Multimodal investigations into the pathophysiology of myoclonus-dystonia

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Response inhibition in Myoclonus Dystonia - an fMRI study

Submitted

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Abstract

*Background:* Myoclonus-dystonia (MD) is a movement disorder characterized by myoclonic jerks, dystonic postures and psychiatric co-morbidity. A mutation in the DYT11 gene underlies half of MD cases. We hypothesize that MD results from a dysfunctional basal ganglia network causing insufficient inhibitory motor control. To test this hypothesis functional MRI (fMRI) was performed using a validated §Go/No go¶ task, in order to localize Blood-oxygen-level dependence (BOLD) effects corresponding to Response Inhibition (RI).

*Methods:* Twenty-four MD patients (fifteen DYT11 positive) and 24 matched controls responded with a button press to Go (Go-Response) or No go cues, resulting in analyses of an accurate response withhold to Stop cue (Stop-Inhibit); and an incorrect response to a Go cue (Go-Inhibit); or to Stop cue (Stop-Response).

*Results:* Response accuracy in patients was impaired due to frequent Go-Inhibit errors. Image analysis of the Stop-Inhibit contrast demonstrated frontal, caudate and cingular activity in both groups. Compared to controls, MD patients showed increased primary motor cortex and insular activation. fMRI analysis (Go-Inhibit) revealed increased activity in the contralateral thalamus (Ventral Lateral Nucleus) and dorsolateral-prefrontal cortex. In a post-hoc analysis comparing MD patients, DYT11 positive patients demonstrated anterior cerebellum hyperactivation on all contrasts and increased putaminal activation the Stop-Respond contrast.

*Conclusions:* This study demonstrates a distinct association of motor symptoms in MD with the ventral lateral nucleus of the thalamus was found. Cerebellar dysfunction distinguishes DYT11 positive and negative patients. We suggest that MD might be best considered as a disorder of the cortico-ponto-cerebello-thalamocortical system.
2.1 Introduction

Myoclonus-dystonia (MD) is a rare clinical syndrome that consists of myoclonic jerks and dystonic movements or postures with predominant involvement the upper limbs and cervical parts of the body\[^{144,68}\]. Symptoms are apparent at rest, but increase during action and (psychological) stress. Psychopathology presumably is a fundamental part of the clinical spectrum of the MD syndrome\[^{67}\]. Anxiety, depression, and alcohol abuse have been reported, although the latter may also be explained by its alleviating effect on the motor symptoms. Cognitive function in MD appears to be normal, as extensive neuropsychological examination indicates normal intelligence, attention, executive functioning, memory and psychomotor speed, irrespective of motor symptoms\[^{67}\]. Mutations in the epsilon-sarcoglycan gene (SGCE, DYT11) have been identified in MD. However, only 50% of MD patients with a definite phenotype demonstrate a DYT11 mutation, suggesting genetic heterogeneity of the disorder\[^{165}\].

A subcortical origin of MD has been postulated, because electrophysiological recordings do not indicate primary cortical dysfunction in MD\[^{117}\]. Jerk-locked back-averaged electroencephalography (EEG) does not reveal cortical spikes preceding the myoclonic jerks and no enlarged cortical somatosensory evoked potentials (SSEP) have been found\[^{117}\]. In addition, transcranial magnetic stimulation (TMS) onto the motor cortices demonstrated normal cortical excitability\[^{205}\]. Involvement of the basal ganglia is supported by neuroimaging studies that indicate putaminal dysfunction\[^{165}\]. Moreover, deep brain stimulation (DBS) of the internal globus pallidus (GPI) provides clinical improvement generally exceeding 50% in both myoclonus and dystonic symptoms\[^{7}\].

In the current study we test the hypothesis that MD results from dysfunction of the inhibition of basal ganglia (BG) by means of a validated Response Inhibition (RI) task, the Go/No go paradigm. Paramount in RI-tasks is the requirement of a motor response on a Go cue and a response-withhold under the ‘No go’ condition\[^{188}\]. The motor response is generally considered to be initiated and controlled by the prefrontal cortex. There, the prefrontal cortex excites the striatum and inhibits the globus pallidus via the premotor cortex. Hence, this response alleviates the inhibition from the thalamus to the primary motor cortex which is excited to produce an intended motor action. Adequate RI originates from the inferior frontal cortex leading to activation of the subthalamic nucleus, which increases the excitation of the pallidum and conversely inhibits the thalamocortical output. This results in inhibition of the primary motor cortex and therefore inhibition of a motor response. In MD patients, with proven normal cognition and no signs of primary cortical deficits, we expect the cognitive cortical circuit of response inhibition to be normal, but the ‘subcortical-to-cortical’ motor pathway to be impaired due to disinhibition. In particular, we expect functional imaging differences in activations in the thalamus, GPI and striatum.

2.2 Materials and methods

2.2.1 Participants

A total of 55 subjects participated in this study after written informed consent and approval by the local AMC ethics committee was obtained. MD patients were selected
from the database of the Academic Medical Centre of Amsterdam (AMC) and invited to participate. All patients were screened for DYT1, DYT6 and DYT11 mutations. Exclusion criteria were age < 18 years, current depression or claustrophobia precluding MRI investigation. Psychiatric co-morbidity was assessed using structured clinical interviews conducted by a trained neuropsychologist blinded for subject status. The Mini International Neuropsychiatric Interview (MINI-Plus) was used and in a few cases the Structured Clinical Interview on DSM-IV diagnostics (SCID-I), as this was used in a previous reported study[67]. Neuro- or psychoactive drugs were abstained one day prior to scanning and last botulinum toxin injections were at least three months earlier. Of 31 MD patients (20 DYT11pos) fulfilling the criteria and willing to participate, seven were excluded from analyses due to interrupted scanning caused by patients’anxiety (2 DYT11pos; 1 DYT11neg) or too much motion artefact upon image analysis (3 DYT11pos; 1 DYT11neg). Patients’ clinical characteristics are summarized in Table 2.1. Twenty-four healthy controls without neurological or psychiatric conditions, and matched to the remaining 24 MD patients for gender, age (± 5 yr), education, and handedness were included. Education was classified using the 7-point Dutch Verhage educational scale, scoring: “1 = less than 6 years of education Dutch primary school” to “7 = specialized degree on University-level”. Handedness was determined with the standard Edinburgh Handedness Inventory[146]. The severity of motor symptoms in MD patients was clinically assessed and recorded on video at the day of scanning. An independent clinician blinded for subject status rated the videos using the motor items of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRSM) and the modified version of the Unified Myoclonus Rating Scale (UMRSM)[33;73].

2.2.2 Response Inhibition task

Participants performed with their dominant hand a “Go/No go” response inhibition (RI) task adopted from Garavan and colleagues with a mixed block-event related design[75;74]. Prior to scanning, the task was explained and subjects performed one complete training session. Subjects were presented with a 1 Hz serial stream of alternating letters, X and Y, and were required to make a button press response to each letter except when the alternation order was interrupted. Subjects were instructed to respond to Go cues (alternating letters) by pressing a button with the index finger of the right hand, and to withhold the button-press with “No Go” cues (here referred to as “Stop”), whenever the previous letter was the same as the current letter (10% of trials). This resulted in four possible trials: (i) an accurate response with a button press to a Go cue (Go-Respond); (ii) an accurate ‘response-inhibition’ to a Stop cue (Stop-Inhibit); (iii) an incorrect ‘response-inhibition’ to a Go cue (Go-Inhibit); or (iv) a incorrect response to a Stop cue (Stop-Respond). The overall task consisted of 268 trials and took 4:49 minutes and 112 scans to complete (i.e., 10 short scanblocks of 11 scans and 2 additional scans at the end). This sequence was further subdivided into 5x2 (AB) scan-blocks, consisting of “A = letter- trials with no stop trials” (i.e., XXYYXYYXYYXY) followed by “B = letter-trials with 20% stop trials” (e.g., XXYYXYYXYYXY). The RI task was performed twice with a minimum of 10 minutes in between tasks. In total, 484 Go stimuli were presented and 52 Stop trials (9:1). Stimulus duration was 800 ms followed by a 200-ms blank screen in between stimuli.
### Table 2.1: Clinical characteristics of MD patients. + indicates: present; - : absent; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; BTX= botulinum toxin, Br= Bromazepam B= Buspiron, Cl= Clomipramine C= Clonazepam, E= Escitalopram, F= Fenobarbital Fl= Flupentixol M= Melitracen, P= Paroxetine Ta= Tamsulosin T= Tri-hexyfenidyl UMRS = Unified Myoclonus Rating Scale.

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<thead>
<tr>
<th>Patient</th>
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<th>Age</th>
<th>BFMDRS</th>
<th>UMRS</th>
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<tr>
<td>2</td>
<td>+</td>
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<td>62</td>
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<td>F</td>
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<td>47</td>
<td>92</td>
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<td>-</td>
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<tr>
<td>24</td>
<td>-</td>
<td>M</td>
<td>52</td>
<td>13</td>
<td>61</td>
<td>C</td>
</tr>
</tbody>
</table>
2.2.3 Data acquisition and preprocessing

Imaging was performed using a 3.0 Tesla (T) Philips Intera scanner with an 8-channel SENSE head coil. Stimuli were generated with a PC running the Presentation software package and were projected onto a screen in front of the scanner table (i.e., white XY-letters centred on a black screen). The projected image was visible through a mirror positioned on the headcoil. An MRI-compatible box with response keys was used to monitor button presses. Foam pads were applied to reduce head motion; earplugs together with a headphone were used to reduce scanner noise. For functional imaging a T2*-weighted echoplanar imaging (EPI) sequence was used, covering the whole brain with 45 interleaved 3-mm-thick/0-mm-gap sagittal slices (TR/TE = 2570/25 ms, SENSE factor 2.4; field of view 214x214 mm^2; scan matrix 96x96 and in plane resolution 2.2x2.2 mm^2). Two sessions of 112 functional scans were recorded and a T1-weighted structural 3D anatomical scan (0.78x0.78x1 mm resolution). Functional images were slice-time corrected, spatially realigned, normalized into the standard space of the MNI-152 Template brain, and smoothed with an 8-mm Gaussian kernel.

2.2.4 Data analysis and Statistics

Behavioural analyses were conducted with non-parametric Mann Whitney U and Kruskal - Wallis tests using the Statistical Package for the Social Sciences (SPSS) software 15.0.1 (significance threshold of p < .05).

General Linear Model (GLM) analysis was performed using the Statistical Parameter Mapping-software package SPM5. In the 1st level analyses, the design consisted of event-related regressors, constructed by convolving column vectors encoding for event-related responses of the RI-task with the canonical Hemodynamic Response Function (HRF). Contrast images encoding for ‘Stop-Inhibit’, ‘Go-Inhibit’ and ‘Stop-Respond’ were created. Due to the high frequency of default responses, ‘Go-Respond’ was not modelled as it is considered an implicit baseline.

Head motion during scanning may induce large Blood-oxygen-level dependence (BOLD) signal changes and hence result in false-positive activation. Therefore, we used the rotation and translation parameters obtained from the spatial realignment to insert motion parameters. In addition, we used scan-nulling regressors into the GLM analysis; these model for changes in the BOLD-signal associated with large inter-scan motion events (head jerks). Second level group analyses were performed to assess the main effect of ‘Stop-Inhibit’ and for group comparisons between MD patients and healthy controls (HC) for ‘Stop-Inhibit’ and ‘Stop-Respond’. A separate one-sample t-test was performed on only MD patients for the Go-Inhibit contrast, as the events of the Go-Inhibit errors in controls were too few to allow for comparison between groups. In a post-hoc analysis, DYT11pos and DYT11neg patients were compared.

A significance threshold of p < 0.005 with a cluster extent of more than 8 voxels was used, except for the main effect, which was p < 0.0001. Small volume (SV) correction (20 mm sphere) of p < 0.005 was applied to correct for multiple comparisons using the a priori hypothesis of activation in the basal ganglia, more specifically the putamen, globus pallidus and caudate nucleus.
2.3 Results

2.3.1 Participants

The data of 48 subjects (15 DYT11pos, 9 DYT11neg, and 24 HC), with a mean age of 40.7 years (SD = 14.3; 26 females) were analyzed (Table 2.1). No statistical differences with respect to age, gender, education and handedness were observed between patient and control subject pairs. One DYT11neg patient was left-handed whereas all DYT11pos patients were right-handed. Within the MD patient group, DYT11pos and DYT11neg differed significantly on UMRS scores (Mann-Whitney U-test; p = .01; median 16 and 29). Psychiatric examination indicated that none of the patients currently classified for an anxiety disorder or depression.

2.3.2 Behavioral findings

Task performance results (means of correct and incorrect responses, and reaction times) are depicted in Table 2.2. Patients made more Go-Inhibit errors compared to controls (i.e., more failures to respond to Go cues). After the scanning session, patients reported their inability to respond to “go” cues due to their motor symptoms. In MD patients, Go-Inhibit trials were preceded significantly more often by default Go-Respond and Stop-Inhibit trials (p < 0.001). In healthy controls, Go-Inhibit error trials were significantly more often the first trial of the task (p < .001).

2.3.3 Imaging findings

The main effect across groups for the Stop-Inhibit contrast showed nine significant clusters, summarized in Table 2.3. Most prominently, ipsilateral frontal gyrus (BA47), precuneus (BA7), inferior parietal (BA40) and caudate activations were found. Also, contralateral cerebellar, insular (BA13) and superior parietal (BA7) activations were observed (See Figure 2.1). Group comparison of the Stop-Inhibit contrast showed an

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of correct trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop-Inhibit</td>
<td>26 (± 10)</td>
<td>31 (± 11)</td>
</tr>
<tr>
<td>Go-Respond</td>
<td>466 (± 19)</td>
<td>475 (± 10)</td>
</tr>
<tr>
<td><strong>Number of error trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop-Respond</td>
<td>25 (± 10)</td>
<td>20 (± 11)</td>
</tr>
<tr>
<td>Go-Inhibit</td>
<td>12 (± 9) *</td>
<td>5 (± 6)</td>
</tr>
<tr>
<td><strong>Reaction times (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop-Respond</td>
<td>380 (± 70)</td>
<td>360 (± 76)</td>
</tr>
<tr>
<td>Go-Respond</td>
<td>407 (± 44)</td>
<td>380 (± 61)</td>
</tr>
</tbody>
</table>

Table 2.2: Behavioral results on Response-Inhibition-task. Means (and SD) are displayed. * significant at p < .0001

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CHAPTER 2. RESPONSE INHIBITION IN M-D WITH FMRI

Figure 2.1: Overview of imaging findings main task effect: A) Stop-Inhibit: both patients and controls have activation in the ipsilateral (i) frontal gyrus (BA47), precuneus (BA7), inferior parietal (BA40) and contralateral cerebellum B) Stop-Inhibit: MD > controls, depicting the insula and primary motor cortex.

increase in activation in the primary motor cortex and insula in MD patients compared to HC. The reverse contrast (HC > MD) showed no significant clusters. The Stop-Respond contrast demonstrated hyperactivation of the ipsilateral premotor cortex, and medial frontal gyrus (BA8) and ipsilateral anterior cingulate (BA32) and putamen in MD compared to controls. Controls had hyperactivation of the dorsolateral prefrontal cortex (DLPFC, BA9) and superior frontal gyrus (BA6) compared to MD patients. The Go-Inhibit contrast was analyzed for MD patients only, because controls had few Go-Inhibit errors. MD patients showed BOLD activation in the contralateral thalamus (Ventral lateral nucleus, VLN), brainstem and medial frontal cortex and ipsilateral dorso-lateral-prefrontal cortex and middle frontal gyrus. Exclusion of the left handed patient and its matched control did not alter significance of the cognitive (ipsilateral findings) and motor clusters. All other possible comparisons displayed no significant clusters.

2.3.4 Post hoc analysis: Between-MD groups comparison

Differences in BOLD activation between the DYT11pos versus DYT11neg MD patient groups were analyzed with a two-sample t-test on the Stop-Inhibit contrast images. The results are illustrated in Figure 2.2 and summarized in Table 2.4. Cerebellar anterior lobe hyperactivation was found in DYT11pos patients with all contrasts (Stop-Inhibit: z = 4.28; p = .0001; Go-Inhibit: z= 3.06; p = .0001 Stop-Response: z = 3.66 =; p = .0001). Cluster activation of the cerebellum remained after exclusion of the left handed patient.
2.3. RESULTS

Table 2.3: Overview of brain regions with significant differences in regional blood flow between MD patients and healthy control subjects per contrast. BA = Brodmann Area; \(K_E\) = minimum voxels; MD = Myoclonus Dystonia patients; HC= healthy controls; C= contralateral; I=ipsilateral; DLPFC= dorsolateral prefrontal cortex; All contrast are displayed as \(p < 0.005\) (SV correction) except for * = \(p < 0.0001\) (SV correction). Voxel extent = 8; All other possible comparisons displayed no significant clusters.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Comparison</th>
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<th>BA</th>
<th>Side</th>
<th>MNI Coordinates</th>
<th>(K_E)</th>
<th>Z score</th>
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<td>Stop-Inhibit</td>
<td>Main effect MD &amp; HC *</td>
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<td>47</td>
<td>I</td>
<td>34,29, -5</td>
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<td></td>
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<td>Superior parietal lobule</td>
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<td></td>
<td>Medial frontal gyrus</td>
<td>8</td>
<td>I</td>
<td>10, -26, 61</td>
<td>28</td>
<td>4.12</td>
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<td></td>
<td></td>
<td>Anterior cingulate</td>
<td>32</td>
<td>C</td>
<td>-16, 37, 2</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td>Putamen</td>
<td>-</td>
<td>C</td>
<td>-21, -6, 13</td>
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<td>MD &lt; HC</td>
<td></td>
<td>DLPFC</td>
<td>9</td>
<td>I</td>
<td>25, 53, 31</td>
<td>46</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus</td>
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<td>C</td>
<td>-5, 24, 61</td>
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<td>Go-Inhibit</td>
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<td>Medial Frontal Gyrus</td>
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<td>I</td>
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<td>-</td>
<td>8, -31, -20</td>
<td>9</td>
<td>3.17</td>
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</table>

*All contrast are displayed as \(p < 0.005\) (SV correction) except for * = \(p < 0.0001\) (SV correction). Voxel extent = 8; All other possible comparisons displayed no significant clusters.*
CHAPTER 2. RESPONSE INHIBITION IN M-D WITH FMRI

Figure 2.2: Imaging findings of error contrast and post-hoc analysis: A) Go-Inhibit: Group effect MD, depicting the ventral lateral nucleus of the thalamus B) Stop-Inhibit: Group effect DYT11pos > DYT11neg, depicting the anterior cerebellum. “i” = ipsilateral.

Table 2.4: Overview of brain regions with significant differences between MD patients with and without DYT11 mutation in regional blood flow per contrast. BA = Brodmann Area; KE = minimum voxels; C= contralateral; I=ipsilateral; DLPFC= dorsolateral prefrontal cortex; DYT11pos = MD with DYT11 mutation; DYT11neg= MD without DYT mutation; All contrast are displayed as p < 0.005 (SV correction), except for * = p < 0.01 (SV correction), Voxel extent = 8; All other possible comparisons displayed no significant clusters.
2.4 Discussion

We investigated whether MD is associated with insufficient BG inhibitory motor control by means of a RI paradigm in a large cohort of 24 MD patients and their matched controls. The behavioral results indicate that both healthy controls and patients subjects were able to perform the task adequately. Cognitive control of RI appears unimpaired in MD. The current findings support the hypothesis that MD is associated with insufficient motor inhibition, indicated by the hyperactivation found in the primary motor cortex in MD patients during Stop-Inhibit trials and activations found in the thalamus in the MD group during Go-Inhibit errors.

2.4.1 Response inhibition

The imaging findings for the main effect of the Stop-Inhibit contrast (inferior frontal, superior parietal, caudate, and middle frontal gyrus) are in line with previous reports\cite{41,9}. RI is considered to be under cognitive inhibitory control of frontal-striatal-thalamic-cortical circuitry. The (pre-) supplementary motor area activation (SMA; premotor cortex; BA 6) is essential for motor response planning and selection. Prefrontal and inferior cortex activity (BA 44, 45, and 47) is essential for general response inhibition and cognitive control. The medial frontal cortex (MFC) is involved and important for higher order executive functioning and decision-making processes\cite{41,188}. We found all these structures in the Stop-Inhibit contrast in the combined group analysis, and activations did not significantly differ between patients and controls in these regions. However, MD patients demonstrate more insular and primary motor cortex activation on the main task effect compared to controls. Anterior insular activation (BA 13) has been associated with attention and interference effects resulting from task-specific demands. Thus, it can be concluded that the cognitive control circuit involved in planning and redirecting action is normal in MD patients, in line with previous reports on the absence of primary cortical changes and normal cognitive functioning in MD patients\cite{67}. This study is the first to test RI during fMRI in dystonia. Previously, response inhibition has been investigated with an anticipated response task in patients with focal hand dystonia\cite{190}. Patients were significantly less successful in inhibiting their responses, but this might be influenced by the incorporation of anticipation in the experimental design. In contrast, in another study with a simple RI task in patients with musician’s dystonia, the number of motor errors was not significantly higher compared to healthy pianists\cite{96}. In a modified Go/No-Go paradigm with EEG, subjects had to play a sequence on the piano on a Go cue. In correct No-Go trials, weaker phase synchronization in the sensorimotor and the premotor cortices was found.

2.4.2 Thalamic involvement in MD

Although the overall task performance on the main task effect (Stop-Inhibit) was well, MD patients did make significantly more motor Go-Inhibit errors than controls (Table 2.3). After scanning, patients reported to have been unable to repeatedly press the response button due to their motor complaints. Therefore, it appears that Go-Inhibit errors are related to the patient’s motor symptoms and we used the Go-Inhibit contrast to investigate motor control during the presence of MD symptoms. We found association with activity of the DLPFC and thalamus (ventral lateral nucleus, VLN).
The VLN is the output relay to the primary motor cortex and is part of the cortico-ponto-cerebello-thalamo-cortical system. All connections from the cerebellum and brainstem project via the pontine nuclei to the VLN. In several cases of MD, deep brain stimulation (DBS) has been performed with the globus pallidus internus (GPI) as target\cite{7}. An alternative DBS target for MD is the thalamic VLN\cite{199}. Thus, our findings suggest a functional relation between MD motor symptoms and the VLN.

### 2.4.3 Cerebellar involvement in MD

Interestingly, differences between MD patient groups were seen including cerebellar hyperactivity in the DYT11pos compared to DYT11neg patients in a post-hoc analysis. Dystonia is currently regarded as a neurodevelopmental circuit disorder, involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways\cite{29}. A recent study demonstrated impaired saccadic adaptation in DYT11 mutation positive MD, also indicating cerebellar dysfunction in MD\cite{98}. Moreover, findings on the expression of the SGCE isoforms also demonstrated that dysfunction of the cerebellum in MD\cite{165}. In addition to cerebellar involvement, Argyelan and colleagues have demonstrated clear differences in cerebello-thalamo-cortical connectivity by means of a DTI study in primary dystonia\cite{8}. Furthermore, it has been shown that both the striatum and the cerebellum have a role in the expression of dystonia, as either (subclinical) lesions of the striatum as well as a surgical removal of the cerebellum in a mouse model alleviated the paroxysmal dystonic attacks\cite{139}. Therefore, our findings are in line with the current view of the pathophysiology of dystonia as a dysfunction of the motor circuit involving the sensorimotor cortices, thalamus, and cerebellum, rather than an isolated basal ganglia disorder.

### 2.4.4 Study limitations

The phenotypical difference of the patients with and without DYT11 gene mutation. The UMRS scores between MD groups differed significantly (DYT11+ median= 16; DYT11neg median = 29; p = .01). On clinical grounds this difference was not as apparent. A clinimetric explanation could lie in the predominant distal myoclonus in DYT11pos (scores low on UMRS) and the relatively more proximal myoclonus in DYT11neg patients (which scores relatively high on UMRS). Both the UMRS and BFMDRS-scaling do not optimally assess MD motor symptoms and a MD specific scale should be developed to score for severity of motor symptoms more accurately. However, this difference in myoclonus severity could influence one of our main findings, the difference in activation of the cerebellum in MD patients. The hypothesis that predominant myoclonus as seen in DYT11neg patients could be related to relative hypoactivation of the cerebellum is an interesting starting point for future studies. Methodological considerations of this study include the exclusion of some patients from analysis due to excessive head motion. This may bias our findings, as those patients were most affected or most influenced by the scanner environment. No patients with claustrophobia were included in the original sample, but anxiety levels were nonetheless high in 3 patients.
2.4.5 Conclusions

Our imaging findings suggest involvement of cortico-ponto-cerebello-thalamo-cortical system in the motor symptoms in MD. Furthermore, the current findings indicate different clinical subtypes of DYT11 positive and negative MD patients. These findings call for additional studies of patients with and without DYT11 mutation and their pathophysiological underpinnings in MD.