CHAPTER FIVE

Physiology of dystonia: Human studies

Petra Fischer[a], Dan Piña-Fuentes[b,c], Panagiotis Kassavetis[d], and Anna Sadnicka[e,f,*]

[a]School of Physiology, Pharmacology and Neuroscience, University of Bristol, Biomedical Sciences Building, University Walk, Bristol, United Kingdom
[b]Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Meibergdreef 9, Amsterdam, The Netherlands
[c]Department of Neurology, OLVG, Amsterdam, The Netherlands
[d]Department of Neurology, University of Utah, Salt Lake City, UT, United States
[e]Motor Control and Movement Disorders Group, St George's University of London, London, United Kingdom
[f]Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, United Kingdom
*Corresponding author. e-mail address: a.sadnicka@ucl.ac.uk

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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.

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1. Introduction

Over the last two decades disease models of dystonia have been dominated by the notion that inhibition and plasticity are abnormal (Hallett, 2011a; Quartarone et al., 2005; Berardelli et al., 1998; Quartarone, Siebner, & Rothwell, 2006). 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 materialize. 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 and sensorimotor integration. Here, clinical observation reassures us that sensory influences are integral to disease models as many patients with dystonia experience sensory-trick phenomena. Finally, we debate the role of abnormal oscillatory behavior 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 hypothesized to be a dominant pathophysiological mechanism of dystonia since the turn of the century (Hallett, 2011a; Berardelli et al., 1998; Nakashima et al., 1989a; Panizza, Hallett, & Nilsson, 1989). 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 (Deuschl et al., 1992; Nakashima et al., 1989a). However, impairment of RI is not specific and has been found in other conditions such as hemiparesis due to stroke (Nakashima et al., 1989a). In addition, impaired RI was found in the non-manifesting limbs in cervical dystonia (Deuschl et al., 1992) but results have been contradictory in non-manifesting limbs in focal hand dystonia (Nakashima et al., 1989a; Chen, Tsai, & Lu, 1995). Impaired RI is not present in non-manifesting DYT1 individuals (Edwards et al., 2003). 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 (Panizza et al., 1989). 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 (Priori et al., 1995). 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 (Tisch et al., 2006). 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 (Espay et al., 2006).

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 (Conte et al., 2013; Grandas et al., 1998; Schwingenschuh et al., 2011; Tolosa, Montserrat, & Bayes, 1988; Valls-Sole, Tolosa, & Ribera, 1991), and cervical dystonia, but not in patients with increased blinking without the typical spasms of blepharospasm (Berardelli et al., 1985; Carella et al., 1994; Pauletti et al., 1993). In patients with extracranial dystonia the recovery cycle of the blink reflex was normal (Pauletti et al., 1993). Of note, the blink reflex recovery cycle in patients with atypical/functional blepharospasm is normal too (Schwingenschuh et al., 2011). The inhibitory masseter reflex itself (stimulation of infraorbital, supraorbital or mental nerve during masseter voluntary contraction) was absent in 5 out of 15 patients with blepharospasm and oromandibular dystonia (Berardelli et al., 1985) but normal in cervical dystonia (Nakashima et al., 1989b). 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 (Pauletti et al., 1993) 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 (Carella et al., 1994; Nakashima et al., 1989b). 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 (Quartarone et al., 2000). The two reflexes are likely mediated via different pathways as the onset of suppression of the SCM after supraorbital nerve stimulation is around 40 ms 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 19 ms 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 (Batla et al., 2015; Bologna & Berardelli, 2017; Sadnicka et al., 2022a; Kaji Bhatia & Graybiel, 2018). 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 5 ms (Daskalakis et al., 2004; Tremblay et al., 2016). 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 (Bologna et al., 2016; Brighina et al., 2009). In cervical dystonia the results are variable (Bologna et al., 2016; Porcacchia et al., 2019; Sondergaard et al., 2021).

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 5 ms) and long intracortical inhibition (LICI) with longer intervals, from 50 to 200 ms (Di Lazzaro et al., 2000; Valls-Sole et al., 1992). SICI has been found to be lost in some studies (Edwards et al., 2003; Espay et al., 2006; Hanajima et al., 1998; Huang et al., 2010; Kanovsky et al., 2003; Ridding et al., 1995) but not others (Brighina et al., 2009; Ganos et al., 2018; Koch et al., 2014; Kojovic et al., 2013; Kroneberg et al., 2018; Stinear & Byblow, 2004). Similarly, the results are mixed for LICI, with some studies showing loss of LICI (Chen et al., 1997; Espay et al., 2006) and others

not (Latorre et al., 2021; Meunier et al., 2012a). 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 (Beck et al., 2009a; Sattler et al., 2014). Dorsal premotor-motor cortical inhibition is shown to be enhanced in writer's cramp and CD patients (Beck et al., 2009b; Pirio Richardson, 2015; Pirio Richardson, Tinaz, & Chen, 2015). Ventral premotor-motor cortical inhibition is normal in writer's cramp (Merchant et al., 2020). The parieto-motor network includes facilitatory and inhibitory connections which seem to be abnormal in writer's cramp (Merchant et al., 2020). Surround inhibition is another type of inhibition, which is thought to be impaired in dystonia (Beck et al., 2008; Sohn & Hallett, 2004). 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 (Hallett, 2011b). 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 (Kassavetis et al., 2018).

As it becomes evident from the above, although loss of inhibition is a 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 (Huang et al., 2005; Stefan et al., 2000). 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 (Siebner et al., 1999). 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 (Quartarone et al., 2003). 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 organization of plasticity responses (Quartarone et al., 2005). 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 (Quartarone et al., 2008). 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 (Kojovic et al., 2011).

Non-invasive brain stimulation (NIBS) protocols were historically thought to modify corticospinal excitability in a *predictable* and *consistent* manner (Pellegrini, Zoghi, & Jaberzadeh, 2018). 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 25 ms (PAS25), (ii) intermittent theta burst

stimulation (iTBS) and (iii) anodal tDCS (Lopez-Alonso et al., 2014). 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 (Lopez-Alonso et al., 2014)). 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 (Lopez-Alonso et al., 2014). 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 (Fratello et al., 2006) (other plasticity paradigms such as tDCS are more stable within individuals (Lopez-Alonso et al., 2015)). There appear to be many causes of variability (Cheeran et al., 2008; Hordacre et al., 2017; Huang et al., 2017; Lopez-Alonso et al., 2014; Muller-Dahlhaus et al., 2008; Wiethoff, Hamada, & Rothwell, 2014). Some appear to be physiological, that we can interrogate through careful experimental work. For example, some of the inter-subject variability in response to each protocol appears to be due to differences in the population of neurons activated by each TMS pulse (Hamada et al., 2012). However, the range of other factors is increasingly large and include non-modifiable and modifiable physiological, technical, and statistical factors (Guerra et al., 2020; Ridding & Ziemann, 2010). Therefore, variability in NIBS studies that try to probe plasticity is a consistent and significant research issue (Guerra et al., 2020).

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 (Quartarone et al., 2003). 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 (Kang et al., 2011; Sadnicka et al., 2014). 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 (Meunier et al., 2012b; Sadnicka et al., 2014). 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) (Belvisi et al., 2013; Weise et al., 2006). 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 (Cheeran et al., 2008). 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 stabilize neuronal activity) (Kang et al., 2011; Karabanov et al., 2015a; Quartarone et al., 2005; Sadnicka et al., 2014). 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. 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 (Terranova et al., 2013), autism (Jung et al., 2013), migraine (Pierelli et al., 2013)). 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 organization across the nervous system. A first step is to decide what phenomena we are trying to explain. Are we looking to characterize the changes in system-level function that underwrite the behavioral 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 (Carson & Kennedy, 2013; Karabanov et al., 2015a, 2015b). This is not easy to resolve but having better clarity of our research question will aid better mechanistic inference from our experimental work.

Finally, whether the abnormalities in plasticity response and inhibition are a causal aetiological factor or a simple consequence of too much movement is very difficult to resolve. 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. 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 (Fedak et al., 2015). Yet our belief in inhibition and plasticity hypothesis for dystonia have been described as 'canonical' rather than evidence-based (Conte et al., 2019; Latorre et al., 2019). 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 (McCloskey & Prochazka, 1994) and for accurately maintaining a stable gaze or posture (Sanes, 1990; Shaikh et al., 2016). 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 (Broussolle et al., 2015; Patel et al., 2014), 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 (Bara-Jimenez et al., 1998), 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 (Sadnicka et al., 2022b). Other studies reported impaired somatosensory spatial discrimination abilities in focal but not generalized DYT1 dystonia (Molloy et al., 2003; Bara-Jimenez, Shelton, & Hallett, 2000).

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 (Aglioti et al., 2003; Bradley et al., 2012; Tinazzi et al., 2004; Sanger, Tarsy, & Pascual-Leone, 2001). Prolonged TDTs have also been detected in clinically unaffected body parts (Fiorio et al., 2003; Morgante et al., 2011), asymptomatic carriers of the DYT-TOR1A gene (Fiorio et al., 2007), and unaffected relatives (Bradley et al., 2009; Kimmich et al., 2011; Kimmich et al., 2014), 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 (Aglioti et al., 2003). The degree of impairment correlated with symptom severity and was also associated with reduced efficacy of sensory tricks (Kagi et al., 2013). However, two more recently published studies found that the ability of dystonia patients to detect brief intervals between sensory stimuli was intact (Ganos et al., 2018; Sadnicka et al., 2017). 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 (Sadnicka et al., 2017).

Additionally, abnormal proprioceptive processing has been demonstrated in studies of the tonic vibration reflex (Desrochers et al., 2019). 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 (Grunewald et al., 1997). Several follow-up studies have confirmed abnormal Ia afferent activity processing (Lekhel et al., 1998; Rome and Grunewald, 1999; Yoneda et al., 2000; Frima, Rome, & Grunewald, 2003) and extended the findings to unaffected first-degree relatives (Frima, Nasir, & Grunewald, 2008). 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 (Brugger et al., 2019).

Intriguingly, vibrotactile stimulation can both exacerbate dystonia symptoms (Kaji et al., 1995; Tempel & Perlmutter, 1990), and alleviate symptoms depending on the stimulation site and pattern (Khosravani et al., 2019; Leis et al., 1992; Lekhel et al., 1998; Rosenkranz et al., 2009; Karnath, Konczak, & Dichgans, 2000; Zhu, Mahnan, & Konczak, 2021). Karnath, Konczak, Dichgans. (2000) 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 (Tang et al., 2007), 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 (Pohl, Happe, & Klockgether, 2002). Cooling slows down peripheral nerve conduction times and increases the cortical 20 Hz drive to muscles in healthy participants (Witham et al., 2011). 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" (Mackay, 1997). 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 (Conte et al., 2020; Meunier et al., 2001; Tisch & Limousin, 2020). 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) (Thompson et al., 2014). 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 (Pesaran et al., 2018). 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 (Pina-Fuentes et al., 2018).

6.1 Low-frequency oscillations in dystonia

Prominent oscillations in the low frequency range (LF, spanning both theta 4 to −8 Hz and alpha 8 to −12 Hz bands) have been consistently found in the internal globus pallidus (GPi) (Pina-Fuentes et al., 2019a; Silberstein et al., 2003; Wang et al., 2018), and the subthalamic nucleus (STN) (Cao et al., 2019; Geng et al., 2017) 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) (Pina-Fuentes et al., 2019a; Silberstein et al., 2003; Wang et al., 2018), and can be modulated by both peripheral stimuli and voluntary movements (afferent and efferent information, respectively) (Liu et al., 2008). 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 (Foncke et al., 2007; Sharott et al., 2008). 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 (Tang et al., 2007). 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 (Miocinovic et al., 2018a). Hypersynchronization in the LF-range has also been observed between the GPi and the motor cortex in patients with dystonia, in the resting state (Averna et al., 2021), and between the STN and the motor cortex (Cao et al., 2019; Johnson et al., 2021).

6.2 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 (Miocinovic et al., 2015; Wang et al., 2016). Increased LF-power in the motor cortex is also normalized after DBS (Sedov et al., 2019). Moreover, DBS is able to normalize the coherence between both the GPi (Barow et al., 2014), and the STN (Johnson et al., 2021) with the motor cortex. When DBS is suspended, LF-oscillations become prominent in both the GPi (Scheller et al., 2019) and the motor cortex (Miocinovic et al., 2018a). 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 (Barow et al., 2014; Miocinovic et al., 2018a; Pina-Fuentes et al., 2020; Scheller et al., 2019). Studies with a long-term follow up are required to investigate the chronic effects of DBS on dystonic motor network activity.

6.3 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 (Jinnah, Neychev, & Hess, 2017). 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 (Jurkiewicz et al., 2006). 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 (Buzsaki, Logothetis, & Singer, 2013). Prominent LF-oscillations and hypersynchronization in the LF-spectrum have been found not only in patients with idiopathic dystonia (Silberstein et al., 2003), but have also been observed in many other types of dystonia, including several types of genetic dystonia (Zhu et al., 2020), secondary dystonia (McClelland et al., 2020) and myoclonus dystonia (Foncke et al., 2007). 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 (Barow et al., 2014; Liu et al., 2006; Yokochi et al., 2018). Besides this, prominent LF-activity has also been detected in other types of hyperkinetic disorders, such as chorea (Jimenez-Shahed et al., 2016; Zhu et al., 2018) and Tourette's syndrome (Jimenez-Shahed et al., 2016). 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 (Chung & Huh, 2016), it is possible that tonic dystonia is defined by distinct neurophysiological characteristics (Liu et al., 2006). Given that it usually takes weeks or months for tonic dystonia to improve after DBS activation (Grips et al., 2007), chronic recordings are necessary to establish the neural correlates of these tonic components.

6.4 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 (Scheller et al., 2019) and Toronto Western Spasmodic Torticollis Rating Scale for cervical dystonia (Neumann et al., 2017), and with the activity of dystonic muscles measured with EMG (Chen et al., 2006a). 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 (Tijssen, Marsden, & Brown, 2000). Secondly, given that the prominent LF-oscillations are spatially confined to the GPi (Chen et al., 2006b), where stimulation is the most effective (Neumann et al., 2017), 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 (Doldersum et al., 2019). 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 (Arlotti et al., 2018; Little et al., 2013; Pina-Fuentes et al., 2019b, 2020), the motor cortex (Johnson et al., 2021), 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 (Pauls et al., 2018) and parkinsonism (Mahlknecht et al., 2018). To achieve this, portable devices that are capable of recording LFPs and simultaneously delivering stimulation are required (Averna et al., 2021), together with systems that allow simultaneous multisite recordings, for example from the GPi or the STN, and the motor cortex (Gilron et al., 2021). However, it is not yet established how such oscillations can be incorporated into aDBS systems. LF-oscillations occur in short-lived bursts (Pina-Fuentes et al., 2019a; Wang et al., 2018), so these bursts could be used to trigger stimulation when those bursts exceed a certain threshold (Johnson et al., 2021; Lofredi et al., 2019). 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) (Thenaisie et al., 2021), especially as those artifacts tend to be more prominent in the lower-frequency spectrum.

6.5 Other sources of osillations in dystonia and oscillations in other frequency bands

Increased LF-activity has not always been found in patients with dystonia (Miocinovic et al., 2015; Wang et al., 2016). 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 (Sedov et al., 2019). 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 (Miocinovic et al., 2018b), and in the contralateral GPi when performing hand movements (Brucke et al., 2012). Synchronization in the high-gamma frequencies have also been observed in the motor cortex (Swann et al., 2016) and the GPi (Brown et al., 2001) 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 (Silberstein et al., 2003). However, they present a lower magnitude than those observed in patients with PD (Pina-Fuentes et al., 2019b), and they do not correlate with dystonic symptoms (Neumann et al., 2017). Therefore, it could be that those oscillations are present due to their physiological role in maintaining the basal resting state (Little & Brown, 2014).

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.

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 characterize 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 behavior.

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 normalization 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 realizable 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.

References

Aglioti, S. M., et al. (2003). Temporal discrimination of cross-modal and unimodal stimuli in generalized dystonia. *Neurology, 60*(5), 782–785.

Arlotti, M., et al. (2018). Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology, 90*(11), e971–e976.

Averna, A., et al. (2021). Pallidal and cortical oscillations in freely moving patients with dystonia. *Neuromodulation*.

Bara-Jimenez, W., et al. (1998). Abnormal somatosensory homunculus in dystonia of the hand. *Annals of Neurology, 44*(5), 828–831.

Bara-Jimenez, W., Shelton, P., & Hallett, M. (2000). Spatial discrimination is abnormal in focal hand dystonia. *Neurology, 55*(12), 1869–1873.

Barow, E., et al. (2014). Deep brain stimulation suppresses pallidal low frequency activity in patients with phasic dystonic movements. *Brain, 137*(Pt 11), 3012–3024.

Batla, A., et al. (2015). The role of cerebellum in patients with late onset cervical/segmental dystonia?–evidence from the clinic. *Parkinsonism & Related Disorders, 21*(11), 1317–1322.

Beck, S., et al. (2009a). Inter-hemispheric inhibition is impaired in mirror dystonia. *European Journal of Neuroscience, 29*(8), 1634–1640.

Beck, S., et al. (2008). Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. *The Journal of Neuroscience, 28*(41), 10363–10369.

Beck, S., et al. (2009b). The role of inhibition from the left dorsal premotor cortex in right-sided focal hand dystonia. *Brain Stimulation, 2*(4), 208–214.
Belvisi, D., et al. (2013). Abnormal experimentally- and behaviorally-induced LTP-like plasticity in focal hand dystonia. *Experimental Neurology, 240*, 64–74.
Berardelli, A., et al. (1985). Patho-physiology of blepharospasm and oromandibular dystonia. *Brain, 108*, 593–608.
Berardelli, A., et al. (1998). The pathophysiology of primary dystonia. *Brain, 121*(Pt 7), 1195–1212.
Bologna, M., & Berardelli, A. (2017). Cerebellum: An explanation for dystonia? *Cerebellum Ataxias, 4*, 6.
Bologna, M., et al. (2016). Effects of cerebellar theta-burst stimulation on arm and neck movement kinematics in patients with focal dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 127*(11), 3472–3479.
Bradley, D., et al. (2009). Temporal discrimination threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia. *Brain, 132*(Pt 9), 2327–2335.
Bradley, D., et al. (2012). Temporal discrimination thresholds in adult-onset primary torsion dystonia: An analysis by task type and by dystonia phenotype. *Journal of Neurology, 259*(1), 77–82.
Brighina, F., et al. (2009). Effects of cerebellar TMS on motor cortex of patients with focal dystonia: A preliminary report. *Experimental Brain Research, 192*(4), 651–656.
Broussolle, E., et al. (2015). Early illustrations of geste antagoniste in cervical and generalized dystonia. *Tremor and Other Hyperkinetic Movements (N Y), 5*, 332.
Brown, P., et al. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *The Journal of Neuroscience, 21*(3), 1033–1038.
Brucke, C., et al. (2012). Scaling of movement is related to pallidal gamma oscillations in patients with dystonia. *The Journal of Neuroscience, 32*(3), 1008–1019.
Brugger, F., et al. (2019). Sensory trick efficacy in cervical dystonia is linked to processing of neck proprioception. *Parkinsonism & Related Disorders, 61*, 50–56.
Buzsaki, G., Logothetis, N., & Singer, W. (2013). Scaling brain size, keeping timing: Evolutionary preservation of brain rhythms. *Neuron, 80*(3), 751–764.
Cao, C., et al. (2019). Cortico-subthalamic coherence in a patient with dystonia induced by chorea-acanthocytosis: A case report. *Frontiers in Human Neuroscience, 13*, 163.
Carella, F., et al. (1994). Exteroceptive reflexes in dystonia: A study of the recovery cycle of the R2 component of the blink reflex and of the exteroceptive suppression of the contracting sternocleidomastoid muscle in blepharospasm and torticollis. *Movement Disorders: Official Journal of the Movement Disorder Society, 9*(2), 183–187.
Carson, R. G., & Kennedy, N. C. (2013). Modulation of human corticospinal excitability by paired associative stimulation. *Frontiers in Human Neuroscience, 7*, 823.
Cheeran, B., et al. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *The Journal of Physiology, 586*(23), 5717–5725.
Chen, C. C., et al. (2006b). Neuronal activity in globus pallidus interna can be synchronized to local field potential activity over 3–12 Hz in patients with dystonia. *Experimental Neurology, 202*(2), 480–486.
Chen, C. C., et al. (2006a). Oscillatory pallidal local field potential activity correlates with involuntary EMG in dystonia. *Neurology, 66*(3), 418–420.
Chen, R., et al. (1997). Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology, 49*(4), 1054–1059.
Chen, R. S., Tsai, C. H., & Lu, C. S. (1995). Reciprocal inhibition in writer's cramp. *Movement Disorders: Official Journal of the Movement Disorder Society, 10*(5), 556–561.
Chung, M., & Huh, R. (2016). Different clinical course of pallidal deep brain stimulation for phasic- and tonic-type cervical dystonia. *Acta Neurochirurgica (Wien), 158*(1), 171–180.

Conte, A., et al. (2020). Advances in the pathophysiology of adult-onset focal dystonias: Recent neurophysiological and neuroimaging evidence. *F1000Res, 9*.
Conte, A., et al. (2013). Is increased blinking a form of blepharospasm? *Neurology, 80*(24), 2236–2241.
Conte, A., et al. (2019). Ten-year reflections on the neurophysiological abnormalities of focal dystonias in humans. *Movement Disorders: Official Journal of the Movement Disorder Society, 34*(11), 1616–1628.
Daskalakis, Z. J., et al. (2004). Exploring the connectivity between the cerebellum and motor cortex in humans. *The Journal of Physiology, 557*(Pt 2), 689–700.
Desrochers, P., et al. (2019). Sensorimotor control in dystonia. *Brain Sciences, 9*(4).
Deuschl, G., et al. (1992). Reciprocal inhibition of forearm flexor muscles in spasmodic torticollis. *Journal of the Neurological Sciences, 113*(1), 85–90.
Di Lazzaro, V., et al. (2000). Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 111*(5), 794–799.
Doldersum, E., et al. (2019). Intermuscular coherence as biomarker for pallidal deep brain stimulation efficacy in dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 130*(8), 1351–1357.
Edwards, M. J., et al. (2003). Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. *Brain, 126*(Pt 9), 2074–2080.
Espay, A. J., et al. (2006). Cortical and spinal abnormalities in psychogenic dystonia. *Annals of Neurology, 59*(5), 825–834.
Fedak, K. M., et al. (2015). Applying the Bradford Hill criteria in the 21st century: How data integration has changed causal inference in molecular epidemiology. *Emerging Themes in Epidemiology, 12*, 14.
Fiorio, M., et al. (2007). Defective temporal processing of sensory stimuli in DYT1 mutation carriers: A new endophenotype of dystonia? *Brain, 130*(Pt 1), 134–142.
Fiorio, M., et al. (2003). Temporal processing of visuotactile and tactile stimuli in writer's cramp. *Annals of Neurology, 53*(5), 630–635.
Foncke, E. M., et al. (2007). Local field potentials and oscillatory activity of the internal globus pallidus in myoclonus-dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 22*(3), 369–376.
Fratello, F., et al. (2006). Modulation of corticospinal excitability by paired associative stimulation: reproducibility of effects and intraindividual reliability. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 117*(12), 2667–2674.
Frima, N., Nasir, J., & Grunewald, R. A. (2008). Abnormal vibration-induced illusion of movement in idiopathic focal dystonia: An endophenotypic marker? *Movement Disorders: Official Journal of the Movement Disorder Society, 23*(3), 373–377.
Frima, N., Rome, S. M., & Grunewald, R. A. (2003). The effect of fatigue on abnormal vibration induced illusion of movement in idiopathic focal dystonia. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*(8), 1154–1156.
Ganos, C., et al. (2018). Cortical inhibitory function in cervical dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 129*(2), 466–472.
Geng, X., et al. (2017). Comparison of oscillatory activity in subthalamic nucleus in Parkinson's disease and dystonia. *Neurobiology of Disease, 98*, 100–107.
Gilron, R., et al. (2021). Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. *Nature Biotechnology, 39*(9), 1078–1085.
Grandas, F., et al. (1998). Blink reflex recovery cycle in patients with blepharospasm unilaterally treated with botulinum toxin. *Clinical Neuropharmacology, 21*(5), 307–311.

Grips, E., et al. (2007). Patterns of reoccurrence of segmental dystonia after discontinuation of deep brain stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(3), 318–320.
Grunewald, R. A., et al. (1997). Idiopathic focal dystonia: A disorder of muscle spindle afferent processing? *Brain, 120*(Pt 12), 2179–2185.
Guerra, A., et al. (2020). Variability in non-invasive brain stimulation studies: Reasons and results. *Neuroscience Letters, 719*, 133330.
Hallett, M. (2011a). Neurophysiology of dystonia: The role of inhibition. *Neurobiology of Disease, 42*(2), 177–184.
Hallett, M. (2011b). Neurophysiology of dystonia: The role of inhibition. *Neurobiology of Disease, 42*(2), 177–184.
Hamada, M., et al. (2012). Cerebellar modulation of human associative plasticity. *The Journal of Physiology, 590*(10), 2365–2374.
Hanajima, R., et al. (1998). Cortico-cortical inhibition of the motor cortical area projecting to sternocleidomastoid muscle in normals and patients with spasmodic torticollis or essential tremor. *Electroencephalography and Clinical Neurophysiology, 109*(5), 391–396.
Hordacre, B., et al. (2017). Variability in neural excitability and plasticity induction in the human cortex: A brain stimulation study. *Brain Stimulation, 10*(3), 588–595.
Huang, Y. Z., et al. (2017). Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 128*(11), 2318–2329.
Huang, Y. Z., et al. (2010). Restoration of motor inhibition through an abnormal premotor-motor connection in dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 25*(6), 696–703.
Huang, Y. Z., et al. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201–206.
Jimenez-Shahed, J., et al. (2016). GPi oscillatory activity differentiates tics from the resting state, voluntary movements, and the unmedicated parkinsonian state. *Frontiers in Neuroscience, 10*, 436.
Jinnah, H. A., Neychev, V., & Hess, E. J. (2017). The anatomical basis for dystonia: The motor network model. *Tremor and Other Hyperkinetic Movements (N Y), 7*, 506.
Johnson, V., et al. (2021). Embedded adaptive deep brain stimulation for cervical dystonia controlled by motor cortex theta oscillations. *Experimental Neurology, 345*, 113825.
Jung, N. H., et al. (2013). Impaired induction of long-term potentiation-like plasticity in patients with high-functioning autism and Asperger syndrome. *Developmental Medicine and Child Neurology, 55*(1), 83–89.
Jurkiewicz, M. T., et al. (2006). Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *Neuroimage, 32*(3), 1281–1289.
Kagi, G., et al. (2013). Sensory tricks in primary cervical dystonia depend on visuotactile temporal discrimination. *Movement Disorders: Official Journal of the Movement Disorder Society, 28*(3), 356–361.
Kaji, R., et al. (1995). Tonic vibration reflex and muscle afferent block in writer's cramp. *Annals of Neurology, 38*(2), 155–162.
Kaji, R., Bhatia, K., & Graybiel, A. M. (2018). Pathogenesis of dystonia: Is it of cerebellar or basal ganglia origin? *Journal of Neurology, Neurosurgery, and Psychiatry, 89*(5), 488–492.
Kang, J. S., et al. (2011). Deficient homeostatic regulation of practice-dependent plasticity in writer's cramp. *Cerebral Cortex, 21*(5), 1203–1212.
Kanovsky, P., et al. (2003). Abnormalities of cortical excitability and cortical inhibition in cervical dystonia evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings. *Journal of Neurology, 250*(1), 42–50.
Karabanov, A., et al. (2015a). Consensus paper: Probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. *Brain Stimulation, 8*(3), 442–454.

Karabanov, A., et al. (2015b). Consensus paper: Probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. *Brain Stimulation, 8*(5), 993–1006.
Karnath, H. O., Konczak, J., & Dichgans, J. (2000). Effect of prolonged neck muscle vibration on lateral head tilt in severe spasmodic torticollis. *Journal of Neurology, Neurosurgery, and Psychiatry, 69*(5), 658–660.
Kassavetis, P., et al. (2018). Reappraising the role of motor surround inhibition in dystonia. *Journal of the Neurological Sciences, 390*, 178–183.
Khosravani, S., et al. (2019). Laryngeal vibration as a non-invasive neuromodulation therapy for spasmodic dysphonia. *Scientific Reports, 9*(1), 17955.
Kimmich, O., et al. (2011). Sporadic adult onset primary torsion dystonia is a genetic disorder by the temporal discrimination test. *Brain, 134*(Pt 9), 2656–2663.
Kimmich, O., et al. (2014). Temporal discrimination, a cervical dystonia endophenotype: Penetrance and functional correlates. *Movement Disorders: Official Journal of the Movement Disorder Society, 29*(6), 804–811.
Koch, G., et al. (2014). Effects of two weeks of cerebellar theta burst stimulation in cervical dystonia patients. *Brain Stimulation, 7*(4), 564–572.
Kojovic, M., et al. (2011). Botulinum toxin injections reduce associative plasticity in patients with primary dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 26*(7), 1282–1289.
Kojovic, M., et al. (2013). Secondary and primary dystonia: Pathophysiological differences. *Brain, 136*(Pt 7), 2038–2049.
Kroneberg, D., et al. (2018). Motor cortical plasticity relates to symptom severity and clinical benefit from deep brain stimulation in cervical dystonia. *Neuromodulation, 21*(8), 735–740.
Latorre, A., et al. (2019). The interindividual variability of transcranial magnetic stimulation effects: Implications for diagnostic use in movement disorders. *Movement Disorders: Official Journal of the Movement Disorder Society, 34*(7), 936–949.
Latorre, A., et al. (2021). The signature of primary writing tremor is dystonic. *Movement Disorders: Official Journal of the Movement Disorder Society, 36*(7), 1715–1720.
Leis, A. A., et al. (1992). Modification of cervical dystonia by selective sensory stimulation. *Journal of the Neurological Sciences, 110*(1–2), 79–89.
Lekhel, H., et al. (1998). Postural responses to vibration of neck muscles in patients with uni- and bilateral vestibular loss. *Gait & Posture, 7*(3), 228–236.
Little, S., & Brown, P. (2014). The functional role of beta oscillations in Parkinson's disease. *Parkinsonism & Related Disorders, 20*(Suppl 1), S44–S48.
Little, S., et al. (2013). Adaptive deep brain stimulation in advanced Parkinson disease. *Annals of Neurology, 74*(3), 449–457.
Liu, X., et al. (2006). Different mechanisms may generate sustained hypertonic and rhythmic bursting muscle activity in idiopathic dystonia. *Experimental Neurology, 198*(1), 204–213.
Liu, X., et al. (2008). The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. *Brain, 131*(Pt 6), 1562–1573.
Lofredi, R., et al. (2019). Pallidal beta bursts in Parkinson's disease and dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 34*(3), 420–424.
Lopez-Alonso, V., et al. (2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimulation, 7*(3), 372–380.
Lopez-Alonso, V., et al. (2015). Intra-individual variability in the response to anodal transcranial direct current stimulation. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 126*(12), 2342–2347.
Mackay, W. A. (1997). Synchronized neuronal oscillations and their role in motor processes. *Trends in Cognitive Sciences, 1*(5), 176–183.

Mahlknecht, P., et al. (2018). Parkinsonian signs in patients with cervical dystonia treated with pallidal deep brain stimulation. *Brain, 141*(10), 3023–3034.
McClelland, V. M., et al. (2020). Abnormal patterns of corticomuscular and intermuscular coherence in childhood dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 131*(4), 967–977.
McCloskey, I. D., & Prochazka, A. (1994). The role of sensory information in the guidance of voluntary movement: Reflections on a symposium held at the 22nd annual meeting of the society for neuroscience. *Somatosensory & Motor Research, 11*(1), 69–76.
Merchant, S. H. I., et al. (2020). The role of the inferior parietal lobule in writer's cramp. *Brain, 143*(6), 1766–1779.
Meunier, S., et al. (2001). Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. *Annals of Neurology, 50*(4), 521–527.
Meunier, S., et al. (2012a). Plasticity of cortical inhibition in dystonia is impaired after motor learning and paired-associative stimulation. *European Journal of Neuroscience, 35*(6), 975–986.
Meunier, S., et al. (2012b). Plasticity of cortical inhibition in dystonia is impaired after motor learning and paired-associative stimulation. *The European Journal of Neuroscience, 35*(6), 975–986.
Miocinovic, S., et al. (2018a). Chronic deep brain stimulation normalizes scalp EEG activity in isolated dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 129*(2), 368–376.
Miocinovic, S., et al. (2018b). Cortical gamma oscillations in isolated dystonia. *Parkinsonism & Related Disorders, 49*, 104–105.
Miocinovic, S., et al. (2015). Patterns of cortical synchronization in isolated dystonia compared with parkinson disease. *JAMA Neurology, 72*(11), 1244–1251.
Molloy, F. M., et al. (2003). Abnormalities of spatial discrimination in focal and generalized dystonia. *Brain, 126*(Pt 10), 2175–2182.
Morgante, F., et al. (2011). Abnormal tactile temporal discrimination in psychogenic dystonia. *Neurology, 77*(12), 1191–1197.
Muller-Dahlhaus, J. F., et al. (2008). Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental Brain Research, 187*(3), 467–475.
Nakashima, K., et al. (1989b). An exteroceptive reflex in the sternocleidomastoid muscle produced by electrical stimulation of the supraorbital nerve in normal subjects and patients with spasmodic torticollis. *Neurology, 39*(10), 1354–1358.
Nakashima, K., et al. (1989a). Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain, 112*(Pt 3), 681–697.
Neumann, W. J., et al. (2017). A localized pallidal physiomarker in cervical dystonia. *Annals of Neurology, 82*(6), 912–924.
Panizza, M. E., Hallett, M., & Nilsson, J. (1989). Reciprocal inhibition in patients with hand cramps. *Neurology, 39*(1), 85–89.
Patel, N., et al. (2014). Alleviating manoeuvres (sensory tricks) in cervical dystonia. *Journal of Neurology, Neurosurgery, and Psychiatry, 85*(8), 882–884.
Pauletti, G., et al. (1993). Blink reflex and the masseter inhibitory reflex in patients with dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 8*(4), 495–500.
Pauls, K. A. M., et al. (2018). Dysarthria in pallidal Deep Brain Stimulation in dystonia depends on the posterior location of active electrode contacts: A pilot study. *Parkinsonism & Related Disorders, 47*, 71–75.
Pellegrini, M., Zoghi, M., & Jaberzadeh, S. (2018). Biological and anatomical factors influencing interindividual variability to noninvasive brain stimulation of the primary motor cortex: a systematic review and meta-analysis. *Reviews in the Neurosciences, 29*(2), 199–222.

Pesaran, B., et al. (2018). Investigating large-scale brain dynamics using field potential recordings: Analysis and interpretation. *Nature Neuroscience, 21*(7), 903–919.
Pierelli, F., et al. (2013). Abnormal sensorimotor plasticity in migraine without aura patients. *Pain, 154*(9), 1738–1742.
Pina-Fuentes, D., et al. (2019b). Direct comparison of oscillatory activity in the motor system of Parkinson's disease and dystonia: A review of the literature and meta-analysis. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 130*(6), 917–924.
Pina-Fuentes, D., et al. (2020). Low-frequency oscillation suppression in dystonia: Implications for adaptive deep brain stimulation. *Parkinsonism & Related Disorders, 79*, 105–109.
Pina-Fuentes, D., et al. (2019a). The characteristics of pallidal low-frequency and beta bursts could help implementing adaptive brain stimulation in the parkinsonian and dystonic internal globus pallidus. *Neurobiology of Disease, 121*, 47–57.
Pina-Fuentes, D., et al. (2018). Toward adaptive deep brain stimulation for dystonia. *Neurosurgical Focus, 45*(2), E3.
Pirio Richardson, S. (2015). Enhanced dorsal premotor-motor inhibition in cervical dystonia. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 126*(7), 1387–1391.
Pirio Richardson, S., Tinaz, S., & Chen, R. (2015). Repetitive transcranial magnetic stimulation in cervical dystonia: Effect of site and repetition in a randomized pilot trial. *PLoS One, 10*(4), e0124937.
Pohl, C., Happe, J., & Klockgether, T. (2002). Cooling improves the writing performance of patients with writer's cramp. *Movement Disorders: Official Journal of the Movement Disorder Society, 17*(6), 1341–1344.
Porcacchia, P., et al. (2019). Abnormal cerebellar connectivity and plasticity in isolated cervical dystonia. *PLoS One, 14*(1), e0211367.
Priori, A., et al. (1995). Physiological effects produced by botulinum toxin treatment of upper limb dystonia. Changes in reciprocal inhibition between forearm muscles. *Brain, 118*(Pt 3), . 801–7.
Quartarone, A., et al. (2003). Abnormal associative plasticity of the human motor cortex in writer's cramp. *Brain, 126*(Pt 12), 2586–2596.
Quartarone, A., et al. (2008). Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(9), 985–990.
Quartarone, A., et al. (2005). Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia. *Brain, 128*(Pt 8), 1943–1950.
Quartarone, A., et al. (2000). Short latency trigemino-sternocleidomastoid response in muscles in patients with spasmodic torticollis and blepharospasm. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 111*(9), 1672–1677.
Quartarone, A., Siebner, H. R., & Rothwell, J. C. (2006). Task-specific hand dystonia: Can too much plasticity be bad for you? *Trends in Neurosciences, 29*(4), 192–199.
Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *The Journal of Physiology, 588*(Pt 13), 2291–2304.
Ridding, M. C., et al. (1995). Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *Journal of Neurology, Neurosurgery, and Psychiatry, 59*(5), 493–498.
Rome, S., & Grunewald, R. A. (1999). Abnormal perception of vibration-induced illusion of movement in dystonia. *Neurology, 53*(8), 1794–1800.
Rosenkranz, K., et al. (2009). Regaining motor control in musician's dystonia by restoring sensorimotor organization. *The Journal of Neuroscience, 29*(46), 14627–14636.

Sadnicka, A., et al. (2022a). A critical investigation of cerebellar associative learning in isolated dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 37*(6), 1187–1192.
Sadnicka, A., et al. (2014). A reflection on plasticity research in writing dystonia. *Movement Disorders: Official Journal of the Movement Disorder Society, 29*(8), 980–987.
Sadnicka, A., et al. (2022b). Intact finger representation within primary sensorimotor cortex of musician's dystonia. *Brain*.
Sadnicka, A., et al. (2017). Mind the gap: Temporal discrimination and dystonia. *European Journal of Neurology: the Official Journal of the European Federation of Neurological Societies, 24*(6), 796–806.
Sanes, J. (1990). Motor representations in deafferented humans: A mechanism for disordered movement performance. In M. Jeannerod (Ed.). *Attention and performance Xiii*. Psychology Press.
Sanger, T. D., Tarsy, D., & Pascual-Leone, A. (2001). Abnormalities of spatial and temporal sensory discrimination in writer's cramp. *Movement Disorders: Official Journal of the Movement Disorder Society, 16*(1), 94–99.
Sattler, V., et al. (2014). Does abnormal interhemispheric inhibition play a role in mirror dystonia? *Movement Disorders: Official Journal of the Movement Disorder Society, 29*(6), 787–796.
Scheller, U., et al. (2019). Pallidal low-frequency activity in dystonia after cessation of long-term deep brain stimulation. *Movement Disorders: Official Journal of the Movement Disorder Society, 34*(11), 1734–1739.
Schwingenschuh, P., et al. (2011). The blink reflex recovery cycle differs between essential and presumed psychogenic blepharospasm. *Neurology, 76*(7), 610–614.
Sedov, A., et al. (2019). The role of pallidum in the neural integrator model of cervical dystonia. *Neurobiology of Disease, 125*, 45–54.
Shaikh, A. G., et al. (2016). Cervical dystonia: A neural integrator disorder. *Brain, 139*(Pt 10), 2590–2599.
Sharott, A., et al. (2008). Is the synchronization between pallidal and muscle activity in primary dystonia due to peripheral afferance or a motor drive? *Brain, 131*(Pt 2), 473–484.
Siebner, H. R., et al. (1999). Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology, 52*(3), 529–537.
Silberstein, P., et al. (2003). Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. *Brain, 126*(Pt 12), 2597–2608.
Sohn, Y. H., & Hallett, M. (2004). Disturbed surround inhibition in focal hand dystonia. *Annals of Neurology, 56*(4), 595–599.
Sondergaard, R. E., et al. (2021). Cerebellar brain inhibition is associated with the severity of cervical dystonia. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*.
Stefan, K., et al. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123*(Pt 3), 572–584.
Stinear, C. M., & Byblow, W. D. (2004). Elevated threshold for intracortical inhibition in focal hand dystonia. *Movement Disorders, 19*(11), 1312–1317.
Swann, N. C., et al. (2016). Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease. *The Journal of Neuroscience, 36*(24), 6445–6458.
Tang, J. K., et al. (2007). Changes in cortical and pallidal oscillatory activity during the execution of a sensory trick in patients with cervical dystonia. *Experimental Neurology, 204*(2), 845–848.
Tempel, L. W., & Perlmutter, J. S. (1990). Abnormal vibration-induced cerebral blood flow responses in idiopathic dystonia. *Brain, 113*(Pt 3), 691–707.

Terranova, C., et al. (2013). Impairment of sensory-motor plasticity in mild Alzheimer's disease. *Brain Stimulation, 6*(1), 62–66.
Thenaisie, Y., et al. (2021). Towards adaptive deep brain stimulation: Clinical and technical notes on a novel commercial device for chronic brain sensing. *Journal of Neural Engineering, 18*(4).
Thompson, J. A., et al. (2014). Clinical implications of local field potentials for understanding and treating movement disorders. *Stereotactic and Functional Neurosurgery, 92*(4), 251–263.
Tijssen, M. A., Marsden, J. F., & Brown, P. (2000). Frequency analysis of EMG activity in patients with idiopathic torticollis. *Brain, 123*(Pt 4), 677–686.
Tinazzi, M., et al. (2004). Timing of tactile and visuo-tactile events is impaired in patients with cervical dystonia. *Journal of Neurology, 251*(1), 85–90.
Tisch, S., & Limousin, P. (2020). Neurophysiological insights in dystonia and its response to deep brain stimulation treatment. *Experimental Brain Research, 238*(7–8), 1645–1657.
Tisch, S., et al. (2006). Changes in forearm reciprocal inhibition following pallidal stimulation for dystonia. *Neurology, 66*(7), 1091–1093.
Tolosa, E., Montserrat, L., & Bayes, A. (1988). Blink reflex studies in focal dystonias: Enhanced excitability of brainstem interneurons in cranial dystonia and spasmodic torticollis. *Movement Disorders: Official Journal of the Movement Disorder Society, 3*(1), 61–69.
Tremblay, S., et al. (2016). Non-invasive brain stimulation as a tool to study cerebellar-M1 interactions in humans. *Cerebellum Ataxias, 3*, 19.
Valls-Sole, J., Tolosa, E. S., & Ribera, G. (1991). Neurophysiological observations on the effects of botulinum toxin treatment in patients with dystonic blepharospasm. *Journal of Neurology, Neurosurgery, and Psychiatry, 54*(4), 310–313.
Valls-Sole, J., et al. (1992). Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalography and Clinical Neurophysiology, 85*(6), 355–364.
Wang, D. D., et al. (2018). Pallidal deep-brain stimulation disrupts pallidal beta oscillations and coherence with primary motor cortex in Parkinson's disease. *The Journal of Neuroscience, 38*(19), 4556–4568.
Wang, D. D., et al. (2016). Subthalamic local field potentials in Parkinson's disease and isolated dystonia: An evaluation of potential biomarkers. *Neurobiology of Disease, 89*, 213–222.
Weise, D., et al. (2006). The two sides of associative plasticity in writer's cramp. *Brain, 129*(*Pt 10*), 2709–2721.
Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimulation, 7*(3), 468–475.
Witham, C. L., et al. (2011). Contributions of descending and ascending pathways to corticomuscular coherence in humans. *The Journal of Physiology, 589*(Pt 15), 3789–3800.
Yokochi, F., et al. (2018). Resting-state pallidal-cortical oscillatory couplings in patients with predominant phasic and tonic dystonia. *Frontiers in Neurology, 9*, 375.
Yoneda, Y., et al. (2000). Abnormal perception of the tonic vibration reflex in idiopathic focal dystonia. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies, 7*(5), 529–533.
Zhu, G., et al. (2018). Characteristics of globus pallidus internus local field potentials in hyperkinetic disease. *Frontiers in Neurology, 9*, 934.
Zhu, G. Y., et al. (2020). Characteristics of globus pallidus internus local field potentials in generalized dystonia patients with TWNK mutation. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 131*(7), 1453–1461.
Zhu, Y., Mahnan, A., & Konczak, J. (2021). Vibro-tactile stimulation as a non-invasive neuromodulation therapy for cervical dystonia: A case study. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2021*, 6314–6317.