Disorganised sensorimotor integration in mutation-positive Myoclonus-Dystonia: a functional MRI study

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Abstract

**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 dystonia patients.

**Patients:** Thirteen clinically affected *SGCE* mutation carriers and 11 control subjects were studied.

**Interventions:** A finger-tapping motor task was performed in a block design using a 3.0 Tesla MRI.

**Results:** In *SGCE* mutation carriers significant hyperresponsiveness in contralateral inferior parietal cortical areas, ipsilateral premotor and primary somatosensory cortex, and ipsilateral cerebellum were observed during the motor task compared to healthy controls.

**Conclusions:** The cortical activation patterns in *SGCE* mutation carriers during this motor task point to a disorganised sensorimotor integration in this uniform group of dystonic patients and is consistent with functional neuroimaging studies in other types of (hereditary) dystonia.
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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 depressed mood or anxiety.1 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 SGCE mutations are lacking, suggesting the involvement of other genes or environmental factors.5

M-D is considered as a dystonia-plus syndrome with the basal ganglia being thought to play a major role in dystonia.6,7 The pathophysiology of M-D is elusive but 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.7 On the other hand, abnormalities of sensory input processing in dystonic patients have been reported and are reflected by the ‘geste antagonistique’.8 Several observations strongly support the idea that sensorimotor integration is impaired in dystonia.6,9 Myoclonus in M-D is also likely to be of subcortical origin, i.e. basal ganglia, because of the lack of stimulus-sensitivity and the absence of giant somato-sensory evoked potentials.10

Functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been previously performed in primary torsion dystonia11-14, focal hand dystonia and writer’s cramp15-19, orofacial20, and laryngeal dystonia.21 Although conflicting results with respect to the activation patterns of different cortical and basal ganglia structures have been reported, all these studies do agree on dysfunction of the striato-pallido-thalamo-cortical circuit in dystonia.

Functional imaging studies in SGCE mutation carriers (MC) are very limited; a single 5-year old M-D patient showed a changes in the motor network when performing a drawing and hand ‘snapping’ task during an fMRI study, specifically in the thalamus and dentate nucleus.22 Recently, a study by our group showed reduced striatal D2 receptor binding in SGCE MC when compared to healthy control subjects.23
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The aim of the present fMRI study was to study the activation patterns in SGCE mutation positive MC 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 controls.

Subjects and Methods

Subjects

We studied 13 clinically affected SGCE MC, (mean age 47, range 19-65). Genetically, one was a ‘de novo’ mutation, 8 MC inherited the mutation from their father, and 4 MC inherited the mutation from their mother. The control group consisted of 11 (one left-handed) neurologically and psychiatrically healthy controls (mean age: 45 years, range: 23-71) and was age and gender matched to the SGCE MC group. Eleven of the 13 SGCE MC have been recently described as part of a large Dutch M-D family (genotype, 619-620del AG). The two remaining subjects were not related (genotype, IVS7+2 C>T and c.179A>C (His>Pro)). In six out of eight patients who inherited the mutation from their father, myoclonus was only distally located on neurological examination. The four patients who inherited the mutation from their mother showed mild axial dystonia. Psychiatric history was positive in nine out of thirteen patients (see Table 1). SGCE MC were clinically scored using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Unified Myoclonus Rating Scale (UMRS). The clinical characteristics of the SGCE MC are summarized in Table 1. Informed consent was obtained in all subjects and the study was approved by the local medical ethics committee.

Methods: 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
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The task consisted of 6 epochs, each task epoch lasted 18s and was preceded by a 16s rest block.

**Functional Magnetic Resonance Imaging Scanning**

Imaging was performed using a 3.0 T Philips Intera scanner with a SENSE head coil. Stimuli were generated using a Pentium PC running the ePrime (http://www.pstnet.com/products/e-prime/) software package 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 (EPI) sequence; TE=30ms, TR=2011ms, 64x64 matrix, 35 slices, 3x3 mm in-plane resolution, slice thickness 3mm with a 1mm interslice gap, covering the entire brain. A session consisted of one EPI session, followed by a T1-weighted structural 3D inversion-recovery MR scan (0.78x0.78x2mm resolution).

The 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 hyper/hyporesponsiveness to indicate that group by task interactions as reported below represent differential changes in neural activity in response to the task performed, but not differences in baseline perfusion.

**Statistical analysis**

Imaging data were analysed using SPM2 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). Spatially, images were realigned, normalised into the standard space of the MNI-152 brain and smoothed with an 8-mm Gaussian kernel. The data were corrected for differences in slice-timing, high-pass filtered and analysed in the context of the General Linear Model. Boxcar regressors, convolved with the canonical haemodynamic response function (HRF), were used to model the response during the task.

Linear contrasts of parameter estimates were computed for main effects of task versus 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.
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groups, as well as interactions between groups. Main effects across groups are reported at $p<0.05$, corrected for multiple comparisons using the False Discovery Rate method\textsuperscript{26}, with a cluster size restriction of 10 voxels. Interaction effects were calculated as $T$ contrasts between SGCE MC and control subjects and are reported at $p<0.001$ uncorrected, masked with the appropriate main effect at $p<0.001$ and a voxel extent threshold of 5 voxels.

**Results**

The clinical characteristics of the SGCE MC are summarized in Table 1.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>BFMDRS/UMRS</th>
<th>Psychiatric Symptoms</th>
<th>Medication</th>
<th>Type of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>2 / 28</td>
<td>Depr</td>
<td>Paroxetine</td>
<td>Fa</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>3 / 8</td>
<td>-</td>
<td>-</td>
<td>Fa</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>0 / 4</td>
<td>Anx</td>
<td>-</td>
<td>Fa</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>F</td>
<td>22 / 80</td>
<td>Depr, Anx</td>
<td>Citalopram</td>
<td>Fa</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>2 / 4</td>
<td>Anx</td>
<td>-</td>
<td>Fa</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>14 / 12</td>
<td>Depr, Anx, OCD</td>
<td>Clomipramin</td>
<td>Fa</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>M</td>
<td>10 / 48</td>
<td>Depr, Anx, OCD</td>
<td>-</td>
<td>‘de novo’</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>M</td>
<td>10 / 43</td>
<td>OCD</td>
<td>-</td>
<td>Fa</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>M</td>
<td>2 / 42</td>
<td>-</td>
<td>-</td>
<td>Fa</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>F</td>
<td>6 / 0</td>
<td>-</td>
<td>-</td>
<td>Mo</td>
</tr>
<tr>
<td>11</td>
<td>53</td>
<td>F</td>
<td>8 / 0</td>
<td>Anx</td>
<td>Venlafaxin</td>
<td>Mo</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>M</td>
<td>6 / 0</td>
<td>-</td>
<td>-</td>
<td>Mo</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>F</td>
<td>6 / 0</td>
<td>Depr, Anx</td>
<td>Clomipramin</td>
<td>Mo</td>
</tr>
</tbody>
</table>


All subjects were able to perform the tasks correctly during the practice outside the scanner. Because the task does not require dexterity, we included one 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.

**Imaging data:**

One SGCE MC (nr 7) data set was discarded from further analysis due to excessive head movement during scanning. Main effects across groups consisted of bilateral,
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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.

Table 2: Main effects across groups: MNI coordinates and Z values for areas with significant activation.

<table>
<thead>
<tr>
<th>Activated brain areas</th>
<th>Brodmann area</th>
<th>MNI</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>-</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 -87 -9</td>
<td>5.59</td>
</tr>
<tr>
<td>Contraletal parietal cortex (SII)</td>
<td>40</td>
<td>39 -42 51</td>
<td>5.58</td>
</tr>
<tr>
<td>Ipsilateral parietal cortex (SII)</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>

Table legend: SII: secondary somatosensory cortex, MNI: Montreal Neurological Institute

Figure 1: Main effects across groups

Figure Legend: Main effects across groups during the finger tapping task, corrected at 0.05 False Discovery Rate (FDR) with a voxel extent threshold of 10.
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Table 3: Motor task: MNI coordinates and Z values for areas with significant differences in activation.

<table>
<thead>
<tr>
<th>Groups compared</th>
<th>Activated brain areas</th>
<th>Brodmann area</th>
<th>MNI</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC &gt; CO</td>
<td>Contralateral parietal (SII)</td>
<td>40</td>
<td>-36 -54 45</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral cerebellum</td>
<td>-</td>
<td>15 -81 -33</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral DLPFC</td>
<td>9</td>
<td>54 6 33</td>
<td>3.58</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral cingulate</td>
<td>24</td>
<td>0 12 27</td>
<td>3.53</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral sensory</td>
<td>3</td>
<td>51 -15 39</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral premotor</td>
<td>6</td>
<td>39 -3 42</td>
<td>3.25</td>
</tr>
<tr>
<td>CO &gt; MC</td>
<td>Contralateral insula</td>
<td>13</td>
<td>-39 9 12</td>
<td>3.49</td>
</tr>
</tbody>
</table>

Table legend: MC: manifesting carriers, CO: control subjects, MNI: Montreal Neurological Institute

In the SGCE MC group, significant cortical hyperresponsiveness of the contralateral secondary somatosensory cortex (S-II, BA40), ipsilateral premotor cortex (BA6), primary somatosensory cortex (BA3), dorsolateral prefrontal cortex (DLPFC, BA9) and the ipsilateral cerebellum was seen as compared to controls (Figure 2).

Figure 2: Hyperresponsiveness in manifesting SGCE gene mutation carriers

Figure legend: SGCE MC: A: significant cortical hyperresponsiveness of the contralateral secondary somatosensory cortex (S-II, BA40), B: ipsilateral premotor cortex (BA6), C: primary somatosensory cortex (BA3), D: dorsolateral prefrontal cortex (DLPFC, BA9) and E: the ipsilateral cerebellum.
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Hyporesponsiveness was found in the contralateral insula (BA13) (Figure 3).

Figure 3: hyporesponsiveness in manifesting SGCE gene mutation carriers

Figure legend: SGCE MC: significant hyporesponsiveness in the contralateral insula (BA13).

This analysis was repeated omitting the four subjects with only slight axial dystonia, who inherited the mutation from their mother, yielding similar results in the same areas (not shown). Linear regression analysis was performed with UMRS and BFMDRS as regressors. No correlation between myoclonus and/or dystonia and BOLD signal was found.

Comment

To our knowledge, the present fMRI study is the first functional imaging study that has been performed in a group of SGCE MC. Our aim was to visualize differences in brain activation patterns specifically in a homogeneous group of patients with dystonia. In the following paragraphs, 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 controls.\textsuperscript{27} The main findings of the motor task in SGCE MC in the present fMRI study include hyperresponsiveness in different
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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 regions has been previously described in different forms of dystonia but not in myoclonus.

First, the hyperresponsiveness of the pre-motor cortex in our study is consistent with the resting state findings in a PET study performed in clinically affected DYT-1 and DYT-6 MC. In dystonia, it has been hypothesized that overactivity of the pre-motor areas reflects cortical hyper-excitability 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 ipsi- and not contralateral pre-motor cortex hyperresponsiveness, suggesting ‘overflow’ of activity, due to decreased inter-hemispherical 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 (BA40 or S-2) is consistent with a PET study in clinically affected DYT-1 and DYT-6 mutation carriers, in which this area was also found to exhibit hypermetabolism. The BA40 or S-II, 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 DLPFC (BA9), presumably the frontal eye-field, which is part of the pre-motor area and encompasses all of BA8 and portions of BA9, 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 due to the simplicity of the task since basal ganglia structures are known to be activated primarily during complex motor tasks.
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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 MC and controls. The proper method to control for myoclonus would be EMG co-registration, which was, however, not available in our lab when the present study was conducted. In future studies EMG co-registrations during fMRI should be performed by directly relating the BOLD signal to the involuntary movements and using the EMG signal to monitor task execution. Because myoclonus was an important symptom in most patients, as is illustrated by their scores on the UMRS, it is possible that our findings could be, at least partly, attributed to phenotype, i.e. 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 (inheriting the mutation from their mother) yielded strikingly similar results, suggesting that the changes are genotype- rather than phenotype specific. The mutation of the four M-D patients who inherited the mutation from their mother have the same type of mutation as the other M-D patients who inherited the mutation from their father, which excludes the possibility of a benign polymorphism. We consider the strength of this study the genotypical homogeneity, rather than phenotypical 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 OCD patients, mainly in the basal ganglia and DLPFC. The observed hyperresponsiveness in the DLPFC may thus be (partly) attributed to the psychiatric co-morbidity and not to the movement disorder itself. Because of the small sample size and 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 the present fMRI study are consistent with previous findings in other forms of inherited dystonia, data has 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, sensorimotor activity. Other genotype specific differences are suggested by regional metabolism differences during resting condition in a PET study between DYT-1 and DYT-6 carriers. Sporadic, mainly focal, forms of
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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{16,17} In orofacial dystonia, activation studies employing a whistling task found deficient motor and enhanced somatosensory activation\textsuperscript{20}, while a study in laryngeal dystonia using a vocal motor task found reduced sensorimotor activation.\textsuperscript{21} Taken together, these findings suggest that brain areas involved in dystonia are comparable for all dystonia patients, but that the hyper- and hyporesponsiveness patterns are pheno- 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 at comparing various other pheno- and genotypic homogeneous diagnostic groups within a single study, using a comprehensive set of scanner tasks. To detect the \textit{SGCE} genotype-specific contribution to the observed brain activation patterns in the present fMRI study, it would be interesting to study non manifesting \textit{SGCE} MC.

Finally, the observed changes in BOLD signal in different cortical areas possibly are the result of changes in functional connectivity between the basal ganglia and different cortical areas. Since 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 hyperresponsivness of the motor cortex in M-D patients is due to decreased inhibition of the striato-pallido-thalamo-cortical circuit. Further studies are needed to further elucidate this important issue.

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References: