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When Blue Turns to Gray: The Enigma of Musician's Dystonia

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Abstract and Keywords

Musician's dystonia (MD) is an enigmatic neurologic disorder that selectively interferes with voluntary motor control required for music performance. In many cases it is evident only in certain passages of certain pieces. This contributes to the challenges of assessment and treatment. Oral medications and botulinum toxin injections have shown some limited efficacy, but with adverse side effects. Physical medicine and rehabilitation strategies generally have a lower risk of adverse side effects and show promise in efficacy but are difficult to incorporate in well-controlled studies. MD shares pathophysiologic features with other forms of focal dystonia, including abnormalities in inhibition, sensorimotor integration, and plasticity at many levels of the central nervous system. Theories for the pathogenesis include multiple etiologic factors, such as genetics, gender, and "use patterns." Ongoing research on assessment, pathophysiology, and pathogenesis should provide rationale bases for managing and even preventing MD.

Keywords: musician, dystonia, isolated dystonia, focal hand dystonia, use patterns

Introduction

Dystonia

Musician's dystonia is a particular form of dystonia. The concept of dystonia has evolved over the past several decades. A recent update to its definition reflects a multiyear effort to achieve some consensus on how it is described:

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Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

(Albanese et al., 2013)

Dystonia can refer to characteristic symptoms that are secondary to a long list of other, mostly neurologic, disorders. Dystonia can also be the primary disorder, referred to as "isolated dystonia." References to dystonia in the remainder of this chapter will refer to the primary, isolated form of dystonia.

There are many forms of dystonia, most commonly differentially characterized by their age of onset and the distribution of body regions that are symptomatic. Dystonias with onset in childhood or adolescence tend to be more general, involving several parts of the body and are more likely to begin in the lower extremities. Adult onset dystonias are much more common and typically involve only a single body region ("focal dystonia") or a small number of contiguous body regions ("segmental dystonia"). The various focal dystonias share several characteristics, including a lack of selectivity in attempts to perform specific movements, such as individual finger movements in the case of focal hand dystonia (FHD). In some cases, focal dystonias also exhibit undesirable co-contraction of antagonistic muscles (Cohen & Hallett, 1988).

Musician's Dystonia

Musician's dystonia (MD) is a specific type of focal dystonia. Onset can range from approximately 18 years old to the seventh decade, but most commonly occurs in the mid-30s (Altenmüller, 2003; Brandfonbrener, 1995; Brandfonbrener & Robson, 2004; Chang & Frucht, 2013; Conti, Pullman, & Frucht, 2008; Jankovic & Shale, 1989; Lederman, 1991; Schuele & Lederman, 2004a). MD is one of the most perplexing forms of dystonia. Documenting a cohort of over 590 MD patients diagnosed between 1994 and 2007 at the Institute of Music Physiology and Musicians' Medicine of the Hanover University of Music, Drama, and Media (Altenmüller, Baur, Hofmann, Lim, & Jabusch, 2012; Jabusch & Altenmüller, 2006a) it has been associated with almost every instrument and in several body regions. In every case MD involves impaired voluntary motor control while a musician is playing the instrument. The symptoms generally appear during movements that are extensively trained. It can affect control of facial, lip, and tongue muscles ("embouchure dystonia," Frucht et al., 2001), lower limbs, or, in the majority of patients, the muscles controlling the arm or hand. MD involving the hand is a form of FHD.

MD is sometimes referred to as "musician's cramp" because it is often described in conjunction with a form of FHD called "writer's cramp." However, the term "cramp" can be misleading; MD rarely involves the maximum intensity contractions associated with cramps (Pesenti, Barbieri, & Priori, 2004; Tubiana, 2000). In the hand, MD is usually associated with loss of fine control and coordination most commonly in heterogeneous subsets of digits 2–5 (Charness, Ross, & Shefner, 1996; Frucht, 2009b; Furuya, Tominaga, Miyazaki, & Altenmüller, 2015; Jankovic & Ashoori, 2008; Jankovic & Shale, 1989). The relative amount of excessive finger flexion or extension depends on the type of instrument (Frucht, 2009b; Conti et al., 2008). Flexion is more common than extension. If multiple fingers are involved, they are usually adjacent fingers. Patients report a feeling of loss of automaticity in previously automatic music performance (Frucht, 2009b). Several examples of abnormal postural configurations are depicted in Fig. 1. MD is painless in most, but not all, patients (Jabusch & Altenmüller, 2006b). Indeed pain may suggest diagnosis of repetitive strain injury or occupational fatigue syndrome rather than MD.



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Figure 1. Representative posture patterns in musician's dystonia.

Reproduced from Hans-Christian Jabusch and Eckart Altenmüller, Epidemiology, phenomenology, and therapy of musician's cramp. In Eckart Altenmüller, Mario Wiesendanger, and Jürg Kesselring (Eds.), *Music, motor control, and the brain*, p. 267, Figure 17.2, doi:10.1093/acprof:oso/9780199298723.001.0001, Copyright © Oxford University Press 2006, reproduced by permission of Oxford University Press.

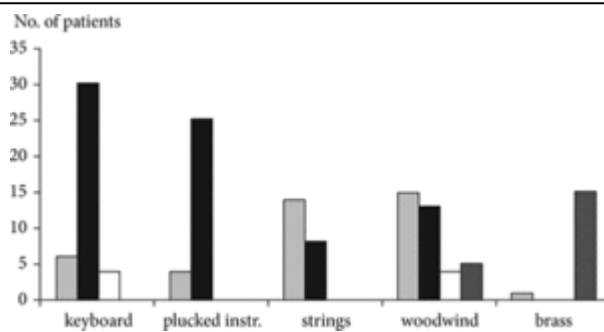
MD is the form of focal hand dystonia with the highest rate of prevalence (Altenmüller & Jabusch, 2009). Curiously, MD is about ten times more prevalent than corresponding focal dystonias in the general public. An estimated 1–2

percent of all musicians develop MD (Altenmüller, 2003). MD is the performance-related medical problem that is most likely to lead to long-term disability in musicians (Schuele & Lederman, 2004b). Because treatments are frequently suboptimal and usually incomplete, and because musicians' identities are strongly intertwined with their profession, news of the MD diagnosis can be devastating. However, it should be mentioned that prognosis has improved the last twenty years, and around 70 percent of musicians suffering from focal dystonia remain in their professions (Lee, Eich, Ioannou, & Altenmüller, 2015a).

Essential Characteristics of Musician's Dystonia

Two characteristics of MD stand out: how symptoms are localized to a specific body part and how symptoms exhibit task specificity. Fig. 2 illustrates how localization of the dystonia in the left versus right hands, and in some cases facial muscles, are differentially involved depending on the type of musical instrument (Frucht, 2009a; Jabusch & Altenmüller, 2006b). Instruments such as keyboards (piano, organ, harpsichord) and plucked instruments (guitar, electric bass) are associated with MD predominantly in the right hand. Bowed string instruments are associated with MD predominantly in the left hand (Altenmüller et al., 2012; Jabusch & Altenmüller, 2006b). It remains unclear to what extent the demands of music performance on the particular type of instrument factor into this lateral asymmetry. Many classical repertoires place great demands on both hands at the keyboard, for example. Fine motor control in other activities of daily living also contributes to susceptibility in the individual's dominant hand (Baur, Jabusch, & Altenmüller, 2011). Naturally, brass players are most likely to exhibit embouchure dystonia. Also, brass players exhibit a higher ratio of embouchure to hand dystonia than woodwind players. This makes sense in light of the motor control demands of the instruments. Brass players precisely control frequency and amplitude of lip vibrations by modulating embouchure muscle tension. The demands for woodwind instruments are different: embouchure adjustments do not require lip vibration but finger movement patterns are more complex, explaining why dystonia is common in the hand in woodwinds but very rare among brass players (Altenmüller et al., 2012).

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Figure 2. Symptom localization among the hands and embouchure in musician's dystonia.

Reproduced from Hans-Christian Jabusch and Eckart Altenmüller, Epidemiology, phenomenology, and therapy of musician's cramp. In Eckart Altenmüller, Mario Wiesendanger, and Jürg Kesselring (Eds.), *Music, motor control, and the brain*, p. 267, Figure 17.3, doi:10.1093/acprof:oso/9780199298723.001.0001, Copyright © Oxford University Press 2006, reproduced by permission of Oxford University Press.

Task specificity refers to the phenomenon whereby symptoms appear only during certain tasks. It is a hallmark of many forms of dystonia, including not only those forms explicitly labeled as “task-specific dystonias,” but also other forms such as cranial and cervical dystonia where symptoms are often sensitive to the task context, such as whether or not a patient is talking. This characteristic is one of the reasons why many of the focal dystonias were

historically considered a psychiatric disorder long before they were considered neurologic (Marsden & Sheehy, 1990). Among the focal dystonias, MD exhibits some of the most exquisite task specificity. For many patients, the symptoms are present only while playing the instrument and, in some cases, only in specific passages of specific pieces (Jabusch & Altenmüller, 2006b; Lee, Tominaga, Furuya, Miyazaki, & Altenmüller, 2015b; Tubiana, 2003). Broadly defined, a “task” context can include other elements of the patient's moment-by-moment sensorimotor state. Thus so called “sensory tricks,” or the “geste antagoniste,” that patients can use to transiently alleviate symptoms, can be viewed as a particular manifestation of task specificity. As with other focal dystonias, some MD patients can benefit from sensory tricks (Paulig, Jabusch, Grossbach, Boullet, & Altenmüller, 2014). For example, some MD patients benefit from playing with a latex glove, or when holding an object such as a rubber gum between the fingers (Jabusch & Altenmüller, 2006a). Collectively the localization and task specificity characteristics of MD are important features to keep in mind when assessing the patient's severity and response to treatment.

Assessment

The Importance of Rating Scales

As with most disorders, it is a common convention to carefully assess the patient before initiating treatment. Compared to characterizing severity, diagnosis is relatively straightforward and is not addressed further here. But evaluating the efficacy of

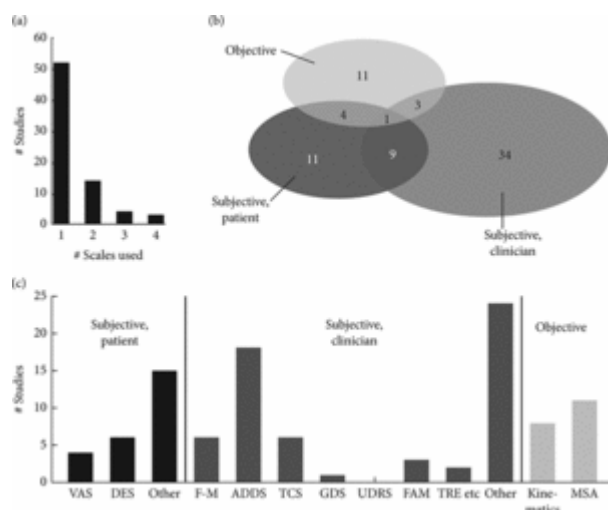
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treatments inherently requires some comparison of severity before and at various time points after treatment. The class of tools used to measure severity are often referred to as "rating scales" because they have historically most commonly involved a human—the clinician or patient or both—making some ratings of severity on a previously agreed upon scale.

Rating scales provide important outcome measures for clinical trials. They also commonly serve stratification purposes in genetic studies or as a regressor for research into pathophysiology. Thus they have become a critical path tool for the whole pipeline of research into new treatments. Tailoring the Dystonia Study Group (Group, 2004) guidelines for musician's dystonia, a maximally useful rating scale for MD should be: (1) reliable and valid, (2) sensitive to change, (3) specifically designed to measure MD, and (4) practical in a clinical setting (Spector & Brandfonbrener, 2005, 2007).

Rating Scales for Musician's Dystonia

Motivated by Spector and Brandfonbrener's initial effort (Spector & Brandfonbrener, 2007), Peterson and colleagues (Peterson, Berque, Jabusch, Altenmüller, & Frucht, 2013) conducted a critical and comprehensive review of MD rating scales in 2013. The latter used considerably less restrictive inclusion criteria to comprehensively review the use of rating scales in 135 articles on MD. They provided complete descriptions of the scales, variations in their use, and their properties relative to the Dystonia Study Group's guidelines for clinical utility. They also systematically evaluated the distribution of each scale's use in the literature, including studies involving various treatment approaches and pathophysiological assays. As shown in Fig. 3, the various scales can be divided into subjective and objective measures, with subjective being further subdivided into patient- or clinician-rated.



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Figure 3. Rating scale use in the musician's dystonia literature. (A) : histogram of number scales used in

each study; (B) : number of studies using each type of scale (subjective by patient, subjective by clinician, objective, or combinations thereof; (C) : number of studies using each scale, grouped by type.

Reproduced from David A. Peterson, Patrice Berque, Hans-Christian Jabusch, Eckart Altenmüller, and Steven J. Frucht, Rating scales for musician's dystonia, *Neurology* 81(6), 589-598, <https://doi.org/10.1212/WNL.0b013e31829e6f72>, Copyright © 2013 American Academy of Neurology.

A noteworthy objective scale is MIDI-based Scale Analysis (MSA). For MSA, keyboardists play 10–15 iterations of two octaves of the C major scale in ulnar and radial directions mezzo forte legato style at a tempo of eight notes per

second. Key press timing is recorded through a standard MIDI interface. Key press and release timing provide measures of tone durations, overlaps, and interonset intervals (IOIs). The standard deviation of IOIs (sdIOI) is used to quantify the temporal evenness with which the scales are performed. The sdIOI has provided excellent sensitivity and become the primary outcome measure in subsequent studies using MSA (Jabusch, Vauth, & Altenmüller, 2004c).

Rating Scale Deficiencies

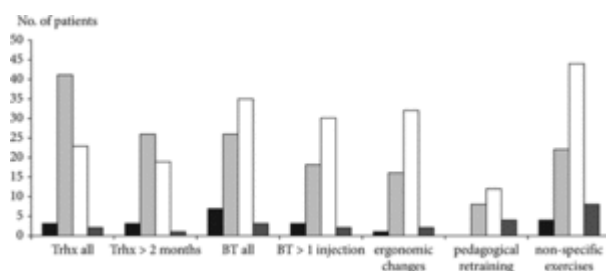
Rating scales have provided a way to strengthen an assessment exercise that is otherwise largely qualitative by supplementing it with measures that are inherently quantitative. Curiously, only about half of all experimental studies in MD used quantitative assessments (Peterson et al., 2013). Unfortunately, none of the scales have been rigorously evaluated against the Dystonia Study Group's criteria for a maximally useful rating scale (Spector & Brandfonbrener, 2007): reliable and valid, sensitive to change, practical in a clinical setting, and specifically tailored to MD. The subjective scales lack the sensitivity needed to compare treatments with similar efficacy because they have high inter-rater variability. They also lack digit-level specificity, which is central for many patients with FHD. Some of the rating scales used in MD—such the Fahn-Marsden (FM) scale, Unified Dystonia Rating Scale (UDRS), and Global Dystonia Scale (GDS)—were originally designed for generalized dystonia or focal forms other than MD. Although they convey “global impressions” based on clinical observation, they are not tailored to task-specific motor impairments (Peterson et al., 2013). A few scales—such as the TCS, FAM, and TRE—incorporate a symptom-evoking performance element. This is key for MD as it is inherently task-specific for most patients. However, only a small minority of past MD research has used these scales.

Objective scales, e.g., based on kinematics or MIDI for hand dystonia or acoustic analysis of the fundamental in embouchure dystonia (Lee, Voget, Furuya, Morise, & Altenmüller, 2016), offer the benefits of mitigating the intra- and inter-rater variability intrinsic to subjective scales. However, objective scales require additional infrastructure, limiting their efficient use in the clinic. Regardless of how MD severity is measured, the relative merits of those techniques should be considered in the context of choosing, evaluating, and updating strategies to treat MD.

Treatment

Treating Musician's Dystonia

Options for treating MD overlap substantially with those for other focal dystonias. Yet MD is one of the most difficult forms of dystonia to treat (Jankovic & Ashoori, 2008; Tubiana & Chamagne, 1993). In general, the treatments are aimed at the symptoms, not the causes or underlying pathophysiology. This is unsurprising given what little is known about the pathogenesis and pathophysiology of focal dystonias. A summary list of the treatments and rough stratification of their efficacy across a wide variety of MD patients is given in Fig. 4.



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Figure 4. Treatment efficacy based on patient ratings. Black bars: deterioration. Gray bars: No change. White bars: alleviation. Hatched bars: no reply. Trhx, trihexyphenidyl; BT, botulinum toxin.

Reproduced from Hans-Christian Jabusch, Dorothea Zschucke, Alexander Schmidt, Stephan Schuele, and Eckart Altenmüller, Focal dystonia in musicians: Treatment strategies and long-term outcome in 144 patients, *Movement Disorders* 20(12), 1623–1626, <https://doi.org/10.1002/mds.20631>, Copyright © 2005 Movement Disorder Society.

The primary oral medication that has been tried is trihexyphenidyl, an anticholinergic. However, at doses sufficient to demonstrate efficacy in adults it usually is accompanied by severe adverse side effects. Botulinum toxin injections into affected muscles have become the mainstay for treating focal dystonias. Their net effect is to block neurotransmission at the neuromuscular junction. In the case of MD, injection

efficacy can be greatly enhanced by carefully selecting the muscle to inject, including by distinguishing primary from compensatory movements (Frucht, 2015) and appropriate incorporation of EMG and ultrasound guidance. The injections can offer some symptomatic relief for many. There are reports of particularly successful cases (e.g., Vecchio et al., 2012). However, botulinum toxins also have several limiting adverse side effects (Frucht, 2009b; Jankovic & Ashoori, 2008; Zeuner & Molloy, 2008), particularly when lateral finger movements are an important part of the motor repertoire. If not carefully planned and administered, they often lead to weakness that limits hand performance. Even with optimal doses and injection locations, efficacy tends to wear off, typically 2–4 months post injection. Thus injections need to be periodically repeated in perpetuity and there is the natural variation in efficacy associated with where one is in the treatment “cycle.”

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For the overwhelming majority of MD patients, currently available treatments are suboptimal. Because many MD patients are professional musicians that play at very high levels, the diagnosis can spell the end of their performance career (Conti et al., 2008; Frucht, 2009a). Thus MD remains as one of the primary challenges in musician's medicine (Jabusch & Altenmüller, 2006a; Rosset-Llobet, Candia, Molas, Cubells, & Pascual-Leone, 2009; Tubiana & Chamagne, 1993).

Physical Medicine and Rehabilitation

Pharmacologic treatment strategies suffer from a lack of specificity that is particularly important in MD. Systemic oral medications have an obvious lack of spatial selectivity. It is highly unlikely, for example, that there is a simple mapping between cholinergic receptors in various brain regions and alterations in brain circuitry that coincide with very specific motor repertoires selectively affected in music performance. There is also a mismatch between the slow pharmacokinetics of oral medications and the rapid temporal dynamics of MD symptoms. In the case of botulinum toxins, they have an inherently good spatial selectivity in the periphery, but again suffer from a mismatch in temporal dynamics. Given these deficiencies of oral medications and botulinum toxin approaches, and the characteristics of symptom localization and exquisite task specificity in MD, it is unsurprising that a diverse set of non-pharmacologic treatment strategies have been attempted.

Prominent among the non-pharmacologic approaches are a variety of techniques under the umbrella of what can be called physical medicine and rehabilitation (PMR). These go by many names, including rehabilitation strategies, behavioral therapies, behavioral interventions, retraining programs, pedagogical retraining, technical exercises, non-specific exercises on the instrument, etc. In each case, they involve some subset of principles from PMR. They have been reviewed for their use in dystonia, including with foci of the hand and wrist, but more often for the writer's cramp form of FHD than for MD per se (Bernstein et al., 2016; Valdes, Naughton, & Algar, 2014). In some cases, PMR approaches have involved temporarily limiting movement. Specifically, they involve immobilizing or modifying the range of motion of the affected motor system with some form of splint for a period of weeks to years (Priori, Pesenti, Cappellari, Scarlato, & Barbieri, 2001; Satoh, Narita, & Tomimoto, 2011), and can produce improvements that are sustained well beyond the end of the intervention (Priori et al., 2001).

The PMR methods have a long history, going at least as far back as to predate recognition of FHD in the musician as dystonia (Hays, 1987). Collectively they are considered useful (Lederman, 2001), but often exhibit benefits that are mixed and/or transient, require months or even years of therapy (Sakai, 2006; Tubiana, 2000), and suffer from varied levels of compliance. The reasons are generally unclear, but for some approaches it may be because the methods are not tailored to each musician's exquisite and very personalized motor repertoire. In the case of most PMR approaches, replicating the

results has either not been attempted or not been successful. Also, the studies have suffered from several design deficiencies, mostly because it is inherently difficult to incorporate careful controls and blinding.

Some research into focal dystonia pathophysiology has been repurposed for therapeutic potential. Prominent examples include non-invasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and direct current stimulation (DCS). They have been tried in isolation and in conjunction with PMR techniques, with the hypothesis that they might amplify, accelerate, or make more persistent the beneficial effects of the PMR approaches in isolation (Furuya, Nitsche, Paulus, & Altenmüller, 2014; Rosset-Llobet et al., 2015). These brain stimulation methods offer the advantage that they can be administered in a control (placebo) fashion, thereby enabling blinded, controlled trials (Rosset-Llobet, Fabregas-Molas, & Pascual-Leone, 2015). TMS and DCS are discussed further in the next section on pathophysiology.

Pathophysiology

Pathophysiology versus Pathogenesis

Even in scientific forums, distinctions between association and causation are sometimes unclear. Characterizations of research in focal dystonia are no exception. One way we have attempted to make this distinction more clear in this chapter is by discussing matters of pathophysiology and pathogenesis in separate sections. Most if not all findings of pathological physiology in FHD, including MD, should be viewed as simple associations. Whether or not they are potential causes or consequences of the disorder is particularly difficult to determine. For example, even evidence that clinical recovery in MD coincides with normalization of receptive field topography (Candia, Wienbruch, Elbert, Rockstroh, & Ray, 2003) does not necessarily suggest that transitions from normal to abnormal receptive field topographies play a causal role.

Classic Concepts on Focal Dystonia Pathophysiology

Most of the information about the pathophysiology of MD is actually inferred from research including cohorts comprised of some (or all) patients with other forms of focal task-specific dystonias, especially writer's cramp. General consensus is that most, but probably not all, physiological features are common across the focal task-specific dystonias. In this section, unless denoted otherwise, the pathophysiological features were found in studies with FHD patients, sometimes but not always including MD patients.

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Over the past few decades, a small handful of recurrent themes have characterized the pathophysiology of FHD (for a good review, see Hallett, 2006). These include abnormalities in inhibition, sensorimotor integration, and plasticity. Aspects of all of these have been documented at various nodes in the brain circuits mediating motor (and sensorimotor) function, as illustrated by fMRI (Haslinger et al., 2017; Oga et al., 2002), diffusion tensor imaging (DTI, Delmaire et al., 2009), and even gamma knife thalamotomies (Horisawa et al., 2017). Roughly speaking, the brain regions implicated include several somatosensory and somatomotor cortical areas, some association cortical areas, several basal ganglia nuclei, portions of the cerebellum, and motor and intralaminar nuclei in the thalamus. Brainstem and spinal circuits may also play a role, and have been indirectly implicated in some studies focused on alterations to reflex systems in paired pulse paradigms.

Investigators have found a decrease in net inhibition at each level of the motor control circuitry. Perhaps more importantly, the decreased inhibition has more specifically been associated with a loss of spatial selectivity, and this has been put forth as a potential endophenotype for focal dystonia (Altenmüller et al., 2012). It has been documented in the spatial domain, as a blurred differentiation of individual digits at the behavioral and the neural levels in FHD (Bara-Jimenez, Catalan, Hallett, & Gerloff, 1998; Delmaire et al., 2005; Sohn & Hallett, 2004), including in MD (Elbert et al., 1998). It has also been documented in the time domain, as in reduced TMS-evoked silent periods (Chen et al., 1997; Ridding, Sheean, Rothwell, Inzelberg, & Kujirai, 1995) and defective compliance with the no-go signal in a stop-signal task (Ruiz et al., 2009). Interestingly, the exact nature of the selective inhibition in the somatosensorimotor system may be different between writer's cramp and MD forms of FHD. Karin Rosenkranz (Rosenkranz et al., 2005) evaluated a TMS-based measure of fast, local inhibition in the cortex—the “short-latency intracortical inhibition” (SICI)—in the context of simultaneous vibratory input to individual hand muscles. She found that although SICI was unchanged for neighboring muscles in writer's cramp patients, it was suppressed selectively in neighboring muscles that are functionally connected with the vibrated muscles in healthy musicians but non-selectively in MD patients. They hypothesized that musicians' extensive practice produces the altered surround inhibition that later progresses into a non-focal pattern seen in MD.

There is also evidence for altered sensorimotor integration in FHD. Part of this characterization stems for the ambiguity regarding when “sensory” ends and “motor” begins in the nervous system—both functionally and anatomically. The lines of demarcation are acutely blurred in music, wherein tight, temporally nested sensorimotor loops are central and critical to music comprehension and production. Notwithstanding semantics, pathological sensorimotor integration has evolved as a consistent theme in focal dystonia pathophysiology. Both the functional manifestations and circuit bases have been recently reviewed (Avanzino, Tinazzi, Ionta, & Fiorio, 2015) and will not be covered in detail here. Notably, although the Rosenkranz (Rosenkranz et al., 2005) study focused on measures of spatial inhibition with the SICI measure of cortical physiology, it also intrinsically investigated sensorimotor integration by combining somatosensory input and motor evoked potentials. The focus of this and other previous sensorimotor integration

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research has been primarily on spatial selectivity, with generally fixed temporal parameters. However, an emergent theme in focal dystonia research is that time and timing may play particularly critical roles.

Dystonia and Disordered Timing

Although intuition would suggest exquisite temporal processing in musicians, and some measures indicate that timing abilities are normal in MD (van der Steen, van Vugt, Keller, & Altenmüller, 2014), there is also evidence for disordered temporal processing in MD. Among the many potential MIDI output variables in Jabusch's MSA rating scale, one of the strongest findings in MD was the variability in the inter-onset key press interval (sdIOI; Jabusch et al., 2004c). Also, the temporal dynamics of pre-movement brain activity are smeared in dystonia relative to controls (Gilio et al., 2003). This isn't surprising given that SICI phenomena show exquisite timing sensitivity (Rosenkranz, 2010) and in light of a recent review triangulating between time processing, motor circuits, and movement disorders including dystonia (Avanzino et al., 2016).

At the intersection of sensorimotor integration and timing is the psychophysical measure known as the temporal discrimination threshold, or TDT. In the case of the auditory TDT, for example, subjects are given two brief auditory tones with rapid onsets and offsets separated by a brief and variable interval. The interval is adjusted in a bi-directional staircase fashion to determine the interval below which subjects cannot distinguish the two separate stimuli and perceive them as one; the TDT.

The visual TDT has been shown to be abnormal (high) in many forms of dystonia (Hutchinson et al., 2013), including MD when musicians rather than non-musicians are used as study controls (Killian et al., 2017). The TDT has also been put forth as a candidate endophenotype (Hutchinson et al., 2013), because it has been shown to be abnormal in non-manifesting carriers of the DYT1-form of familial dystonia (Fiorio et al., 2007) and it is present in the unaffected hand, suggesting it is not secondary to symptoms (Bara-Jimenez, Shelton, Sanger, & Hallett, 2000; Fiorio, Tinazzi, Bertolasi, & Aglioti, 2003).

Plasticity

Plasticity is an overused and sometimes misinterpreted term in the neurosciences. In the simplest sense, it refers to the ability of the system to change. It has manifestations at behavioral and several physiological levels, and likely has bases at the circuit and molecular levels, historically couched in terms of changes in the network of synapses among neurons, and the molecular signaling pathways that modulate the strength of those synapses at different timescales.

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In the context of dystonia, plasticity can refer to the near-real time adaptations of sensorimotor systems, as for example a greater response than normal to paired associate stimulation protocols, whereby the relative timing of sensory stimuli and exogenous stimulation of motor cortical areas can strengthen that sensory system's subsequent ability to evoke the motor response within the same experimental session. Plasticity can also refer to the systems-level homologues of synaptic plastic process of long-term potentiation and depression (LTP and LTD), in the form of high- and low-frequency repetitive stimulation with TMS to potentiate or depress subsequent cortical excitability. At a drastically slower timescale, plasticity can refer to the slow, often insidious changes in brain circuitry that likely underlie the pathogenesis of dystonia. There are also the notions of "metaplasticity" and "homeoplasticity" which, among other things, are thought to regulate the primary plastic processes already discussed.

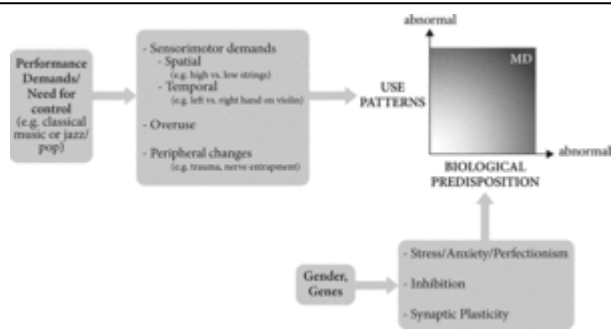
In the case of MD, one theory is that musical practice in healthy musicians is associated with (indeed, likely relies upon) beneficial plastic adaptation in the motor cortex, including for example a reduction in motor thresholds and increase in motor excitability, and that in MD patients these processes have progressed too far and begin to compromise, rather than enhance, movement patterns (Altenmüller & Jabusch, 2010b). Thus musicians may have (or take advantage of) greater primary plastic capabilities and MD patients may have dysfunctional metaplastic processes that regulate the primary plastic processes in an abnormal way. A great mystery in MD research is how such dysfunctional plastic processes are initiated and used in generating the disorder.

Pathogenic Theory

Biological Predisposition

With relatively rare exceptions, most central nervous system disorders, including most forms of dystonia, likely arise from some complex combination of genetic and environmental factors. In the adult onset dystonias, this is usually conceptualized as a genetic predisposition followed by some environmental "trigger." In this chapter, we formulate a theoretical framework for the pathogenesis of MD that is organized in a similar fashion: biological predisposition and "use patterns" (see Fig. 5). Biological predispositions include of course genetics but also gender. "Use patterns" is a broad umbrella term that refers to how the sensorimotor systems are used over protracted periods of time. As such, it can be considered a category of "environmental" factors.

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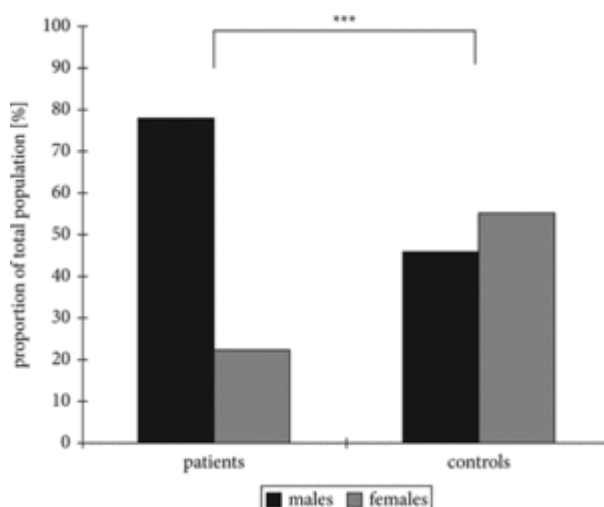
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Figure 5. A theoretical framework for pathogenic factors. The probability of developing MD increases with increasing abnormality in use patterns and/or biological predisposition. Several factors influence use patterns, including the spatiotemporal demands of the instrument, overuse, and situations that modify peripheral constraints, which in turn are variously influenced by the performance demands on the patient. Biological predisposition consists of innate characteristics of the patient, from the personality profile down to the level of properties of inhibition in brain circuits and the intricate molecular underpinnings of synaptic plasticity, all in turn influenced by the patient's gender and genetics.

Early studies described positive family history of dystonia as a risk factor for development of MD (Jankovic & Shale, 1989; Lim & Altenmüller, 2003; Schmidt et al., 2006), and this connection has been strengthened in multiple subsequent studies, including findings compatible with a pattern of autosomal-dominant inheritance (Baur et al., 2011; Jabusch & Altenmüller, 2006b; Schmidt et al., 2009). But specific abnormal genes specifically associated with MD have remained elusive.

Genetics are also probably implicated in personality traits, and MD patients tend to exhibit exaggerated perfectionism and social phobias not seen in healthy musicians (Jabusch & Altenmüller, 2004; Jabusch, Müller, & Altenmüller, 2004a).

Another aspect of biological predisposition is gender. For practically all other forms of dystonia, the M:F ratio ranges from 1:2 to 1:4. Curiously, however, the overwhelming majority of MD patients are male (Lederman, 1991), and this has been confirmed in large cohorts (Jabusch & Altenmüller, 2006b; Lim & Altenmüller, 2003). Indeed, the 5:1 M:F ratio is corrected to 6:1 when taking into account the slight predominance of female musicians in the musician's population in Germany (see Fig. 6) (Lim & Altenmüller, 2003).



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Figure 6. Gender distribution of 591 patients and 2651 healthy musicians, in relative ratios.

Reproduced from Eckart Altenmüller, Volker Baur, Aurélie Hofmann, Vanessa K. Lim, and Hans-Christian Jabusch, Musician's cramp as manifestation of maladaptive brain plasticity: Arguments from instrumental differences, *Annals of the New York Academy of Sciences* 1252, 259-265, doi:10.1111/j.1749-6632.2012.06456.x Copyright © 2012, John Wiley and Sons.

The mechanisms by which genetics and gender contribute to MD pathogenesis are an almost complete mystery, but they likely involve differential hormonal contributions to synaptic plasticity and neuronal

inhibition, as well as macroscopic personality traits like stress, anxiety, and perfectionism (Altenmüller et al., 2012), which appear to be present at higher levels in MD (Altenmüller & Jabusch, 2010a). Since the first description of musician's dystonia, in the case of Robert Schumann (Altenmüller, Kesselring, & Wiesendanger, 2006) psychological triggering factors have been discussed. Indeed when tested carefully, musicians suffering from dystonia can be clustered into two groups, those with pre-existing anxiety disorders and dysfunctional psychological coping strategies, leading to stressful personalities and those with no pathophysiological signs (Ioannou & Altenmüller, 2014; Ioannou, Furuya, & Altenmüller, 2016). Interestingly, in musicians with anxiety disorders dystonia manifests itself about eight years earlier (Ioannou et al., 2016). Thus it seems that MD is not a uniform nosological entity, but can instead be classified into two forms: a predominantly "motor" manifestation and a manifestation with accompanying non-motor symptoms, such as constraints, anxiety, etc. Intriguingly, these two types of manifestations are not a dichotomy but may overlap (Ioannou et al., 2016). Whether this dimension depends on gender remains to be determined. Curiously, gender appears to influence the TDT (Williams et al., 2015), and this sexual dimorphism is also age-related (Butler et al., 2015). Endophenotypes like altered spatiotemporal inhibition and the TDT may play a critical intermediary role in discovering MD pathogenesis, helping to provide a link between biological predisposition, the contribution of use patterns, and the phenotypic characteristics of the disorder.

Use Patterns

Several features of MD suggest that *how* the sensorimotor systems are used in music performance may be a factor contributing to the development of MD. Motor workload and movement complexity appear to be risk factors. MD is more likely to appear in the hand with higher demands of spatiotemporal precision, such as the right hand on keyboards and plucked instruments, and the left hand in bowed string players. Among the string instruments, MD appears to be more prevalent on string instruments with shorter string lengths, such as the violin versus double-bass (Altenmüller et al., 2012; Jabusch & Altenmüller, 2006b). In fact, the relative absence of MD documented in double bassists may be due to a lack of simultaneous finger action (Conti et al., 2008). Another apparent risk factor is the type of musical performance. Classical musicians seem to be more at risk of developing MD than pop or jazz musicians. A hypothesized reason why is that

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classical music involves higher expectations of temporally precise reproduction and less opportunity for improvisation than pop and jazz (Jabusch & Altenmüller, 2006b). Professional classical musicians have also typically undergone many tens of thousands of hours of practice, involving movements that are extensively trained, representing an “oversampling” of a disproportionately narrow part of the space of possible sensorimotor mappings. Finally, in some cases, peripheral issues such as prolonged pain syndromes, nerve entrapment, and subclinical range of motion limitations (Charness et al., 1996; Leijnse, Hallett, & Sonneveld, 2015) that can precede MD onset may induce compensatory changes in use patterns that are pathogenic and would not otherwise occur in a healthy musician's motor repertoire. Furuya (Furuya & Hanakawa, 2016) suggests that such dysfunctional adaptations of body representations in somatosensory and motor systems may be an intermediate point on the path toward full MD development. It should be noted that these are all retrospective observational results and there have been no controlled, prospective studies regarding these factors.

As with genetics and gender, the mechanisms by which use patterns contribute to MD pathogenesis are unclear. But having a theoretical framework can help provide a rational basis for future experimental research.

Future Directions

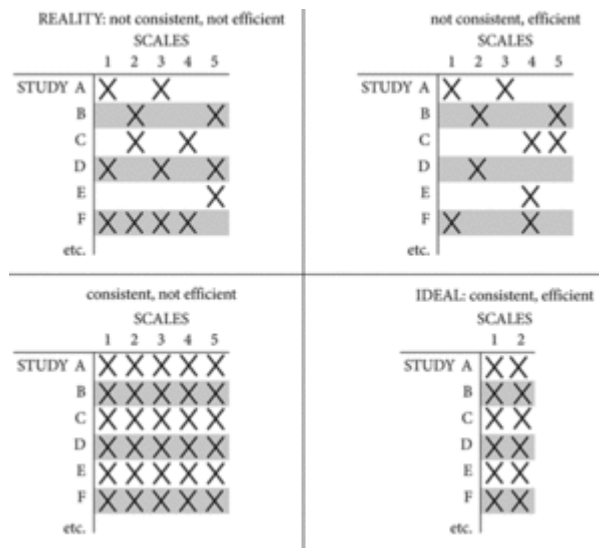
Better Assessment

Among the numerous unmet needs in dystonia (Albanese, 2017), one of the designated research priorities in focal task-specific dystonias is more precise methods for characterizing and assessing the phenotype (Richardson et al., 2017). This is acutely evident for MD. For over a decade dystonia researchers have suggested that a new rating scale for MD that is reliable, valid, sensitive, and specific to MD is sorely needed (Jankovic and Ashoori, 2008; Spector & Brandfonbrener, 2007). Peterson and colleagues (Peterson et al., 2013) comprehensively summarized the state of affairs in rating scale use for MD. As alluded to in the section “Rating Scale Deficiencies,” none of the existing scales have been completely and rigorously evaluated for reliability and validity, sensitivity to change, practical use in a clinical setting, *and* specifically tailored to MD. Exacerbating the concerns about reliability and sensitivity to change, most of the existing rating scales are based on human judgments, making them inherently subjective. Further developments in objective rating instruments that would make them more readily applicable in the clinical setting would help mitigate these issues.

As evident in the MD rating scale review (Peterson et al., 2013), there appears to be no standard choice for rating scale(s) in MD research; most studies use only one or two rating scales but the scales used vary widely from one study to the next. When trying to

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compare and reconcile multiple treatment studies, this makes it difficult to discern between treatment effects and measurement effects. Likewise non-standard selection of rating scales diminishes the collective research value of pathophysiology studies.



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Figure 7. Toward ideal rating scale use. Upper left: current rating scale use is neither consistent across studies nor efficient. Upper right: efficient rating scale use would minimize the number of scales used in each study (in this example depiction, to two scales per study). Lower left: consistent rating scale use would ensure that the same rating scales are used across all studies. Lower right: the ideal scenario would be both consistent and efficient by pushing the envelope on both: a consistent application of the minimal number of scales across all studies.

In summary, as depicted in Fig. 7, we suggest that the migration to a more ideal mode for assessing MD severity would include two categories of improvements: (1) standardizing the choice of rating scale(s) used across studies, and (2) increasing the efficiency with which a small number of rating scales can completely cover the conceptual space of measurements one wants to make in the disorder. This mode would accelerate research into both the pathophysiology of MD and improved treatments.

New Treatments

Another designated research priority in focal task-specific dystonias is innovative clinical trial design that takes into account the tremendous heterogeneity in the presentation of these dystonias from one patient to the next (Richardson et al., 2017). Despite concerted efforts to evaluate an array of new treatment approaches, most have involved small, unblinded, retrospective studies. Clearly we need new trials that are controlled, blinded, prospective, and randomized. Unfortunately, these designs are very difficult to implement in the space of PMR treatments. This poses a creative challenge for the field of MD, given the likely prominent role of PMR in MD treatment. Relatedly, given the heterogeneity in MD manifestation, treatments should logically be tailored to the individual patient. This is also challenging in the context of the common research goal of reproducibility.

Yet there is a persistent need for new therapies for MD. Although many patients manage to stay in the field with currently available therapies, most have to make substantial

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compromises in their level of music performance. And outcomes are particularly limiting for patients with embouchure dystonia (Frucht et al., 2001; Jabusch & Altenmüller, 2006b).

Given the central theme of disordered temporal processing in MD, we hypothesize that the highly refined timing characteristics of the sensorimotor systems in professional musicians are critical to not only understanding the disorder but also optimizing treatment. Simply put, patients get stuck in patterns of inappropriate motor sequences and greater attention to the critical role of time in related auditory perception and motor performance could help them overcome these dysfunctional patterns. Future treatment research should evaluate novel non-pharmacological interventions for MD that are focused on timing and determine whether and how their efficacy is related to psychophysical measures of temporal processing, such as the TDT.

With respect to the motor performance aspect of timing, one form of PMR-style intervention explicitly focused on timing is slow-down exercises (SDE; Sakai, 2006). SDE is an MD rehabilitation strategy that has patients slow down the tempo of their symptom-evoking performance pieces until symptoms resolve, and then gradually increase the tempo back to the original speed as long as symptoms do not return. To our knowledge, groups independent of the original developers have not evaluated SDE. And the original application of SDE required many weeks of retraining to establish effects. Nevertheless, approaches like SDE merit further systematic, controlled investigation by independent groups.

TMS offers a non-invasive method to not only study MD but also, typically in the form of repetitive TMS (rTMS), modulate it. rTMS (and its surface voltage counterpart transcranial Direct Current Stimulation, tDCS) have been evaluated as potential treatments for FHD, mostly with writer's cramp (Cho & Hallett, 2016; Obeso, Cerasa, & Quattrone, 2016) but also with MD (Furuya et al., 2014; Kieslinger, Holler, Bergmann, Golaszewski, & Staffen, 2013). Because it inherently involves stimulation with temporal precision at millisecond timescales, TMS provides a potentially complementary physiologic counterpart to the PMR methods that operate at behavioral timescales. Although research on their combined utility as FHD therapy has thus far shown only mixed results (Kimberley, Schmidt, Chen, Dykstra, & Buetefisch, 2015), we expect further trials in the near future.

Although stereotactic surgeries, especially deep brain stimulation (DBS) in the globus pallidus internum (Gpi), have demonstrated efficacy in generalized dystonia, there are relatively fewer reported series in focal dystonias, and to our knowledge none in MD. Future advances in DBS technology, including closed loop designs, may be able to incorporate task context (either behaviorally or physiologically) and facilitate symptom reduction that is appropriately context-dependent for focal task-specific dystonias. However, as with the botulinum toxin injections, the exquisite spatiotemporal demands of music performance will make MD probably one of the last indications for the treatment.

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Although lesion methods have fallen out of favor with the advent of DBS, there is one successful reported case of a thalamotomy for an MD patient that was refractory to oral medications and botulinum toxin (Horisawa et al., 2017).

Endogenous cannabinoid receptors play an important role in, among other things, synaptic plasticity processes in the basal ganglia. Thus, they are a rational target for dystonia. Jabusch reported positive though transient benefits from a single dose of THC in a pianist with MD (Jabusch, Schneider, & Altenmüller, 2004b), but subsequent controlled studies in more broadly defined movement disorders populations have since produced mixed results (Kluger, Triolo, Jones, & Jankovic, 2015; Koppel et al., 2014).

Since successful treatment is still a challenge, preventing musician's dystonia is important. Although prospective studies are lacking, avoidance of triggering factors, such as chronic pain, overuse, anxiety, and mechanical repetitions are important and may prevent manifestation of MD, especially in those musicians with genetic susceptibility.

Research on Pathophysiology

The sensorimotor systems employed during music performance operate at high rates and with great temporal precision. Thus future basic and clinical research in MD should specifically measure and modulate the motor control system with a focus on timing. The TDT is one obvious paradigm for pursuing this. But the TDT is usually measured in the visual or somatosensory domains. Yet the auditory modality is particularly important for musicians. So future work should include the auditory TDT to measure the temporal precision of auditory processing in MD patients.

Research into temporal processing in MD should also be carefully integrated with previous themes in pathophysiology, such as altered surround inhibition. We expect that the TDT deficits in dystonia that have been interpreted as a time-domain version of reduced surround inhibition (Tamura et al., 2009) are not independent from but actually interact with alterations in the precision of "spatial" surround inhibition processes.

Recent evidence that surround inhibition can be modulated by attention (Kuhn, Keller, Lauber, & Taube, 2018) provides a timely segue to our other recommendation for future MD pathophysiology research: we should allocate some resources to attention. Although difficult to assay in non-human primates, attention may have been a factor in a monkey model of FHD (Byl, Merzenich, & Jenkins, 1996). And differential use of attention seems to be a factor in PMR approaches to MD (Brian Hays, personal communication).

And attentional modulation has likely been a key element in what is sometimes labeled as psychogenic dystonia because it is often based on tests of distractibility. If a symptom is modulated when attention is directed to or away from a motor function, is it still organic dystonia? Regardless of what we call it, attention seems to play a role. Indeed allocation of attention has itself been considered a form of action selection, and therefore attentional focus can be considered part of the task-dependent aspect inherent in most

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focal dystonias. Unfortunately, attention can be difficult to measure and is often not considered in evaluating overt motor function. But simple gaze monitoring may provide a reasonable first step.

The brain circuits mediating attention are widespread but likely rely heavily upon thalamic systems that have thus far been relatively understudied in neuroscience. Yet the thalamus is a central node mediating communication among many motor systems including the cerebellum, cortex, striatum, and of course brainstem. Indeed Hutchinson and colleagues (Hutchinson et al., 2013) have postulated that the projection from the superior colliculus to the striatum via the intralaminar nuclei of the thalamus mediates the TDT. So future pathophysiology in research on dystonias, including MD, should redirect attention to timing, attentional focus, and the thalamus.

Research on Pathogenic Mechanisms

The framework of pathogenic theory we discussed earlier motivates a few directions for future research into pathogenic mechanisms. An implied but not explicit element in the framework is reinforcement learning (RL). Similar to that laid out for the cranial dystonias (Peterson & Sejnowski, 2017), we hypothesize that the pathogenesis of MD results from a pathological RL process influenced by both the biological predisposition and use pattern categories of pathogenic factors. In the simple computational theory of RL, there is a mapping from states to actions that is learned through trial and error and biased by reinforcement signals. The concept is particularly appropriate for task-specific dystonias such as MD, because action selections (i.e., the next motor output) is explicitly influenced by the current "state," encompassing not only sensory state but also context of the instrument and current "task" (e.g., performing a certain piece) (Altenmüller & Müller, 2013). In its neural instantiations, RL systems are composed of a network of neurons whose matrices of synaptic connections represent that state-to-action mapping, and whose weight changes correspond to the learning process. Reinforcement signals are thought to come from rewards and "punishments," which can be exogenous and/or endogenous. Some consider music as a language of emotions, covering a spectrum from negative to positive valence. These are experienced not only by the music consumer, but also the producer. Professional classical musicians experience both the fear of failure in a system that emphasizes precision and reproducibility yet also the joy of performing (Altenmüller & Jabusch, 2009). These factors may influence and amplify endogenous reward signals used in the brain's RL systems.

Much, but likely not all, of the brain's implementation of RL involves dopamine-mediated signaling in the primary input nucleus of the basal ganglia, the striatum. One of the most classic interpretations of phasic dopamine signaling has been the encoding of unpredicted levels of reward, i.e., "reward prediction errors" (Schultz & Dickinson, 2000). And there is a large, diverse body of literature suggesting that dopamine dynamics in the striatum may play some role in a wide variety of dystonias (Peterson, Sejnowski, & Poizner, 2010), and this has subsequently been supported by genetic evidence in some

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focal dystonias (Fuchs et al., 2013). Structural and functional abnormalities have been found in the basal ganglia in FHD (Peller et al., 2006; Zeuner et al., 2015), and the projections from cortex to striatum likely play a critical role in representing temporal information at behavioral timescales (Meck, Penney, & Pouthas, 2008). Unsurprisingly then, the striatum has also been implicated as a key structure related to the TDT (Bradley et al., 2009; Pastor, Macaluso, Day, & Frackowiak, 2008). We suggest that future research into MD (and, for that matter, more broadly defined focal dystonias) take into account this theoretical framework for designing future experiments as well as computational model simulations of the system, as has already been done coding malleable sensory representations with neighborhood preserving self-organizing maps that simulate the task-dependence of MD (Altenmüller & Müller, 2013).

Progress in genomics has enabled whole-exome sequencing at ever decreasing costs. However, the relatively low number of MD patients limits what might be inferred from an unbounded search from whole genomes. If, however, appropriate priors are taken into account, the search for statistically meaningful genetic associations with MD may be tractable. Such priors could be informed by, for example, (1) genetic findings from other focal dystonias, which likely share many aspects of biological predisposition with MD, (2) genes associated with molecular pathways that are sexually dimorphic, (3) genes associated with molecular pathways that underlie and influence cellular and circuit-level physiology such as synaptic plasticity and altered neuronal inhibition.

Given the high dimensionality and complexity of not only the genomics but also the rich motor repertoires inherent in a musician's "use patterns," theoretical frameworks and computational models may help provide a tractable path forward for simulating and studying what gives rise to MD. Ultimately, this knowledge should in turn provide guidance on how to reverse and prevent the disorder.

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