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Physiology of Dystonia: Human Studies

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**Abstract**

In this chapter, we discuss neurophysiological techniques that have been used in the study of dystonia. We examine traditional disease models such as inhibition and excessive plasticity and review the evidence that these play a causal role in pathophysiology. We then review the evidence for sensory and peripheral influences within pathophysiology and look at an emergent literature that tries to probe how oscillatory brain activity may be linked to dystonia pathophysiology.

**Keywords**

Dystonia, inhibition, plasticity, sensory, proprioceptive, oscillations, neurophysiology, pathophysiology

# 1. Introduction

Over the last two decades disease models of dystonia have been dominated by the notion that inhibition and plasticity are abnormal [1-4]. Both theories have their origins in data generated through neurophysiological interrogation of brain circuits in humans. Yet, treatments that build directly from these theories have failed to materialise. We discuss how although there is much evidence for shifts in excitability of sensorimotor circuits, we still lack direct confirmation that inhibition and plasticity are causally linked to the pathophysiology of dystonia. We then focus on another dominant research theme, the role of sensory feedback. Here, clinical observation reassures us that sensory influences are integral to disease models as many patients with dystonia experience a sensory-trick phenomenon. Finally, we debate the role of abnormal oscillatory behaviour in dystonia pathophysiology as access to recordings of deep nuclei from patients treated with deep brain stimulation have offered us new windows into human neurophysiology.

# 2. Inhibition

Loss of inhibition has been hypothesised to be a dominant pathophysiological mechanism of dystonia since the turn of the century [3-6]. Most of the evidence on inhibition in dystonia is generated with neurophysiological techniques that test inhibitory networks in several levels of the CNS, including the spinal cord, brainstem, cerebral cortex and cerebellar inhibitory connections which we discuss in turn.

In the spinal cord, impaired reciprocal inhibition (RI) is thought to drive co-contractions of agonist-antagonist muscle [6, 7]. However, impairment of RI is not specific and has been found in other conditions such as hemiparesis due to stroke [6]. In addition, impaired RI was found in the non-manifesting limbs in cervical dystonia [7] but results have been contradictory in non-manifesting limbs in focal hand dystonia[6, 8]. Impaired RI is not present in non-manifesting DYT1 individuals [9]. RI testing is heavily dependent on the consistency of H-reflex. Any factor that can affect the H-reflex amplitude (such as background activity) can affect RI measurements. For that reason, it is technically difficult to measure RI in patients with involuntary muscle contractions such as in dystonia [5]. Importantly, loss of RI in the level of the spinal cord can be due to impairment at the level of the Ia inhibitory interneurons or its influence from supraspinal input (corticospinal descending axons), but it remains unclear where the abnormality occurs in dystonia. Notably, botulinum toxin injections reverse the abnormally low second phase of RI in upper limb dystonia [10]. Also, bilateral globus pallidus internus deep brain stimulation (GPi DBS) in idiopathic isolated (‘primary torsional’) dystonia reverses abnormalities in the first and second phase of RI[11]. Overall, given that RI is impaired in non-affected limps and is normalized by interventions that provide clinical improvement but have very different mechanisms, it seems that RI is not a primary abnormality but rather a correlate of impaired dystonic motor control. Interestingly, RI is also reduced in functional dystonia which also suggests that impaired RI is not a specific pathophysiological abnormality in idiopathic isolated dystonia [12].

At the level of brainstem, most of the evidence originates from studies on the blink reflex (tested with two stimuli that trigger blink reflex and measuring the inhibitory effect of the first stimulus on to the second stimulus) . The recovery cycle of the blink reflex has been found to be abnormally hyperexcitable in patients with blepharospasm [13-17], and cervical dystonia, but not in patients with increased blinking without the typical spasms of blepharospasm [18] [19, 20]. In patients with extracranial dystonia the recovery cycle of the blink reflex was normal [19]. Of note, the blink reflex recovery cycle in patients with atypical/functional blepharospasm is normal too [16]. The inhibitory masseter reflex itself (stimulation of infraorbital, supraorbital or mental nerve during masseter voluntary contraction) was absent in 5 out 15 patients with blepharospasm and oromandibular dystonia [18] but normal in cervical dystonia [21]. Its recovery cycle (tested with paired stimuli) was impaired (similarly to the blink reflex) in cranial, cervical and generalized dystonia but not in limb dystonia [19] which suggests a somatotopic distribution of the abnormality. The exteroceptive suppression of EMG activity in the contracting sternocleidomastoid muscle (SCM) by electrical stimulation of the supraorbital nerve is reduced in cervical dystonia and blepharospasm [20, 21]. A short latency reflex can be evoked in SCM by stimulating the infraorbital nerve and is bilaterally abnormal in cervical dystonia but not in blepharospasm [22]. The two reflexes are likely mediated via different pathways as the onset of suppression of the SCM after supraorbital nerve stimulation is around 40ms suggesting a polysynaptic pathway (likely involving synapses that are impaired in both cervical dystonia and blepharospasm), but the latency of EMG responses after infraorbital stimulation is around 19ms suggesting an oligo-synaptic pathway (likely *not* involving synapses that are involved in blepharospasm, but only in cervical dystonia).

The cerebellum has been implicated in the pathophysiology of dystonia more recently although its exact role is unclear and the topic remains controversial [23-26]. The inhibitory influence of the cerebellum over the motor cortex has been tested with a TMS paradigm, commonly described as cerebellar brain inhibition (CBI). The usual set up includes a cerebellar stimulation preceding the motor cortical stimulation by about 5ms [27, 28]. The cerebellar input then inhibits the cortical excitability supposedly through the cerebellothalamocortical pathway. In patients with focal hand dystonia, this effect is lost which suggests impairment of cerebellar modulation of motor cortex excitability [29, 30]. In cervical dystonia the results are variable [30-32].

Local inhibitory networks within the motor cortex have been studied with TMS when paired stimulation is applied through the same coil in the same area of the cortex. With this technique GABAergic inhibition has been studied. Short intracortical inhibition (SICI) is tested with intervals of a few milliseconds (less than 5ms) and long intracortical inhibition (LICI) with longer intervals, from 50 to 200 ms [33, 34]. SICI has been found to be lost in some studies [9, 12, 35-38] but not others [29, 39-43]. Similarly, the results are mixed for LICI, with some studies showing loss of LICI [12, 44] and others not [45, 46]. Other corticocortical networks have been studied between distal cortical targets such as transcallosal interhemispheric inhibition (IHI) or within the same hemisphere premotor-motor or parietal-motor connections. The loss of IHI seems to be related to the clinical presence of mirror dystonia, which is defined as appearance of dystonic movement in the affected dystonic limb induced by a specific task performed by the unaffected contralateral limb [47, 48]. Dorsal premotor-motor cortical inhibition is shown to be enhanced in writer’s cramp and CD patients [49-51]. Ventral premotor-motor cortical inhibition is normal in writer’s cramp [52]. The parieto-motor network includes facilitatory and inhibitory connections which seem to be abnormal in writer’s cramp [52]. Surround inhibition is another type of inhibition, which is thought to be impaired in dystonia [53, 54]. Normally, SI is thought to play an important role in active inhibition in surround muscles during a motor task. When SI is lost, overflow activation of surround muscles causes the dystonic symptoms [55]. One study proposed that SI is more variable in focal hand dystonia and larger sample sizes may be necessary to draw firm conclusions on SI in dystonia [56].

As it becomes evident from the above, although loss of inhibition is prominent theory that is commonly discussed on the topic of the pathophysiology of dystonia, the data is not always consistent. The variability of the techniques and the heterogeneity of the disease can explain some of the variable results. Unfortunately, the rarity of dystonia does not allow large studies that could potentially resolve the conflicting results. The neurophysiological studies are inherently noisy and can be technically very challenging especially in a population with abnormal movements. The paradox in the studies of inhibition in dystonia is that a bias towards more noisy data in the patient group (for example due increased background activation) can result in a positive study, as the patient groups would show no significant modulation of the measures (i.e. loss of inhibition) in contrast to the control group. This effect is even more pronounced in small sample size studies. For this reason, interpretation of the results need caution. Despite the overwhelming number of publications that report some level of impaired inhibition in dystonia, this knowledge has not led to a more cohesive description of the pathophysiological substrate of dystonia or development of therapies.

# 3. Plasticity

Repetitive TMS and transcranial direct current stimulation (tDCS) are techniques that aim to modulate cortical excitability over a time period that outlasts the period of brain stimulation and are considered experimental tools by which we can probe and modulate synaptic plasticity itself [57, 58]. Changes in excitability are usually quantified by applying single pulses of TMS to the motor cortex to elicit motor evoked potentials (MEPs) in the muscles of the contralateral hand before and after the plasticity protocols.

Several influential publications have suggested that abnormal plasticity may be an important causal mechanism of dystonia. For example, low frequency repetitive TMS was tested by Siebner et al in patients with writing dystonia [59]. Rather than the expected *decrease* in the averaged MEP, patients showed a significant *increase* in MEPs, suggesting that increased excitability of the motor cortex was important. Quartarone then consolidated this work by applying a paired associative stimulation plasticity (PAS) protocol in writing dystonia in a landmark publication in which they found stronger facilitation of MEP amplitudes in patients compared to controls [60]. Later, publications in writing dystonia suggested that not only was the magnitude of response excessive but that patients also had abnormal temporal properties and spatial organisation of plasticity responses[1]. When other dystonia subtypes were tested, such as the cranial and cervical dystonias, these groups were also found to have excessive motor cortex plasticity responses using paradigms which tested the hand muscles [61]. Thus, abnormal excitability was not confined to clinically affected circuits and excessive plasticity was proposed as an endophenotypic trait for dystonia. Another supportive finding was that effective treatment of cervical dystonia with botulinum toxin injections was mirrored by shifts of excessive plasticity responses towards those of controls at the peak of treatment efficacy[62].

Non-invasive brain stimulation (NIBS) protocols were historically thought to modify corticospinal excitability in a *predictable* and *consistent* manner [63]. However, increasingly inter-individual variability has been observed. For example, in one study over 50 subjects were studied with the three most used paradigms to *facilitate* corticospinal excitability; i) paired associative stimulation with an interstimulus interval of 25ms (PAS25), ii) intermittent theta burst stimulation (iTBS) and iii) anodal tDCS [64]. Despite the large sample size, there was no significant effect for any of these paradigms on MEP amplitude across the whole group (or other neurophysiological markers of excitability [64]). Within this null result, cluster analysis revealed a bimodal response pattern and that only 39%, 45% and 43% of subjects responded with a facilitatory response *as expected* to PAS25, anodal tDCS and iTBS respectively [64]. The stability of plasticity responses at an individual level is also poor. For example, if individuals have their plasticity response tested at two different sessions using PAS25, the magnitude of evoked plasticity responses can be entirely unrelated across the two sessions [65] (other plasticity paradigms such as tDCS are more stable within individuals [66]). There appear to be many causes of variability[64, 67-71]. Some appear to be physiologically, that we can interrogate through careful experimental work. For example, inter-subject variability in response to each protocol appears to be due to differences in the population of neurons activated by each TMS pulse [72]. However, the range of other factors is increasingly large and include non-modifiable and modifiable physiological, technical, and statistical factors [73, 74]. Therefore, variability in NIBS studies that try to probe plasticity is a consistent and significant research issue [74].

Variability in clinical groups is likely to be higher than normative control groups. Factors such as duration and severity of disease, number and type of treatments all have the potential to influence plasticity responses. A comparative review of published studies in dystonia does reveal evidence of variability. For example, early studies within the dystonia literature clearly described large excessive effects with plasticity protocols [60]. However, other studies failed to find any group effect of PAS protocols in patients with focal dystonia or no difference between the response of healthy subjects and those with dystonia [75, 76]. Interestingly, if directly compared, the magnitude of excessive plasticity response documented in some studies that *did* find a significant difference between controls and patients with dystonia was less than excessive plasticity responses quantified in other studies that found *no significance* between groups [76, 77]. Others have suggested that the abnormality in dystonia may be subtler than a simple increase in plasticity and that the spatial specificity of the response was the core abnormality (for example, patients may have a greater spread of the effect to non-target muscles) [78, 79]. However, in healthy individuals, plasticity is no longer considered to be specific to the target muscle; arguments that dystonia has a greater spread of response must also account for this finding in healthy subjects [71]. More recently more complex plasticity profiles have been documented in dystonia, some have observed shifts in meta-plasticity (a synaptic or cellular activity that primes the ability to induce subsequent synaptic plasticity) or homeostatic plasticity (range of plasticity mechanisms that stabilise neuronal activity) [1, 75, 76, 80]. However, some of these failed to replicate earlier ‘core’ plasticity findings and thus the foundations of the plasticity hypothesis remain variably documented.

**4. Limitations of Inhibition and Plasticity Hypothesis**

The preceding discussion reveals several limitations with the inhibition and plasticity hypothesis for dystonia pathophysiology. There are several priority issues to need to be explored and better understood to gain greater clarity.

Reproducibility of findings is one major issue. The strength and the consistency of the association between neurophysiological responses and dystonia is often too uncertain. If we continue to sample highly variable outcome parameters with numbers that are too low to adequately power studies, results will continue to confuse. For example, recently another experimental neurophysiological paradigm, eye-blink conditioning, was highlighted as problematic [25]. When larger numbers of patients were evaluated with an analysis that allowed for co-variates such as age and sex, previously documented abnormalities in conditioning resolved into the inherently high variability of response seen in both control and dystonia populations.

Specificity is another issue. Our currently broad descriptions of ‘reduced’ inhibition and ‘abnormal’ plasticity response are not unique to dystonia. For example, abnormalities in plasticity responses have been demonstrated in a multitude of unrelated central nervous system disorders (for example: Alzheimer’s disease [81], autism [82], migraine [83]). There is also broad agreement that most subtypes of isolated dystonia are likely to represent a network disorder. Many neurophysiological paradigms are readouts from the motor cortex, and average of motor evoked potentials from primary motor cortex. Such paradigms look in relative isolation at a single node within the sensorimotor cortex, its data presumably reflecting interactions with other nodes within the dystonic network. Our readout parameter, the motor evoked potential, is a noisy parameter which varies across trials and across individuals. Do current techniques offer too limited capacity to get insight into the broader dystonic network? A low dimensional outcome metric, such as change in MEP, will be unlikely to capture dynamic activity across a network. It will also be unable to account for the diversity of disease process that abnormal plasticity has been linked to, and the specificity of findings will likely be limited until more complex or composite measures of brain function are used.

It is also critical that we do not use neurophysiology as an assumptive link, a process that is relevant to all levels of organisation across the nervous system. A first step is to decide what phenomena we are trying to explain. Are we looking to characterise the changes in system-level function that underwrite the behavioural phenotype dystonia, a correlate to the abnormal dystonic movement observed in response to a range of causal diseases? Or alternatively are we searching for a marker of an aetiologically homogenous groups such as DYT-*TOR1A* dystonia? In the latter case our hypothesis would be that the genetic mutation has a specific effect over the molecular machinery responsible for implementing cellular synaptic plasticity and we will try to sample this effect by testing neuronal circuits at the whole brain level with human neurophysiology. The length of this last sentence and the number of assumptions contained gives some indication of how tenuous and indirect such approaches can become. For example, it cannot be assumed that changes in the motor cortex measured by shifts in mean MEP are a simple analogue of synaptic plasticity at the cellular level [80, 84, 85]. This is not easy to resolve but having better clarity of our research question will aid better mechanistic inference from our experimental work.

Finally, the chicken and its egg raise their head and vertex. Most broadly, dystonia is a hyperkinetic movement disorder in which there is too much movement with abnormal muscle contractions which lead to abnormal postures. The motor cortex as the common final output that controls movement is therefore likely to be comparatively hyperexcitable as too much movement for given context is being produced. Whether the abnormalities in plasticity response and inhibition are a causal aetiological factor, a simple consequence of too much movement is very difficult to resolve. Similarly, compensatory mechanisms that try and counteract dystonia are also likely to be active. Changes in inhibition and plasticity could also be a by-product of a system trying to compensate for abnormal movements.

Currently, any criteria for causal inference are poorly satisfied by our current neurophysiological literature [86]. Yet our belief in inhibition and plasticity hypothesis for dystonia have been described as ‘canonical’ rather than evidence-based [87, 88]. Collective commitment to hypothesis can then have the serious repercussions of both implicit and explicit biases. The manner with which outlying data are treated, how experiments are planned, which datasets are pushed and accepted for publication can all be influenced. There is a danger that new research will continue to be framed in traditional disease models. Rather, we need to review the underpinning evidence analytically and continuously.

# 5. Peripheral contributions and disrupted sensorimotor integration

Sensory feedback is essential for guiding voluntary movement [89] and for accurately maintaining a stable gaze or posture [90, 91]. The striking phenomenon of sensory tricks, where a light touch of a body part alleviates muscle contractions – suggests that peripheral feedback is one important factor in dystonia. Sensory tricks have been observed in various variations in all forms of idiopathic isolated dystonia (e.g. cervical dystonia, task-specific dystonia) and genetic isolated dystonia (e.g. DYT-TOR1A related dystonia) dystonia [92, 93], and is thus a unifying feature. In the next section, we will review studies discussing altered processing of peripheral feedback to evaluate the idea that dystonia is a disorder of dysfunctional sensorimotor integration.

Early studies have found abnormal somatotopic organization in focal hand dystonia in the form of overlapping somatosensory evoked potentials [94], and disorganized finger representations . The latter was most pronounced in asymptomatic limbs and resulted in speculations that disorganized finger representations might be endophenotypic. Only recently more robust analyses methods applied to fMRI data showed that finger representations in musicians with dystonia appear to be intact when compared with healthy musicians [95]. Other studies reported impaired somatosensory spatial discrimination abilities in focal but not generalized DYT1 dystonia [96, 97].

Among the most widely studied measures of sensory dysfunction in dystonia are prolonged temporal discrimination thresholds (TDTs), capturing an impaired ability to detect the presence of two sensory stimuli when they are only separated by very brief intervals [98-101]. Prolonged TDTs have also been detected in clinically unaffected body parts [102, 103], asymptomatic carriers of the DYT-TOR1A gene [104], and unaffected relatives [105-107], suggesting this altered form of sensory processing precedes symptom onset. In temporal discrimination tasks that require multimodal integration of visual and tactile stimuli, patients performed worse than in unimodal discrimination tasks [98]. The degree of impairment correlated with symptom severity and was also associated with reduced efficacy of sensory tricks [108]. However, two more recently published studies found that the ability of dystonia patients to detect brief intervals between sensory stimuli was intact [40, 109]. Discrimination accuracy and reaction time data was used to compute models that can reveal latent decision-making factors, which suggest that abnormal decision-making thresholds may be an alternative explanation for prolonged TDTs in dystonia [109].

Additionally, abnormal proprioceptive processing has been demonstrated in studies of the tonic vibration reflex [110]. In these studies, a limb movement is triggered by vibration that mimics muscle stretch by activating muscle spindles, causing a compensatory contraction of the vibrated muscle. When visual information is withheld, participants can only rely on proprioceptive information to estimate whether their arm has moved. To assess the accuracy of the proprioceptive percept, blindfolded participants are asked to mirror the perceived movement with the limb contralateral to the vibrated side. Patients with focal dystonia were able to mirror passive displacements of their arm, but failed to accurately mirror movements triggered by the vibration reflex, which selectively activates Ia afferents [111]. Several follow-up studies have confirmed abnormal Ia afferent activity processing [112-115] and extended the findings to unaffected first-degree relatives [116]. Yet more recently, a study detected abnormal vibration-induced postural responses only in cervical dystonia patients that did not benefit from sensory tricks, suggesting that Ia afferent processing is less affected in patients benefiting from sensory tricks [117].

Intriguingly, vibrotactile stimulation can both exacerbate dystonia symptoms [118, 119], and alleviate symptoms depending on the stimulation site and pattern [114, 120-124]. Karnath et al. (2009) showed in a patient with spasmodic torticollis that vibration of the affected muscles alleviated involuntary head torsion, whereas haptic stimulation or transcutaneous electrical stimulation resulted only in marginal improvements. This observation points towards a causal role of proprioceptive afferent activity in the pathogenesis of dystonia.

What is the mechanism behind symptom attenuation via sensory stimulation? The temporal structure and degree of synchronization of neural sensorimotor network activity seems to play a key role in dystonia, as will be discussed in detail in the next section on oscillations. Effective sensory tricks seem to attenuate excessive 6-8 Hz basal ganglia and sensorimotor cortex synchronization [125], although it is unclear whether the attenuation is simply driven by the coincident reduction in motor symptoms. Interestingly, when two patients who found sensory tricks to be ineffective performed a similar gesture, their symptoms got worse and synchronization increased. Another trick to temporarily reduce dystonia symptoms is to cool the affected limb in a water bath [126]. Cooling slows down peripheral nerve conduction times and increases the cortical 20 Hz drive to muscles in healthy participants [127]. The temporal characteristics of neural activity thus might be an important point to consider in future studies concerning dystonia.

In a seminal article, Shaikh et al. (2016), proposed that cervical dystonia might be caused by malfunctioning of a “head neural integrator” system - a system that is key for integrating visual, proprioceptive, and cerebellar inputs. The idea was based on the observation that gaze and head rotations drift back toward a default “central null” resting position when brainstem “integrator” structures are disrupted. Malfunction may be caused by alterations intrinsic to the integrator circuits, alterations in either cerebellar, basal ganglia or peripheral feedback, or a combination of factors. The various possible factors are difficult to disentangle, but - as briefly discussed above - the temporal structure and degree of synchronization between afferent and efferent activity might be key for understanding how sensorimotor integration is disrupted in dystonia. More than 20 years ago, William MacKay already suggested that “synchronous oscillatory activity may be an integrative sensorimotor mechanism for gathering information that can be used to guide subsequent motor actions” [128]. The extent to which disorderly integration of multiple sensory streams and disrupted temporal coordination of neural activity causes dystonia symptoms remains to be tested in future studies.

In summary, a considerable body of studies suggests that altered sensory processing is an endophenotypic trait and might be a predisposing factor for dystonia [129-131]. Studies investigating alterations in temporal integration windows for sensory processing and for sensorimotor coordination could become pivotal in our quest to understanding and treating dystonia.

# 6. Oscillations in dystonia

The introduction of deep brain stimulation (DBS) as a treatment for dystonia, has allowed the neurophysiological study of deep regions of the motor network, which are usually not accessible to superficial techniques, such as electroencephalography (EEG) [132]. In patients with dystonia treated with DBS, it is possible to record the local electrical activity of the nuclei where the DBS electrodes are implanted. This activity, the ‘local field potentials’ (LFP), represents the summation of postsynaptic potentials from the neurons surrounding the electrodes [133]. By looking at the characteristics of these LFP’s during different disease states (for example when dystonic movements are present, or before and after DBS), or their relationship with other brain or body regions, it has been possible to infer which components are associated with dystonia features. Specifically, aberrant oscillations that are embedded in the LFPs and synchronized throughout the dystonic motor network have been identified [134].

### Low-frequency oscillations in dystonia

Prominent oscillations in the low frequency range (LF, spanning both theta 4 to-8 Hz and alpha 8 to -12Hz bands) have been consistently found in the internal globus pallidus (GPi) [135-137], and the subthalamic nucleus (STN) [138, 139] of patients with dystonia in the resting state. Given their deep location, it is yet to be described how LF-oscillations behave in the healthy brain. However, these oscillations are increased when compared to those of patients with other diseases, such as Parkinson’s disease (PD) [135-137], and can be modulated by both peripheral stimuli and voluntary movements (afferent and efferent information, respectively) [140]. It has been observed that LF-oscillations are coherent with electrical activity in the LF-range of dystonic muscles, measured through electromyography (EMG). The direction in which the dystonic drive in the LF-range appears to be transmitted primarily from the GPi to the affected muscles [141, 142]. Nevertheless, an afferent drive (from the dystonic muscles to the GPi) has also been observed, albeit to a lesser extent. This drive could represent sensorimotor feedback which is aberrant in dystonia. This is further supported by the fact that an effective sensory trick suppresses abnormal LF synchronization [125]. Such suppression may suggest that a sensory trick beneficially modulates the aberrant feedback present in dystonia. Furthermore, increased oscillations in the alpha band have been identified in the resting-state motor cortex of patients with dystonia, compared to healthy controls [143]. Hypersynchronization in the LF-range has also been observed between the GPi and the motor cortex in patients with dystonia, in the resting state[144], and between the STN and the motor cortex [139, 145].

### The effect of DBS on LF-oscillations

High-frequency DBS is able to suppress the abnormally increased LF-oscillations in the GPi of patients with phasic dystonia [146, 147]. Increased LF-power in the motor cortex is also normalized after DBS [148]. Moreover, DBS is able to normalize the coherence between both the GPi [149], and the STN[145] with the motor cortex. When DBS is suspended, LF-oscillations become prominent in both the GPi [150] and the motor cortex [143]. These observations indicate that one of the mechanisms that lead to the improvement of dystonia during DBS is the normalization of the prominent LF-oscillations and their hypersynchronization in the motor network. Up to now it is unclear what the long-term effects of DBS on LF-activity are, but an immediate post-stimulation LF suppression has been observed after DBS, which indicates that the effect of DBS could remain present even after chronic DBS is switched off [143, 149-151]. Studies with a long-term follow up are required to investigate the chronic effects of DBS on dystonic motor network activity.

### Significance of prominent LF oscillations

The motor system is composed of several central structures (which include the cerebral cortex and basal ganglia, among others) that are in charge of transmitting information to the motor units, in order to initiate, maintain or terminate movements [152]. While these structures interact directly with each other through synaptic connections, it has been observed that they are also able to generate and transmit oscillatory activity related to different movement states [153]. These oscillations are part of the healthy motor system, but they might become aberrant in the presence of a movement disorder, such as LF-oscillations in dystonia [154]. Prominent LF-oscillations and hypersynchronization in the LF-spectrum have been found not only in patients with idiopathic dystonia[135], but have also been observed in many other types of dystonia, including several types of genetic dystonia [155], secondary dystonia[156]and myoclonus dystonia [142]. These findings suggest that prominent LF-oscillations and hypersynchronization in the LF-band are ubiquitous in patients with dystonia, regardless of the dystonia type. However, these oscillations have been mostly related to the phasic dystonic components[149, 157, 158]. Besides this, prominent LF-activity has also been detected in other types of hyperkinetic disorders, such as chorea [159, 160] and Tourette’s syndrome[160]. For this reason, it is likely that LF synchrony reflect a hyperkinetic state in the motor network, rather than being pathognomonic of dystonia. The relationship between tonic dystonia and LF-synchronization is less clear. Since phasic and tonic components of dystonia react differently to DBS [161], it is possible that tonic dystonia is defined by distinct neurophysiological characteristics [157]. Given that it usually takes weeks or months for tonic dystonia to improve after DBS activation [162], chronic recordings are necessary to establish the neural correlates of these tonic components.

### Clinical implications of LF-oscillations in dystonia

The magnitude of the LF-oscillations measured in the GPi positively correlates with the clinical severity of dystonia measured with the Burke‐Fahn‐Marsden Dystonia Rating Scale [150] and Toronto Western Spasmodic Torticollis Rating Scale for cervical dystonia [163], and with the activity of dystonic muscles measured with EMG [164]. Therefore, the identification of abnormal oscillations in dystonia can be used for several clinical applications. Firstly, since the LF-drive is only present in patients with dystonia, it could be possible to use EMG or EEG-EMG coherence to differentiate dystonia from other (functional) movement disorders [165]. Secondly, given that the prominent LF-oscillations are spatially confined to the GPi [166], where stimulation is the most effective [163], they could be used either for intraoperative mapping to help selecting the optimal target for electrode placement, or for optimal contact selection during DBS programming [167]. Lastly, given their correlation with clinical symptoms, LF-oscillations could be used as feedback signal for adaptive DBS (aDBS) devices, in which stimulation is delivered based on the magnitude of LF-oscillations in the basal ganglia [151, 168-170], the motor cortex [145], or possibly a measure of synchrony (i.e. coherence) with other brain or body parts affected by dystonia. By modulating the total amount of stimulation delivered, it could be possible to tackle side effects from DBS, such as stimulation-induced dysarthria [171]and parkinsonism [172]. To achieve this, portable devices that are capable of recording LFPs and simultaneously delivering stimulation are required [144], together with systems that allow simultaneous multisite recordings, for example from the GPi or the STN, and the motor cortex [173]. However, it is not yet established how such oscillations can be incorporated into aDBS systems. LF-oscillations occur in short-lived bursts [136, 137], so these bursts could be used to trigger stimulation when those bursts exceed a certain threshold [145, 174]. Furthermore, stepwise approaches, in which stimulation is gradually ramped up or down, can also be explored. An important aspect of the use of LF-oscillations as feedback for aDBS devices, is that such devices should be able to correctly filter stimulation, movement and other types of physiological artifacts (e.g. cardiac artifacts) [175], especially as those artifacts tend to be more prominent in the lower-frequency spectrum.

### Other sources of osillations in dystonia and oscillations in other frequency bands.

Increased LF-activity has not always been found in patients with dystonia [146, 147]. Given that dystonia is a complex movement disorder, several nodes from the motor network have been implicated in the emergence of dystonia, including nuclei from the thalamus, cerebellum, and midbrain [148]. It is likely that these nuclei also play a role in the modulation of LF-activity, but due to their location direct recordings have been seldom reported. Besides this, oscillations in other frequency bands also play a role in the emergence of dystonic movements. High-gamma oscillations (60-90 Hz) have been observed in the motor cortex in the presence of dystonic posturing [176], and in the contralateral GPi when performing hand movements [177]. Synchronization in the high-gamma frequencies have also been observed in the motor cortex [178] and the GPi [179]of patients with PD treated with levodopa. This might indicate the prokinetic nature of those oscillations. However, more studies in dystonia are warranted to establish their significance. Oscillations in the beta band have also been observed in the GPi of patients with dystonia [135]. However, they present a lower magnitude than those observed in patients with PD [168], and they do not correlate with dystonic symptoms [163]. Therefore, it could be that those oscillations are present due to their physiological role in maintaining the basal resting state [180].

In summary, abnormal oscillations have been detected in the motor system of patients with dystonia. Particularly hypersynchronization in the LF-range has been consistently found. These oscillations seem to play a role promoting a hyperkinetic state, which could facilitate the development of dystonic movements. Furthermore, the characterization of these oscillations could have some clinical applications, such as facilitating DBS programming and the development of aDBS systems, which are able to titrate stimulation according to the magnitude of LF-activity.

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# 7. Conclusions

In this chapter we have overviewed topics that have dominated our literature exploring the human neurophysiology of dystonia. Like all methods there are limitations to neurophysiology and by acknowledging and exploring all features of the data we will approach better approximations for disease pathophysiology. For inhibition and plasticity to maintain their key positions within dystonia pathophysiological frameworks we have discussed several factors that need to be better understood. Without deeper understanding reduced inhibition and abnormal plasticity may remain descriptive, indirect observations that poorly motivate therapeutic translation. Embracing new initiatives such as open science data publication will also offer greater transparency and data sharing collaborations will increase our ability to fully power studies to capture and characterise the full diversity of neurophysiological responses. Similarly, we need to drill down deeper into the precise processing abnormalities in the sensory domain and the wealth of new data revealing shifts in oscillatory behaviour.

Experimentally neurophysiological methods remain powerful tools by which to probe network function in dystonia. The increasing number of methods and evolution of analytical methods equip us with the toolkit we need to discover the axes of dystonia mechanism. Modulation of circuit function and normalisation of pathophysiological drivers is also feasible with both central and peripheral neuro-modulatory techniques. Developing methods to cure or significantly improve the trajectory of non-degenerative forms of dystonia thus is a realisable and attainable goal. This makes for an exciting future with the promise that our neurophysiology research can directly feed back into the design of the treatments we can offer our patients.

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