The role of dopamine and serotonin in cervical dystonia

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STRUCTURAL, FUNCTIONAL AND
MOLECULAR IMAGING OF THE BRAIN
IN PRIMARY FOCAL DYSTONIA
– A REVIEW


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Chapter 2

ABSTRACT

Primary focal dystonias form a group of neurological disorders characterized by involuntary, sustained muscle contractions causing twisting movements and abnormal postures. The estimated incidence is 12-25 per 100,000. The pathophysiology is largely unclear but genetic and environmental influences are suspected. Over the last decade neuroimaging techniques have been applied in patients with focal dystonia. Using structural, functional and molecular imaging techniques, abnormalities have been detected mainly in the sensorimotor cortex, basal ganglia and cerebellum. The shared anatomical localisations in different forms of focal dystonia support the hypothesis of a common causative mechanism. The primary defect in focal dystonia is hypothesised in the motor circuit connecting the cortex, basal ganglia, and cerebellum. Imaging techniques have clearly enhanced current knowledge on the pathophysiology of primary focal dystonia and will continue to do so in the future.
INTRODUCTION

Dystonia is a syndrome characterized by involuntary, sustained muscle contractions causing twisting movements and abnormal postures. Epidemiological studies are limited: in two service-based studies performed in a total of nine European countries the incidence was estimated to be 12-25 per 100,000. The only population-based study performed in Austria, found an incidence of 732 per 100,000. It is the third most common movement disorder after Parkinson’s disease (prevalence 65.6-12,500 per 100,000) and tremor disorders (prevalence 900 per 100,000).

Dystonia can be classified based on different characteristics. An important division is between primary or idiopathic and secondary dystonia: patients with primary dystonia have no brain abnormalities on conventional imaging with CT or MRI, while lesions such as lacunar infarcts, iron depositions or hemorrhage in the basal ganglia may be seen in patients with secondary dystonia. Another frequently used classification is based on topographic distribution, including focal dystonia (one body region), segmental dystonia (two or more adjacent regions), multifocal dystonia (two or more nonadjacent regions), hemidystonia (ipsilateral arm and leg) and generalized dystonia. The most common forms of focal dystonia include cervical dystonia (dystonia of the neck), blepharospasm (dystonia of the eyelids) and task-specific or focal hand dystonia (dystonia of one or both hands).

Until a few decades ago it was believed that dystonia was a psychiatric condition. Currently, we consider it a neurological disease. Yet, the pathophysiology of several forms of dystonia is still an enigma. Seventeen, mainly autosomal dominantly inherited dystonic syndromes have been described, defined as DYT1-17 and thus far 7 genes have been identified. These inherited forms are usually young onset, generalised forms of dystonia and include, among others, primary generalised dystonia (DYT1), myoclonus dystonia (DYT11) and dopa-responsive dystonia (DYT5). In this review we focus on the most frequent occurring group: the primary focal dystonias, usually starting at later age (40-60 years). No causative genes have been detected yet, although in about 30% of these patients a positive family history has been described, with multiple family members with focal dystonia, and sometimes even more than one form of focal dystonia. Therefore, it seems likely that focal dystonias may have a common, but presently unknown, cause, and that the clinical manifestations of the focal dystonias may be heterogeneous.

Since the 1990s, several imaging techniques including MRI and scintigraphic techniques have been used to study several forms of primary focal dystonia. These different imaging techniques have been used to study different aspects of the pathophysiology of focal...
dystonia. For example, diffusion-tensor imaging has been used to study connectivity in the white matter, functional MRI to study activation of certain brain areas and PET and SPECT to study altered cerebral blood flow, glucose metabolism, or concentrations of neurotransmitters or receptors such as dopamine (receptors). Several structural, functional and molecular abnormalities were found and these results have increased our understanding of the pathophysiology of focal dystonias. In this review, first the results from published imaging studies in patients with focal dystonia will be outlined, where after the current concepts on the pathophysiology of focal dystonia will be discussed.

### Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1985 until April 2010 with combinations of the terms (“focal dystonia”, “cervical dystonia”, “blepharospasm”, “writer’s cramp”, “focal hand dystonia”, “laryngeal dystonia”, “oromandibular dystonia”) and (“MRI”, “VBM”, “DTI”, “fMRI”, “PET”, “SPECT”, “MEG”, “EEG”). Articles were further identified from the reference lists of found articles. Only papers in English were reviewed.

### Imaging studies in focal dystonia

In the following sections, the different imaging techniques used in patients with primary focal dystonia will be explained and subsequently the results of studies using these techniques will be summarized and shortly discussed if required. Patients with DYT1 dystonia or myoclonus-dystonia (DYT11) can sometimes have a phenotype with only focal dystonia, for example writer’s cramp. We will not discuss results from studies on these patient groups, but we will focus on studies in genetically unexplained primary focal dystonias. For a more detailed overview of the included studies, see tables 1-3. All the studies we identified were case-control studies. In general, the abnormalities that we will discuss can be divided in three groups: abnormalities in the basal ganglia and thalamus, in the sensorimotor cortex and in the cerebellum.

- **MRI-techniques**
  
  **Voxel-based morphometry**
  
  Voxel-based morphometry (VBM) is an image technique that allows comparison of regional brain volumes between two groups on T1-weighted magnetic resonance imaging (MRI) scans, usually a group of patients and a group of sex- and age-matched controls. Using VBM it is possible to detect and quantify differences in gray and white matter volume that are not visible with the naked eye. The biggest advantage of VBM is that it involves the whole brain instead of preset regions of interest (ROIs), making it less time-consuming and more objective than other MRI techniques.¹⁰
Eight papers were identified that used VBM in focal dystonia patients (table 1). All these studies compared a group of patients with focal dystonia to a group of healthy age- and sex-matched controls. With respect to findings in the basal ganglia, a bilateral increase in putaminal gray matter up till 10% has been found in patients with blepharospasm (BLS), focal hand dystonia (FHD), patients with different forms of focal dystonia (cervical dystonia, focal hand dystonia, spasmodic dysphonia and musician’s dystonia), and in patients with orofacial dystonia. An increase in putaminal gray matter has also been found in patients with abnormal temporal discrimination threshold (TDT). TDT is the minimum time between two stimuli, for example electrical stimulation (tactile) or light flashes (visual), that makes it possible to perceive these stimuli as asynchronous. In the above named study by Bradley and co-workers, TDT was measured with both visual and tactile stimuli. Abnormal TDTs have been described in a number of conditions in the past, including different forms of focal and generalized dystonia, Parkinson’s disease and multiple system atrophy. It has been proposed as an endophenotype of these disorders. Therefore, it is possible that abnormal TDT is an indicator of abnormal basal ganglia function. Interestingly, also relatives of patients with different types of focal dystonia that had increased TDT had an increase in putaminal gray matter, in contrast to relatives with normal TDT.

It seems that a bilateral increase in putaminal gray matter is a consistent finding among different forms of focal dystonia; although one study found a significant bilateral decrease in gray matter in the putamen together with a bilateral increase in the gray matter in the caudate nucleus in patients with cervical dystonia (CD) and BLS compared to controls. There is no clear explanation for this contrasting result, since the patient groups among the different studies are comparable. Abnormalities in other parts of the basal ganglia and the thalamus have also been described. These consist of an increase in gray matter in the right globus pallidus interna in CD, a bilateral decrease in gray matter in the thalamus in FHD, and a bilateral increase of gray matter volume in the nucleus accumbens and the globus pallidus interna in patients with CD and FHD.

In the primary sensorimotor cortex (SMC) a bilateral increase of gray matter volume in the motor cortex has been reported in patients with CD. In patients with FHD the gray matter volume in the PMC was also increased, but only contralateral to the affected hand. An increase in gray matter volume in the primary sensory cortex has been described in patients with writer’s cramp (WC) and FHD both bilaterally as well as contralateral to the affected hand.
**Table 1.** Characteristics of VBM studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type*</th>
<th>N*</th>
<th>Ageb</th>
<th>M/Fb</th>
<th>Increased volumed</th>
<th>Decreased volumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black et al</td>
<td>1998</td>
<td>BLS/FHD</td>
<td>13</td>
<td>56±15</td>
<td>4/9</td>
<td>Putamen</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5 BLS, 8 FHD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley et al</td>
<td>2009</td>
<td>PTD</td>
<td>35</td>
<td>53 (35-73)</td>
<td>UKc</td>
<td>Putamen</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20 CD, 13 FHD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delmaire et al</td>
<td>2007</td>
<td>WC</td>
<td>30</td>
<td>50±13</td>
<td>9/21</td>
<td>-</td>
<td>L SMC, thalamus, cerebellum</td>
</tr>
<tr>
<td>Draganski et al</td>
<td>2003</td>
<td>CD</td>
<td>10</td>
<td>44±11</td>
<td>3/7</td>
<td>PMC, cerebellum, R GPi</td>
<td>R SMA, R prefrontal cortex, R visual cortex</td>
</tr>
<tr>
<td>Egger et al</td>
<td>2007</td>
<td>CD/FHD</td>
<td>22</td>
<td>CD 49±9; FHD 42±16</td>
<td>14/8</td>
<td>GPI, nu accumbens, prefrontal cortex, L inf parietal lobe</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11 CD, 11 FHD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etgen et al</td>
<td>2006</td>
<td>BLS</td>
<td>16</td>
<td>67±4</td>
<td>4/12</td>
<td>Putamen</td>
<td>L inf parietal lobe</td>
</tr>
<tr>
<td>Garraux et al</td>
<td>2004</td>
<td>FHD</td>
<td>36</td>
<td>53±10</td>
<td>21/15</td>
<td>PSC, PMC</td>
<td>-</td>
</tr>
<tr>
<td>Obermann et al</td>
<td>2007</td>
<td>CD/BLS</td>
<td>20</td>
<td>CD 58±7; BLS 53±11</td>
<td>6/14</td>
<td>Thalamus (CD), caudate head, sup temp lobe, L cerebellum</td>
<td>Putamen, thalamus (BLS)</td>
</tr>
</tbody>
</table>

Unless stated otherwise detected abnormalities are bilateral. Studies are named in the same order as in the text.

*BLS = blepharospasm, CD = cervical dystonia, FHD = focal hand dystonia, MuD = musician's dystonia, PTD = primary torsion dystonia, SD = spasmodic dysphonia, WC = writer's cramp

bAge is depicted as mean ± SD where possible. If information was insufficient, median and range are depicted, M/F=Male/Female

cUK = unknown

dGPI = globus pallidus interna, PMC = primary motor cortex, PSC = primary somatosensory cortex, SMA = supplementary motor area, SMC = sensorimotor cortex
Abnormalities in the cerebellum consist of a bilateral increase in gray matter volume of the cerebellar flocculus in patients with CD\(^1\) and bilateral structural abnormalities in the sensorimotor territory of the cerebellum in patients with FHD.\(^2\)

Other abnormalities include a bilateral increase in gray matter volume of the prefrontal cortex in patients with CD and FHD\(^1\)\(^8\) and a decrease in gray matter of the left inferior parietal lobe in patients with BLS\(^1\)\(^2\).

All together, using VBM, abnormalities have been found in the basal ganglia, especially in the putamen, the thalamus, sensorimotor cortex and cerebellum of patients with focal dystonia.

**Diffusion-tensor imaging**

Diffusion-tensor imaging (DTI) is a relatively new MRI technique that measures macroscopic axonal organization in nervous system tissues by measuring water diffusion. In white matter the water diffusion parallel to the fibers is less restricted compared to perpendicular to the fibers, because of axonal membranes and myelin sheaths. The discrepancy between the restriction parallel and perpendicular to the fiber is expressed in the fractional anisotropy (FA) parameter. By definition, FA is low in the cortex, as nerve terminals are not aligned in the same direction. DTI therefore, is mainly useful to detect abnormalities in the white matter and to assess connectivity of different brain regions.\(^2\)\(^0\) In patients with focal dystonia a few small DTI studies (n=6 studies) have been performed and abnormalities were detected in pathways to and from the basal ganglia and the sensorimotor cortex.

In a study by Colosimo and co-workers, in patients with CD (n=15) a decreased FA was found in the corpus callosum, as well as the left pallidum, left putamen and caudate nucleus bilaterally when compared to healthy controls. An increased FA was found bilaterally in the putamen.\(^2\)\(^1\) Similarly, in 18 patients with CD, DTI showed increased FA in the putamen bilaterally, decreased FA in the corpus callosum, increased mean diffusivity (MD) in the prefrontal cortex bilaterally and the left SMA and decreased MD in the right caudate and left putamen. These findings are consistent with increased fibre coherence and more ordered tissue, possibly indicating increased cellularity in the basal ganglia, including the putamen in patients. Besides, it suggests loss of neurons in the prefrontal cortex, SMA and the corpus callosum.\(^2\)\(^2\) In contrast to this, Bonilha and co-workers found an increase in FA in the thalamus, basal ganglia and adjacent white matter and significant decreased FA in the frontal projections in 7 patients suffering mainly from CD.\(^2\)\(^3\) In a later study, the same group found disrupted thalamic-prefrontal pathways in 7 patients with mainly CD compared to controls.\(^2\)\(^4\) Patients with BLS (n=16) did not
show abnormalities compared to healthy controls.\textsuperscript{22} Blood et al. used DTI to examine white matter abnormalities in patients with CD (n=4) and FHD (n=2) before and after treatment with botulinum neurotoxin (BoNT). They found that patients with dystonia had unilateral increased FA, consistent with subcortical white matter abnormalities in the ansa lenticularis, compared to controls, that disappeared 4 weeks after BoNT treatment. The ansa lenticularis is a distinct bundle of neurons that projects from the globus pallidus to the thalamus. The white matter asymmetry observed in the ansa lenticularis of dystonia patients before treatment may have reflected activity-dependent microstructural changes in the projection fibers of neurons exhibiting abnormal activity. According to the authors, it is unlikely that the observed normalisation after BoNT treatment is a permanent change, because the asymmetries that were observed after earlier BoNT injections were not associated with clinical effectiveness.\textsuperscript{25}

One study comparing 26 WC patients with controls, found an increase in FA in the fiber tracks connecting the primary sensorimotor areas to subcortical structures, including the corticospinal tract.\textsuperscript{26}

In summary, studies using DTI have shown abnormalities in the fiber tracks connecting the basal ganglia, cortex and cerebellum. Increased FA could be attributed to increased cellular density, with increased fiber coherence and more ordered tissue, containing large numbers of similarly aligned neurons, in the basal ganglia. The observed FA decrease in the corpus callosum might, however, be related to a decreased number of axons connecting cortical regions of the two cerebral hemispheres to each other.\textsuperscript{21, 22}

\textit{Magnetic resonance spectroscopy}

Magnetic resonance spectroscopy (MRS) is an MRI technique used to measure regional variations in neurochemistry and display concentrations of various brain metabolites in preset regions of interest (ROIs) in the brain.\textsuperscript{27} In one study in 7 patients with WC it was used to quantify gamma-aminobutyric acid (GABA) in different ROIs. GABA is an inhibitory neurotransmitter that influences the dopaminergic system. In the study by Levy and co-workers, there was a significant decrease in GABA levels in the motor cortex and lenticular nucleus contralateral to the affected hand compared to controls. These findings suggest that GABAergic neurons are non-uniformly affected and that a decreased inhibition of the dopaminergic system may play a role in the pathophysiology of patients with WC.\textsuperscript{28}

\textit{Functional MRI}

Functional MRI (fMRI) is the most commonly used imaging technique in studies in patients with focal dystonia to date. Blood-oxygen-level dependence (BOLD) is the most widely used MRI contrast. The MRI signal is weighted by the ratio of
oxyhemoglobin (oxygenated and isomagnetic) and deoxyhemoglobin (deoxygenated and paramagnetic) and therefore relates in an indirect manner to regional cerebral blood flow and neural activity. In most applications the BOLD signal is measured when a patient is performing a task. This allows for a statistical comparison of the fMRI signal and the task design, eventually yielding activation maps of the entire brain. The different designs combined with different tasks allow studying dystonia as a dynamic condition, instead of the static results obtained with for example VBM and DTI.

Numerous tasks can be performed during fMRI scanning, such as writing, drawing or hand movements (WC and FHD) and blinking (BLS), but visual and tactile stimulation tests have also been used in studying focal dystonias. An important distinction must be made between tasks that do or do not induce dystonia, especially when comparing patients to healthy controls. Tasks that induce dystonia are likely to show dystonic activity in motor cortex and associated areas during fMRI, where tasks that do not induce dystonia are believed to show primary changes in the brain or longstanding consequences of dystonia. We will discuss the different tasks and results below. For an overview of the studies see table 2.

- **Writer’s cramp, tasks that did not induce dystonia**
  During wrist movements, Oga and co-workers found decreased activity of the sensorimotor cortex (SMC) and supplementary motor area (SMA) associated with voluntary muscle contraction, but also with muscle relaxation in WC compared to controls. This finding strongly supports the view that an impairment of the excitatory as well as inhibitory motor control mechanism may be an underlying mechanism inducing dystonia. In this study, no basal ganglia abnormalities were observed. In contrast, Blood et al. found mainly basal ganglia activity in their study and no cortical activity, comparing patients with FHD to healthy controls during and after finger tapping. After performing the task, there was sustained basal ganglia activity in patients compared to controls. This effect was observed after tapping with the non-dystonic hand, uncorrelated to dystonic severity in the right lentiform nucleus and not observed in the primary sensorimotor cortex. In a study by Delmaire and co-workers, FHD patients and healthy controls performed flexion/extension of the right and left fingers and toes and contraction of the lips. The somatotopic representation of the body in the putamen contralateral to the affected limb was disrupted in subjects with WC compared to controls.
### Table 2. Characteristics of fMRI studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type</th>
<th>N</th>
<th>Agea</th>
<th>M/Fb</th>
<th>Increased activationd</th>
<th>Decreased activationd</th>
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<tbody>
<tr>
<td><strong>Tasks that did not induce dystonia</strong></td>
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</tr>
<tr>
<td>Baker et al</td>
<td>2003</td>
<td>BLS</td>
<td>5</td>
<td>50-62</td>
<td>1/4</td>
<td>Ant visual cortex, ant cingulate cortex, PMC, thalamus and cerebellum</td>
<td>-</td>
</tr>
<tr>
<td>Blood et al</td>
<td>2004</td>
<td>WC</td>
<td>5</td>
<td>31-58</td>
<td>2/3</td>
<td>Basal ganglia</td>
<td>-</td>
</tr>
<tr>
<td>De Vries et al</td>
<td>2008</td>
<td>CD</td>
<td>8</td>
<td>30-55</td>
<td>2/6</td>
<td></td>
<td>Imagining: parietal, left premotor and cingulate cortex Motor execution: right putamen, insula, and cingulate cortex</td>
</tr>
<tr>
<td>Delmaire et al</td>
<td>2005</td>
<td>WC</td>
<td>14</td>
<td>54±10</td>
<td>4/10</td>
<td>Altered somatotopic organization in the contralateral putamen</td>
<td>-</td>
</tr>
<tr>
<td>Dresel et al</td>
<td>2006</td>
<td>BLS/Meige</td>
<td>26</td>
<td>49-71</td>
<td>UK</td>
<td>Both; Bilateral SSA, caudal SMA, Only Meige; PMC and premotor cortex</td>
<td>-</td>
</tr>
<tr>
<td>Islam et al</td>
<td>2009</td>
<td>WC</td>
<td>17</td>
<td>23-67</td>
<td>4/13</td>
<td>-</td>
<td>PMC, primary SSC, SMA, secondary SSC</td>
</tr>
<tr>
<td>Oga et al</td>
<td>2002</td>
<td>WC</td>
<td>8</td>
<td>22-58</td>
<td>5/3</td>
<td>-</td>
<td>L SMC and SMA</td>
</tr>
<tr>
<td><strong>Tasks that did induce dystonia</strong></td>
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<tr>
<td>Haslinger et al</td>
<td>2005</td>
<td>LD</td>
<td>12</td>
<td>53±9</td>
<td>7/5</td>
<td>Primary SMC, premotor and sensory association cortex</td>
<td></td>
</tr>
<tr>
<td>Hu et al</td>
<td>2006</td>
<td>WC</td>
<td>10</td>
<td>45±12</td>
<td>6/4</td>
<td>Contralateral basal ganglia and motor cortex, ipsilateral cerebellum</td>
<td>-</td>
</tr>
<tr>
<td>Preibisch et al</td>
<td>2001</td>
<td>WC</td>
<td>12</td>
<td>25-57</td>
<td>6/6</td>
<td>Ipsilateral cerebellum, primary SMC, PMA, thalamus</td>
<td>-</td>
</tr>
<tr>
<td>Pujol et al</td>
<td>2000</td>
<td>WC</td>
<td>5</td>
<td>24-50</td>
<td>4/1</td>
<td>L SMC</td>
<td>PMA</td>
</tr>
<tr>
<td>Schmidt et al</td>
<td>2003</td>
<td>BLS</td>
<td>6</td>
<td>32-67</td>
<td>2/4</td>
<td>Putamen, frontal and parietal operculum, SMA, SMC, visual areas and cerebellum</td>
<td>-</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Typea</td>
<td>N</td>
<td>Ageb</td>
<td>M/Fb</td>
<td>Increased activationd</td>
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<tr>
<td>Butterworth et al</td>
<td>2003</td>
<td>WC</td>
<td>9</td>
<td>18-72</td>
<td>8/1</td>
<td>-</td>
<td>Decreased separation (and reverse representation) of digits Reduced activation of the SSC and posterior parietal area</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>2009</td>
<td>WC</td>
<td>12</td>
<td>29-63</td>
<td>7/5</td>
<td>-</td>
<td>Reduced inter-digit representation, reversals and overlapping activation. Reduced activation of PSC</td>
</tr>
<tr>
<td>Peller et al</td>
<td>2006</td>
<td>WC</td>
<td>17</td>
<td>24-71</td>
<td>8/9</td>
<td>Putamen, caudate nucleus, GPI, thalamus, visual cortex, L ant insula, R intraparietal sulcus, cerebellum</td>
<td></td>
</tr>
</tbody>
</table>

Unless stated otherwise detected abnormalities are bilateral. Studies are named in the same order as in the text.

aBLS = blepharospasm, CD = cervical dystonia, LD = laryngeal dystonia, WC = writer’s cramp
bAge is depicted in years as mean ± SD where possible. If information was insufficient, median and range are depicted
UK = unknown
dGPI = globus pallidus interna, PMA = premotor areas, PMC = primary motor cortex, PSC = primary somatosensory cortex, SMA = supplementary motor area, SMC = sensorimotor cortex, SSA = somatosensory areas, SSC = somatosensory cortex
Disease severity correlated with decreased activation in the altered putamen in these patients. In another study, patients with WC show decreased activation in the primary sensorimotor cortex and the secondary somatosensory cortex, during tapping and index finger flexion without showing signs or reporting feelings of dystonia compared to controls. Overall, activation was more often bilateral in patients compared to controls, although this was not the case in all the above named areas. These changes were observed in a study using motor tasks performed with the dystonic and the clinically asymptomatic hand and compared to healthy controls performing these tasks with both hands. The cortical activation pattern differed between tapping and flexion in the within-subject comparison: the abnormalities were more widespread while performing the repetitive movement tapping even though there were no dystonic muscle contractions.

- **Writer’s cramp, tasks that did induce dystonia (visually checked)**

Preibisch and co-workers showed significant activation of the contralateral thalamus, extended activation of the primary sensorimotor cortex with a maximum of activation in the premotor area, and greater activation of the ipsilateral cerebellum during writing in patients with WC when compared to healthy controls. These findings were replicated in a study by Hu and co-workers. They compared patients with WC to controls while writing with a pencil and writing with a finger. They found significant activation of contralateral basal ganglia (especially the putamen), sensorimotor cortex (primary sensory cortex, supplementary motor cortex, premotor cortex) and ipsilateral cerebellar hemisphere when patients with WC wrote with a pencil and data were compared with healthy controls performing the same task. There was no obvious difference in writing with a finger between controls and patients, but writing with a finger did not induce dystonia while writing with a pencil did. No within-subject comparisons were made in this study. One slightly different study compared patients with guitar-induced hand dystonia to healthy professional guitar players while playing guitar. There was increased primary sensorimotor cortex activation contralateral to the dystonic hand in dystonia-producing exercises in patients with hand dystonia compared to reference musicians. Premotor activation was notably reduced with respect to reference musicians and to the normal hand trials in each patient. A shift from premotor activation to primary sensorimotor activation was detected in the guitarists engaged in dystonia-producing exercises compared to the healthy musicians.
Neuroimaging in focal dystonia

- **Writer’s cramp, tasks with somatosensory stimuli**

In a study comparing patients with WC, FHD and focal arm dystonia to healthy controls during processing of vibrotactile stimulation of individual digit tips there was a reduced separation between digits 2 and 5 in the dystonic patients. Digital representations were compressed and disordered. These findings were replicated in a later study that found a reduction in the cortical distance between digits that are functionally related to the task of writing (digits 1-3), during sensory stimulation via vibration, in patients with WC compared to controls. The thumb representation is shifted into the cortical region normally occupied by digit 2. In one study completely different results were found: no abnormalities in digital representation, but increased activation of the basal ganglia. Discrimination of tactile input from the affected limb appeared to be associated with a widespread overactivation of the basal ganglia and lateral thalamus in patients with WC compared to controls. The increased activity in the basal ganglia was not specifically linked to the execution of the task and was less prominent in patients who had long-standing WC. Task-related activity was altered in other brain regions: there was a relative overactivity in posterior visual areas, left anterior insula and right intraparietal sulcus but not in the primary or secondary sensory cortex. A bilateral pontocerebellar cluster showed a linear decrease in task-related activity with increasing severity of dystonia.

- **Blepharospasm**

In patients with BLS, Baker and co-workers found bilateral increased activation of the visual cortex and area prostriata, primary motor cortex, cingulated cortex, posterior putamen, central thalamus, and the superior cerebellar hemispheres and vermis during spontaneous and voluntary blinking in patients with BLS compared to controls. Patients did not experience eyelid spasms during these tasks. The activated regions are normally engaged in spontaneous blinking. The finding of increased activation in brain regions associated with blinking has been replicated in another study that found unilateral or bilateral activation of the putamen during eyelid spasms in patients with BLS compared to controls. Primary and associative visual cortices were activated during voluntary blinking in patients and control subjects and have previously been reported to be activated during voluntary eye blinking. Dresel and co-workers compared patients with Meige’s syndrome (a syndrome with BLS and oromandibular dystonia) to patients with BLS and healthy controls while whistling. The whistling task activated a common distributed network including the sensorimotor and ventral premotor cortex, basal ganglia and rostral paravermal cerebellum in all groups. Patients with Meige’s syndrome showed deficient activation of the primary motor and ventral premotor cortex in the area that represents the mouth when compared to controls and patients with isolated BLS. Compared to controls, both the patients with BLS and Meige’s syndrome had relative
overactivity of the bilateral post-central gyrus and the caudal SMA during whistling. BoNT therapy partly reversed the overactivity of the post-central gyrus and caudal SMA in Meige's syndrome, but not in BLS.42

- **Other forms of focal dystonia**

Haslinger and co-workers compared patients with laryngeal dystonia pre- and post-BoNT to controls during vocalization, whispering, and rest. Reduced activation was detected in the right inferior primary motor and somatosensory cortices as well as left superior sensorimotor cortex in patients with laryngeal dystonia compared to controls during vocalization pre-BoNT as well as partly during whispering pre- and post-BoNT.43

In the only fMRI study in patients with CD, de Vries and co-workers compared patients to healthy controls during execution and imagination of hand movements. They found that CD was associated with impaired cerebral activation of the parietal cortices, cingulated cortex/SMA and ipsilateral putamen during both execution and imagining of non-dystonic right-hand movements.44

All together, in fMRI studies regions that show abnormalities are consistent among different forms of focal dystonia and consist of the primary sensory and motor cortex, accessory motor cortices, the basal ganglia, thalamus, and the cerebellum. Generally speaking, tasks that induce focal dystonia usually lead to an increase in activation, whereas tasks that do not induce dystonia lead to a decrease in activation of the above named areas. Other findings that stand out in fMRI studies are activation of the visual and visual association cortices while blinking, but also during tactile stimulation, and disorganisation of the hand area on the primary sensory cortex. The latter is especially present in patients with WC and consists of overlap of the areas representing different digits, mainly digits 1-3.38 The results suggest that dystonic symptoms are specific to digits that show reduced inter-digit separation, and that mere shifts in digit representation do not predict motor impairments.

- **Encephalographic techniques**

*Magnetoencephalography and electroencephalography*

Magnetoencephalography (MEG) and electroencephalography (EEG) studies in patients with focal dystonia show a considerable overlap with findings from neuroimaging studies, using fMRI and PET. We will give a short overview of studies using EEG and MEG in patients with focal dystonia. For more extensive information we refer to the references.
Neuroimaging in focal dystonia

EEG is a technique in which external electrodes are used to monitor cortical activity and reactivity.\textsuperscript{45} We identified four studies using EEG in patients with focal dystonia. In patients with FHD an increased Bereitschaftspotential during voluntary, non-dystonic contraction of wrist muscles compared to controls was detected.\textsuperscript{46} Furthermore, movement-related desynchronization (20-30 Hz) over the contralateral and midline cortical regions was deficient.\textsuperscript{47} Both studies point towards decreased cortical inhibition in focal dystonia. Other EEG studies in FHD, musician’s dystonia and CD found abnormalities in the beta band of the EEG signal.\textsuperscript{48-50} Interestingly, these abnormalities could be reduced by applying a sensory trick.\textsuperscript{50}

MEG is a technique that can be used to record magnetic fields generated by the brain. Because it is also possible to do depth recording, three-dimensional information can be gathered.\textsuperscript{51} The most consistent finding in studies using MEG in patients with WC and/or FHD is a disordered cortical representation of digits on the somatosensory cortex.\textsuperscript{52-56} The total surface representing the hand and different digits on the somatosensory cortex is decreased in some studies\textsuperscript{52 53 57} and increased in others\textsuperscript{52 54 55}. One study found similar results for patients with embouchure dystonia (task-specific dystonia of the mouth and jaw in musicians), namely altered lip and digit representation on the somatosensory cortex and a decreased cortical distance between hand and lip representations.\textsuperscript{57} Abnormalities are more pronounced in patients with more severe dystonia.\textsuperscript{53 56}

In three more recent MEG studies in patients with WC and/or FHD, oscillatory networks showed overall reduced high frequency oscillations in patients compared to controls.\textsuperscript{58} Furthermore, excessive coupling between the SMC bilaterally and reduced coupling between ipsilateral cerebellum and contralateral posterior parietal cortex during dystonic writing was found in patients compared to controls.\textsuperscript{59} The involvement of the parietal cortex was replicated in a study by Tecchio and co-workers.\textsuperscript{60} The EEG and MEG findings support the hypothesis of reduced inhibition and disturbed sensory-motor integration in focal dystonia patients.

- **Scintigraphic techniques**
  
  **Positron emission tomography**

  Positron emission tomography (PET) is a scintigraphic technique that uses radiopharmaceuticals emitting positrons. Shortly after a positron has been emitted, it will annihilate with an electron, after which 2 photons (in opposite direction of each other) will be emitted, which can be detected by a PET camera. The two radiopharmaceuticals commonly used in PET studies on focal dystonia are \( ^{18}\text{F}\)-fluorodeoxyglucose (\( ^{18}\text{F}\)-FDG) and \( ^{15}\text{O}\)-H\(_2\)O. These tracers are both used to quantify activity within brain regions. \( ^{18}\text{F}\)-FDG uptake reflects regional glucose metabolism
and \(^{15}\text{O}\)-H\(_2\text{O}\) quantifies regional cerebral blood flow (rCBF). Other tracers that have been used in studies on focal dystonia, are \(^{11}\text{C}\)-N-methyl-spiiperone (\(^{11}\text{C}\)-NMSP) and \(^{18}\text{F}\)-spiiperone (\(^{18}\text{F}\)-SP); radiopharmaceuticals that bind to dopamine D\(_{2/3}\) receptors (D2/3R) which are expressed intensively in the striatum. Dopamine is believed to play an important role in the pathophysiology of dystonia. One argument for the role of dopamine is the rare dystonia-plus syndrome dopa-responsive dystonia. Patients with this condition have a form of dystonia that can successfully be treated with levodopa.\(^{61}\) Other important arguments are the co-existence of dystonia in patients with Parkinson's disease, especially when they are treated for longer periods with levodopa\(^{62}\) and the possibility of developing dystonia after use of neuroleptics which are D2/3R blockers.\(^{63}\)

We will discuss the results of these techniques separately, for an overview of the studies see table 3.

- **Glucose metabolism**

Using \(^{18}\text{F}\)-FDG PET, increases and decreases in FDG uptake have been found in the basal ganglia, cerebellum and sensorimotor cortex of patients with focal dystonia. A bilateral increase in glucose metabolism in the lentifom nucleus has been found in patients with CD compared to controls.\(^{64}\) There was an increase in glucose metabolism in the striatum and thalamus of patients with BLS and Meige's syndrome compared to controls.\(^{65}\) Hutchinson and co-workers found increased glucose metabolism in the cerebellum and the pons in patients with BLS compared to controls. Furthermore, the authors of this study found that during induced sleep, patients with BLS showed glucose hypometabolism in the superior-medial aspect of Brodmann area 8 compared to controls. This region is associated with supranuclear control of eyelid opening.\(^{66}\) The glucose hypermetabolism in the cerebellum and the pons has been replicated in a study that examined patients with BLS after BoNT treatment. In this study, Suzuki and co-workers found a bilateral glucose hypermetabolism in the thalamus and the pons of patients with BLS compared to controls and a trend towards glucose hypermetabolism in the putamen bilaterally. Patients with incomplete suppression of BLS on BoNT had glucose hypermetabolism in the cerebellum and the pons compared to patients with complete suppression.\(^{67}\) Kerrison and co-workers found a complex network of cortical and subcortical regions with increased and decreased metabolism in patients with BLS compared to controls. There was increased metabolism in the inferior frontal gyri, right posterior cingulated gyrus, left middle occipital gyrus, fusiform gyrus of the right temporal lobe, left anterior cingulate gyrus and the caudate nucleus. Decreased glucose metabolism was found in the inferior frontal gyri, left cerebellar hemisphere, and thalamus. Lateralization of activation of the frontal and temporal cortex to the right with contralateral deactivation of the left cerebellum suggests a connection mediated by the corticopontocerebellar pathway.\(^{58}\)
Regional cerebral blood flow

Where the above described studies using $[^{18}\text{F}]-\text{FDG}$ found abnormalities in glucose metabolism mainly in the basal ganglia, the abnormalities in rCBF as measured with $[^{15}\text{O}]-\text{H}_2\text{O}$ are mainly cortically localized. Similar to findings of fMRI studies, $[^{15}\text{O}]-\text{H}_2\text{O}$ PET is often used in task-related studies on WC patients. The main advantage of $[^{15}\text{O}]-\text{H}_2\text{O}$ PET when compared to fMRI is that $[^{15}\text{O}]-\text{H}_2\text{O}$ PET is able to quantify regional cerebral blood flow. In addition, due to the short half lifetime of the radiotracer ($t_{1/2} = 2$ minutes), repeated studies can be performed in a short time period.\textsuperscript{69}

A study by Ceballos-Baumann and co-workers showed impaired activation of the primary motor cortex and greater activation in frontal and parietal association areas in WC patients compared to controls while writing. BoNT treatment failed to normalize the impaired activation of primary motor cortex, but did enhance activation of parietal cortex and accessory motor areas.\textsuperscript{70} In a study by Ibanez and co-workers, patients with WC also showed reduced rCBF in sensorimotor and premotor structures in different tasks compared to controls. Certain regions were significantly abnormal for individual tasks. Patients showed significantly less rCBF in the contralateral vs ipsilateral primary sensorimotor cortex, during sustained flexion or extension of the wrist. There was a significant decrease of rCBF in the left premotor cortex with writing, but there were no differences during tapping.\textsuperscript{71} Lerner and co-workers found a significant increase in rCBF of the primary sensory cortex and decrease of rCBF of the supplementary motor area (SMA) in patients with WC during writing and tapping compared to controls. Increased blood flow of the primary sensory cortex found in this study might reflect more intense processing of the sensory information or possibly expanded cortical representation of the hand area. The investigators also found increased flow in the right cerebellum of patients with WC compared to controls.\textsuperscript{72} In patients with CD using a sensory trick, a significant decrease of motor cortical blood flow contralateral to the side toward which the head tends to rotate was found. This modulation includes the SMA (anterior part), part of the precentral gyrus, and the primary sensorimotor cortex (SMC). In addition, the sensory trick leads to an increased activation of the parietal cortex ipsilateral to the direction of dystonic head rotation and bilateral occipital cortex.\textsuperscript{73} A study of patients with facial dystonia (blepharospasm and oromandibular dystonia) showed a significantly reduced primary sensorimotor area (PSA) blood flow response to vibration of the lower face in patients with facial dystonia compared to healthy controls. The peak activations the authors observed in this study were centered in the precentral gyrus, adjacent to the central sulcus, consistent with the primary motor cortex.\textsuperscript{74}
### Table 3. Characteristics of PET studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type</th>
<th>N</th>
<th>Age</th>
<th>M/F</th>
<th>Increased signals</th>
<th>Decreased signals</th>
</tr>
</thead>
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<tr>
<td><strong>Glucose metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Esmaeli-Gutstein et al</td>
<td>1999</td>
<td>BLS/ Meige</td>
<td>11</td>
<td>50-85</td>
<td>5/6</td>
<td>Striatum, thalamus</td>
<td>-</td>
</tr>
<tr>
<td>Hutchinson et al</td>
<td>2000</td>
<td>BLS</td>
<td>6</td>
<td>63±11</td>
<td>UK^c</td>
<td>Cerebellum and pons</td>
<td>Sup-med frontal cortex</td>
</tr>
<tr>
<td>Kerrison et al</td>
<td>2003</td>
<td>BLS</td>
<td>11</td>
<td>44-80</td>
<td>2/9</td>
<td>Inf frontal gyri, R post cingulate gyrus, L middle occipital gyrus, fusiform gyrus of the R temporal lobe and L ant cingulate gyrus R caudate</td>
<td>Inf frontal gyri, L inf cerebellum and thalamus</td>
</tr>
<tr>
<td>Magyar-Lehmann et al</td>
<td>1997</td>
<td>CD</td>
<td>10</td>
<td>36-71</td>
<td>4/6</td>
<td>Lentiform nucleus</td>
<td>-</td>
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<tr>
<td>Suzuki et al</td>
<td>2007</td>
<td>BLS</td>
<td>25</td>
<td>53±10</td>
<td>8/17</td>
<td>Thalamus, cerebellum and pons</td>
<td>-</td>
</tr>
<tr>
<td><strong>Regional cerebral blood flow</strong></td>
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<td></td>
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<tr>
<td>Ceballos-Baumann et al</td>
<td>1997</td>
<td>WC</td>
<td>6</td>
<td>35-66</td>
<td>4/2</td>
<td>Frontal association cortex</td>
<td>Contralateral PMC</td>
</tr>
<tr>
<td>Feiwell et al</td>
<td>1999</td>
<td>BLS</td>
<td>14</td>
<td>65±8</td>
<td>4/10</td>
<td>After BoNT: parietal cortex and caudal SMA</td>
<td>-</td>
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<tr>
<td>Ibanez et al</td>
<td>1999</td>
<td>WC</td>
<td>7</td>
<td>42±5</td>
<td>4/3</td>
<td>Primary SMC</td>
<td>Primary SMC, Less correlation between putamen and premotor cortical regions.</td>
</tr>
<tr>
<td>Lerner et al</td>
<td>2004</td>
<td>WC</td>
<td>10</td>
<td>31-58</td>
<td>6/4</td>
<td>PSC, PMC</td>
<td>-</td>
</tr>
<tr>
<td>Naumann et al</td>
<td>2000</td>
<td>CD</td>
<td>7</td>
<td>28-76</td>
<td>5/2</td>
<td>Ipsilateral superior and inferior parietal lobe, bilateral occipital cortex</td>
<td>Contralateral SMA and primary SMC</td>
</tr>
<tr>
<td>Odergren et al</td>
<td>1998</td>
<td>WC</td>
<td>4</td>
<td>35-51</td>
<td>2/2</td>
<td>L primary SMC, L premotor cortex, cerebellum (mainly R)</td>
<td>L supramarginal and angular gyri, inf part of the L temporal lobe</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Typea</td>
<td>N</td>
<td>Ageb</td>
<td>M/F</td>
<td>Increased signald</td>
<td>Decreased signald</td>
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</tr>
<tr>
<td>Leenders et al.</td>
<td>1993</td>
<td>CD</td>
<td>6</td>
<td>18-63</td>
<td>3/3</td>
<td>Contralateral striatum</td>
<td>-</td>
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<tr>
<td>Perlmutter et al.</td>
<td>1997</td>
<td>Cranial/FHD (cranial), 7 (FHD)</td>
<td>14</td>
<td>56±14</td>
<td>5/16</td>
<td>-</td>
<td>Putamen</td>
</tr>
</tbody>
</table>

Unless stated otherwise detected abnormalities are bilateral. Studies are named in the same order as in the text.

a BLS = blepharospasm, CD = cervical dystonia, FHD = focal hand dystonia, WC = writer’s cramp

b Age is depicted as mean ± SD where possible. If information was insufficient, median and range are depicted

c UK = unknown

d PMC = primary motor cortex, PSC = primary sensory cortex, SMA = supplementary motor area, SMC = sensorimotor cortex
The only study using $[^{15}\text{O}]$-butanol in patients with WC found increased blood flow in the contralateral thalamus and primary sensorimotor and premotor cortical areas, but also in the ipsilateral cerebellum as the patients with WC invoked progressively greater dysfunction by a longer duration of writing.$^{75}$

- **Dopamine receptor availability**

Two PET studies looked at D2/3R availability in patients with focal dystonia. Leenders and co-workers found no difference in striatal $[^{11}\text{C}]$-NMSP binding in patients with mainly CD when compared to healthy controls. A trend was observed regarding the side to side differences: specific binding of the tracer tended to be higher in the striatum contralateral to the side to which the head was turning to.$^{76}$ Another study showed decreased $[^{18}\text{F}]$-SP binding in the putamen of patients with hand and facial dystonia. There was no significant difference between patients with hand and facial dystonia.$^{77}$

In summary, using PET abnormalities have been shown in glucose metabolism, rCBF and D2/3R availability of patients with focal dystonia. Glucose metabolism was increased in the basal ganglia, thalamus, cerebellum and pons in the different studies. One study found an increase in glucose metabolism in a large cortico-subcortical network of which the meaning is not yet known. Abnormalities in rCBF were less consistent than the changes in glucose metabolism. Most studies found a decreased rCBF in the PMC, SMC, SMA and PSA and an increase in rCBF in frontal and parietal association areas. However, one study found an increase in rCBF in the PSC.$^{72}$ The authors stipulate that this could have been caused by more intense processing of the sensory information or expanded cortical representation of the hand area. One study found results that were completely the opposite of what the other studies found, namely an increased rCBF in the PMC, PSC, premotor areas, thalamus and cerebellum.$^{75}$ This was the only study that used a different tracer, namely $[^{15}\text{O}]$-butanol, but it is unlikely that this would have caused this difference. The involvement of the striatum and putamen has not only been shown by increased glucose metabolism but also using radiotracers for the D2/3R: a trend towards higher tracer binding in the striatum contralateral to the affected body side and decreased binding in the putamen of patients with hand and facial dystonia was found.

One striking abnormality that was shown in one study was the bilateral activation of the visual cortex in CD patients that used a sensory trick. This suggests that this region is part of the network responding to the application of a trick manoeuvre.$^{73}$ The visual cortex proved to be involved in non-visual tasks in the past, such as tactile object recognition and tactile orientation, Braille reading in the congenitally blind and visual imagery.$^{78}$ The sensory trick in patients with CD might help to determine the position of
the head relative to the rest of the body and therefore improve the position of the head. The visual cortex could play a role in this process in the same way it plays a role in tactile object recognition.

**Single-photon emission computed tomography**

Single-photon emission computed tomography (SPECT) is a technique very similar to PET. The most important differences between SPECT and PET are different tracers and the higher resolution of clinical PET images. With SPECT a radioactively labelled tracer (radiopharmaceutical) is injected and binds to specific receptors or transporters in the brain, or reflects blood flow. Most studies in patients with focal dystonia used radiopharmaceuticals that image the dopamine system, especially the postsynaptic D2/3R.

Hierholzer and co-workers found in 10 patients with CD that the average specific striatal binding to D2/3Rs, measured with $[\text{^{123}I}]$-iodobenzamide ($[\text{^{123}I}]$-IBZM) SPECT, was not significantly different from the control group. However, patients exhibited a more asymmetric striatal binding compared to controls and 50% of the patient group did show a higher receptor binding in the striatum contralateral to the direction of head rotation. The difference in binding was statistically significant for this patient group. This is in accordance with the increased dopamine receptor binding in the contralateral striatum found in the PET study in patients with CD mentioned above and has also been found in other SPECT studies. For example a tendency for a reduced IBZM binding in the dorsal portion and an increase in the ventral parts of the striatum contralateral to the side of head rotation was found by Becker and co-workers in 10 CD patients, but these results did not reach statistical significance, probably because of small study size (n=10). The abnormally low IBZM binding contralateral to the side of head deviation may indicate a reduced postsynaptic D2/3 receptor density within the lentiform nucleus. These findings may point towards the medial lentiform nucleus or pallidothalamic pathway as the site of pathology in CD. One study evaluated both the pre- and postsynaptic dopaminergic system in 10 patients with CD, using $[\text{^{123}I}]$-epidepride (a tracer for D2/3R) and $[\text{^{123}I}]$-β-CIT (a tracer for the presynaptic dopamine transporter = DAT). Striatal D2/3R binding was bilaterally significantly reduced in patients compared to controls, but there was no difference in striatal DAT binding.

In a study evaluating 10 patients with WC, Horstink and co-workers found that the striatal D2/3R binding was bilaterally decreased in patients compared to controls. Another SPECT study evaluated 5 patients with WC pre- and post-biofeedback-based
sensorimotor training with $^{[123]}$I-IBZM SPECT and also found decreased striatal binding. The training made patients more confident to write with a relaxed limb, writing improved and striatal D2R-binding restored to nearly normal levels.$^{84}$

Albin and co-workers performed the only study that evaluated integrity of cholinergic nerve terminals in 13 patients with CD using $^{[123]}$I-iodobenzovesamicol ($^{[123]}$I-IBVM), a SPECT tracer that binds to the vesicular acetylcholine transporter (VACHT). They found a reduced IBVM binding in the putamen as well as in the whole striatum in patients with CD compared to controls.$^{85}$

In summary, the findings in SPECT studies implicate a role for the striatal dopaminergic system and the basal ganglia in the pathophysiology of focal dystonia.

**DISCUSSION**

Different studies using different imaging techniques find abnormalities in the sensorimotor cortex, the basal ganglia and the cerebellum. This suggests that all these structures play a role in the pathophysiology of dystonia, although it is not possible to implicate one of these structures as the source of dystonia based on the current studies. It is likely that findings are related, as they share a pathophysiological basis. As such, the findings of the different imaging modalities each contribute supplementary information. For example, increased connectivity from the basal ganglia to the cortex and the cerebellum may also show as an increase in basal ganglia volume and could lead to increased metabolism in these regions. Moreover, if increased volume in the basal ganglia is based on increased cellularity, which is the most common hypothesis, this could also lead to increased levels of endogenous dopamine and consequently lower binding to postsynaptic D2/3R in the basal ganglia. Interestingly, until now only one study examined the integrity of nigrostriatal neurons by examining binding to striatal DATs.$^{82}$ Although this study did not find differences in striatal DAT, this does not exclude that endogenous dopamine levels are increased in focal dystonia.

It is striking to see that the found abnormalities are more or less consistent in all forms of focal dystonia. This suggests that there is a common underlying pathophysiological mechanism that can manifest itself in a body part, leading to one of the focal dystonias. However, there are some abnormalities that are only detected in a specific form of focal dystonia and this might give insight in what causes one patient to develop cervical dystonia and the other blepharospasm.$^{86}$ Most of these abnormalities are caused by the task that is performed and are linked to the affected body part. For example,
increased activation of visual association areas during blinking in patients with BLS, and altered activation of the motor cortex in patients with WC during writing tasks. Of more interest are the less predictable differences between different forms of focal dystonia. BLS stands out as an exception compared to the other forms of focal dystonia with almost all used techniques. One DTI study compared patients with CD and BLS to healthy controls. Patients with CD had abnormalities in white matter tracks of the basal ganglia, corpus callosum and ansa lenticularis compared to controls, however patients with BLS had no abnormalities. Another outstanding difference is the activation of the PMC in patients with BLS measured with fMRI. In studies using a task that did not induce dystonia in patients with CD, FHD, WC and SD a decrease in activation of the PMC and/or SMC is found. However, in patients with BLS an increase of activation in the PMC and SMC was found in two studies. These conflicting results might mean that BLS has a different pathophysiological mechanism than the other forms of focal dystonia, but the data are too limited to draw any definite conclusions. It would be interesting, however, to compare patients with BLS to patients with other forms of focal dystonia in future imaging studies.

According to the proposed shared underlying pathophysiologic mechanism in all focal dystonias, the primary defect is likely to be located somewhere in the motor circuit connecting the cortex to the basal ganglia and the cerebellum. More specific, the discussed studies support the concept of increased grey matter volume of the basal ganglia, mainly the putamen, and increased connectivity of the basal ganglia to the cortex and of the cortex to the cerebellum. These pathways could be responsible for the generation of abnormal movements. At this stage, however, it is not possible to exclude that the changes are consequences of dystonia rather than the cause. At the same time there is decreased connectivity of the hemispheres and a disturbed sensorimotor reflection on the cortex (increased activity of the sensorimotor cortex and compressed and disordered digital representation). The last feature is especially well described in patients with WC where several digits overlap on both the motor and the sensory cortex. Disturbed sensorimotor reflection has not been investigated in other forms of dystonia, so it is unknown if this is a common feature.

The studies we discussed above have several limitations, most of which are ubiquitous to studying relatively rare conditions. First, most of the studies have a small sample size. It could be that with a larger, more appropriate sample size other small but relevant differences would have been found, on top of the changes described in this review. Small differences are usually considered not relevant, but they might complete pathophysiological views. Second, these studies were retrospective studies with a case-control design. A case-control design is sensitive to differences caused by selection
bias or confounding between the patient and the control group that could lead to distortion of results. Third, most studies, especially the older ones, did not correct for multiple comparisons. This significantly increases the risk of false positive results. Fourth, the groups that were investigated differed between different studies on clinical characteristics and ROIs selected for the imaging. Therefore, results of different studies are difficult to compare to each other. Fifth and finally, in only one of the fMRI studies the task was monitored with EMG. This way, it is unknown whether tasks were correctly executed, when tasks were performed and whether dystonic activity occurred.

In conclusion, imaging studies found abnormalities in the basal ganglia, thalamus, sensorimotor cortex and cerebellum of patients with focal dystonia, making it highly likely that the primary defect in focal dystonia lies somewhere in the sensory-motor circuit connecting these regions. When treating patients with focal dystonia with deep brain stimulation (DBS) in the subthalamic nucleus, globus pallidus or thalamus this sensory-motor circuit is interrupted, leading to a decrease in symptoms. The significance of the involvement of this sensory-motor circuit is yet to be determined. In the future it would be helpful to conduct studies with appropriate sample sizes using multiple imaging techniques in the same patients, for example structural and functional MRI and SPECT or PET, to better link different findings together. We would like to make a strong argument for co-registration of EMG during functional imaging studies. EMG co-registration would add scientific value to fMRI studies and PET studies measuring metabolism, especially if tasks were performed during these studies. Using EMG co-registration it is possible to see if the task is being performed and if there is dystonic activity in muscles. Furthermore, it creates an opportunity for backaveraging of the imaging signal to investigate which activation precedes the task and which activation occurs during the task. As a final remark, we think it would be interesting to conduct larger imaging studies in families with focal dystonia. However, in some families multiple family members are affected, raising the suspicion of at least an underlying genetic vulnerability. This suspicion is strengthened by the fact that many imaging studies in genetic forms of dystonia find similar results (e.g. increased cortical-cerebellar connectivity) as the studies we described in this review, suggesting a common pathophysiological mechanism. It would be of interest to conduct imaging studies in both patients and asymptomatic family members that are at risk to develop focal dystonia, to optimize research on the pathophysiology of dystonia and clarify the causative and secondary changes.
REFERENCES


Chapter 2


