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Task-Specific Dystonias: A review.

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Abstract: Task-specific dystonias are primary focal dystonias characterized by excessive muscle contractions producing abnormal postures during selective motor activities that frequently involve highly skilled, repetitive movements. Historically these peculiar postures were considered psychogenic but have now been classified as forms of dystonia. Writer’s cramp is the most commonly identified task specific dystonia and has features typical of this group of disorders. Symptoms may begin with lack of dexterity during performance of a specific motor task with increasingly abnormal posturing of the involved body part as motor activity continues. Initially, the dystonia may manifest only during the performance of the inciting task, but as the condition progresses it may also occur during other activities or even at rest. Neurological exam is usually unremarkable except for the dystonia-related abnormalities. Although the precise pathophysiology remains unclear, increasing evidence suggests reduced inhibition at different levels of the sensorimotor system. Symptomatic treatment options include oral medications, botulinum toxin injections, neurosurgical procedures, and adaptive strategies. Prognosis may vary depending upon body part involved and specific type of task affected. Further research may reveal new insights into the etiology, pathophysiology, natural history and improved treatment of these conditions.
Introduction

Task-specific dystonias present as focal excessive muscle contractions that develop in parts of the body involved in highly skilled, over-learned tasks like writing, typing or playing a musical instrument and occur almost exclusively during the performance of those activities. In general, dystonias may be classified etiologically into primary dystonias, in which dystonia is the main sign and the cause is genetic or unknown; and secondary dystonias, in which dystonia may be one of several disease manifestations and the cause may be identifiable.\(^1\)\(^2\) Primary dystonia is further classified based on age of onset. Childhood-onset dystonia (<28 years of age) usually starts in the lower limbs, trunk or upper extremities and frequently spreads to the rest of the body.\(^3\) Adult-onset usually begins in the upper half of the body with a risk of spread to other body parts depending upon the anatomic site of onset.\(^4\) Dystonias also can be classified by body part affected as focal (one body part), segmental (two or more contiguous body parts), multifocal (two non-contiguous areas), hemidystonia, or generalized.\(^5\)\(^6\) Moreover, dystonias can be classified as to whether they are constant, intermittent or situational, the latter including task-specific dystonias.

History

Bernardino Ramazzini provided one of the first descriptions of task-specific dystonia in 1713 in a book of occupational diseases.\(^7\) In chapter II of this book’s “Supplementum” Ramazzini noted that “Scribes and Notaries” may develop “incessant movement of the hand, always in the same direction…the continuous and almost tonic strain on the muscles…[that] results in failure of power in the right hand.” A report from the British Civil Service also contained an early description of writer’s cramp.\(^8\) In 1864, Solly coined the term scrivener’s palsy for this affliction.\(^9\) These historical reports usually attributed the etiology of the motor abnormalities to overuse. Then, in 1911 Oppenheim introduced the term “dystonia,” to describe abnormal increased of muscle tone and contractions that characterize these disorders. For much of the 20\(^{th}\) century, however, task-specific dystonias were considered psychogenic and called occupational neuroses due to the task specific nature of the manifestations, frequent immediate relief with sensory tricks (like touching a specific body part during the dystonia) and exacerbation by stress.\(^10\) Writer’s cramp was recognized in the 1970’s as a form of idiopathic dystonia and related to dysfunction of the basal ganglia.\(^11\) In 1978 Donald Hunter described more than 50 different occupations associated with dystonia during performance of a relevant specific task.\(^12\) Then in 1982, Sheehy and Marsden described the dystonic features and lack of psychopathology in their series of patients with writer’s, pianist’s and typist’s cramps and concluded that the symptoms were due to organic abnormalities.\(^13\)\(^14\)

Phenomenology

The usual age of onset of task-specific dystonias spans the third to sixth decade.\(^13\)\(^14\) Initial symptoms may include a feeling of painless tightness, fatigue, and lack of
dexterity with subsequent development of uncontrollable activation of surrounding muscles and abnormal movements during a specific, highly skilled motor task. Other activities requiring the same muscles may be performed normally, at least initially. Tremor in the affected body parts may also occur particularly during the inciting task in as many as half of the patients. We will now review the phenomenology of the most common task-specific dystonias following a cranio-caudal anatomical distribution.

Lower facial muscles may be involved in task-specific dystonias. Embouchure is a musical term to describe the interface between facial muscles and the mouthpiece of a woodwind or brass instrument needed to control air flow to the instrument. The coordinated and highly specific activation of each of the muscles involved is fundamental for the creation of proper pitch and volume with the musical instrument. Embouchure dystonia is a task-specific dystonia that affects these facial muscles. The average age of onset is in the fourth decade, and symptoms typically begin an average of 25 years (range 7-45 years, SD 13) after starting to learn the instrument. Initial symptoms were usually limited to one range of notes or style of playing, but this tended to progress to other sounds and even to non-task-specific movements. Patients complained of mouth tremor, lip fatigue, abnormal jaw opening and excessive and incomplete lip closure. However, facial pain was uncommon (12%). Frucht and colleagues classified embouchure dystonia into embouchure tremor, involuntary lip movements, and jaw movement abnormalities. Interestingly, about 10% of the patients described by Frucht had a hand task-specific dystonia, which preceded the embouchure dystonia by as many as 19 years. Embouchure dystonia may spread in about 25% of patients to involve other facial muscles. Once present, embouchure dystonia does not usually remit, and responds only poorly to pharmacologic interventions and chemodenervation. Prognosis is therefore poor, and the majority of patients are unable to earn a living playing their instrument.

The next part of the body affected by task-specific dystonia is the larynx. Although the laryngeal dystonias are not typically considered task-specific dystonias, they do meet our criteria since excessive muscle activity occurs only with selected vocal tasks. Laryngeal dystonia affects the quality and strength of voice. The two main forms are adductor laryngeal dystonia and the less common abductor laryngeal dystonia. The adductor type produces tight, strained, strangled speech due to excessive adduction of the vocal cords. Voice is typically worse with speaking and much better with whispering, singing, talking while yawning, shouting or changing pitch. Voice produced in connected speech as compared with sustained vowels may provoke more frequent and severe laryngeal spasms, and this task-specificity may help differentiate adductor dystonia from other laryngeal conditions. Breathing is almost always normal. Abductor laryngeal dystonias, characterized by excessive breathiness, seem even more task-specific with worse function with voiceless consonants (p, t, l, s, f, h, th). Sounds, such as ‘s,’ ‘h,’ or ‘k,’ preceding open vowels in words like ‘coffee’ and ‘cake’ usually are affected most. But many patients are able to perform these sounds normally while singing, laughing, humming, shouting, yawning, or just by changing the pitch of the speech. The risk of spread in laryngeal dystonias is relatively low (12%). Laryngeal dystonias can be disabling, depending on the patience’s reliance on voice for working. Laryngeal
Dystonias are 3 times more common in females, and the average age of onset is on the fifth decade.19

We found only one clearly task-specific cervical dystonia case report.20 This patient had bilateral arm amputations, and learned to write and draw holding a pen with his mouth. After 20 years of frequent and extensive writing, he developed slowly progressive cervical dystonia. Initially, symptoms were present only while writing but after more than 10 years these progressed to be present constantly and without relationship with the initial inciting task.

Upper extremity task-specific dystonias include a wide variety of disorders, many related with labor, including shoemaker’s dystonia, tailor’s dystonia, pianist’s cramp, writer’s cramp, hairdresser and telegraphist’s cramps. Upper extremities task-specific dystonias related to sports include the golfer’s yips,21,22 pistol-shooter’s cramp,23 and petanque players arm dystonia.24 We will now review the clinical manifestations of the most common task-specific dystonias of the upper extremities.

Writer’s cramp is a task-specific dystonia of writing, characterized initially by an abnormally tight grip while writing with progressive difficulty in performing the task as writing continues. Usually distal muscles of the dominant hand are the first affected. Tight grip of the pen is typical, and hand-wrist flexors are more commonly involved than extensors, even though hyperextension of the distal phalanges or even the fingers have been seen.13 Excessive muscle spasms may progress to more proximal muscles around the elbow and shoulder producing abduction of the arm. Symptoms appear at a mean age of 38 years and may be painless or accompanied by painful hand and forearm cramping.25 Slowly, handwriting becomes less legible. Sensory tricks like rubbing the back of the hand may diminish writer's cramp. An initial classification divided the patients in two groups, simple and dystonic writer’s cramp, based on the absence or presence of dystonia while performing other tasks.13 However, about half of the patients with simple cramps progress to having dystonia with other activities. About a third of patients with writer’s cramp have intermittent symptoms that are not disabling. However, the rest have constant abnormal writing that can become illegible. Remissions are uncommon, and symptoms can progress to the contralateral hand.4,13,25 Some general features that are associated with poor prognosis include secondary dystonia, tremor, long duration or progressive symptoms.26

Typist’s cramp is a task-specific dystonia characterized by excessive flexion or extension of the fingers that produces slow and laborious typing. Hand and wrist pain while typing is common. Excessive finger extension can be either the primary abnormality or a compensatory behavior. Excessive thumb flexion has also been reported.13

Golfer’s cramp or the “yips” may be a task-specific dystonia. The 'yips' are manifested by symptoms of jerks, tremors or freezing in the hands and forearms mostly while putting. These symptoms impair golf performance and contribute to attrition in golf. Many 'yips'-affected golfers decrease their playing time or quit to avoid exposure to this embarrassing problem. If this is the main physical activity that the patient is performing, this could lead
to depression and sedentary life-related comorbidities. Early studies demonstrated a lack of psychopathology in these patients.\textsuperscript{27} Adler and colleagues evaluated the neurophysiological characteristics of the excessive motor activation that impairs function and found evidence of co-contraction on affected golfers and not in controls.\textsuperscript{28} The yips may be classified into two different types, dystonic (Type I) and anxiety-related (Type II).\textsuperscript{29}

Musicians practice and perform highly skilled motor tasks that may lead to development of focal hand dystonias specific to playing the relevant instrument such as piano, guitar, clarinet, flute, horn, harp and the tabla.\textsuperscript{30,31} Both professional and amateur players are at risk.\textsuperscript{17} The mean age of presentation is in the fourth decade.\textsuperscript{32-34} Musician’s task-specific dystonias rarely occur during the initial training period but rather more commonly develop at the peak professional stage.\textsuperscript{17} Sensory complaints are rare.\textsuperscript{32} The most commonly affected muscles are those heavily involved in the performance and most often in the hand that performs the most demanding tasks.\textsuperscript{37,32,34} In pianists the right hand is more commonly involved, typically with fourth and fifth finger excessive flexion, which are the same fingers affected on the left hand of violin players.\textsuperscript{33} If the bowing hand of violinists is affected, then it is usually associated with abnormalities of wrist posture.\textsuperscript{14} The right hand is more commonly involved on guitarists. This lateralization is not as prominent in woodwind players probably due to the equivalent complexity of movements in both hands.\textsuperscript{17} While guitar players have a hyperflexion of the third right finger, clarinetists tend to have hyperextension.\textsuperscript{33} Some musicians have task-specific dystonias while playing one instrument, but not while playing others. The prognosis is poor for musician’s cramp, as these task-specific dystonias impair performance forcing as many as half of musicians to stop professional playing.\textsuperscript{35} Prognosis may be worse for string players who have dystonia of the bowing arm, as treatment is less effective.\textsuperscript{36}

Task specific dystonias of the lower extremities are rare. For example, children with DYT1 dystonia may begin with foot dystonia only when walking forward that is not present when walking backwards or while running or swimming. However, this specificity is frequently lost as the condition progresses. There are some reports of lower extremity task-specific dystonias. In one of those reports, a patient had walking-induced equino-varus deformity only when the leg was at the end of the swing phase.\textsuperscript{37} Lo and Frucht reported two cases of patients that had dystonia of the lower extremities only while walking down steps.\textsuperscript{38} Interestingly, an interoceptive sensory trick (imagining walking in a different modality) led to temporary improvement. Some adult-onset primary lower limb dystonia can be relatively task-specific and be present only during walking or running but not while standing or sitting.\textsuperscript{39,40}

**Evaluation and Differential Diagnosis**

The purpose of the physical exam on task-specific dystonias is to confirm diagnosis, identify the specific triggers of the dystonia, determine the muscles involved in the movement and exclude other potentially confounding conditions. The key features of the history include identification of the precipitating actions that lead to the dystonic
movement. The specific characteristics of the movements should be elicited. Other factors that may mitigate the task-specific dystonia should be sought. Detailed questions are important to determine whether dystonia has affected other body parts or activities. The examination should first observe whether dystonia is present in the relevant body part while at rest, during a specific task or with other tasks. It is also helpful to determine whether performing other unrelated motor activities like walking precipitates it. During the performance of the precipitant task, the patient should be asked to do it with and without the use of the behavioral adaptations that have been beneficial.

Other components of the exam should be normal except for occasional tremor or less likely myoclonus or chorea during the task-specific dystonia. Occasionally, the affected limb might have increased tone or reduced ipsilateral arm swing.13,14 About one third of patients will have an abnormal posture of the affected region at rest or with voluntary movements of other body parts. Some patients with task specific dystonia of one limb develop abnormal postures while performing the precipitant action with the contralateral limb, so called mirror dystonia. Ascertainment of mirror dystonia can be useful in dissecting the true dystonic muscles from otherwise compensatory behavior.41

Neurophysiologic studies of patients with writer’s cramp, typist’s cramp, pianist and guitarist’s cramp have shown the simultaneous activation of agonist and antagonist muscles (co-contraction), activation of muscles that are usually not involved on the task (overflow), and excessive contraction.42,42-44 Co-contraction is not specific for dystonia as anyone voluntarily holding the limb stiffly could have similar electromyographic findings. However, a study examined the mechanisms underlying co-contraction in patients with writer’s cramp, indicating that co-contraction in dystonia is neurophysiologically different from voluntary co-contraction and could be produced by abnormal synchronization of presynaptic inputs to antagonist motor units.45

Although not routinely recommended for diagnosis, nerve conduction and electromyography studies may help identify other peripheral nervous system abnormalities like carpal tunnel syndrome that could be exacerbated by focal dystonia.6 Brain imaging for diagnostic purposes is not routinely recommended.6 Differential diagnosis includes non-task related dystonias, parkinsonism-associated dystonias, carpal tunnel syndrome, neuropathies, plexopathies, repetitive stress injury, thoracic outlet syndrome and other vascular insufficiencies, reflex sympathetic dystrophy and psychogenic movement disorder.46

**Epidemiology and risk factors**

Most focal dystonias begin in adulthood.5 The prevalence per million for early and late onset dystonia has been estimated to be between 11 to 50 and 101 to 430 respectively.47 However, population-based studies of people examined by movement disorders experts have provided higher prevalence rates of late-onset primary dystonia, up to 7,320 per million.48 Writer’s cramp and laryngeal dystonias are the most common forms of task-
specific dystonias. Prevalence estimates of task-specific dystonias ranges between 7 and 69 per million in the general population.\textsuperscript{49,50} The prevalence of task-specific dystonias in German musicians has been calculated to be as high as 0.5\% and may be one of the most common causes of hand complaints in musicians.\textsuperscript{17}

There are some epidemiological differences between task-specific and other types of dystonia. Although adult-onset focal primary dystonias in general are more common in females,\textsuperscript{49,51} task-specific dystonias may be more common in males.\textsuperscript{34,52,53} Also musician’s cramp tends to begin at younger ages than other adult-onset primary dystonias.\textsuperscript{17,54,55}

There is a paucity of data on risk factors for task-specific dystonias. A positive family history is one of the most important risk factors for primary dystonias\textsuperscript{47} although most patients with adult-onset focal dystonia do not have an identifiable gene defect.\textsuperscript{56} Ten to twenty percent of patients with task-specific dystonias have a positive family history.\textsuperscript{57} In fact, three families with a dominant pattern of inheritance have been described with a proband having musician’s cramp and other family members having writer’s cramp.\textsuperscript{58} However, reliability of proband-provided family history is known to be poor.\textsuperscript{59} Interestingly, DYT1 gene mutations that typically cause childhood onset generalized dystonia also can occasionally cause focal hand dystonia or a task-specific dystonia.\textsuperscript{60-64} However, in general the DYT1 mutation is uncommon in patients with task-specific dystonia.\textsuperscript{63,64} Other genetic abnormalities, including DYT6, DYT7, DYT13, and abnormalities linked to Chromosome 18 have been found in patients with task-specific dystonias.\textsuperscript{65,65,66} The etiology of the majority of adult-onset primary dystonias, including task-specific ones, remains unclear and may include polygenetic abnormalities associated with environmental factors.\textsuperscript{67}

The role of environmental triggers for task-specific dystonia also remains unknown. The most likely trigger is the highly skilled over-learned task but this remains to be proven. Several studies have addressed the role of trauma. Sheehy and colleagues reported that only 5\% of 91 patients with writer’s cramp had a history of a hand injury in the preceding 3 months of the appearance of the dystonia.\textsuperscript{25} Yet, focal trauma due to repetitive motor tasks have been linked with task-specific dystonias.\textsuperscript{17} Moreover, the presence of ulnar neuropathy, as well as preceding trauma has been associated with musician’s task-specific dystonias.\textsuperscript{68,66} However, small surveys of embouchure dystonia patients have not found an association with preceding trauma, dental work, or exposure to neuroleptics.\textsuperscript{16} Head trauma does not seem to be associated with cranial dystonias either.\textsuperscript{70}

**Pathophysiology**

Investigations of the pathophysiology of task-specific dystonia have found abnormalities within the basal ganglia or its connections, decreased inhibition at various levels of sensorimotor systems, abnormal plasticity and impaired sensorimotor processing. Some clinical similarities across the different task specific dystonias suggest that there may be
commonalities of pathophysiology yet different anatomic sites of involvement, different demographics of affected individuals and different prognoses indicate that all may not share the same pathophysiologic or etiological basis.\textsuperscript{53,71,72}

**Regional Pathophysiology:**

In this section we will review structural abnormalities found in some people with task-specific dystonias, summarize resting state and physiologic activation studies that have attempted to localize regional dysfunction and then describe relevant neurochemical and pharmacologic activation studies.

Although structural abnormalities have been found in many areas beyond the basal ganglia,\textsuperscript{73-76} mostly basal ganglia lesions have been found in the few studies that addressed task specific dystonias. Volumetric analysis of magnetic resonance (MR) images demonstrated increased size of the putamen by about 10\% in those affected by primary cranial or hand dystonia (primarily task specific hand dystonia).\textsuperscript{77} Similar MR-based volumetric techniques in 36 people with task-specific hand cramp have shown increased volume of the grey matter in the hand area of the left primary sensorimotor cortex, bilateral posterior thalamus and cerebellum.\textsuperscript{78} However, another study in 30 patients with writer’s cramp found reduced volume in those regions,\textsuperscript{79} These discrepancies may, in part, be explained by methodological and interpretative issues.\textsuperscript{80} One study of patients with focal hand dystonias and other primary focal dystonias, showed increased grey matter in globus pallidus, caudate, accumbens and prefrontal cortex bilaterally, as well as left inferior parietal lobe using voxel-based morphometry analysis.\textsuperscript{81} MR-based diffusion tensor imaging (DTI) in people with cervical dystonia and hand cramp have identified abnormal fractional anisotropy in a region between pallidum and thalamus that may reflect abnormal BG connections.\textsuperscript{82}

Abnormal function in various brain regions may contribute to the pathophysiology of task specific dystonia despite normal appearing structure. Functional neuroimaging using either PET or fMRI has been used for this purpose. PET measurements of regional blood flow or metabolism are thought to reflect neuronal input into a brain region or local neuronal activity within that region.\textsuperscript{83} Resting state PET studies have found changes in function of the putamen and other components of basal ganglia-cortical circuits in patients with primary and secondary dystonia, consistent with dysfunction of lenticular nuclei and premotor areas.\textsuperscript{84-87} However, it is important to appreciate that abnormal regional function found in people with dystonia compared to normals could indicate a regional abnormality that is pertinent to the pathophysiology of dystonia or could reflect abnormal feedback to that brain region due to abnormal motor behavior during the “resting state” study. Eidelberg and colleagues avoided this confound by studying people that carried the DYT1 gene that may cause dystonia in about 30-40\% of people with this defect. They used a principal components analysis to measure a movement-free pattern in non-manifesting DYT1 carriers that was also present in manifesting carriers during sleep.\textsuperscript{88} There have not been similar studies in task-specific dystonias.
Most studies have not found selective functional abnormalities in people with dystonia at rest although, as noted above, there are exceptions that used principal components analysis to identify abnormal patterns of resting flow or metabolism. Moreover, since task specific dystonias are usually not present at rest, it is reasonable to use an activation paradigm during a neuroimaging study to determine whether there are abnormal responses. The main caveat with this approach is to ensure proper controls for abnormal motor behavior by the dystonic group compared to normals. Otherwise, a change in an imaging measured response in the brain to a specific motor pattern (like writing with writer’s cramp) may reflect either the feedback related to motor performance or indicate alterations in brain function that lead to the differences in motor behavior. This confound is called the “chicken and egg” problem and must be considered when interpreting these types of studies. For example, a number of studies have shown that hand movements in normals activate contralateral primary motor and sensory cortex, ipsilateral cerebellum, premotor cortex and bilateral supplementary motor area. However, people with task-specific dystonias may have either hyper or hypometabolism of the premotor area while performing a hand motor task. One activation study found in people with writer’s cramp deficient blood flow activation of the premotor cortex and decreased correlation between premotor cortical regions and putamen. The authors concluded that the findings suggest a dysfunction of the premotor cortical network in patients with writer’s cramp possibly arising from basal ganglia dysfunction. In task-specific dystonias and other dystonic patients, most tasks have been associated with a reduced response in the sensorimotor cortex with increased activity in the lateral prefrontal regions. Writer’s cramp patients had writing induced greater activation of the ipsilateral cerebellum and thalamus, in addition to an extensive activation of the sensorimotor cortex consistent with increased basal ganglia output via the thalamus to the motor and premotor cortical areas.

In contrast, a fMRI study of guitarists with and without musician’s cramp showed that the dystonic patients (while playing the instrument) had a significantly larger activation of the contralateral primary sensorimotor cortex with an associated bilateral underactivation of premotor areas, when compared to the resting state and to non-dystonic guitarist. Other studies have found similar results however each of these studies is potentially confounded by possible differences in performance of the task between the dystonics and normals.

Two groups have tried to avoid this confound by analyzing imaging data collected after motor activity stopped. In one fMRI study, people with hand cramp had an abnormal signal in striatum during a finger tapping task that persisted after the finger tapping stopped suggesting that this reflected a defect in inhibitory control. Another group used event-related fMRI in people with laryngeal dystonia to analyze BOLD signal responses to vocal tasks at a time when there was no task performance or during whispering when there was no abnormal performance and found reduced activation of primary sensorimotor and premotor area. However, in both of these latter two studies lack of electromyographic monitoring of muscle activity limit how confidently one can be regarding lack of abnormal motor activity during these times.

Another approach to avoid this potential motor behavioral confound is to investigate brain responses to sensory stimulation in which people with dystonia and normals have
the same behavioral activity. This was first done by measuring PET-based blood flow responses to hand vibration in people with dystonia on just one side of the body. In that study, people with dystonia had reduced response in contralateral sensorimotor cortex and interestingly a similar reduced response to vibratory stimulation of the “uninvolved side.” A follow up investigation in people with writer’s cramp confirmed these reduced responses in sensorimotor cortex and also identified a similarly reduced response in supplementary motor area (SMA). Subsequent studies using fMRI and magnetoencephalography have found abnormal sensory fields in people in task-specific hand dystonia. All the above suggests that there is a baseline sensory abnormality in patients with dystonia. Interestingly, preliminary data in one person with dopa-responsive dystonia suggest that this abnormal cortical response may be corrected by administration of levodopa. This effect of levodopa may be mediated by its action in basal ganglia but does not prove it since there are cortical dopamine receptors.

Several studies of PET dopaminergic radioligand binding have identified dopaminergic defects in basal ganglia. Nonhuman primates treated with intracarotid MPTP, which selectively destroys dopaminergic neurons, develop transient hemidystonia prior to chronic hemiparkinsonism. During the dystonic period, there is a transient decrease in D2-like receptor number (about 30% decrease) in the putamen. Interestingly, PET measurements revealed a similar putaminal decrease in patients with cranial and focal hand dystonias (again mostly task-specific dystonia). A similar reduction in putaminal specific binding has been reported in cervical dystonia and non-manifesting carriers of the DYT1 mutation, although these were not people with task-specific dystonia.

A defect in GABA level in the lenticular nucleus contralateral to the affected hand has been found in people with writer’s cramp using magnetic resonance spectroscopy. It is not clear if these focal biochemical changes are secondary to dysfunction of other areas or may be related to changes in dopaminergic dysfunction.

In summary, current evidence demonstrates defects in basal ganglia pathways that may reflect or include dysfunction of dopaminergic pathways that influence basal ganglia-cortical circuits. The role of other pathways, like cerebellum or other biochemical systems, is less certain.

**Loss of inhibition:**

Loss of inhibition at different levels may contribute to the excessive motor activity in focal dystonia patients. Loss of reciprocal inhibition (the normal inhibition of antagonist muscles during a movement) in the arms of patients with writer’s cramp could be consistent with a loss of inhibition at a spinal level, as this reflex depends on the activity of the agonist muscle Ia sensory afferents. Importantly, long-lasting voluntary handgrip in normals reduces reciprocal inhibition, suggesting that excessive motor activity that occurs in task specific dystonias could act in the same manner.

Transcranial magnetic stimulation (TMS) studies in patients with task-specific dystonia have revealed defects consistent with reduced cortical inhibition. Short intracortical
inhibition is reduced in bilateral cortices of patients with unilateral writer’s cramp, suggesting that this defect occurs in the affected and unaffected sides like defects in vibrotactile responses. Patients with writer’s cramp also have a significant reduction of the long intracortical inhibition only in the contralateral hemisphere and only during muscle activation. Patients with focal hand dystonia also have impairment of the normal modulation of the intracortical inhibition expected during performance of a manual task. Task-specific dystonias patients have increased corticospinal excitability and lack of inhibition of corticospinal excitability after exposure to subthreshold 1Hz repetitive TMS. A peripheral conditioning stimulus normally induces a inhibitory response that correlates with the intracortical inhibition to paired-pulse TMS. Using stimulation of the median nerve as a conditioning response produces a normal response in people with cranial dystonia. However, people with focal hand dystonia have an excitatory response rather than inhibitory one. Abnormal intracortical inhibition may contribute to a lack of specificity in the output from the cortex and the development of unwanted motor activation. Reduced GABA levels in the sensorimotor area of patients with hand dystonia found with MRS also is consistent with reduced inhibition at a cortical level but does not prove that this is the primary site of pathology. Of course, all of these findings could indicate adaptive responses to dystonia rather than a cause of dystonia.

An important contribution was provided by Rosenkranz and colleagues, who studied the pathophysiological differences between musician’s and writer’s cramp using transcranial magnetic stimulation. They compared the spatial pattern of sensorimotor organization in the motor cortex of these patients with normal musicians and non-musicians controls. They used focal vibration of a single hand muscle and measured the corticospinal excitability to that muscle and other hand muscles. In the vibrated muscle of healthy non-musicians, vibration increased the amplitude of the motor-evoked potentials and decreased the short-latency intracortical inhibition. But it had the opposite effects on the other hand muscles, which could be interpreted as focal facilitation with surround inhibition. Vibration had little effect on patients with writer’s cramp, but it notably reduced short-latency intracortical inhibition in all hand muscles. Importantly, in the vibrated muscle of normal musicians, the results were intermediate between the healthy non-musicians and the dystonic musicians. The authors concluded that musical performance leads to some physiological changes in organization of the motor cortex, that when exaggerated causes dystonia. This difference could be at least in part due to the considerably higher practice that is needed for instrumental performance. They also added that it seems that sensory input had greater importance in musician’s cramp than in writer’s cramp.

The loss of surround inhibition could explain some of the abnormal motor activations that happen in task-specific dystonias. Surround inhibition, as revealed by studies using TMS, seems to be impaired in focal hand dystonia patients when compared to normals. Tinazzi and colleagues also evaluated the concept of surround inhibition using somatosensory evoked potentials on patients with dystonia. They compared evoked potentials produced by median vs ulnar stimulation and then they evaluated simultaneous stimulation. No significant difference was found between SEP for individually stimulated
median and ulnar nerves in dystonic patients and normal subjects, but the patients had a significantly higher percentage ratio (median + ulnar response x 100) for mainly central components. These findings suggest that the inhibitory integration of afferent inputs from adjacent body parts is abnormal in dystonia.

In summary, lack of inhibition at multiple levels could explain the unintended activation of muscles and the resulting abnormal movements in patients with task-specific dystonia.121

**Excessive Plasticity:**

Plasticity or changes in how brain pathways respond to various stimuli may contribute to the development of task-specific dystonia. Cortical TMS may provide some insights into this mechanism.122 In normals, peripheral nerve stimulation increases the motor response to TMS and the motor facilitation is limited to the muscles innervated by the peripheral nerve that was stimulated. This response is larger in patients with task-specific dystonias and spreads to muscles not innervated by the stimulated nerve.115 Task-specific dystonia patients also have an attenuated reinforcement of the intracortical inhibitory circuits that generate the cortical silent period after the associated stimulation. This lack of cortical inhibition could produce a less precise system that also could contribute to dystonia.

Task-specific dystonias are frequently associated with repetitive movements. One hypothesis that could connect repetitive movement with dystonia would be that excessive plasticity causes repetitive movements to abnormally lower stimulus threshold for activation of a specific circuit. Repetitive motor activities can change the sensorimotor cortex and lead to dystonia in animal models.123 Current evidence shows that there is increased plasticity in brains of patients with task-specific dystonias, associated with an abnormal homeostasis, as the normal limits of excitability are not preserved.124 A study that illustrates this combined low-frequency repetitive transcranial magnetic stimulation (rTMS) with transcranial direct current stimulation (TDCS) to probe regional homeostatic plasticity of the left M1 in writer cramp patients and normals. In normals the response to anodal TDCS over M1 enhances the inhibitory effect of subsequent 1 Hz rTMS on corticospinal excitability. Conversely, preceding cathodal TDCS reversed the after effect of 1 Hz rTMS, producing an increase in corticospinal excitability. In writer cramp patients the effects of this preconditioning were very different. Following TDCS, 1 Hz rTMS induced no consistent changes in corticospinal excitability, and the normal inhibitory effect of preconditioning with cathodal TDCS was absent. The authors concluded that the homeostatic mechanisms that stabilize excitability levels are abnormal in writer’s cramp. Quartarone and colleagues suggest that repetitive skilled motor practice leads to excessive formation of associations between the sensory input and motor outputs (abnormal potentiation) and a failure to weaken existent associations (deficient depotentiation).122 However, most people that frequently repeat a specific motor activity develops task-specific dystonias. Thus, there must be a permissive state or pre-existing condition that makes an individual vulnerable to a task-specific dystonia producing event. This “double-hit” model has been advanced by an animal model of craniofacial dystonia. In that model, striatal dopamine deficiency caused by a prior injection of 6-OHDA made
rodents vulnerable to a simple peripheral injury that leads to development of facial twitches that mimic cranial dystonia.\textsuperscript{125}

The role of these changes in plasticity remains still unknown. They could be the result of loss of inhibition, as reduced GABA could lead to changes in plasticity by itself.\textsuperscript{126} However, whether increased plasticity causes dystonia or dystonia produces increased plasticity remains to be determined.

**Changes in sensory function:**

The potential contribution of abnormal sensorimotor processing to the pathophysiology of dystonia in general and task-specific dystonia in particular has gained increasing attention.\textsuperscript{118,127} Clinical observations have been suggestive. Sensory complaints may precede onset of motor symptoms; at least this has been reported in a small series of patients with craniofacial dystonia.\textsuperscript{128} It also is well known that many patients can ameliorate dystonic spasms by varying sensory inputs to involved or nearby parts of the body. These so-called sensory tricks are sometimes known as “geste antagoniste” and were initially thought to be psychogenic. A recent physiologic study has suggested that sensory tricks may modify sensorimotor processing, a critical step that could modulate dystonic symptoms.\textsuperscript{127}

Patients with focal hand dystonia may have sensory abnormalities including deficient graphesthesia,\textsuperscript{129} and temporal and spatial discrimination ability,\textsuperscript{130,131} whereas those with DYT1 generalized dystonia have normal spatial discrimination.\textsuperscript{132} The abnormalities in temporal discrimination relate specifically to cutaneous and not musculo-skeletal proprioceptive pathways.\textsuperscript{133} However, a recent study found decreased sensory threshold in pianists without dystonia raising the question as to whether the sensory abnormality is specific for dystonia rather than a response to training a highly learned and skilled motor task.\textsuperscript{134}

Evidence of defective central sensorimotor processing in people with task-specific dystonia include the reduction in sensorimotor cortex blood flow responses to hand vibration, as discussed above.\textsuperscript{97,98} Abnormal sensory inputs or abnormal central processing of normal afferents can change motor activity.\textsuperscript{135} For example, muscle vibration can induce focal hand dystonia, likely by activating muscle spindles and the tonic vibration reflex, which can be attenuated by local injection of lidocaine.\textsuperscript{136} Vibratory stimulation can produce an illusion of movement in normals, but this response is diminished in people with task-specific dystonias.\textsuperscript{137} These findings suggest, but do not prove, that an abnormal muscle spindle function could contribute to dystonia. In contrast, sensory evoked potentials (SEP) at rest and the latency of primary cortical responses are normal in dystonia indicating normal lemniscal system function and normal primary sensory cortex excitability.\textsuperscript{127} However, a recent study using SEP found impaired modulation of pre-movement sensory input with loss of the normal attenuation of SEPs in preparation for movement in people with writer’s cramp.\textsuperscript{138}
Repetitive motor activities may broaden sensory fields in sensorimotor cortex associated with development of dystonia in nonhuman primate model of repetitive use-induced dystonia. fMRI studies also suggest that there may be broadened sensory fields in people with hand dystonia. Broadening of sensory field may extend beyond cortical regions. Microelectrode recordings of the pallidum and thalamus reveal enlarged sensory receptive fields in patients with generalized dystonia that are having implantation of deep brain stimulator electrodes. Less segregation could be associated with spreading and overflow during motor activities. However, it remains unknown whether this overlap of sensory fields precedes the motor abnormalities or is a consequence of overtraining or excessive muscle activity associated with dystonia.

One could expect that the major changes on sensation caused by a continuous and abnormal activation of muscles could induce the sensory abnormalities that have been described. In fact, it has been shown that co-contraction can cause changes in cortical plasticity and sensory function in normal individuals. However, the sensory discrimination abnormalities are found on the contralateral limb in people with unilateral writer’s cramp, and on hands of patients with blepharospasm and cervical dystonia. Moreover, sensory abnormalities have been found on unaffected family members of patients with familial adult-onset Primary Torsion Dystonia. Also, a study using PET showed that there was abnormal functional coupling between brain regions of DYT1 patients and also their non-dystonic siblings, suggesting a sensory abnormality at a more fundamental level. Studies using magnetoencephalography to evaluate sensory cortex in subjects with task-specific dystonias have shown a clear disarray of the non-dystonic hand representation, another sign of endophenotypic rather than adaptive sensory dysfunction. Also reciprocal inhibition is defective on both the affected and the non-affected arm in writer’s cramp patients. All the above suggests that there is a baseline sensory abnormality in patients with dystonia.

In summary, abundant evidence indicates sensory processing defects in task specific dystonias. Several lines of evidence suggest that this may be a key part of the pathophysiology of the condition.

**Integration of Pathophysiology:**

A brief review of the anatomy and physiology of basal ganglia will be provided here since this is germane to integrating the various aspects of the pathophysiology of dystonia. The major input area of the basal ganglia is the striatum composed of caudate and putamen. These structures receive glutamatergic input from wide spread cortical regions, from intralaminar thalamic nuclei and dopaminergic input from substantia nigra pars compacta. Another main source of glutamatergic input from cortical regions goes directly to subthalamic nucleus. The classic model of the basal ganglia is characterized by two major pathways connecting the striatum to the globus pallidus pars interna (GPi), the major output of the basal ganglia. The direct pathway from striatum is an inhibitory GABAergic connection to GPi, while the indirect pathway includes a GABAergic inhibitory connection to globus pallidus externa (GPe) which subsequently projects to subthalamic nucleus (STN) via inhibitory GABAergic connection. Post-synaptic D1-like
receptors are expressed preferentially on the striatal neurons that project to GPi; whereas D2-like post synaptic receptors are expressed preferentially on those that project to GPe\(^{147-150}\) although some striatal neurons have both D1-like and D2-like receptors.\(^{151}\) STN, in turn, projects directly to GPi via an excitatory glutamatergic connections as well as back to GPe and then to GPi. The GPi sends inhibitory GABAergic projections to motor thalamus, which projects to cortical motor areas. The cortico-STN-GPi route is faster and stronger than the direct striatal pathway.\(^{152}\) Also, the indirect pathway projects onto GPi in a less selective fashion than the direct pathway.\(^{153,154}\) This provides the anatomic basis for selected facilitation and surround inhibition modulated by the basal ganglia.\(^{155}\)

As noted above, a primary function of the indirect pathway may be to broadly inhibit unwanted muscle activation during an intended movement.\(^{156}\) Dystonia is characterized by a lack of inhibition of excessive or unwanted muscle contractions during the intended target task, which could be viewed as a dysfunction of the indirect pathway. Inhibited indirect pathway or excessive direct pathway could lead to a decreased output from GPi and lack of focus on motor activation. After inactivation of internal segment pallidal neurons with the GABA agonist muscimol, dystonic postures can develop with a reaching task, which supports the idea that decreased GPi output is associated with dystonia.\(^{157}\) Also, many reports of patients with primary or secondary dystonia are consistent with a relatively inhibited GPi.\(^{143,158}\) PET measures of dopaminergic receptor binding in people with task-specific hand dystonia (and cranial dystonia) and in an animal model with transient dystonia suggest that dystonia may preferentially affect D2-mediated pathways, which also implicates the indirect pathway.\(^{102,103,159}\) Alternatively, a change in firing patterns in GPi may be more important than a change in rate, as suggested by recordings in a hamster model of idiopathic paroxysmal dystonia.\(^{160}\) Either way, dysfunction at multiple sites within the indirect pathway could alter surround inhibition and produce dystonia.

More recently it has been recognized that cerebellar control over tone could play a role in task specific dystonia. Excitation of gamma and alpha motor neurons occur independently from each other. It has been hypothesized that a repetitive, prolonged practice of a motor plan, as done by musicians, could lead to an increased gamma drive, independent of alpha drive. This could initially increase the speed and performance of highly demanding task, but also could produce an increased reflex gain spreading across muscles as an unwanted byproduct that could lead to a task specific dystonia.\(^{161}\) Some studies have suggested that the cerebellum has the capacity to exert a specific drive to gamma motor neurons, separate from the drive to alpha motor neurons.\(^{162,163}\) However, the cerebellum is connected with the striatum, and therefore the interplay between these structures makes specific localization complex.\(^{164}\)

In summary, substantial evidence suggests that dysfunction of the indirect pathway may lead to reduce surround inhibition of an intended motor activity but it is not clear how this may relate to sensory abnormalities. The potential role of the direct pathway remains unknown. Whether cerebellar dysfunction contributes to this condition remains to be proven. Furthermore, the precise details of how this relates to altered cortical
inhibition are unclear. Finally, the pathophysiologic differences between the task-specific dystonias and other primary dystonias needs further study.

**Treatment**

**Pharmacological alternatives**

We are not aware of any randomized-controlled trials for pharmacological treatments of task-specific dystonias. Anticholinergic, dopaminergic and GABAergic medications have been used empirically with some inconsistent success for generalized dystonia and severe focal dystonia.\(^{165,166}\) Use of trihexphenidyl on patients with musician’s cramp has been reported subjectively useful in one third of the patients.\(^{167}\) Although oral medications have provided benefits in selected patients, these drugs have often dose-limiting side effects.

**Botulinum toxin injections**

Chemodenervation with botulinum toxin type A injections was approved by the FDA in 1989 and has become a common treatment for task-specific dystonias.\(^{168-170}\) Randomized, double-blind, placebo-controlled trials of BNT-A for writer’s cramp have shown benefit after a single or multiple injection.\(^{171-174}\) Long-term follow up on patients with writer’s cramp treated with chemodenervation, are consistent with normalized writing in half of the patients, and partial benefit in another 10%, lasting a mean of six months after the procedure.\(^26\) and this approach has been shown to be safe.\(^{168}\) However, the main challenge is to provide adequate benefit without loss of function associated with weakness. This is particularly important in those that still expect high level fine motor control with the affected limb.\(^{19,175}\) The same cautions apply to botulinum treatment of laryngeal dystonia – at least for adductor type. Botulinum neurotoxin A is probably effective for the treatment of adductor-type laryngeal dystonia.\(^{176}\) There are insufficient data to make recommendations regarding treatment of abductor laryngeal dystonia.\(^{173}\)

In case series of musician’s cramp been treated with chemodenervation, 50-69% of the patients experienced improvement from the injections and 36% reported long-term benefit in their performance ability.\(^{167,177}\) The limitations of some of these studies include been open-label, with subjective assessment of the results, and without the use of placebo controls.

Botulinum neurotoxin (BNT) may block gamma motor neurons preferentially over the alpha motor neurons, decreasing the muscle activity on the spindle more than the extrafusal fibers.\(^{178}\) This may explain how BNT can alleviate excessive contraction without causing weakness. It is not clear if these peripheral alterations lead to central changes that could improve or worsen the abnormal pattern of activation. The known attenuation of the reciprocal inhibition seen in patients with task-specific dystonias seems to normalize partially after injections with BNT.\(^{179}\) Another study showed that by altering the peripheral feedback, botulinum toxin injections could potentially produce reorganization of the intracortical circuits leading to changes of the excitability of the
motor cortex in patients with dystonia. However, other studies have shown that even though botulinum toxin injected into involved muscles reduced dystonic posturing in writer’s cramp, it does not normalize the usual task-specific dystonias patterns of cortical responses, and it is clear that is far from curative.

**Surgical options**

Both pallidotomy and pallidal deep brain stimulation have been effectively used for dystonia. There are few reports of surgical approaches for disabling task-specific dystonias. In one study of 12 patients with disabling symptoms due to task-specific hand dystonia, stereotactic nucleus ventro-oralis thalamotomy was performed. All patients had disappearance of dystonic symptoms sustained during the follow-up period (3 - 33 months, mean 13.1 months).

**Sensorimotor retraining, rest and other rehabilitation therapies**

Many patients with task-specific dystonias alter the normal way they perform activities in an attempt to improve performance. Specially designed splints or thicker pens may help writer’s cramp. It has been thought that by immobilizing the dystonic limb the abnormal sensorimotor pattern could be reversed, helping reduce focal dystonia symptoms. This has provided some benefit to task-specific dystonias patients after immobilization for a mean of 4.5 weeks. Benefit persisted in the majority of patients after 20 weeks, but longer term follow up and cost-effectiveness analysis of the immobilization have not been reported.

Few patients with embouchure dystonia can respond to rebuilding their embouchure. If lack of normal homeostatic control of plasticity contributes to the pathophysiology of task-specific dystonia that is triggered by over-learned highly skilled tasks then intensive retraining could be deleterious in the long run. This rationale has prompted some to recommend to those patients with embouchure dystonia that were not dependent on performing, to consider quitting to minimize the risk for spreading into other activities like eating or speaking, although they recognized the lack of conclusive evidence on this regard. The role of retraining remains to be determined.

Sensorimotor re-tuning is a rehabilitation intervention using splinting of unaffected fingers that has been shown to help pianists and guitarists with task-specific dystonias, but not woodwind players. Two months of training provided benefit for up to two years in some of these musicians. When effective, these context-specific training protocols may return sensorimotor cortical processing towards normal as measured by whole-head magnetoencephalography. Byl and colleagues have shown that sensory retraining, non-stressful hand rehabilitation and other non-pharmacological techniques can be useful in patients with task-specific dystonias. Jabusch et al reported benefit on about half of the patients with musician’s cramp by using pedagogical retraining, unmonitored technical exercises and with ergonomic changes. However, studies with a large patient base, with long-term benefit ascertainment, controlled, and under blinded assessments are lacking.
In summary, oral medications have been anecdotally beneficial in some patients. Botulinum toxin injections have provided greater benefit to many but still have substantial limitations. The role of surgery and rehabilitation approaches remains to be determined, but are areas of active investigation.

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