Chapter 1

General introduction and aims of this thesis
Structural and functional neuroimaging in Myoclonus-Dystonia

Background

Myoclonus-Dystonia (M-D) is a rare hyperkinetic movement disorder, characterized by dystonic postures and myoclonic jerks.\textsuperscript{1,2} It usually becomes apparent in the first two decades of life and stabilizes after a few years of progression of symptoms. The main symptom is myoclonus of the upper part of the body. The dystonia can be apparent anywhere in the body, though spasmodic torticollis appears to be most prevalent. A striking feature is the almost complete resolution of symptoms after alcohol ingestion. Several psychiatric conditions are considered part of the M-D phenotype, such as anxiety, obsessive compulsive disorder and depression.\textsuperscript{3} M-D is considered a dystonia plus syndrome, designated DYT-11.\textsuperscript{2}

No etiological treatment is yet available for M-D. Clonazepam might be effective for myoclonus, while injections with botulinum toxin (BTX) have been shown to be a very effective treatment for (cervical) dystonia in a large number of clinical trials.\textsuperscript{4} Deep brain stimulation (DBS) of the globus pallidus internus (GPi) or the thalamic nucleus ventralis intermedius (VIM) is currently the most promising technique for treatment of patients with medically refractory dystonia.\textsuperscript{5,6}

Genetics

In about half of all M-D patients, the disease is autosomal dominantly inherited and caused by single mutations in the epsilon-sarcoglycan gene (\textit{SGCE}) on chromosome 7q21 (DYT-11).\textsuperscript{1,7} In a French study, 37\% of mutations consisted of deletions, 20\% of nonsense mutations, 20\% of splice site mutations, 14\% of missense mutations, and 9\% of insertions.\textsuperscript{8} The function of this protein remains incompletely understood. \textit{SGCE} is a member of a gene family including alpha, beta, gamma and delta sarcoglycans. Mutations in these other sarcoglycans can result in various types of limb-girdle muscular dystrophies. A new M-D locus has been mapped to chromosome 18p11 in one family.\textsuperscript{9} Furthermore, single mutations in the dopamine D2 receptor (\textit{DRD2}) and DYT-1 genes have been described in combination with \textit{SGCE} mutations in two M-D families.\textsuperscript{10-12} In many patients with the M-D phenotype DYT-11 mutations are lacking, suggesting the involvement of other genes or environmental factors.\textsuperscript{13}

Penetration of M-D is highly dependent on the parental origin of the disease allele, resulting from maternal imprinting, i.e. the paternal allele is always the one
expressed, while the maternal allele is silenced. The consequence is that only mutations inherited from the father will cause the clinical picture of M-D. In the literature however, some patients exhibit a mild phenotype while inheriting the mutation from their mothers.

**Pathophysiology**

M-D patients with an *SGCE* gene mutation constitute a homogeneous group of patients with clinical symptoms of both myoclonus and dystonia and can therefore be used as a human model to study the pathophysiology of dystonia and myoclonus.

Different theories exist on the pathophysiology of dystonia. The first functional theory is based on neuronal models of dystonia suggesting excessive motor cortex excitation due to hyperactivity of the direct putamino-pallidal pathway with reduced inhibitory output of the internal segment of the globus pallidus (GPI), and subsequently increased thalamic input to the (pre-) motor cortex. Strong support for this theory comes from an *SGCE* knock-out mouse model in which the mice not only showed phenotypical characteristics of M-D, but on post-mortem examination also showed higher striatal concentrations of dopamine and its metabolites.19

The second theory proposes abnormalities in sensorimotor integration and is supported by the ‘geste antagonistique’. Regarding the theory of defective sensorimotor integration, the strongest support for this theory comes from a study using corticography in monkeys, showing altered representation of sensorimotor areas in animals with repetitive movement-induced focal hand dystonia.22

The third theory consists of a relatively new idea: that the involuntary movements could lead to (micro)-anatomic changes through cortical plasticity. On the other hand, it has been shown that excess voluntary movement can lead to structural changes in gray and white matter volumes. It is therefore unclear whether found changes are the cause or the effect of a movement disorder. Over the last few years there is growing evidence that the cerebellum plays a role in dystonia as well.25

None of these theories are conclusive as yet.

Little is known about the pathophysiology of myoclonus in M-D. The myoclonus in M-D is thought to be of subcortical origin, because of the lack of stimulus sensitivity and the absence of a giant somatosensory evoked potential on neurophysiological testing.
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Structural and functional neuroimaging

Imaging techniques can be divided into structural and functional imaging techniques. Structural techniques are applied to investigate the structural integrity of the studied tissue. Newer, functional imaging techniques, add a dimension by investigating a measure of its function, for instance regional blood flow, glucose metabolism or a neurotransmitter receptor. In M-D, no structural abnormalities can be observed on computed tomography (CT) or magnetic resonance imaging (MRI) scans with the naked eye. More sensitive structural imaging techniques that have been evolving over the past few years are voxel based morphometry (VBM) and diffusion tensor imaging (DTI).

VBM allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping (SPM). VBM registers every three-dimensional T1-weighted MRI image to a template to correct for most of the large differences in brain anatomy among the different subjects after which the image volume is compared across brains at voxel-level. With this technique, it is possible to detect differences in gray and white matter volume that with normal visual assessment would remain undetected. This technique has two important advantages over “classic” morphometry: VBM is more objective and takes less time compared to manually drawing preset regions of interest.

Diffusion tensor imaging (DTI) is a technique that enables the measurement of restricted diffusion of water in tissue in order to describe axonal organization in nervous system tissues. Using DTI, each voxel contains information on two parameters: First, the mean diffusion rate usually designated MD. To avoid confusion with the studied disease it will be abbreviated as MeanD in this thesis. The second parameter that can be used describes the direction of diffusion, i.e. the number of neurons aligned in the same direction, this is known as fractional anisotropy (FA). Because alignment of fibers in the same direction is mainly found in white matter, the main usefulness of the technique is to detect abnormalities in white matter. Because DTI seems to be more sensitive in detecting subtle white matter abnormalities than VBM, abnormalities can be referred to as micro-structural, as opposed to the macro-structural abnormalities detected with VBM.

In functional neuroimaging, the most popular techniques rely on regional blood flow, glucose metabolism or transporter/receptor ligands. Functional MRI assumes that activated brain regions have a larger blood flow and relies on the principle of a difference in magnetic properties of oxygenated hemoglobin vs. deoxygenated
hemoglobin. This difference can be translated into a blood oxygenated level dependent (BOLD) signal. Usually, in a first level analysis the images during resting state are compared to an active state –e.g. a motor task- for each individual subject. The second level analysis then compares these substracted images in groups of subjects –e.g. patients vs. control subjects-. In this way, hyperresponsive and hyporesponsive brain areas can be detected.

Single photon emission computed tomography (SPECT) is a molecular imaging technique using gamma rays emitted from a radionuclide and detected by a gamma camera. A radiopharmaceutical consisting of molecules of two different attached compounds is injected into the bloodstream of a subject. The first compound is known as the radionuclide; this is the gamma ray-emitting compound that allows detection using the gamma-camera. The second compound is the ligand, which has specific affinity for transporters or receptors of neurotransmitters. Because of this affinity, the ligand binds to a specific place in the brain, for instance the striatal dopamine D2 receptor if [123-I]iodobenzamide (IBZM) is used, and its concentration is measurable by detecting the gamma rays emitted by the attached radionuclide.

Structural and functional neuroimaging in M-D patients is very limited. One fMRI study describes a 5-year old girl compared to a single control subject, and shows changes in sub-cortical structures, specifically in the thalamus and dentate nucleus.

Significantly more literature is available on structural and functional neuroimaging in other types of inherited and idiopathic dystonias. Among the inherited dystonias, which are genetically homogeneous groups of dystonia patients, DYT-1 and DYT-6 mutation carriers -exhibiting a clinical picture of early onset idiopathic torsion dystonia- are studied most widely. Functional imaging studies using [18-F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) found increased glucose metabolism in the putamen, globus pallidus, cerebellum and supplementary motor area (SMA) of DYT-1 mutation carriers. All clinically affected DYT-1 and DYT-6 mutation carriers showed metabolic increases in the pre-SMA and parietal association regions. These results support the hypothesis of altered sensorimotor integration in inherited dystonia. [11-C]Raclopride PET studies found significant reductions in striatal dopamine D2 receptor availability in asymptomatic DYT-1 mutation carriers as well as symptomatic DYT-1 and DYT-6 mutation carriers, implying increased endogeneous striatal dopamine regardless of clinical penetrance. In a structural imaging study using DTI, reduced
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cerebello-thalamo-cortical connectivity in DYT-1 and DYT-6 dystonia gene carriers was found in the dorsal brainstem and in the white matter surrounding the deep cerebellar nuclei, supporting altered structural connectivity due to neuronal plasticity.\textsuperscript{39}

In addition to the imaging studies in the hereditary homogeneous forms of dystonia, a significant amount of studies is available on non-inherited focal dystonias such as cervical dystonia, focal hand dystonia and blepharospasm.\textsuperscript{33,40-52} These studies seem to yield conflicting results, possibly reflecting different pathophysiological mechanisms, but all agree on abnormalities in the sensorimotor system.

Aims and outline of this thesis

The aims of this thesis were to use existing and novel structural and functional neuroimaging techniques in a monogenic DYT-11 mutation positive carrier group to investigate existing theories on the pathophysiology and maternal imprinting mode of inheritance of (Myoclonus)-Dystonia and thereby contributing to our understanding of dystonia in general and M-D specifically. As mentioned earlier, different theories exist regarding the pathophysiology of dystonia. First, to test the theory of the hyperactive putamino-pallidal pathway, ultimately resulting in excessive motor cortex excitation we used [123-I]IBZM SPECT scanning to examine dopamine metabolism in vivo in patients. To further test this hypothesis, patients having undergone deep brain stimulation of the globus pallidus were re-scanned after surgery.

The second theory of defective sensorimotor integration in M-D was tested by using functional MRI to compare activation of sensorimotor areas in patients and controls using a simple motor task.

Thirdly, the neuronal plasticity theory: to investigate whether the involuntary excess movement in M-D leads to altered gray and white matter volumes two structural imaging techniques were used: voxel based morphometry and diffusion tensor imaging.

Regarding the maternal imprinting mechanism of inheritance in M-D, we used fMRI to investigate whether this encompasses a strictly dichotomous mode of inheritance or rather a biased gene expression based on parent of origin.
General introduction

Outline of this thesis

**Chapter 2** describes a functional MRI study in a large group of clinically affected DYT-11 mutation carriers. In **chapter 3** a similar study is performed on subjects inheriting the same mutation from their mother with only minor or no symptoms at all. **Chapter 4** discusses a molecular imaging study investigating the dopamine 2 receptor binding capacity in M-D patients, investigating the hypothesis of a hyperactive putamen in dystonia. In **chapter 5**, the same technique was applied to patients having undergone deep brain stimulation (DBS) of the globus pallidus internus (GPI), investigating whether this intervention changes clinical symptoms and/or striatal dopaminergic metabolism. **Chapter 6** concerns a structural MRI study using voxel-based morphometry investigating whether the actual structure of the gray matter is different in M-D patients compared to control subjects, either as a cause or as the result of their ailment. In **chapter 7**, this technique and diffusion tensor imaging (DTI) are used on white matter volume of M-D patients to detect macrostructural and microstructural changes respectively. **Chapter 8** describes the clinical similarities, and therefore diagnostic challenges to clinically distinguish between M-D and SCA 14, illustrated by 4 patients. The results of the different studies are discussed in **chapter 9** and suggestions for future research are proposed.
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References


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