders and as yet not in M-D.

1.1.3 Goals

The main goal of this thesis is to expand current pathophysiological understanding of M-D. To this end we developed and adapted several multimodal techniques. We will describe the current knowledge on the pathophysiology in dystonia and in myoclonus in general. We will follow up what is known in M-D and what remains currently unclear. Subsequently, the multimodal techniques used in this thesis are described. Finally, the focus and outline of this thesis are given.

1.2 Pathophysiology of M-D

The generation of dystonia has been associated with a dysfunction in deep brain nuclei known as the basal ganglia\[168\]. Direct and indirect pathways connect the different structures of the basal ganglia. A commonly used hypothesis in movement disorders is that a disturbance between these pathways leads to abnormal commands from the basal ganglia to the cortex. Both pathways, involved in initiation or terminations/inhibition of movement instructions respectively, consist of several interconnected nuclei, which can inhibit or excite one another through neuronal bursting patterns with different frequencies\[154;218\]. The direct pathway consists of the putamen, globus pallidus externus and the thalamus. The indirect pathway consists of the putamen, globus pallidus internus, subthalamic nucleus, the globus pallidus externus and (also) the thalamus. The putamen receives the cortical input to the basal ganglia, and the globus pallidus externus together with the thalamus generates the output back again to the cortex. Consequently, they function as regulators or pacemakers of cortical function. Their function is not only for the processing of motor commands, but for sensory processing, cognition and association as well\[130;150\]. Normal control is achieved as the direct pathway excites wanted movement (up-regulates the cortex) and the indirect pathway inhibits the unwanted ones (down-regulates the cortex)\[212;100\]. In dystonia, a dysfunction in this mechanism could be linked to loss of inhibition, defects in sensorimotor integration, and maladaptive neural plasticity\[158;29\],
however in M-D patients it is less well known how these dysfunctions could lead to the dystonia symptom.

The generation of myoclonus has been associated with a dysfunction in either cortical or sub-cortical brain regions\(^{[161;40;187;174]}\). In some forms of cortical myoclonus, the cerebellum also seems to play a role\(^{[197;209]}\), however in M-D it is currently not exactly known which regions of the brain are involved. Loss of inhibition, defects in sensorimotor integration and maladaptive neural plasticity likely also play a role in the generation of myoclonus in M-D patients, but it is not known to what extent.

In M-D, there are findings that support a role for the basal ganglia. In patients which have been implanted with ‘deep brain stimulation’ electrodes, during surgery, recordings from the globus pallidus have found an unusual type of oscillatory activation\(^{[65]}\). This oscillation has also been found to be present as a ‘common drive’ that innervates muscles, when signals from two or more muscles are investigated using electromyography (EMG) and a frequency analysis technique called EMG-EMG coherence is used\(^{[66]}\). Deep brain stimulation of the thalamus or globus pallidus has been found to be beneficial for the M-D symptoms\(^{[118;85;107;99]}\). However, as the thalamus and globus pallidus are very ‘general’ structures, it is still unclear whether or not these are the primary structures causing the movement disorder, or some other structure might even be more implicated. The localization of the primary defects in the brain in M-D are not investigated fully yet.

In this thesis, we will examine four hypothesis in M-D. The first three deal with the pathophysiology of M-D; loss of inhibition, defects in sensorimotor integration and maladaptive neural plasticity. The fourth hypothesis deals with the location of brain regions involved in myoclonus; i.e. that it is sub-cortical in M-D.

### 1.2.1 Loss of inhibition

The first hypothesis deals with a loss of inhibition in motor control, to which the excess movements in (general) dystonia are attributed and which is also referred to as ‘disinhibition’\(^{[1;210]}\). The main idea is that the nervous system is composed of excitatory and inhibitory circuits that are in balance with each other. When making a movement, the motor command signal is both an excitatory command for the desired movement and an inhibitory one for the undesired ones. This inhibitory command is called surround inhibition\(^{[89]}\). Usually TMS protocols, combined with EEG and EMG, are used to check for cortical signs of loss of inhibition\(^{[88]}\).

Using TMS and EEG, many findings have been reported that support a loss of inhibition at a cortical level in various forms of dystonia\(^{[86]}\). In M-D, however, no conclusive findings have been found with standard TMS and EEG methods\(^{[205]}\). Only one study reported a subtle change in cortical inhibition in M-D patients\(^{[125]}\), but this has not been reproduced in other studies.

More recently, two imaging studies pointing to a sub-cortical marker for disinhibition have been performed, with conflicting results. In the first study, using single positron electron computed tomography (SPECT), a reduced level of dopamine receptors has been found in the putamen\(^{[18]}\), which could indicate increased levels of dopamine and consequently hyperactivity in the basal ganglia. In the second study, using fMRI, blood oxygenation level dependent (BOLD) hyperactivity has been found in cortical, but not sub-cortical areas\(^{[20]}\). In conclusion, disinhibition in M-D could function quite differently from other types of dystonia, and therefore the hypothesized
disinhibition in M-D needs to be clarified.

### 1.2.2 Defects in sensorimotor integration

The second hypothesis pertains to a dysfunctioning sensorimotor integration \[^{[1;28]}\]. Sensory information from proprioceptive or cutaneous nerves is important for the control of movements. It provides feedback of the environment needed to adjust postures and movements. Several experiments exist that probe the ‘sensorimotor integration’; in most of these experiments, the influence of peripheral sensory inputs (electrical, proprioceptive or cutaneous) on an aspect of the motor system, such as a motor response, is assessed (using EMG or EEG, or TMS protocols) \[^{[88]}\]. Other experiments try to assess sensory discrimination ability in dystonia patients, i.e. if dystonia patients notice the difference in time or location between two stimuli, measured by forced choice \[^{[30]}\].

In dystonia, there are several findings that point to a defect in sensorimotor integration in the brain. Some examples are the sensory trick (also called the ‘geste antagoniste’), in which the dystonia can be ‘unlocked’ by a touch of the hand to the chin \[^{[52]}\]. This has led to the suggestion that dystonia can be ‘stimulus sensitive’. Another example of this is that vibrations of the arm have been reported to induce dystonia in patients with focal hand dystonia \[^{[102]}\]. Finally, there are many findings which indicate that electrical stimuli to the arms interfere with motor responses in dystonia, as measured with TMS \[^{[163]}\], EMG or EEG protocols \[^{[91;132]}\]. In M-D, the presence of the sensory trick is generally not reported in literature. Furthermore, the abnormal movements in M-D do not seem to be stimulus-sensitive in the majority of cases \[^{[173;103]}\], but five cases of stimulus-sensitivity have been reported to auditory or cutaneous stimuli \[^{[117;125]}\]. Studies that assess sensorimotor integration using cortical long-latency reflexes (C-reflex) showed no abnormalities \[^{[117;173;125]}\].

The relative lack of conclusive findings in M-D with respect to sensorimotor integration warrants further investigation. Most findings in (general) dystonia point to a cortical involvement in the defect in sensorimotor integration, i.e. the absence of findings in M-D point to sub-cortical process. With normal electrophysiological protocols not being able to probe sub-cortical dysfunction, one possible marker to investigate a sensory component to the (dys)function of the motor system is the ‘common drive’ mentioned at the start of chapter 2. This has been found to be associated with activity in the basal ganglia in M-D \[^{[65]}\]. As the basal ganglia also process sensory information, proprioceptive stimuli could possibly affect this common motor drive.

### 1.2.3 Maladaptive neural plasticity

The third pathophysiological hypothesis is maladaptive neural plasticity. Normally, neural connections are formed (potentiation) and broken down (depotentiation) in an ongoing ‘naturally-driven’ (homeostatic) regulation to prevent the neural connections from getting out of control. By keeping stronger connections and removing weaker ones, motor skills can be learned and maintained \[^{[57]}\]. Maladaptive neural plasticity means that this down-regulation is defective, leading to a disruption in ‘synaptic homeostasis’. Neural connections more easily ‘pile up’ \[^{[158]}\], which can lead to disorders in the motor system. If this is combined with an excessive use of the motor system (perhaps due to an occupation that requires prolonged use of fine motor...
skills), the usage of motor system and the reduced down-regulation work in tandem to cause a disorder. A movement disorder occurs when the system reaches a point where neuronal motor engrams for different movements start to overlap each other, leading to maladaptive regulation of the motor system, inducing dystonia\textsuperscript{[157;159]}. Both abnormal synaptic homeostasis and abnormal use of the motor system play a role in (general) dystonia; as genetic and environmental factors, respectively. Experiments that probe maladaptive neural plasticity are generally TMS experiments that test for learning effects or specificity of peripheral stimuli. In addition, fMRI is used to probe for increased BOLD activations, or BOLD activation in regions of the brain which are not normally activated. Finally, structural imaging techniques, such as voxel-based morphometry (VBM) to probe for enlarged brain volumes in brain grey or white matter and diffusion tensor imaging (DTI) to probe for microstructural changes in white matter are also commonly used.

In several types of dystonia, maladaptive neural plasticity is supported by excessive repetitive movement patterns (such as in musicians or writers) can result in a focal dystonia\textsuperscript{[3;175]}, a finding which has been reproduced in monkeys as well\textsuperscript{[34]}. Using TMS protocols, maladaptive neural plasticity has also been demonstrated as a loss of sensitivity to (prolonged) electrical stimuli between two locations of the arm\textsuperscript{[157;214]}. Furthermore, impaired ability to condition motor responses (a marker for impaired plasticity) to auditory stimuli has been demonstrated in focal dystonia (in the hand and the neck)\textsuperscript{[195]}. In addition, there are several imaging findings that demonstrate a lack of organization in the activation in cortical areas (PET, fMRI)\textsuperscript{[35]}, changes in the size of deep brain nuclei in dystonia\textsuperscript{[22]} or strength of the connections between brain areas\textsuperscript{[8]}. Only a few functional imaging studies have been performed that show cortical hyperexcitability\textsuperscript{[19;142]}. Structural imaging studies have not been performed yet that could provide information on a structural basis for the functional deficits in M-D.

Neural plasticity has not yet been assessed in M-D as well in other types of dystonia. Structural imaging studies that probe for altered brain volumes or changes in the connections between brain regions would be beneficial in further understanding maladaptive neural plasticity. In this thesis, we will investigate whether in M-D these changes occur in the brain.

### 1.2.4 Myoclonus

The fourth hypothesis is the sub-cortical involvement of myoclonus. In general, myoclonus can be roughly subdivided into ‘cortical’ and ‘sub-cortical’ myoclonus \textsuperscript{[161;40;187;174]}. In some forms of cortical myoclonus, the cerebellum also seems to play a role\textsuperscript{[197;209]}. Myoclonus is often hypothesized to be caused by hyperexcitability of affected brain regions. Whether or not myoclonus is cortical is usually assessed using EEG, in particular by ‘jerk-locked’ back-averaging\textsuperscript{3}. Additional techniques include the somatosensory-evoked potentials to check for cortical hyperexcitability, and long-loop C-reflexes\textsuperscript{4}, to see if myoclonus can be evoked through electrical stimuli\textsuperscript{[191]}. In cortical myoclonus, EMG muscle recordings show myoclonic bursts which are

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\textsuperscript{3}Jerk-locked back-averaging is a technique whereby the EEG signal is averaged in a time window around myoclonus events, that are detected with surface EMG. Myoclonus can be seen as a deflection in this averaged EEG signal\textsuperscript{[117;186]}.

\textsuperscript{4}If an electrical stimulus to one arm induces a reflex movement in the other arm, the cortex is ‘hyperexcitable’\textsuperscript{[40;187]}.
generally short (< 100 ms). EEG “jerk-locked back-averaging” can detect a cortical transient prior about 10 to 40 ms before the myoclonus. Somatosensory evoked potentials show an enlarged EEG component, and there is a presence of a long-loop C-reflex \[40;187\]. In sub-cortical myoclonus, EMG muscle recordings show longer (> 100 ms) myoclonic bursts. Importantly, jerk-locked back-averaging cannot detect cortical EEG transients that precede myoclonus \[186;40\]. There are no long-loop C-reflexes, but myoclonus can sometimes be elicited through acoustic stimuli \[31;32\], suggestive for a stimulus-sensitivity which is more subtle and harder to detect. In M-D, the typical reported mean EMG burst duration is about 100 ms, with a range between 25 and 250 \[125;173\] but greater ranges of 30-750 ms \[117;135\] have also been reported. Jerk-locked back-averaging does not reveal any transient EEG waves preceding the myoclonus in M-D, and somatosensory evoked potentials and long-loop C reflexes are normal \[103;173\]. Myoclonus has been reported to be sensitive to acoustic stimuli or touch in a few (4) M-D patients \[125;117\], and M-D patients also have been reported to have a heightened blink reflex recovery curve \[125\], which are clinically typical signs of a brainstem involvement. In addition, impaired adaptation of eye movements in a conditioning experiment has also been found in M-D, which point to cerebellar involvement, as well \[98\].

In M-D, with the absence of many of the ‘cortical’ findings, myoclonus is considered to be sub-cortical. However, sub-cortical is still too unspecific. In one review, it is further sub-divided into 3 levels (pure cortical, cortical-subcortical and subcortical-supraspinal \[40\]). The exact locations in the brain that induce myoclonus need to be further elucidated, which we plan to do using combined of electromyography with functional magnetic resonance imaging (EMG-fMRI).

### 1.3 Multimodal methods

Multi-modal approaches, by allowing data from one modality to be used in the analysis of the (simultaneously acquired) data from other modalities, enable to conduct experiments that were previously not possible. Thereby, they can be used to probe pathophysiology of M-D (and other dystonias) in new ways. However, they require specialized hardware and software as well as purpose-tailored experimental designs and analyses \[47;109\]. In this work, we used three combined techniques; combined electromyography (EMG) and electroencephalography (EEG) with wrist perturbations, combined diffusion tensor imaging (DTI) with voxel-based morphometry (VBM) and combined EMG with functional magnetic resonance imaging (fMRI).

#### 1.3.1 Combined wrist perturbations with EMG/EEG

The system analysis technique is a new methodology to quantify reflexes \[203;180;181\]. Reflexes are generally indicative for function and malfunction of the peripheral (sensory - motor) nervous system. This system is affected by ‘supra-spinal’ (i.e., cortical) input as well, which can modulate the size and threshold of muscle reflexes. By measuring reflexes and using system analysis techniques, conclusions can be drawn with respect to (abnormalities in) peripheral reflexes, a marker for the spinal sensorimotor system. Conclusions on their (cortical) modulation are more difficult to draw \[203\]. In system analysis experiments, the instruction generally is to ‘minimize displacements’
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of the arm while disturbances are applied by a mechanical apparatus. Both the applied disturbances (the input; force and position) and the mechanical behavior of the arm (the output; position, force and EMG) are monitored. Subsequently, input and output are analyzed to determine to what extent reflexes and intrinsic properties of the arm (mass, stiffness, viscosity) play a role in generating the output.

Normally, the system analysis technique uses only position, force and EMG as output parameters and therefore can only analyze reflexes which occur at the spinal level. It cannot probe into the central nervous system (CNS) and is therefore limited in its ability to answer questions about sensorimotor integration. However, M-D patients have an inter-muscular drive that has been associated with basal ganglia activity (see second paragraph of 2), which could be used to probe sensorimotor integration in the brain. If proprioceptive input could manipulate the intermuscular drive (see 1.2.2), an experiment could be constructed that could assess central sensorimotor integration in M-D.

1.3.2 Combined VBM with DTI

Structural imaging techniques such as VBM and DTI are well suited to answer questions about maladaptive neural plasticity in the grey and white matter of the brain. Normally, separate templates images are used for VBM and for DTI, causing the normalization to a standardized brain to be slightly different between the two modalities. This needs to be addressed before the two modalities are combined. The combined methods may allow a better insight into of brain abnormalities than either one of the methods, as both macrostructural changes (i.e., volumetric increases or decreases in WM) and microstructural changes (i.e., fractional anisotropy (FA) and mean diffusion (MeanD)) can be assessed simultaneously. Combined VBM-DTI could be used to assess neural plasticity in brain white matter in M-D, and provide insights in addition to those from conventional VBM studies.

1.3.3 Combined EMG with fMRI

Combined EMG with fMRI is a promising technique that, unlike combined EEG-fMRI, is currently not extensively used in the field of neuroimaging. In this technique, information regarding the pathological movements is taken from the EMG and used in the fMRI imaging analysis to detect areas in which the Blood Oxygenation Level Dependent (BOLD) signal is associated directly with those movements. In this way, it combines the spatial resolution from fMRI with the temporal resolution from the EMG that is three orders of magnitude faster (fMRI operates on a $\sim 1$ sec timescale, while EMG operates on a $\sim 1$ msec timescale). Combined EMG-fMRI allows, in a motor or a cognitive task, to distinguish BOLD activation due to task performance from BOLD activation due to involuntary movements performed during execution of that task. Furthermore, it allows monitoring of the involuntary movements and locating brain regions responsible for those movements.\cite{208}

For movement disorders the addition of the EMG is especially crucial, since the EMG offers far better monitoring of movements during fMRI scanning than (the usual) visual inspection alone. Unlike in normal motor fMRI experiments where subjects can be ‘trusted’ to move as instructed, movements in M-D (and other dystonias) are involuntary and cannot be predicted or instructed.
There are two main problems with simultaneous EMG-fMRI acquisition, however. Firstly, MRI ‘scanner-artifacts’ are present in the EMG signal (caused by changes in the magnetic field that are generated by the MRI scanner in order to measure the MRI signal) and are that large (about 50-100 times larger than the EMG signal of interest), that without removal they would obstruct EMG analysis. Normally, these MRI artifacts are repetitive artifacts with a common shape, enabling their removal with template subtraction algorithms. There are several MRI artifact subtraction algorithms available, and EEG artifact removal is still a separate research field in which new developments are ongoing. The main problem with current MRI removal algorithms is that they are not designed for use with subjects that have a movement disorder; movements in the MRI scanner also change the shape of the MRI artifacts and partly invalidate the assumptions underlying template removal. Secondly, movements inside the MRI scanner have also move wires in the (strong) 3T magnetic field; this introduces additional ‘movement artifacts’ in the EMG signal that need to be removed. Therefore, reducing the MRI artifacts and movement artifacts require special attention. We needed to construct a new and better MRI artifact removal algorithm, to produce an EMG that is optimally free of artifacts so that myoclonus can be detected.

There have been studies that used EMG-fMRI to investigate movement disorders, but subcortical myoclonus is a specific type of movement disorder not investigated before and needs another type of analysis. To our knowledge, EMG-fMRI has not been used in subcortical myoclonus before and it would be ideally suited to investigate the localization of the sub-cortical generator for subcortical myoclonus in M-D patients. Combining the EEG-fMRI work on epilepsy, as well as a more optimal signal obtained from the EMG, the design and methods could be tailored to analyze myoclonus in M-D with EMG-fMRI.

### 1.4 Focus and outline of the present thesis

The main objective is to further elucidate the pathophysiology of Myoclonus-Dystonia in a homogeneous sample of DYT-11 (SGCE) positive patients. In summary, loss of inhibition is assessed in Chapter 2 (by using a normal fMRI study with an inhibition task), defects in sensorimotor integration in Chapter 3 (by using wrist perturbations combined with EMG/EEG), maladaptive neural plasticity in Chapters 4 and 5 (by using a conventional VBM study, as well as combined VBM with DTI), and myoclonus in Chapter 7 (by using combined EMG-fMRI). Chapter 6 entails the algorithms to remove the MRI artifact from the EMG. Chapter 2 reports an fMRI experiment to examine inhibition in a group of M-D patients and healthy controls. Subjects were instructed to press a button (respond) on very frequent ‘Go’ cues in order to create a strong inclination to respond, while infrequent ‘Stop’ cues were presented in which they had to inhibit their response. We examined which brain regions were associated with this inhibition, both in M-D patients and controls. Chapter 3 describes an experiment in which sensorimotor integration was examined. We applied several types of proprioceptive stimuli to the hands of M-D patients within different frequency bands (around 3-7 Hz, the frequency of the intermuscular drive). We examined if the proprioceptive stimuli could change the dystonic common drive in frequency or power. In addition, we also analyzed the contents of the EEG signal to see if the perturbations were processed at cortical level. In Chapter 4, neural plasticity in grey matter
has been assessed using structural imaging, and voxel-based morphometry. We investigated whether enlarged grey matter volumes could be found in M-D patients, relative to healthy control subjects. Furthermore, we investigated whether there are grey matter brain regions in M-D patients whose volume correlated with clinical scales for dystonia and myoclonus. In Chapter 5, neural plasticity in white matter has been assessed using combined DTI-VBM. Using this combined technique, microstructural and macrostructural white-matter differences were assessed. M-D patients were compared to healthy controls. In Chapter 6, our goal was to develop and implement a new artifact correction for the purpose of removing the MRI artifacts from the EMG signal during combined EMG-fMRI. Movements inside the scanner introduce movement artifacts and changes in the MRI artifacts. These artifacts are assessed and the correction procedure is subsequently designed to minimize its impact on the quality of the EMG signal. Chapter 7 reports the neural correlates of myoclonus in M-D patients. Twelve DYT-11 positive M-D patients were scanned with combined EMG-fMRI while performing a simple motor task. The methodology described in Chapter 6 was used to remove the MRI artifact from the EMG signal. In addition to locating BOLD activation in brain regions associated with performing the motor task (block design), BOLD activation in brain regions associated with myoclonus was detected; to this end, the EMG was used to extract timing information about the myoclonus which was subsequently used in the imaging analysis (event-related design). Chapter 8 contains the general discussion, which summarizes the findings, discusses how they fit into the current theories relating to hyperkinetic movement disorders and provides suggestions for future research.