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Chapter 7

White matter abnormalities in mutation positive Myoclonus-Dystonia: a VBM and DTI study

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Submitted

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Abstract

Background: Myoclonus-Dystonia is an autosomal dominantly inherited movement disorder clinically characterized by myoclonic jerks and dystonic movements of the upper body. Functional imaging and structural gray matter imaging studies in M-D suggest defective sensorimotor integration and an association between putaminal volume and severity of dystonia, possibly due to neuronal plasticity. As we expect changes in the connections between the cortical and subcortical regions we performed a combination of white matter voxel based morphometry (wVBM) and diffusion tensor imaging (DTI) to detect respectively macro- and microstructural white matter changes.

Objective: To study white matter volume and integrity changes in a genetically defined homogeneous group of M-D patients.

Patients: Sixteen clinically affected DYT-11 mutation carriers and 18 control subjects were studied.

Interventions: wVBM and DTI were performed using a 3.0 Tesla MRI scanner.

Results: In DYT-11 mutation carriers, an increase in white matter volume and FA and a decreased mean diffusivity was found in the sub-thalamic area of the brainstem, including the red nucleus. Furthermore, decreased mean diffusivity was found in the subgyral cortical sensorimotor areas.

Conclusions: The white matter changes found in the sub-thalamic area of the brainstem, connecting the cerebellum with the thalamus, are compatible with the hypothesis that abnormal function in M-D involves a network that includes the cerebellum, brainstem and basal ganglia. Whether these changes are causative or an effect of M-D requires further study.
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Background

Myoclonus-Dystonia is a movement disorder clinically characterized by myoclonic jerks and dystonic postures or movements of the upper body, often combined with psychiatric symptoms such as depression or anxiety.\(^1\) It usually becomes clinically manifest within the first two decades and is often responsive to alcohol. M-D is autosomal dominantly inherited and is caused by mutations in the epsilon-sarcoglycan gene (SGCE) on chromosome 7q21 (DYT-11) in about half of all patients.\(^2,3\) Penetrance of M-D is highly dependent on the parental origin of the disease allele, resulting from maternal imprinting.\(^4\) In many patients with the M-D phenotype DYT-11 mutations are lacking, suggesting the involvement of other genes or environmental factors.\(^5\)

M-D is considered a dystonia-plus syndrome and the pathophysiology of M-D is still not well understood. In dystonia the basal ganglia are hypothesized to play a major role\(^6,7\) and neuronal models of dystonia have postulated hyperactivity of the direct putamino-pallidal pathway with reduced inhibitory output of the internal segment of the globus pallidus (Gpi). This subsequently leads to increased thalamic input to the (pre) motor cortex, and results in excessive motor cortex excitation.\(^6\) On the other hand, the sensory system is also likely to play a role, reflected by the “geste antagoniste”.\(^8\) One can further assume that myoclonus in M-D is of subcortical origin, because of the lack of stimulus-sensitivity and the absence of giant somato-sensory evoked potentials.\(^3\) A functional MRI study in M-D patients during a simple motor task found functional changes in both sensory as motor areas, suggesting disorganized sensorimotor integration.\(^9\) Structural changes on the other hand, have also been reported, possibly due to neuronal plasticity.

Cortical plasticity can be examined by investigating relative volumes of grey matter with voxel-based morphometry (VBM), an imaging technique that can quantify volumes of brain structures.\(^10\) VBM studies have revealed that cortical plasticity in the grey matter of the brain appears to play a major role in hyperkinetic movement disorders.\(^11,12\) In a group of M-D patients a voxel based gray matter morphometry study showed putaminal gray matter abnormalities, correlated with severity of dystonia.\(^13\) In other types of dystonia VBM gray matter studies have been published, producing conflicting results but agreeing on abnormalities in sensorimotor structures.\(^14-20\)
Changes in the brain due to plasticity not only affect grey matter, but can affect white matter connecting grey matter areas of the brain as well. Changes in white matter due to plasticity can be measured with VBM (wVBM), in which case the macrostructural white matter volumes are examined. In addition, white matter can be examined with diffusion tensor imaging (DTI). DTI is a technique specifically used for investigating microstructural properties of white matter, such as structure and integrity. DTI allows for quantification of diffusion of water molecules, expressed as mean diffusivity (abbreviated as MeanD to avoid confusion with the affliction investigated) for water diffusion magnitude and as fractional anisotropy (FA) for the directionality of water diffusion at the axonal level.\(^{21}\) When –due to plasticity—more connections are made between grey matter regions, an increased number of axons and myelin are generated and would induce an increased white matter volume that is detected with wVBM, as well as lower mean diffusion (MeanD) as water is more contained. If the increased number of axons would all be in the same direction, higher FA is expected\(^{22}\), but axonal growth could also potentially also reduce FA if axons are not increased consistently in the same direction.

Several DTI and wVBM studies investigating structural white matter abnormalities in different groups of dystonia patient have been published; all studies report abnormal connectivity between basal ganglia, cerebellum and sensorimotor and (pre)frontal cortices.\(^{23-29}\) However, in dystonia, there are no studies as of yet that use combined DTI and wVBM in the study of white matter changes. We investigated white-matter changes in M-D with the combination of the two techniques wVBM and DTI. Based on the sub-cortical pathophysiology of M-D, we hypothesized to find white matter abnormalities in tracts between sensorimotor and prefrontal cerebral cortex, basal ganglia and cerebellum. Based on previous plasticity studies\(^{10}\), due to the constant hyperkinetic state of M-D patients we hypothesized to find increased white-matter volume, decreased MeanD, and increased fractional anisotropy (FA) in the aforementioned white matter tracts.

**Methods**

**Subjects**

We recruited 16 genetically confirmed M-D patients (mean age 43.5 years, range 18-66 years, 8 males) and 18 healthy age and sex matched control subjects (mean
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age 43.6 years, range 21-71 years, 9 males). The study was approved by the local Medical Ethics Committee; all participants were capable of giving written informed consent and did so, after receiving full information on the study. Patients were clinically examined and recorded on video on the day of scanning and clinically scored from the video by a blinded observer using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Unified Myoclonus Rating Scale (UMRS). The clinical characteristics of the M-D patients are summarized in Table 1.

Table 1: patient characteristics

<table>
<thead>
<tr>
<th>subject</th>
<th>gender</th>
<th>age</th>
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<th>BFMDRS</th>
<th>Psychiatric Symptoms</th>
<th>Relevant medication</th>
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<td>6</td>
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<td>28</td>
<td>30</td>
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<td>propanolol</td>
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<td>26</td>
<td>Anx</td>
<td>clonazepam, phenobarbital propanol</td>
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</table>


Mask for the sensorimotor system

In order to constrain our analysis to the sensorimotor system, we created a white-matter mask for use in normalized space that contained all white-matter tracts between the grey matter regions associated with the sensorimotor system. In order to do so, fiber-tracking was performed in the International Consortium for Brain Mapping (ICBM) Tensor atlas. To select the grey-matter regions for the fiber tracking analysis, the Wake Forest University (WFU) PickAtlas (www.fmri.wfubmc.edu/cms/software) was used to create predefined regions of interest.
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(ROIs). Cortical regions, basal ganglia, brainstem and cerebellum were bilaterally selected. The cortical regions included Brodmann areas 1 through 7, 9, 16, 24 and 40. The basal ganglia regions included putamen, caudate, globus pallidus, subthalamic nucleus and the thalamus. The brainstem region included the entire brainstem and pons. The cerebellar region contained the entire cerebellum. Fibers were tracked between these regions and converted into masks. All masks created by the fiber tracking were combined into a single white-matter mask for further analysis (see Figure 1).

MRI data acquisition

For the voxel based morphometry analyses, T1-weighted 3D anatomical images of the entire brain were obtained with a 3.0 Tesla MRI system (Philips Intera, Best, the Netherlands) using the following sequence parameters: field of view 256x256 mm²; scanning matrix 256x256; 170 slices; slice thickness 1 mm; sagittal slice orientation; TE/TR = 4.6/25 ms; SENSE-factor 2.5.

DTI data were acquired using multi-slice spin echo single shot echo-planar imaging using the following parameters: TE/TR = 94/4834 ms; diffusion sensitivities of \( b = 0 \) and \( b = 1000 \) s/mm²; 32 diffusion gradient directions; 45 continuous (no inter-slice gap) slices, slice thickness 3 mm, field of view 229x229 mm²; acquisition matrix 128x128; acquisition voxel size 1.79x1.79x3 mm.

Data processing

All acquired images were converted to Analyze format and processed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK), in MATLAB version 7.3.0 (2006b) (The Mathworks, MA, USA). The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)³⁴ tools, included in SPM8, were used for the inter-subject spatial normalization to an existing DARTEL template in MNI space. This template was derived from 550 healthy European subjects of average age in the IXI-database (http://www.brain-development.org). The normalization with DARTEL improves the inter-subject analyses as it is more accurate in warping both cortical and subcortical regions than standardized normalization included in SPM.³⁵
VBM: White Matter volume (WM)

T1-weighed images were checked for scanning artifacts, gross anatomical abnormalities and rigidly aligned to the pre-existing template. The images underwent an initial segmentation process using VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) to extract WM probability images. Using DARTEL, flow fields were applied to the WM images to warp them to the common MNI template, and modulated using the Jacobian determinants to account for local volume changes. Covariance across the sample was checked prior to smoothing to exclude images with artifacts, and finally the images were smoothed with a Gaussian kernel of 8 mm full width at half-maximum (FWHM).

DTI: Fractional Anisotropy (FA) and Mean Diffusivity (MeanD)

The DTI data were processed using in-house software to create FA value maps encoding for white matter directionality, and MeanD images encoding for the magnitude of diffusion. Image distortions in DTI data induced by eddy currents and head motion were corrected for by applying a full affine alignment of each diffusion image to the mean no-diffusion-weighted image. The FA images were rigidly co-registered to the unwarped WM image of the corresponding subject. Subsequently, the FA images were warped into MNI space by applying the corresponding DARTEL flow fields. Both transformations were also applied to the MeanD images. Covariance across the sample was checked for both FA and MeanD, and the images were smoothed with an 8 mm FWHM Gaussian filter.

Voxel-Based Analysis of FA, MeanD and WM-Volume

To test for FA, MeanD and WM volume differences between M-D patients and controls, voxel-wise statistics were performed using independent-sample t-tests implemented in the general linear model approach of SPM8. The white-matter mask was used as a mask to constrain the analysis to areas related to the sensorimotor system for all three measures – WM, FA and MeanD. Age and gender were run as covariates, peak statistical threshold was set to $p<0.001$ (after masking) with a voxel extent threshold of 20 voxels. Further small volume correction using the a priori hypothesis of involvement in the sensorimotor system in the predefined white matter mask ($p_{FWE} < 0.05$, 10 mm$^3$ sphere) was used to correct for multiple comparisons.
Figure 1: regions of interest

A) Definition of regions of interest (ROI’s) for subsequent fiber-tracking. Cortical regions comprised Brodmann areas 1 through 7, 9, 16, 24 and 40. The basal ganglia comprised the Putamen, Caudate, Globus Pallidus, Sub-thalamic Nucleus and Thalamus. B) Fibers were tracked between the connected brain regions and converted into ROI image was written for each connection. C) The combined tracking between cortex and basal ganglia and between basal ganglia and brainstem is shown in blue. The total WM mask (both yellow and blue combined) was composed of all individual ROI images.

Results

The ROIs orientations to create a white-matter mask are depicted in Figure 1 (a). Figure 1 (b) and (c) illustrate the creation of the WM-mask using tractography in the tensor atlas. To illustrate the inter-subject normalization, the average WM-, MeanD and FA-volumes after registration, as well as the WM mask, are depicted in Figure 2.
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Figure 2: inter-subject normalization

Figure Legend: Average warped FA, MeanD and WM images, for the entire sample of 34 subjects, as well as the WM mask. The WM mask used for the statistical voxel-based analysis consisted of white-matter between motor areas. For FA and WM, the image intensities correspond to values between 0 (black) and 0.9 (white). For MeanD, image intensity is between 0 (black) and 0.0002 (white).

Voxel based group comparisons of M-D patients with healthy control subjects (see Figure 3 and Table 2) showed an increase in white matter volume bilaterally in the sub-thalamic area of the brainstem, which includes the red nucleus (R: x=2, y=-21, z=-8, Z score 3.24, cluster size 35, L: x=-4, y=-21, z=-8, Z score 3.13, cluster size 52). The DTI analyses showed increased FA in the right sub-thalamic area of the brainstem (x=3, y=-22, z=-8, Z score 3.50, cluster size 20) and thalamocortical tract (x=15, y=-55, z=48, Z score 3.32, cluster size 27). Decreased MeanD was found near the right thalamus (x=18, y=-24 z=-2, Z score 5.01, cluster size 1289), in the bilateral sub-thalamic area of the brainstem (x=-12, y=-24, z=-14, Z score 4.21, cluster size 560 as well as near cortical sensorimotor areas (see Table 2 and Figure 3).
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Figure 3: areas of abnormalities

Figure Legend: Areas of abnormalities found in common brainstem/lower thalamic area. Left panel: increase of white matter volume, middle panel: increased fractional anisotropy, right panel: decrease of mean diffusivity.

Table 2: regions of abnormalities.

<table>
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<tr>
<th>Analysis</th>
<th>Comparison</th>
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<th>Z score</th>
<th>Corrected p</th>
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<td>CO &gt; M-D</td>
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<td>-</td>
<td>-</td>
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<td>M-D &gt; CO</td>
<td>Brainstem R (red nucleus)</td>
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<td>-</td>
<td>-</td>
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<tr>
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<td>Putamen R</td>
<td>38 3 -5</td>
<td>3.44</td>
<td>0.013</td>
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</table>

Table legend: M-D: Myoclonus-Dystonia patients, CO: control subjects, MNI: Montréal Neurological Institute, DLPFC: dorsolateral prefrontal cortex. Corrected p = Family Wise Error corrected at p 0.005 with a sphere of 10mm.

Discussion

In the present study combining wVBM and DTI, we clearly demonstrate abnormalities in white matter tracts in M-D patients. The genetically homogeneous study population and the relatively large number of participants add to the reliability of this study. Differences were mainly localized in the sub-thalamic region of the brainstem, a region that contains connections between the cerebellum and
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the basal ganglia. We also showed decreased mean diffusivity in the white matter close to cortical sensorimotor areas.

We detected abnormalities in the sub-thalamic area of the brainstem. In M-D the most prominent and characteristic feature is the multifocal myoclonus. Little is known about the pathophysiology of M-D and its generation of myoclonic jerks. Hypotheses in the literature regarding associated brain regions for subcortical myoclonus in general point towards several brainstem areas. One reason is the resemblance of myoclonus to startle-like jerky movements, whose ‘generator’ is thought to be located in the lower brainstem. Furthermore, the sub-thalamic area of the brainstem is part of the cerebello-thalamo-cortical pathway that is hypothesized to be involved in dystonia. Abnormal connectivity in the sub-thalamic region of the brainstem was also seen in a small group of primary torsion dystonia (DYT-1 and DYT-6) patients using DTI; however, in contrast to our study, a reduction in FA was reported. Possibly, the relatively more prominent myoclonus in M-D could account for this. Another reason might be that increased plasticity in M-D causes more directional axonal growth, resulting in an increase of FA, where axonal growth in DYT-1 and DYT-6 might have been more divergent. In the study in DYT-1/DYT-6 patients, no wVBM was performed and no mean diffusion data was reported.

Our results show increased FA and WM, and reduced MeanD in the sub-thalamic region of the brainstem. Nuclei within this region act as a relay station between cerebellum and basal ganglia. Cerebellar involvement in M-D is suggested as a brain specific isoform of SGCE has been found to be notably highly expressed in the cerebellum in M-D. Furthermore, cerebellar BOLD hyperactivation has been detected with fMRI in M-D patients during a motor task. This fits well with a recently proposed model for dystonia in which malfunctions in a network of brain regions including the cerebellum are associated with dystonia.

We detected decreased MeanD, but no changes in FA or WM, in the sub-gyral cortical sensorimotor areas in M-D. In these areas, a reduction in FA was reported for primary torsion dystonia (DYT-1 and DYT-6), suggesting abnormal connectivity with other brain regions. The reduction in MeanD without changes in FA or WM might indicate a more subtle change in cortical neural plasticity for M-D. This is in accordance with electrophysiological findings; while cortical reduced inhibition has been reported for several types of dystonia, in M-D reduced inhibition is absent.
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DTI studies in other types of dystonia do not show a consistent pattern of affected brain areas. In cervical dystonia and blepharospasm, an increase in FA in the putamen, corpus callosum, prefrontal cortex and supplementary motor area (SMA) has been reported, consistent with increased connectivity in the basal ganglia and loss of neurons in the prefrontal cortex SMA and the corpus callosum. Using DTI probabilistic tractography, in idiopathic cervical dystonia found disrupted thalamic prefrontal pathways. In patients with writer’s cramp, increased FA was detected bilaterally in the white matter of the posterior limb of the internal capsule and adjacent structures, involving fiber tracts connecting the primary sensorimotor areas with subcortical structures. Taken together, findings in different types of dystonia suggest the most common brain regions involved are cortical sensorimotor regions. However, vastly different findings are generally reported and could indicate different pathophysiological mechanisms underlying the different dystonias. Furthermore, MeanD is often not reported at all. The detected decreased mean diffusivity in the white matter close to cortical sensorimotor areas in M-D is consistent with increased FA findings in the same regions in other forms of dystonia, but might indicate a more subtle alteration.

In conclusion, the most prominent changes in connectivity in our study are located in the sub-thalamic region of the brainstem. How these changes relate to the involuntary movements in M-D is unclear, but our findings are consistent with brainstem involvement in the pathophysiology of dystonia, and a malfunction in the network for hyperkinetic movement disorders involving the cerebellum, brainstem and basal ganglia. Whether these changes are specific for M-D remains unclear and would be an interesting hypothesis to test in a larger group of dystonic and myoclonic patients.
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References

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