Could the musical world hold the key to understanding dystonia?

Focal dystonia (FD) is thankfully an uncommon disorder, affecting some 29 per 100,000 of the USA population. However, focal task-specific dystonia (FTSD), a subtype of FD, is much more prevalent amongst musicians with as many as 1% affected. This disparity between the general population and the musician population is striking. Why exactly is it that this type of FD is so common amongst musicians? Is it purely due to the physical demands of being a musician and hence environmental factors or is there a role for genetics? This essay will attempt to answer these questions and in doing so, will determine whether musician’s dystonia can shed light on the causes of other forms of FD.

What is musician’s dystonia?

Dystonia is a debilitating syndrome characterised by the production of abnormal postures, twisting or repetitive involuntary movements as a result of the sustained contraction of antagonistic muscle pairs. Dystonia is divided into subtypes using three different systems of classification: on the basis of anatomical distribution (thus it can be focal, generalised, segmental and hemidystonia), whether the dystonia is primary or secondary in origin, and age of onset. FTSDs are a form of FD that affect individuals who practice repetitive movements that require high levels of accuracy. In musicians and writers this syndrome is known respectively as musician’s dystonia (MD) and writer’s cramp (WC).

MD is task-specific and results in the loss of voluntary control over highly-trained, fine movements performed during playing an instrument, leading to involuntary contractions and abnormal postures. MD is classified based on the body part that is affected. Typically this is the hand in violinists and pianists but it can also manifest as embouchure dystonia where there are abnormalities in coordination of the tongue, lips, and facial and cervical muscles. This form is found in wind and brass players.
A disease of excess practice?

MD has long been thought of as a purely occupational phenomenon. In support of this, associations between a number of aspects relating to musical performance and the development of MD have been found. There is a correlation between length of time practicing and the prevalence of MD as it occurs later in life, at around the fourth decade of life. Information from patients suggests that development of dystonia often follows periods of increased rehearsal or during preparation of a particular challenging piece. This is in line with a slightly different, yet related finding that certain musician types are more at risk than others. Data from a German retrospective study found that MD is more commonly seen in classical musical soloists, with particular attention to pianists and wind instruments. This observation has been linked to work load as soloists are under a greater level of physical and mental strain. Furthermore, localisation of the dystonia is nearly always related to the body part where the instrument is manipulated the most. Musicians who pluck instruments and those who use keyboards are generally affected on their right hand which is in line with the fact that these instruments have a higher right-hand workload.

A disease of abnormal plasticity?

The rigorous nature of musical training which requires practising of repetitive, fine-motor control movements for prolonged periods of time, has structural consequences for the organisation of the primary somatosensory cortex (S1). Plasticity of this cortical region allows use-dependent changes to occur resulting in the expansion of the cortical domain representing the digits (in hand musicians). Alongside this, tactile receptive fields of the fingers decrease in size and their threshold of discrimination lowers making them more sensitive to tactile changes. Enlargement of the hand area in the motor cortex has also been observed. These changes allow the increased motor control
of the fingers and improve their sensory processing capabilities and thus are adaptive to the performer.

However, evidence suggests that these changes can become maladaptive in conditions of high speed and high repetitive work load, leading to superimposition of tactile receptive fields in S1. In a primate model of repetitive strain injury, Byl et al (1997) found that single digital receptive field had spread to areas of S1 previously sub-served by other digits, following intensive training in highly stereotyped and fast movements. These findings have been confirmed in human studies using magnetoencephalography and sensory evoked potentials. These cortical changes are mirrored in neurological clinical examination. MD sufferers show impaired 2-point discrimination when compared with non-musician, healthy controls. In addition to poor spatial resolution in MD, temporal resolution is also impaired. Abnormal somatosensory organisation can also result from injury, a prior history of which is frequently reported in MD.

It is important to determine whether this altered somatosensory organisation is a consequence or a cause of MD. Symptoms of MD are associated with this disorganisation suggesting a correlation, but a more causal relationship is indicated by the fact that normal somatosensory topography is restored with clinical improvement.

The findings of abnormal somatosensory organisation therefore suggest something rather counter-intuitive; namely that a typically considered disorder of motor output has a basis in disordered sensory processing. Nonetheless, only a minority of musicians develop MD and not all who train rigorously do so, therefore other dysfunctional processes must contribute to this abnormal plasticity.

One such other process is abnormal inhibition. This has been observed at cortical, subcortical and spinal levels for both sensory input and motor output. Reduced inhibition, in the form of
surround inhibition may explain the observed ‘overflow’ phenomenon, whereby there is co-contraction of neighbouring muscles in addition to the desired muscle.\textsuperscript{25} Impaired lateral inhibition has also been demonstrated in the sensory domain in patients with focal hand dystonia where co-stimulation of the median and ulnar nerve lead to a multiplicative somatosensory-evoked potentials (SSEPs) instead of reduced SSEPs as seen in normal controls.\textsuperscript{26} These findings are suggestive of a widespread error of inhibition.

Altered sensorimotor integration are also present. The interplay between motor output and sensory input can be demonstrated using a paired associative stimulation (PAS) paradigm which utilises the principle that there is an increase in the motor-evoked potential when TMS is paired with peripheral sensory stimulation.\textsuperscript{27} In a study using this method,\textsuperscript{28} paired-pulse TMS was administered following vibrations to three different hand muscles and short-interval intracortical inhibition (SICI) evaluated in each. People with MD showed a reduction in SICI in all muscles even when only one was stimulated with vibrations, whereas this finding was only seen in the stimulated muscle amongst non-musicians. The findings from MD participants suggests that there is no distinction between sensory input coming from any muscle leading to motor output that is not focalised. In normal musicians, slightly reduced inhibition of neighbouring muscles was found but this is believed to be adaptive for fine motor control.

Altered sensorimotor integration is in keeping with the phenomena of sensory trickery seen in MD. This is the observation that improvement in motor control can be seen when a musician wears a glove or holds something in their fingers.\textsuperscript{29}

Tying in these 3 main observations, we can appreciate how abnormal sensory input, in the form of injury or intense practice, can drive maladaptive somatosensory organization as a result of abnormal
plasticity. The latter may have its’ origins in reduced inhibition. Abnormal sensory organization could then trigger non-focalised motor output, again on the basis of impaired inhibition.

Is it all to do with practising and plasticity?

In addition to the influence of intensive training regimes and deranged plasticity, other aetiological factors deserve consideration. The importance of psychological factors in dystonia have long been recognised. A psychogenic mechanism was believed to underlie the pathophysiology of dystonia as late as 1982, at which time a study revealed that psychiatric abnormality was not greater in its’ 29 participants with WC, compared to the normal population. Evidence from this time until present day however suggests it may be incorrect to disregard the psychological aspects of MD, despite its’ primary neurological origin.

Psychological issues were explored in a large German study looking at musicians with MD, healthy musicians and musicians with chronic pain. Findings showed that musicians with MD, compared with healthy musicians, had a greater level of social phobia and other specific phobias. Anxiety disorders were also more common in MD, as was perfectionism. Data from personal recollection indicated that these traits predated the development of MD, although this form of assessment is significantly under the influence of recollection bias.

There is immense pressure associated with performing music. Fear of failure or wrong notes is a great worry for many performers, particularly those with high background levels of anxiety and perfectionism. It has been suggested that an early dystonic movement may cause stress-induced memory consolidation via activation of the basolateral amygdala. This region is particularly important for reward and punishment processing and has reciprocal connections to the primary motor connections where motor programmes are stored. This would then result in the consolidation of the dystonic movements as an abnormal motor programme.
An alternative explanation of how stress may trigger MD lies in the fact that reduced GABA activity has been found to increase sensitivity to stress. Not only this but chronic stress leads to a decrease in GABA levels.\textsuperscript{35-36} This could explain how stress and pressure of the musical world might contribute to the reduced inhibition noted from neurophysiological studies.

\textbf{What about the role of nature?}

The genetic basis of dystonia has received much attention following the identification of genetic loci in inherited forms of primary dystonia, particularly at the loci DYT-1, DHY-6, DYT-7 and DYT-13.\textsuperscript{40} Recent genetic linkage studies carried out in families of MD sufferers suggests that genetics may also be relevant in this form of task-specific dystonia which questions the notion that the origin of MD lies solely in an occupational nature.\textsuperscript{6,41}

Around 10\% of sufferers of MD report a family history of dystonia.\textsuperscript{2} This has been confirmed in a genetic linkage study looking at 3 families that demonstrate a putative autosomal dominant pattern of inheritance of FTSD.\textsuperscript{41} These findings were explored systematically in a larger genetic study of 28 families with musician’s cramp where relatives were both interviewed and clinically examined to determine their dystonia status.\textsuperscript{6} Of the 28 families, 18 were found to be multiplex families with 2-4 family members affected over 1-3 generations. This study demonstrates the importance of clinical examination alongside using confirmed diagnosis as only 7/19 of the cases in relatives were previously diagnosed. A pattern in line with an autosomal dominant pattern of inheritance was found in 12 of the 18 families.

Interestingly, this study revealed that over half of the MD individuals were found to have other forms of dystonia, and that there was particularly high levels of WC clustered in the families of MD patients. By no means definitively, this suggests the possibility of a shared genetic basis amongst focal dystonias.
So have any gene loci been implicated to date? The DYT-1 mutation has not been found in two genetic studies so far\(^6,4^1\) whereas information for the DYT-7 locus is mixed\(^4^1\), with insufficient evidence to determine whether linkage was present. The problem in this study was that there were too few family members affected to perform the analysis. Previous studies have however implicated this gene locus in two families with focal dystonia, but not specifically with FTSD.\(^4^2,4^3\)

Although an autosomal dominant expression pattern has been found in some families, often not enough family members demonstrate MD to confirm a Mendelian inheritance pattern and to confirm linkage to a particular genotype, which suggests the disorder manifests from multiple genetic loci.\(^4^4\) Perhaps, if an alternative analysis was performed, looking at not just family members with MD, but all focal dystonias, this may be more fruitful. The evidence from intra-familial heterogeneity of phenotype described above suggests that these loci may be shared amongst other adult-onset focal dystonias.

The genetic basis has not been fully studied in MD but information from other forms of focal dystonia suggest that the genetic underpinnings may lie in reduced inhibition.\(^4^4\) The presence of increased cortical excitability has been found across all forms of focal dystonia. This observation is seen in unaffected body parts and in the relatives who are unaffected by the disease which suggests that this may be part of the genetic basis of the disease.\(^4^5\) In focal dystonia, D2 receptors have been found to be deficient in the putamen\(^4^6\) which could lead to the reduction in dopamine-potentiated GABA inhibition of the external globus pallidus leading to increased cortical excitability.

Furthermore common concurrent observations in sufferers of focal dystonia and unaffected relatives are suggestive of endophenotypic traits. These traits include abnormal sensory processing, impaired spatial and temporal discrimination, increased psychiatric abnormalities and impaired mental rotation.\(^4^4\)
What can musician’s cramp tell us about other forms of dystonia?

Evidence described above details that current key aetiological factors implicated in MD appear to be psychological, behavioural (level of practice) and genetic. These observations can be unified using a heuristic model that states that on the basis of a genetic predisposition, a strong enough environmental trigger (in the form of abnormal sensory input or psychological factors or both), will lead to the expression of MD. Alongside this, neurophysiological data shows that there are clear abnormalities in cortical plasticity related to changes in inhibition, sensory processing and sensorimotor integration in MD. It appears that abnormalities of inhibition may represent the genetic basis of MD and consequently contribute to the abnormal sensorimotor integration and plasticity observed. Furthermore psychological stressors may further dampen the impaired inhibition via reduced GABA transmission thus showing how environmental factors can interact with genetic susceptibility.

Does this model fit in with other forms of focal dystonia and can a difference in one or more factors explain the increased prevalence amongst musicians? Genetics appears important in other focal dystonias and as stated earlier, evidence points towards shared genetic susceptibility amongst different forms of focal dystonia. A review of 13 genetic linkage studies in families with focal dystonia, found that 8 families showed heterogeneity of dystonia phenotype. Furthermore the same genetic loci have been implicated in genetic linkage studies of different dystonia types. It is also well accepted that abnormal sensory organisation, reduced inhibition and impaired sensory-motor integration are widespread features in other forms of dystonia, pointing towards a shared underlying pathophysiology.

Whilst the factors considered thus far seem to be shared amongst focal dystonias, this does not reveal why musicians get this subtype of FD more frequently. If both genetic susceptibility and...
abnormal neurophysiological processes discussed earlier are needed for manifestation of focal dystonia, then what else is needed that can explain why musicians are so much more susceptible to this disorder?

Psychiatric disturbances are frequent in focal dystonia, in addition to their prevalence in MD. A case-control study in 89 patients with a variety of FDs revealed that 57.3% had psychiatric conditions, compared to 24.1% of healthy participants. There was a high incidence of depression particularly in belpharospasm (BSP), and cervical dystonia (CD) whereas no difference in OCD and anxiety were found compared to the healthy controls. Psychiatric disturbances overall however, are more frequent amongst musicians than in the general population, which may represent a causal factor explaining why musicians are more susceptible to dystonia. One theory already discussed is that reduced-inhibition mediated by stress could further disrupt the genetically impaired inhibition. This is supported by the observation that the psychiatric conditions in the majority of cases pre-date the development of dystonia, both in MD and other forms of focal dystonia. Alternatively psychiatric disorders may represent an endophenotype that is common to all dystonias and therefore does not trigger the manifestation of this disease but is part of its genetic heritability.

We have also seen that work load, practice time, instrument type and being a soloist show higher levels of dystonia. These things can be seen as abnormal sensory inputs. Abnormal sensory inputs could be in the form of repetitive action (as in MD) or trauma. In some forms of focal dystonia, there is evidence of abnormal sensory input as a consequence of injury preceding the motor impairment. For example, there is evidence of prior neck trauma in people with CD. A similar case exists for BSP, where a case-control study reported prior eye problems, particularly dry eye syndrome. Abnormal sensory input in the form of repetitive stimulation was found in a study of participants with WC, where the condition was associated with hours spent writing and a sudden increase in time spent writing in the year preceding WC development. These abnormal sensory inputs could lead to the
abnormal somatosensory cortical changes and errors of sensorimotor integration, all underpinned by a genetic basis of abnormal inhibition. It could be argued therefore that non-musicians may not experience the same sensory demands on temporal and spatial processing and thus lack these key triggers. This is supported by the prior observation that musicians who do develop MD tend to play instruments associated with high workload and complex movements.51

The study of a discrete form of focal dysphonia known as musical dysphonia has revealed the importance of both environmental and genetic factors in its pathogenesis. Evidence supports a model whereby a genetic predisposition, combined with environmental triggers such as work load and psychological factors, lead to the manifestation of the disorder. This model may also be appropriate for other forms of focal dystonia. More evidence is needed to conclude that the aetiology of MD and other focal dystonia’s are shared, but trying to understand why MD is so common provides a useful way of understanding whether the same factors are relevant to other forms of FD. Findings discussed here suggest that MD is more frequent amongst musicians than focal dystonias are in the general population, because despite a similar genetic predisposition seemingly routed in impaired inhibition, musicians fulfil the extrinsic criteria required to demonstrate the disease, primarily in the forms of psychological stressors and abnormal sensory input. It is a sad irony that for some, it is the very practice of the instrument they love that could rob them of its expression.

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References


