Chapter 11
Neuroimaging of Dystonia

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Introduction

The primary dystonias are movement disorders characterized by involuntary muscle contractions that produce abnormal posture of a specific body part. While there can be debilitating dysfunction of movement, no specific pathology has been identified. Neuroimaging plays a role in trying to define where pathology might be, although, in general, the findings are subtle. Neuroimaging does not presently have a clinical role except to rule out secondary dystonias, in which dystonia is a result of defined central nervous system lesions. When primary dystonia presents in childhood, it is most frequently generalized, and when it presents in adult life, it is most frequently focal, affecting only one or few body parts. The prevalence of dystonias was estimated to be 0.5/100,000 for the general population and 6/100,000 for the Ashkenazi Jewish population [1]. A random sample of individuals aged 50 and older suggested prevalence could be as high as 732/100,000 for older populations [2].

The most common childhood generalized dystonia is DYT1, in which symptoms usually start in the legs. DYT1 dystonia may manifest in young adulthood and more rarely in adult life [3]. DYT1 has a penetrance of only 30 %. One can compare manifesting and nonmanifesting carriers to noncarrier dystonia patients and healthy controls to separate genetic traits from disease traits. There are four common primary focal dystonias, and, while there is likely some genetic basis, they usually are sporadic. Named for the body part affected, these common adult onset dystonias are blepharospasm, cervical dystonia, spasmodic dysphonia, and focal hand dystonia. Most imaging information with regard to primary dystonias relates to these five conditions, and this chapter will emphasize them.

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Clinical Overview of Primary Dystonias

Blepharospasm, also called benign essential blepharospasm, presents as an involuntary eye closure due to either spasms of the orbicularis oculi or a contraction failure of the levator palpebrae muscles (previously called apraxia of eyelid opening) [4, 5]. It is more prominent in females (2.8:1); 93 % of a patient series in the USA were white; median age of diagnosis was 53 years [6].

Cervical dystonia (CD), also called spasmodic torticollis, manifests with an abnormal twisting and squeezing of the neck muscles that can extend to the shoulders, producing an awkward neck and head posture. It affected 0.28 % of the population in a general population questionnaire, where it was more prominent in females (79 %) and whites (92 %) [7].

Spasmodic dysphonia (SD) is a vocal dysfunction marked by uncontrolled voice breaks and effort while speaking due to spasms in the vocal cords. Most commonly, the adductor muscles are affected, interfering with vowel sounds; when the abductor muscles are affected, it interrupts voice onset after voiceless consonants [8]. These patients have no problems with other laryngeal functions such as breathing or swallowing. It is more prominent in females (60–80 %) [9, 10], and has a 0.98 % prevalence in the general population seeking medical care [10].

Focal hand dystonia commonly presents as an occupational cramp with cocontraction of antagonist hand muscles when performing a very well-learned and practiced task such as writing or playing a musical instrument. The same hand can perform other tasks without being affected; thus, focal hand dystonia is often task-specific. It has a high prevalence in musicians (1/500), is more prominent in males, and onset is in young adulthood [11]. Even when presenting as a specific and focal disorder, focal hand dystonia can generalize to other tasks and involve more widespread muscles.

Using Neuroimaging to Understand Dystonia Pathophysiology

Several lines of evidence indicate that there are likely deficits of the basal ganglia, thalamus, sensorimotor cortices, and cerebellum of patients. However, there is no overt pathology or biomarker for the primary dystonias. This chapter will present findings from imaging studies of each of the five types of dystonias in an attempt to better understand the disorder as a group and its different manifestations. These studies use different imaging modalities, aiming to understand the structural and functional deficits the patients might have. Structural changes in gray matter are studied with T1-weighted MRI images and morphometric techniques [12]. Changes in white matter are measured with diffusion tensor imaging (DTI) [13] and the structural connectivity is modeled using tractography methods [14, 15].Changes in blood flow, function, and metabolism are measured with radioligands in positron emission tomography (PET) [16]. Metabolic changes are measured with magnetic resonance spectroscopy (MRS) [17]. Functional magnetic resonance imaging (fMRI) is used to analyze brain function [18] and connectivity [19].

DYT1

One of the core regions-of-interest (ROI) in dystonias is the basal ganglia. Using voxel-based morphometry (VBM), Draganski et al. [20] compared the size of gray matter structures in manifesting and nonmanifesting carriers of the DYT1 gene to healthy volunteers and non-DYT1 carrier dystonia patients. They found an interaction between putamen size and the disorder. Nonmanifesting DYT1 carriers and non-DYT1 carrier primary dystonia patients have enlarged basal ganglia volumes. In manifesting DYT1 carriers, basal ganglia size was inversely proportional to severity of dystonia symptoms. Interestingly, the manifesting carriers, on average, did not differ in basal ganglia size from the healthy volunteers. These results suggest two different mechanisms for the changes in basal ganglia size. For DYT1 carriers, enlarged basal ganglia might be a compensatory mechanism preventing the manifestation of the dystonia. Furthermore, the enlarged basal ganglia in non-DYT1 carrier dystonia patients could either be a compensatory mechanism as well, since dystonic symptoms are not severe for this group and onset is late in life, or could be part of the disease pathological process. Consequently, the dystonia trait is not directly related to basal ganglia size.

DTI studies showed that some deficits are related to the presence of the DYT1 gene while others are related to the dystonia itself. Manifesting and nonmanifesting DYT1 carriers differed from noncarrier healthy controls in the fractional anisotropy (FA) values of the precentral cortex [21], basal ganglia, supplementary motor area (SMA), and cerebellum [22]. Both groups of DYT1 carriers had decreased integrity of the proximal segment of the cerebellar-thalamo-cortical pathway, as evidenced by a reduced FA. Penetrance was reflected in a trend in the distal portion of these fibers, where nonmanifesting carriers had lower FA than healthy volunteers, and manifesting carriers had values in between the other two groups [23]. The authors proposed a model where the difference in integrity of the proximal and distal sections of the pathway represented cerebello-cortical inhibition and suggested this measure as a marker of penetrance.

In the same study, all DYT1 carriers displayed a positive correlation between cerebellar connectivity and cerebellar regional blood flow response to a motor task. Conversely, there was an inverse correlation between their cerebellar connectivity and the thalamus, sensorimotor cortex, and SMA regional cerebral blood flow (rCBF) change elicited by the task [23]. These findings suggest that structure and function of the different components of the cerebellar-thalamo-cortical loop are affected and interrelated.^{18}F-fluorodeoxyglucose (FDG) PET studies indicated that DYT1 carriers, irrespective of penetrance, have increased resting glucose metabolism in basal ganglia, SMA, and cerebellum [21, 24, 25]. Manifesting DYT1 carriers also had increased activity in pre-SMA and parietal association areas [21]. These findings are in concordance with the DTI studies, where cerebellar changes were related to the presence of the DYT1 gene, and distal or cortical changes depended on the penetrance.

Dystonic patients, despite genetic status, had a decreased number of GABAa receptors, measured with ^{11}C-flumazenil, in the bilateral sensorimotor cortex, left

premotor cortex, and left anterior cingulate cortex when compared with healthy volunteers; there was no difference in GABAa receptors between carrier and noncarrier patients [26]. These results support the concept of inhibition as a major factor in disease manifestation [27]. D2 receptors, measured with ^{11}C raclopride, were decreased in the striatum of nonmanifesting DYT1 carriers [28]. In another study, manifesting and nonmanifesting carriers had similarly decreased D2 receptors in the caudate nucleus, putamen, and thalamic nucleus [29]. Secondary dystonias may occur at peaks and troughs of dopamine in idiopathic Parkinson disease (iPD) patients, suggesting a pharmacological effect of dopamine in the manifestation of dystonic symptoms [30]. However, for DYT1 carriers, dopamine receptor levels do not appear to explain the manifestation.

There is evidence that some of the clinical deficits seen in manifesting carriers are also present in nonmanifesting carriers, even if subtle. For example, nonmanifesting carriers had impaired right hand sequence-learning skills, when compared with healthy controls. The behavioral deficit was accompanied by increased $H_2{}^{15}O$ PET signal in the right SMA, left lateral premotor cortex, and inferior parietal cortex. During a kinematically controlled motor task, the nonmanifesting carriers had an increased signal in the left sensorimotor cortex, left premotor cortex, SMA, ventral thalamus, posterior cerebellum, and inferior occipital cortex that could indicate a compensatory mechanism since the performance is not affected in this group [31]. Patients also had diminished activation of their dorsolateral prefrontal, motor cingulate, and dorsal premotor cortices [32]. The nonmanifesting carriers' cerebellar activity was increased during sequence learning [32], but decreased in during motor execution [31].

Since the penetrance of the DYT1 mutation is reduced, there must be other factors involved in manifestation of the dystonia besides this gene. Structural imaging studies show several metrics where manifesting and nonmanifesting carriers differ. Deficits are not always more pronounced in the manifesting carriers. On the contrary, putaminal size [20] and cerebellar-thalamo-cortical pathway connectivity [23] show larger differences in nonmanifesting subjects, suggesting compensatory mechanisms may be at play. Cerebellar abnormalities appear to be similar in manifesting and nonmanifesting DYT1 carriers, so these might be a direct gene effect. Basal ganglia, thalamic, and cortical changes depend on the penetrance; therefore, they reflect an interplay of compensation and manifestation mechanisms.

Blepharospasm

Blepharospasm was thought to be solely a basal ganglia disorder, but now there is evidence from electrophysiology and imaging indicating that the cerebral cortex also plays an important role in the genesis and manifestation of the disorder. In a number of VBM studies, blepharospasm patients had gray matter changes in the putamen [33, 34],inferior parietal cortex (BA40) [33], thalamus, head of caudate, and cerebellum [34]. Recent studies report additional changes at the cortical level, including

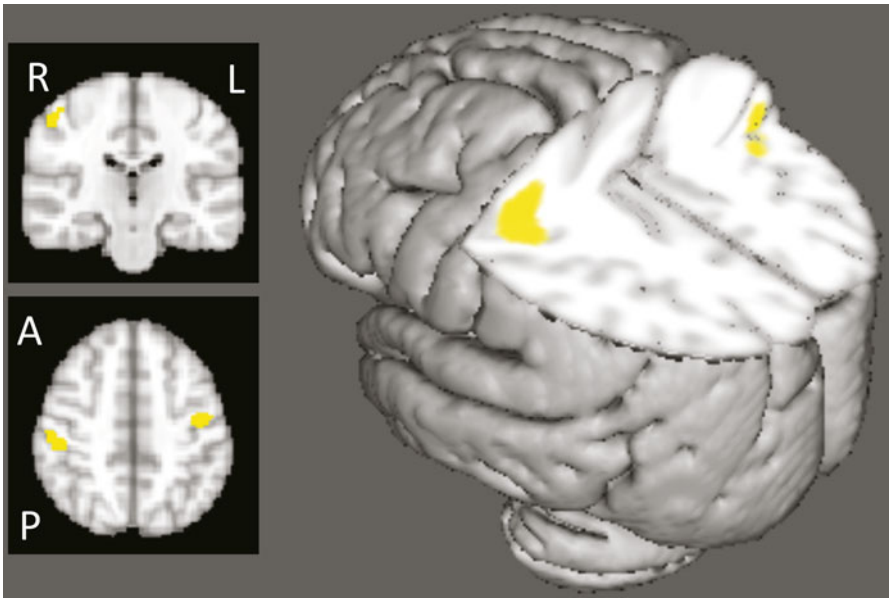

Fig. 11.1 Gray matter volume changes in blepharospasm patients. Significant differences in gray volume, detected using voxel-based morphometry are seen in the sensorimotor area (data from [37]). Regions are shown on *axial* and *coronal* slices and on a 3D reconstructed brain

the right middle frontal gyrus, left superior temporal gyrus, left postcentral gyrus [35], bilateral sensorimotor area, and cingulate gyrus (Fig. 11.1) [36, 37]. Suzuki et al. [38] found a strong correlation between the changes in gray matter volume of the sensorimotor cortex and the duration and activity index indicative of severity, suggesting that the changes might be secondary to the disorder. The variability in the different studies is striking and may be due to differences in imaging sequences or the populations studied. White matter of healthy volunteers and blepharospasm patients had similar FA and mean diffusivity (MD) values [37, 39]. However, the peak connectivity of the corticobulbar tract was lower in blepharospasm patients than in healthy controls [37]. Fiber tracking from a single subject is shown in Fig. 11.2.

Similar to the changes in gray matter, metabolic changes in the resting state were seen in several areas known to be related to blink production and control. Glucose metabolism, measured with ^{18}F-FDG PET, was increased in cortical regions, including inferior frontal gyri, right posterior cingulate gyrus, left middle occipital gyrus, right fusiform gyrus, and left anterior cingulate gyrus. Subcortical areas were also affected, with increased metabolism in the right caudate and decreased in the left inferior cerebellar hemisphere and thalamus [40]. Glucose hypermetabolism in the thalamus and pons was observed in patients treated with botulinum toxin, suggesting these changes are intrinsic to the disorder and not dependent on sensory feedback from the eyelid spasms [41]. In another study, however, metabolic changes in the

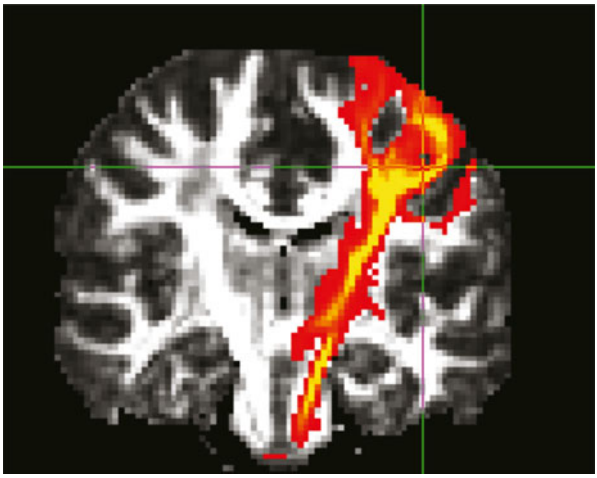

Fig. 11.2 Probabilistic tractography on individual subject data (data from [37]). Left corticobulbar bundle traced on diffusion-weighted images using the motor region shown in Fig. 12.1 as the initiation point and the pons as the endpoint

thalamus correlated with disease severity [36]. Thalamic hypermetabolism (in ventral anterior (VA) and ventral lateral (VL)) was more pronounced in blepharospasm patients with photophobia compared with those without photophobia. Nonphotophobic blepharospasm patients also had decreased metabolism in their midbrain [42].

Some metabolic studies have explored changes in different brain states. rCBF, measured with $H_2{}^{15}O$ PET, was decreased in the primary sensorimotor area in response to lower face stimulation [43]. The sleep–wake cycle also affects metabolism in patients. During wakefulness, there was increased metabolism in the cerebellum and pons. During sleep, when blepharospasm movements are suppressed, there was decreased metabolism in the superior-medial frontal cortex, an area associated with eyelid control [44]. These studies showed that metabolism is sensitive to the precise state of the patient and likely the frequency of eye blinking; this may explain some of the variability of the metabolic studies done "at rest."

There are suggestions of abnormal sensory integration and basal ganglia function with studies not focused on eyelid control. fMRI studies of blepharospasm patients evaluated brain activity elicited by nondystonic motor tasks. During handgrip, the thalamus, caudate nucleus, putamen, and globus pallidus were more active in patients than in controls [45]. During whistling, blepharospasm patients have increased activity in the postcentral cortex and caudal supplementary motor cortex bilaterally, left dorsolateral prefrontal cortex, and left paravermal cerebellum [46]. Using fMRI, activation with patients' blink spasms was compared with healthy volunteers' volitional blinks. Blink spasms increased activation in the putamen [47]; when patients

added volitional blinks to their spasms, cortical areas related to blink production (anterior visual cortex, anterior cingulate, primary motor cortex, thalamus, and superior cerebellum) were more active than in the controls [48]. Forehead stimulation produced increased activation in the putamen that was reversed by botulinum toxin treatment [49].

There is great variability in the results from the different imaging modalities and even within modalities. The variability maybe, in part, due to the inhomogeneity of the population sampled and the different sensitivity of each modality utilized. In addition, different imaging parameters or processing methods used within the same modality can lead to different results. However, put together, these studies find structural, functional, and metabolic deficits in areas seen to produce secondary blepharospasm, such as thalamus [50], basal ganglia [51], cortical areas involved in blink control such as sensorimotor cortex and anterior cingulate among others, and in the cerebellum, an area thought to have a role in dystonia [52].

Cervical Dystonia

One goal of neuroimaging studies is to find the sites of pathology. Neuropathology studies, which would be the most direct method, in all the primary dystonias are few and findings are scarce. A report from four postmortem brains showed subtle changes in the midbrain and cerebellum [53], with absence of anomalies in other brain areas presumed affected in dystonias such as basal ganglia, thalamus, or cerebral cortex. Another postmortem study showed increased concentrations of copper and manganese in the putamen of dystonia patients [54]. Transcranial sonography of the lentiform nucleus of CD patients showed a slight hyperechogenicity contralateral to the head deviation in 9 of 10 subjects [55].

A VBM study reported that CD patients have increased gray matter volume in the thalamus, caudate head bilaterally, superior temporal lobe, and left cerebellum and decreased gray matter in bilateral putamen [34]. Trends toward significant changes were also seen in the globus pallidus, bilateral orbitofrontal cortex, SMA, medial frontal gyrus, and cingulate cortex [56]. Another study reproduced the left caudate and putamen findings and found additional changes in the bilateral premotor and primary sensorimotor cortices [57]. While no correlations were found with disease duration, severity, or age in a cross-sectional study, the left sensorimotor cortex was further reduced when patients were tested/retested 5 years after [57]. The different results between cross-sectional and longitudinal studies highlight the great degree of variability existent across subjects. Additional longitudinal studies of dystonia are needed, since they allow for more controlled evaluation of these changes.

White matter in patients also shows some alterations. Based on small ROI drawn in the white matter between putamen and thalamus, Blood et al. [58] reported that patients had more asymmetry than controls in the FA values. These changes were reversed after botulinum toxin treatment, suggesting the abnormalities were related to the symptoms and that the connection between basal ganglia and thalamus displays

plasticity. Another study found no changes in FA, but reported increased MD in the white matter adjacent to pallidum, caudate, and putamen bilaterally in patients [59]. In an ROI analysis, another study found that FA in CD patients was significantly reduced in the body of the corpus callosum and bilateral putamen. MD was reduced in the right caudate, left putamen, bilateral prefrontal cortex, and left supplementary motor cortex [39]. ROI analyses, while less specific on the location, increase the power and compensate for variability between subjects, both in anatomy and in the manifestation of the dystonia, thus, providing more robust results. In line with the midbrain-cerebellum changes seen in postmortem brains, tractography showed altered connections between the pallidal output fibers and the brainstem [60]. There was a right/left hemisphere asymmetry in the tracts, in accordance with the asymmetric clinical manifestation of the disorder.

Using single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS), basal ganglia NAA/Cr and NAA/Cho were reduced in patients [61]. NAA/Cr is a marker of neuronal integrity, and NAA/Cho a possible indicator of membrane dysfunction, suggesting, in this situation, loss of dopaminergic terminals or abnormal function of the striatal neurons. Because drugs that block dopamine receptors can produce dystonia, particularly of the head and neck, it is believed that the dopaminergic pathways can be involved in the etiology of the disorder. Indeed, an ^{11}C-N-methyl-spiperone PET study showed that while there were no significant differences between healthy controls and patients, patients had a trend toward higher tracer uptake in the hemisphere contralateral to the symptoms [62]. Using ^{123}I iodobenzamide SPECT, there were no differences in radiotracer uptake in basal ganglia between healthy controls and patients, but an interstriatal analysis showed that the basal ganglia contralateral to the direction of the torticollis had a higher binding to D2 receptors than the ipsilateral one [63]. A SPECT study compared the presynaptic striatal dopamine receptors, measured as ^{123}I beta-CIT binding, with the postsynaptic dopamine receptors, measured with ^{123}I-epidepride [64]. While the presynaptic receptor binding was similar for healthy controls and patients, the postsynaptic binding was lower in the CD group. The decreased postsynaptic D2 receptors could explain the lack of inhibition of the thalamo-cortical (indirect) pathway, and also explain the relative increased number of presynaptic receptors seen in other studies [63].

Patients' glucose metabolism, measured with ^{18}F-FDG PET, was increased in the basal ganglia-thalamo-cortical loop, including the basal ganglia, thalamus, premotor and motor cortex, and cerebellum [65], and bilaterally in sensorimotor areas when compared with controls [66]. A recent exploratory study showed that most of the sensorimotor differences were reverted when symptoms were alleviated following epidural premotor cortical stimulation [66]. These results are in line with the notion of CD being a disorder not only of the basal ganglia, but rather representing a more complex association with the sensorimotor network, including sensorimotor cortex, thalamus, and cerebellum.

fMRI studies have shown that nondystonic tasks impair activity in CD patients. As seen in blepharospasm patients, basal ganglia activity was altered during handgrip in CD patients. CD patients' handgrip resulted in increased activity in basal ganglia,

caudate nucleus, putamen, and thalamus [45]. On the other hand, patients' movement imagery produced less activity than healthy volunteers in bilateral parietal, left premotor, and anterior cingulate cortices; movement execution showed impaired activation in the ipsilateral putamen, insula, and cingulate cortex [67]. As a response to passive movement of nondystonic areas, CD patients showed increased activation in primary and secondary sensory cortices contralateral to the stimulation, cingulate cortex, and bilateral cerebellum [68]. Several studies explored the correlation between botulinum toxin and fMRI activity. SMA activity in response to passive movements was positively correlated with botulinum toxin dosage and negatively correlated with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score, suggesting a general disinhibition of the somatosensory system [68]. Similar results are seen during finger tapping, where SMA was abnormally hypoactive in CD patients, and improved toward normal after botulinum toxin treatment [69]. In response to median nerve stimulation, secondary somatosensory and insular cortices were less active in CD patients; however, these changes were reverted 4 weeks after botulinum toxin treatment [70]. These functional findings reinforce the notion of CD as a disorder of the sensorimotor system extending beyond the representation of the affected area. They also show that changes in symptoms, even induced peripherally by botulinum toxin, affect not only primary sensory areas, but also the secondary sensory association areas, SMA, and insula. The abnormalities in these areas are presumably not indicators of the underlying etiological pathology since they revert with botulinum toxin treatment.

Spasmodic Dysphonia

As in the other primary dystonias, there are no consistent radiological findings to explain SD, supporting the idea it is a heterogeneous voice disorder [71]. Similar to other primary dystonias, in addition to basal ganglia involvement, cortical contribution has been suspected. SD patients show changes in cortical thickness, gray matter volume and function in areas related to speech control, including the laryngeal sensorimotor cortex, inferior frontal gyrus, superior and middle temporal cortices, supramarginal gyri, and cerebellum [72]. In these patients, DTI findings indicate patients have decreased FA in the genu of the right internal capsule, a site confirmed in one histopathological examination, and increased MD bilaterally in the lentiform nucleus, ventral thalamus, and cerebellum. These changes correlated positively with severity of the clinical symptoms [73].

While no resting metabolism data are available in SD patients, there are several functional studies with PET and fMRI that found cortical, thalamic, basal ganglia, and cerebellar deficits. An early $H_2{}^{15}O$ PET case study suggested a reduction in SMA during phonation [74]. However, during speech-related activity, patients had hyperactivity in a network including the right dorsal precentral gyrus, cerebellar hemisphere and vermis, primary auditory cortex, anterior cingulate, and anterior insula [75]. The unimodal and heteromodal association areas, including the posterior

supramarginal area and posterior middle temporal gyri and the dorsal postcentral gyrus, were hypoactive in the same patients [75]. These changes reverted after botulinum toxin treatment [75]. The improvement provided by the treatment correlated with increased sensorimotor activity and decreased activity in areas unrelated to motor control. The decreases in posterior auditory association cortex and the right ventral precentral gyrus and increases in SMA proper, heteromodal sensory areas (anterior middle temporal gyrus), and periaqueductal gray matter were not affected by the treatment, thus, considered traits of the disorder. During narrative whispering, increased activity was limited to the SMA proper. Treatment produced changes in the pre-SMA, right dorsal precentral gyrus, caudate, anterior putamen, ventral thalamus, pulvinar, cerebellar hemisphere, and vermis. Therefore, basal ganglia function is not particularly different between healthy volunteers and SD patients, but it is one of the areas where botulinum toxin treatment shows a marked effect.

SD patients showed increased extent of activation in the primary sensorimotor cortex, insula, and superior temporal gyrus during symptomatic and asymptomatic tasks and decreased activation extent in the basal ganglia, thalamus, and cerebellum only during asymptomatic tasks. The extent of activation in the primary sensorimotor cortex and ventral thalamus during a symptomatic task, and in the inferior temporal cortex and cerebellum during symptomatic and asymptomatic voice production, was greater in patients with the abductor form of dysphonia than for those with the adductor form [76].

All aspects of the speech control system [77], including unimodal and heteromodal cortices, basal ganglia, and SMA, have altered function and structure in SD. Pathways extending from the motor cortex to the midbrain are also affected.

Focal Hand Dystonia

Among all the dystonias, focal hand is the most studied one using imaging techniques. Most studies find deficits in the sensory and motor circuits. The gray matter volumes as assessed with VBM of the basal ganglia [78] and the sensorimotor cortices [79] of focal hand dystonia patients differ from those of healthy volunteers. Some of the structural changes are shared with other dystonia types. For example, the volume of the globus pallidus internus and the orbitofrontal cortex are less in dystonic patients than healthy volunteers, but these changes are not specific to focal hand dystonia [56]. Volume changes might be related to plasticity. Evidence for this is that the volume of the middle section of the putamen gray matter in pianists, with and without dystonia, covaries with the variability of their keystroke timing during scale playing. Patients have more variability, and the volume of the middle section of the right putamen is larger in patients than in healthy piano players [80].

Plasticity of the morphological changes is also observed in the white matter. FA values of the corticospinal tract were shown to be larger for musicians than nonmusicians [81], suggesting that practice can effect changes independent of disease. An ROI comparison of FA values of the small white matter region between the basal

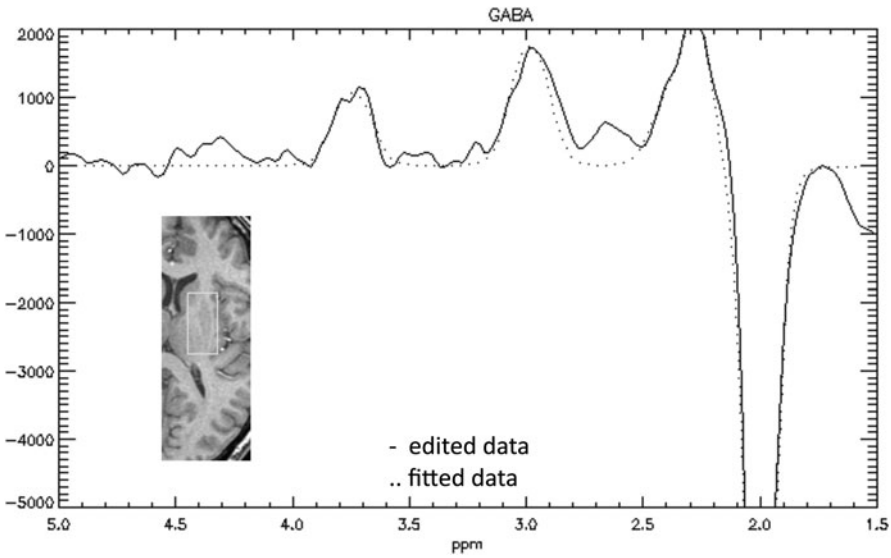

Fig. 11.3 Magnetic resonance spectroscopy. Example of the spectra for GABA (g (gamma)-aminobutyric acid) edited signal from a single subject (data from [85]). *Inset* brain section shows voxel location. *Trace* shows edited MRS with the GABA peak at 3.0 ppm, and the inverted NAA peak at 2.0 ppm

ganglia and thalamus showed left/right asymmetry in two patients with focal hand dystonia before treatment that reversed after botulinum toxin treatment [58]. Writer's cramp patients had increased FA values bilaterally in the posterior limb of the internal capsule and adjacent structures, involving tracts connecting primary sensorimotor areas and subcortical structures [82].

Sensorimotor cortex and basal ganglia of patients were reported to have reduced levels of GABA measured with MRS [83]. This would be in accordance with the concept of reduced inhibition seen in electrophysiological studies [84]. However, the voxel size for GABA MRS is rather large (on the order of tens of cubic centimeters), making it difficult to detect signals when different tissues are part of the region of observation (Fig. 11.3). An attempt to confirm these findings in a second MRS study with improved technique observed only a trend [85]. MRS showed no differences in N-acetylaspartate/creatine or lactate/creatine in the lentiform nucleus [85, 86] or the sensorimotor area [85].

Several studies looked at CBF and metabolism during performance of tasks that generate or do not generate dystonic postures. During a writing task, writer's cramp patients had impaired activation in the contralateral primary motor cortex and enhanced frontal activation. Improvements in writing, seen after botulinum toxin treatment, were accompanied by increases in parietal cortex and caudal SMA activations; however, the impairment persisted in the primary motor cortex [87]. In another study, the primary sensory cortex was overactive in writer's cramp patients

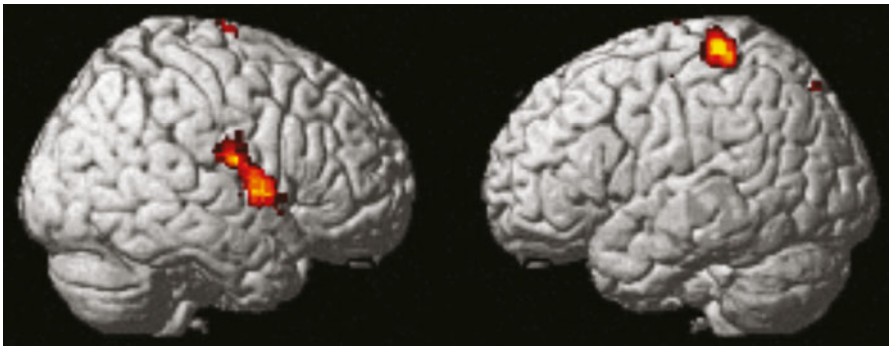

Fig. 11.4 [^{15}O] H_2O PET in focal hand dystonia patients (data from [88]). Regional cerebral blood flow in primary and secondary sensory areas correlates with patients' subjective dystonia score

during a writing task. This change in rCBF, measured with $H_2{}^{15}O$ PET, correlated with subjective patients' scores (Fig. 11.4). The activity in the primary sensory and motor cortices correlated with electromyography (EMG) activity during writing. The sensory changes suggested a possible dysfunction of sensory feedback [88]. When vibrotactile stimulation was applied to either arm, the rCBF response, measured with $H_2{}^{15}O$ PET, was decreased bilaterally in sensorimotor cortices and SMA, even though patients had unilateral symptoms. These changes did not depend on muscle cocontraction, since healthy volunteers had even larger responses when stimulation was applied during muscle contraction [89, 90]. Putamen rCBV measured with $C^{15}O$, rCBF, and $H_2{}^{15}O$ show no functional alteration in patients; however, D_2 binding measured with ^{18}F-spiperone is decreased in patients [91]. Nevertheless, ^{18}F-N-methyl-benperidol (NMB), a more selective D2 receptor that excludes serotonin receptors (5-HT_{2A}), failed to reproduce D2 receptor changes [92]. These results indicate a complex mechanism for the disorder where there are subclinical brain deficits and unclear neurotransmitter alterations.

Several fMRI studies compared task performance and brain activations between healthy volunteers and focal hand dystonia patients. They found differences in brain activity even when performance was matched [93–95]. A comparison between guitar players with and without dystonia found the patients' group to have increased activity in the contralateral sensorimotor cortex and decreased activity bilaterally in the premotor areas when performing hand movements, irrespective of whether the task triggered dystonia or not [94]. Extension or relaxation of the wrist resulted in decreased activation of the sensorimotor cortex and the SMA in writers' cramp patients compared with controls, suggesting deficits both in inhibitory and excitatory mechanisms [95]. When patients tried to control an isolated finger movement, they had less activation in the primary sensory area, associative parietal areas, and right sensorimotor area of the cerebellum than when they were moving two fingers together (Fig. 11.5). These decreases were significantly more pronounced in patients than in healthy volunteers. Nevertheless, patients had increased functional connectivity between the left posterior putamen, left sensorimotor cortex, and left cerebellum. The left anterior putamen connectivity also differed in the bilateral SMA, bilateral

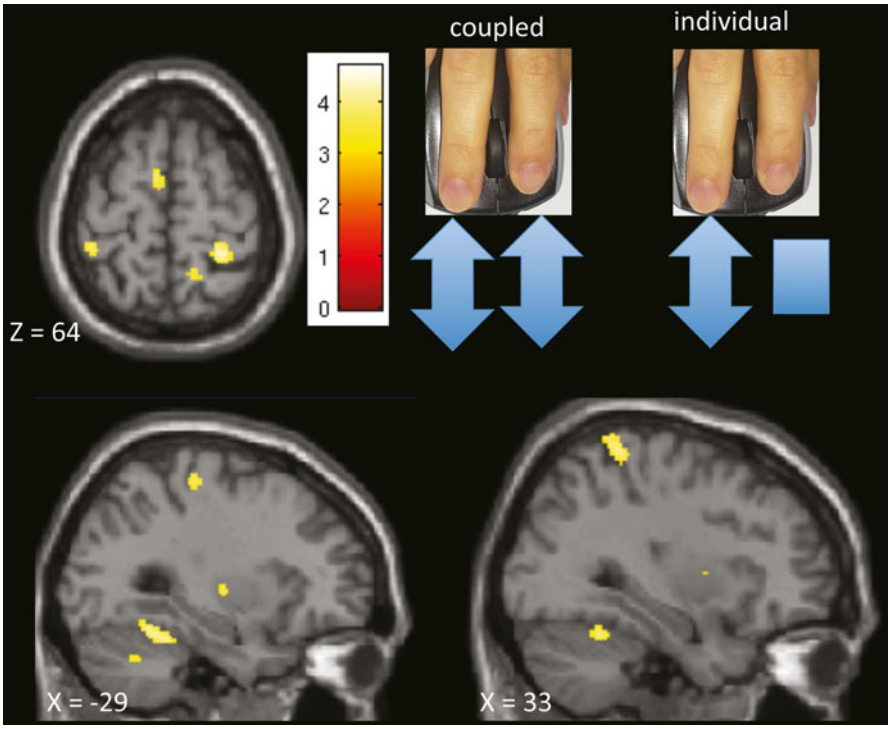

Fig. 11.5 fMRI study of focal hand dystonia (FHD) patients (data from [93]). Compared with healthy volunteer activations, FHD patients show widespread deficits when controlling individual finger movements compared with performing the same movement with both fingers. Healthy volunteers have more activation in the supplementary motor area (SMA), cerebellum, bilateral putamen and bilateral sensory cortex when performing different tasks with each finger (individual task) than when both fingers do the same. Patients show less difference in these areas, suggesting lack of surround inhibition in the FHD

motor cingulate area, left primary motor area, premotor cortex, and left cerebellum, suggesting a compensatory mechanism [93].

Somatosensory finger representation is less demarcated in patients than in controls. It differs between dystonic musicians and healthy nonmusician controls, with patients having smaller distances between individual finger representation [96]. Sensory representation of the fingers had lower spatial separation for patients; the order of the representation was also reversed in the secondary sensory cortex and posterior parietal cortex in patients compared with controls [97]. Another study showed that digits involved in writing (D1, D2, and D3) had smaller interdigit separation in area 3b and overlapping activity, while the distance for asymptomatic digits was preserved. The cluster location, closer to the symptomatic digits, suggested that dystonic symptoms could arise from reduced cortical spacing. In another study, sensory input elicited a lower response in patients' area 3a [98]. Somatotopy is also affected in patients' basal ganglia. Another fMRI study showed that, in patients, the representation

of hand, lip, and toe movements was disorganized in the left putamen, contralateral to the affected side, and to a lesser extent, on the ipsilateral side [99]. Moreover, while the brain response to sensory stimulation of individual fingers predicts the activation from combined stimulation with a 12 % error for the healthy controls, prediction error is 30 % for patients, suggesting a nonlinear interaction [100].

Repetitive transcranial magnetic stimulation (rTMS) of patients' primary sensory cortices can produce a subjective benefit in writing quality. In one study, these improvements were paralleled by bilateral increases in the blood oxygen level-dependent (BOLD) signal on fMRI in the primary sensory cortex, parietal cortex, and SMA. There were neither behavioral nor imaging changes after sham stimulation [101]. Basal ganglia also have abnormal responses to motor tasks. One study showed that after performing a motor task, BOLD signal in the motor area returned to baseline; however, the basal ganglia activation level remained elevated in patients [102]. In another study, basal ganglia and thalamus were hyperactive during tactile stimulation of the index finger of writer's cramp patients, suggesting a deficit in the center-surround inhibition within their circuits. Basal ganglia and thalamus interaction is also affected in musicians with focal hand dystonia; they were active in healthy volunteers, but not in patients during finger tapping [103]. Basal ganglia and thalamic deficits may lead to compensation with augmented activations in cerebellum and cortical areas. This was seen in a study showing increased activity in the posterior vermis, right paramedian cerebellar hemisphere, and dorsal pons, which correlated with disease severity [104]. Patients also had hyperactivity in areas of the visual cortex, anterior insula, and intraparietal sulcus.

Several studies compared finger tapping in healthy volunteers and focal hand dystonia patients. One of them found that while cerebellum and contralateral sensorimotor and premotor areas were active in both groups, ipsilateral activation in the premotor area was larger in patients during tapping with the affected hand, and left cerebellar activation was reduced in patients when tapping with either hand [103]. Another study reported that the execution of simple or complex finger-tapping activates primary motor cortex, primary sensory cortex, SMA, left insula, and bilateral cerebellum. In this study, musicians and writer's cramp patients activated the same network as controls, but to a lower level for both the symptomatic and nonsymptomatic hands [105]. To avoid confounds due to symptomatic task execution in focal hand dystonia patients, a couple of studies explored motor imagery of different hand movements in patients and healthy controls. One study compared imagery of grasping a pencil and writing with grasping the same pencil to sharpen it. Writing imagery produced larger activation than sharpening imagery in the left dorsal premotor area, an area involved in task planning. But, when the grasping was evaluated, healthy volunteers used more of the ventral premotor cortex, while focal hand dystonia patients relied on the dorsal premotor cortex [106]. A second study compared the imagery of writing from a kinesthetic perspective with the observation of a hand performing the movement subjects were asked to imagine. In patients, writing imagery produced an activation deficit of the left sensorimotor cortex, mesial SMA, and left premotor cortex, bilateral putamen, and bilateral thalamus when compared with the writing observation condition [107]. As in the other dystonias, focal hand dystonia affects

structure and function of the components of the motor control circuit and the sensory networks. These alterations are observed as structural changes in white and gray matter. Functional changes are seen not only for tasks triggering dystonia, but also for a variety of tasks not related to the dystonia.

Conclusions and Future Directions

The basal ganglia, originally thought to be the sole origin of dystonia, can now be seen as one player in a more widespread dysfunction. Involvement of the cerebral cortex, in particular, sensorimotor, SMA, and parietal association areas, are consistent in all the primary dystonias. The cerebellum is also affected in all the dystonias discussed here. Unfortunately, there is a large variability of results found in imaging studies across groups and modalities. There are a number of reasons for this, including variation in patient characteristics, MRI hardware, and sequences employed; but, some results are also likely false positives due to small sample sizes. Till date, imaging has not produced a biomarker of dystonia, but has been helpful in expanding our understanding of the brain areas affected. Electrophysiology and imaging studies support the concepts of surround inhibition, compensation, and network imbalance as mechanisms for the disorder. Basal ganglia-thalamo-cortical, cerebellar-thalamo-cortical circuits, and the communication between sensory and motor areas seem to play key roles. What is not yet clear is which of the observed changes are the root causes of the dystonia and which ones are consequences. The ability to study manifesting and nonmanifesting carriers of the DYT1 gene or musicians with and without dystonia is helping to separate the plasticity that compensates for a deficit from the maladaptive plasticity that could result in dystonia. As noted at the outset, the main clinical role for neuroimaging in dystonia, at present, is to identify a secondary cause.

Key elements for further advances in understanding the pathophysiology of dystonias will come from multimodal strategies, where neuroimaging is expected to keep playing a pivotal role. Current studies pinpointed areas of interest, which not only can be studied with pathology, but also guide new imaging studies. It is expected that images obtained at high magnetic field (7 T or higher) will provide an increased signal-to-noise ratio and allow for higher resolution that could help solve the discrepancies seen in morphometric studies. High-order fields also will have an impact on what can be learned from MRS studies.

Another aspect that will improve our understanding the dystonias is having larger populations and longitudinal studies. The latter will be fundamental to delineate which features are causal and which are consequences of the disorder. Finally, as the dystonias are focal and action related, dynamic studies, either based on PET with new radioligands or on more specific fMRI designs, will clarify our understanding of network interactions.

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