Disorganized Sensorimotor Integration in Mutation-Positive Myoclonus-Dystonia

A Functional Magnetic Resonance Imaging Study

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Background: Myoclonus-dystonia is an autosomal dominantly inherited movement disorder clinically characterized by myoclonic jerks and dystonic postures or movements of the upper body. Functional imaging studies in other, mainly heterogeneous groups of dystonia do agree on dysfunction of the striato-pallido-thalamo-cortical circuit.

Objective: To study cerebral activation patterns with functional magnetic resonance imaging in a genetically defined homogeneous group of patients with dystonia.

Design, Setting, and Patients: Thirteen clinically affected SGCE mutation carriers and 11 control subjects were studied in a case-control study.

Intervention: A finger-tapping motor task was performed in a block design using 3.0-T magnetic resonance imaging.

Main Outcome Measures: Blood oxygenation level-dependent signals were compared between groups.

Results: In SGCE mutation carriers, we observed significant hyperresponsiveness in contralateral inferior parietal cortical areas, ipsilateral premotor and primary somatosensory cortex, and ipsilateral cerebellum during the motor task compared with healthy control subjects.

Conclusions: The cortical activation patterns in SGCE mutation carriers during this motor task point to a disorganized sensorimotor integration in this uniform group of patients with dystonia and are consistent with functional neuroimaging studies in other types of (hereditary) dystonia.

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Myoclonus-dystonia (M-D) 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 depressed mood or anxiety. It is autosomal dominantly inherited and is caused by mutations in the ε-sarcoglycan gene (SGCE [GenBank AC069292]) on chromosome 7q21 (DYT11 [OMIM 159900]) in about one-third of all patients. Penetrance of M-D is highly dependent on the parental origin of the disease allele, resulting from maternal imprinting. The SGCE mutations are lacking in many patients with the M-D phenotype, suggesting the involvement of other genes or environmental factors.

Myoclonus-dystonia is considered a dystonia-plus syndrome with the basal ganglia being thought to play a major role in dystonia. The pathophysiology of M-D is elusive but neuronal models of dystonia have postulated hyperactivity of the direct putamen-pallidal pathway with reduced inhibitory output of the internal segment of the globus pallidus. This subsequently leads to increased thalamic input to the (pre)motor cortex and results in excessive motor cortex excitation. On the other hand, abnormalities of sensory input processing in patients with dystonia have been reported and are reflected by the geste antagonistique. Several observations strongly support the idea that sensorimotor integration is impaired in dystonia. Myoclonus in M-D is also likely to be of subcortical origin, ie, basal ganglia, because of the lack of stimulus sensitivity and the absence of giant somatosensory evoked potentials.

Functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been previously performed in primary torsion dystonia and focal hand dystonia and writer’s cramp. Oropharyngeal dystonia, laryngeal dystonia, and laryngeal dystonia...
Although conflicting results with respect to the activation patterns of different cortical and basal ganglia structures have been reported, all of these studies do agree on dysfunction of the striato-pallido-thalamo-cortical circuit in dystonia.

Functional imaging studies in SGCE mutation carriers (MCs) are very limited; a single 5-year-old patient with M-D showed changes in the motor network when performing a drawing and hand “snapping” task during an fMRI study, specifically in the thalamus and dentate nucleus. Recently, a study by our group showed reduced striatal D2 receptor binding in SGCE MCs when compared with healthy control subjects.

The aim of the present fMRI study was to investigate the activation patterns in SGCE MCs during execution of a simple motor task. Based on current neuronal models of myoclonus and dystonia, we hypothesized that patients would exhibit abnormal activation patterns in basal ganglia and cortical sensorimotor areas compared with healthy control subjects.

**METHODS**

**SUBJECTS**

We studied 13 clinically affected SGCE MCs (mean age, 47 years; age range, 19-65 years). Genetically, 1 MC had a de novo mutation, 8 MCs inherited the mutation from their father, and 4 MCs inherited the mutation from their mother. The control group consisted of 11 neurologically and psychiatrically healthy MCs (mean age, 47 years; age range, 23-71 years) and was age- and sex-matched to the SGCE MC group. Eleven of the 13 SGCE MCs have been recently described as part of a large Dutch family with M-D (genotype, 619-620del AG). The 2 remaining subjects were not related (genotypes, IVS7 + 2 C > T and c.179A > C [His > Pro]). In 6 of the 8 patients who inherited the mutation from their father, myoclonus was only distally located on neurological examination. The 4 patients who inherited the mutation from their mother showed mild axial dystonia. Psychiatric history was positive in 9 of the 13 patients (Table 1). The SGCE MCs were clinically scored using the Burke-Fahn-Marsden Dystonia Rating Scale and the Unified Myoclonus Rating Scale. The clinical characteristics of the SGCE MCs are summarized in Table 1.

**TASK PARADIGM**

The task consisted of finger tapping at a rate of 2 Hz performed in the right upper extremity. Finger tapping is a widely used active motor condition in fMRI studies, consisting of a simple open-close action for which no learning is required. An illustrative image was projected onto a screen to instruct the subjects when to perform the task during scanning. Before scanning, subjects were carefully instructed to practice the task outside the scanner to ascertain that the task was performed correctly. This practice session was carefully monitored and subjects were visually monitored during scanning to check accurate performance of the task. The task consisted of 6 epochs; each task epoch lasted 18 seconds and was preceded by a 16-second rest block.

**fMRI SCANNING**

Imaging was performed using a 3.0-T Philips Intera scanner (Philips, Eindhoven, the Netherlands) with a SENSE head coil (Philips). Stimuli were generated using a Dell Pentium 4 computer (Dell Inc, Round Rock, Texas) running the ePrime software package (PST Inc, Pittsburgh, Pennsylvania [http://www.pstnet.com/products/e-prime/]) and projected on a screen in front of the scanner table. The projected image was seen through a mirror positioned above the subject’s head.

Axial multislice T2*-weighted images were obtained with a gradient–echo planar imaging sequence (echo time, 30 milliseconds; repetition time, 2011 milliseconds; 64 × 64 matrix; 35 slices; 3 × 3-mm in-plane resolution; slice thickness, 3 mm; 1-mm interslice gap) covering the entire brain. A session consisted of 1 echo planar imaging session followed by a T1-weighted structural 3-dimensional inversion recovery magnetic resonance scan (0.78 × 0.78 × 2.00-mm resolution).

The blood oxygenation level–dependent (BOLD) effect on which fMRI is predicated is due to fluctuations in blood oxygenation level, and there is ample evidence that this in turn reflects regional changes in neural activity. We chose the term hyperresponsive/hyporesponsive to indicate that group × task interactions as reported later represent differential changes in neural activity in response to the task performed but not differences in baseline perfusion.
Table 2. Main Effects Across Groups

<table>
<thead>
<tr>
<th>Activated Brain Area</th>
<th>Brodmann Area</th>
<th>MNI Coordinates</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral motor cortex</td>
<td>4</td>
<td>−39, −18, 54</td>
<td>6.56</td>
</tr>
<tr>
<td>Ipsilateral cerebellum</td>
<td>NA</td>
<td>30, −48, −33</td>
<td>6.45</td>
</tr>
<tr>
<td>Contralateral premotor cortex</td>
<td>6</td>
<td>0, 0, 60</td>
<td>6.08</td>
</tr>
<tr>
<td>Ipsilateral sensory cortex</td>
<td>3</td>
<td>60, −15, 30</td>
<td>5.77</td>
</tr>
<tr>
<td>Right visual cortex</td>
<td>18</td>
<td>3, −67, −9</td>
<td>5.59</td>
</tr>
<tr>
<td>Contralateral parietal cortex (secondary somatosensory cortex)</td>
<td>40</td>
<td>39, −42, 51</td>
<td>5.58</td>
</tr>
<tr>
<td>Ipsilateral parietal cortex (secondary somatosensory cortex)</td>
<td>40</td>
<td>45, −36, 45</td>
<td>5.40</td>
</tr>
<tr>
<td>Ipsilateral sensory cortex</td>
<td>3</td>
<td>51, −18, 39</td>
<td>5.39</td>
</tr>
<tr>
<td>Ipsilateral motor cortex</td>
<td>4</td>
<td>42, −9, 54</td>
<td>4.93</td>
</tr>
<tr>
<td>Ipsilateral premotor cortex</td>
<td>6</td>
<td>39, 0, 54</td>
<td>4.91</td>
</tr>
</tbody>
</table>

Abbreviations: MNI, Montreal Neurological Institute; NA, not applicable.

The MNI coordinates and Z scores are shown for areas with significant activation.

STATISTICAL ANALYSIS

Imaging data were analyzed using Statistical Parametric Mapping 2 software (Wellcome Department of Cognitive Neurology, London, England; http://www.fil.ion.ucl.ac.uk/spm). Spatially, images were realigned, normalized into the standard space of the Montreal Neurological Institute 152 brain, and smoothed with an 8-mm Gaussian kernel. The data were corrected for differences in slice timing, high-pass filtered, and analyzed in the context of the general linear model. Boxcar regressors convolved with the canonical hemodynamic response function were used to model the response during the task.

Linear contrasts of parameter estimates were computed for main effects of task vs baseline for each subject. The resulting contrast images were subsequently used for a second-level analysis, and main effects for task load were assessed across groups as well as for interactions between groups. Main effects across groups are reported at P < .05 corrected for multiple comparisons using the false discovery rate method, with a cluster size restriction of 10 voxels. Interaction effects were calculated as T contrasts between SGCE MCs and control subjects and are reported at P < .001 uncorrected, masked with the appropriate main effect at P < .001 and a voxel extent threshold of 5 voxels.

RESULTS

The clinical characteristics of the SGCE MCs are summarized in Table 1. All subjects were able to perform the tasks correctly during the practice outside the scanner. Because the task does not require dexterity, we included 1 left-handed subject in the analysis. During hand movements, no movements of the contralateral limb were observed. The presence of proximal myoclonus could not be visually checked during scanning. Mild infrequent distal myoclonus was noted during the activity blocks.

The data set from 1 SGCE MC (patient 7) was discarded from further analysis owing to excessive head movement during scanning.

Main effects across groups consisted of bilateral, predominantly right-sided cerebellar, visual cortex, and parietal activation as well as bilateral sensory and motor cortex activation (Table 2 and Figure 1). Interaction effects between groups are summarized in Table 3.

In the SGCE MC group, significant cortical hyperresponsiveness of the contralateral secondary somatosensory cortex (Brodmann area [BA] 40), ipsilateral premotor cortex (BA 6), primary somatosensory cortex (BA 3), dorsolateral prefrontal cortex (BA 9), and ipsilateral cerebellum was seen as compared with control subjects (Figure 2). Hyporesponsiveness was found in the contralateral insula (BA 13) (Figure 3). This analysis was repeated omitting the 4 subjects with only slight axial dystonia who inherited the mutation from their mother, yielding similar results in the same areas (data not shown).

Linear regression analysis was performed with Unified Myoclonus Rating Scale and Burke-Fahn-Marsden Dystonia Rating Scale scores as regressors. No correlation between myoclonus and/or dystonia and BOLD signal was found.

COMMENT

To our knowledge, this fMRI study is the first functional imaging study that has been performed in a group of SGCE MCs. Our aim was to visualize differences in brain activation patterns specifically in a homogeneous group of patients with dystonia. Here we will discuss our findings within the context of imaging studies in other dystonia syndromes, although it should be noted that myoclonus is the more prominent feature of M-D.

The motor task data in control subjects showed robust main effects, in agreement with previous studies in healthy control subjects. The main findings of the motor task in SGCE MCs in the present fMRI study include hyperresponsiveness in different brain regions known to take part in the integration of voluntary movement. These differences cannot be explained by age differences as there were no significant differences in age between the groups. Hyperresponsiveness in the aforementioned brain

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regions has been previously described in different forms of dystonia but not in myoclonus.

First, the hyperresponsiveness of the premotor cortex in our study is consistent with the resting state findings in a PET study performed in clinically affected DYT1 and DYT6 MCs. In dystonia, it has been hypothesized that overactivity of the premotor areas reflects cortical hyperexcitability of the motor planning areas with subsequent overactivity of the primary motor cortex during voluntary movements. It should be noted, however, that our results show predominantly ipsilateral and not contralateral premotor cortex hyperresponsiveness, suggesting overflow of activity due to decreased interhemispheral inhibition. The hyperresponsiveness in the primary somatosensory cortex is consistent with other fMRI studies regarding writer’s cramp, a form of focal dystonia. In these studies, increased sensorimotor response was detected with finger tapping.

Second, the hyperresponsiveness of the contralateral inferior parietal cortex (BA 40, or secondary somatosensory cortex) is consistent with a PET study in clinically affected DYT1 and DYT6 MCs, in whom this area was also found to exhibit hypermetabolism. The BA 40/secondary somatosensory cortex, also known as the parietal operculum, receives projections from the temporal motor areas and is believed to be part of the supplementary sensory cortex. This supports the hypothesis of defective sensorimotor integration in the pathophysiology of (myoclonus-)dystonia.

Third, the hyperresponsiveness of the ipsilateral cerebellum indicates abnormal activation in other parts of the motor circuitry in M-D. This is consistent with studies involving other types of inherited forms of dystonia. The visual cortex activation is most likely due to the projection of images instructing the subjects when to perform the task. The activation found in the posterior ipsilateral dor-

### Table 3. Montreal Neurological Institute Coordinates and Z Scores for Areas With Significant Differences in Activation During the Motor Task

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>Activated Brain Area</th>
<th>Brodmann Area</th>
<th>MNI Coordinates</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCs &gt; control subjects</td>
<td>Contralateral parietal cortex (secondary somatosensory cortex)</td>
<td>40</td>
<td>−36, −54, 45</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral cerebellum</td>
<td>NA</td>
<td>15, −81, −33</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral dorsolateral prefrontal cortex</td>
<td>9</td>
<td>54, 6, 33</td>
<td>3.58</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral cingulate cortex</td>
<td>24</td>
<td>0, 12, 27</td>
<td>3.53</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral sensory cortex</td>
<td>3</td>
<td>51, −15, 39</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral premotor cortex</td>
<td>6</td>
<td>39, −3, 42</td>
<td>3.25</td>
</tr>
<tr>
<td>Control subjects &gt; MCs</td>
<td>Contralateral insula</td>
<td>13</td>
<td>−39, 9, 12</td>
<td>3.49</td>
</tr>
</tbody>
</table>

Abbreviations: MCs, mutation carriers; MNI, Montreal Neurological Institute; NA, not applicable.

**Figure 2.** Images from the second-level analysis comparing all SGCE mutation carriers with all control subjects. The images show significant cortical hyperresponsiveness of the contralateral secondary somatosensory cortex (Brodmann area 40) (A), ipsilateral premotor cortex (Brodmann area 6) (B), primary somatosensory cortex (Brodmann area 3) (C), dorsolateral prefrontal cortex (Brodmann area 6) (D), and contralateral cerebellum (E).
solar prefrontal cortex (BA 9), presumably the frontal eye field, which is part of the premotor area and encompasses all of BA 8 and portions of BA 9.\textsuperscript{29,30} may represent changes in eye-hand coordination. The interpretation of the changes found in the insula, however, remains speculative. No differences in activation were found in the basal ganglia. This might be owing to the simplicity of the task because basal ganglia structures are known to be activated primarily during complex motor tasks.

The present fMRI study has several limitations. An important potential limitation is the lack of objective measurements of involuntary movement during scanning. Mild infrequent myoclonus was noted in patients during the activity blocks; therefore, this may have contributed to the observed differences in activation patterns between SGCE MCs and control subjects. The proper method to control for myoclonus would be electromyographic coregistration, which was, however, not available in our laboratory when this study was conducted. In future studies, electromyographic coregistrations during fMRI should be performed by directly relating the BOLD signal to the involuntary movements and using the electromyographic signal to monitor task execution. Because myoclonus was an important symptom in most patients, as illustrated by their scores on the Unified Myoclonus Rating Scale, it is possible that our findings could be at least partly attributed to phenotype, ie, myoclonus rather than dystonia. However, the linear regression analyses yielded no correlation between myoclonus and/or dystonia and BOLD signal. Furthermore, the analysis omitting the 4 subjects with only slight axial dystonia (inherting the mutation from their mother) yielded strikingly similar results, suggesting that the changes are genotype specific rather than phenotype specific. The 4 patients with M-D who inherited the mutation from their mother have the same type of mutation as the other patients with M-D who inherited the mutation from their father, which excludes the possibility of a benign polymorphism. We consider the strength of this study to be the genotypic homogeneity rather than phenotypic homogeneity. Another possible limitation of this study is the high number of psychiatric symptoms in the genotypic homogeneity. Another possible limitation of this study is the high number of psychiatric symptoms in the SGCE MC group considered to be part of the M-D phenotype. Functional changes in cortical activity have been described in patients with obsessive-compulsive disorder, mainly in the basal ganglia and dorsal prefrontal cortex.\textsuperscript{30,31} The observed hyperresponsiveness in the dorsal prefrontal cortex may thus be (partly) attributed to the psychiatric comorbidity and not to the movement disorder itself. Because of the small sample size and the heterogeneous nature of psychiatric comorbidity, a post hoc analysis of subgroups was considered to be of very limited value and therefore not performed.

Although the areas of abnormal activity identified in this fMRI study are consistent with previous findings in other forms of inherited dystonia, data have been inconsistent with regard to the direction of these abnormalities. In patients with primary torsion dystonia, finger tapping was associated with decreased rather than increased somatosensory activity.\textsuperscript{12,13} Other genotype-specific differences are suggested by regional metabolism differences during the resting condition in a PET study between DYT1 and DYT6 MCs.\textsuperscript{19} Sporadic, mainly focal forms of dystonia also may have their own specific patterns of activation. In writer’s cramp, patients’ increased sensorimotor responses were detected using a finger-tapping paradigm.\textsuperscript{15,16} In orofacial dystonia, activation studies using a whistling task found deficient motor and enhanced somatosensory activation,\textsuperscript{10} while a study in laryngeal dystonia using a vocal motor task found reduced sensorimotor activation.\textsuperscript{17} Taken together, these findings suggest that brain areas involved in dystonia are comparable for all patients with dystonia but that the hyperresponsiveness and hyporesponsiveness patterns are phenotype and genotype specific. On the other hand, these inconsistencies may be explained by a number of methodological differences across studies, including patient selection criteria, imaging modality (PET vs fMRI), and differences in task paradigms. To resolve this issue, future studies should aim to compare various other phenotypic and genotypic homogeneous diagnostic groups within a single study using a comprehensive set of scanner tasks.

To detect the SGCE genotype-specific contribution to the observed brain activation patterns in our fMRI study, it would be interesting to study nonmanifesting SGCE MCs. Finally, the observed changes in BOLD signal in different cortical areas are possibly the result of changes in functional connectivity between the basal ganglia and different cortical areas. Because the myoclonus in M-D is thought to be of subcortical origin and the basal ganglia are involved in the pathophysiology of dystonia, one may consider that the hyperresponsiveness of the motor cortex in patients with M-D is due to decreased inhibition of the striato-pallido-thalamo-cortical circuit. Additional studies are needed to further elucidate this important issue.

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Author Contributions: Drs Beukers and Foncke equally contributed to this article. Dr Beukers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Foncke, Nederveen, and Tijssen. Acquisition of data: Beukers, van der Meer, Nederveen, de Ruiter, and Bour. Analysis and interpretation of data: Beukers, Foncke, van der Meer, de Ruiter, Bour, Veltman, and Tijssen. Drafting of the manuscript: Beukers. Critical revision of the manuscript for important intellectual content: Foncke, van der Meer, Nederveen, de Ruiter, Bour, Veltman, and Tijssen. Statistical analysis: Beukers and de Ruiter. Obtained funding: Beukers, Foncke, and Tijssen. Administrative, technical, and material support: Foncke, van der Meer, Nederveen, and Bour. Study supervision: Veltman and Tijssen.

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REFERENCES


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