Delineating the electrophysiological signature of dystonia.

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Abstract

Over the last 30 years, the concept of dystonia has dramatically changed, from being considered a motor *neurosis,* to a pure basal ganglia disorder, to finally reach the definition of a network disorder involving the basal ganglia, cerebellum, thalamus, and sensorimotor cortex. This progress has been possible thanks to the collaboration between clinicians and scientists, and the development of increasingly sophisticated electrophysiological techniques able to non-invasively investigate pathophysiological mechanisms in humans. This review is a chronological *excursus* of the electrophysiological studies that laid the foundation for the understanding of the pathophysiology of dystonia and delineated its electrophysiological signatures. Evidence for neurophysiological abnormalities are grouped according to the neural system involved, and a unifying theory, bringing together all the hypothesis and evidence provided to date, is proposed at the end.

Introduction

At the beginning of the 20th century, under the influence of the recent development of the psychoanalytic theory, neurology and psychiatry evolved into separate disciplines: the former focussed on brain diseases with a recognizable organic component, while the latter on pathologic conditions thought to originate from the mind. The subtle boundary between the two favoured the development of conflicting theories about aetiology and pathogenesis of certain disorders. This is true for dystonia which, at the time of the schism, was retained amongst organically unaligned or functional conditions and then classified as a motor *neurosis* (Newby et al. 2017). David Marsden, with his brilliant intuition, removed dystonia from this unclear classification and recognized it as a basal ganglia (BG) disorder. Marsden's concept was based on two main arguments: 1) the clinical observation of typical dystonic pattern in the context of damage to the BG and 2) the evidence of physiological abnormalities by using non-conventional electrophysiologic techniques, which pointed towards the loss of normal BG inputs onto spinal and brainstem interneurons (Marsden and Rothwell 1987). It was, in fact, the implementation of new neurophysiological investigations and the encounter between a great clinician and scientist, David Marsden, and an enthusiastic physiologist, John Rothwell, that laid the foundation for the understanding of the pathophysiology of dystonia.

In this review we chronologically retraced the steps that, over 30 years, have led to the understanding of the pathophysiological mechanisms causing dystonia, investigated with electrophysiological techniques. To facilitate reading, evidence for neurophysiological abnormalities are grouped according to the neural system involved. We conclude discussing the most recent concepts on the pathophysiology of dystonia and by proposing a unifying theory that brings together all the hypotheses and evidence provided to date.

Spinal cord and brainstem

The classical electromyographic (EMG) pattern of dystonia often consists of a simultaneous activation of agonist and antagonists muscles, described as co-contraction (Rothwell et al. 1983); therefore, abnormalities in the spinal cord circuitry were first considered as possible pathophysiological hallmarks of dystonia. Stretch reflex, H-reflex, reciprocal inhibition of H-reflex and ballistic movements at a single joint were therefore investigated. In summary, the results of these early studies showed increase in duration of both long-latency stretch reflex and the first burst of agonist EMG activity in ballistic arm movements (Rothwell et al. 1983; Marsden and Rothwell 1987), reduction in the amount of presynaptic inhibition in the spinal cord (Rothwell et al. 1988; Nakashima et al. 1989), and overflow

of activity to muscle not directly involved in the action during voluntary and reflex movements (Rothwell et al. 1983). These results suggest a general lack of inhibition in both reflex and voluntary movements in dystonia, likely due to defective descending control on spinal cord (Marsden and Rothwell 1987; Sheehy et al. 1988). Similar conclusions have been drawn studying brainstem reflexes in patients with different forms of dystonia. Although the reflex arcs and the neural structures which mediate the blink and corneal reflexes were considered to be intact, one study showed an abnormal excitatory drive to the facial motoneurons and interneurons mediating facial reflexes in patients with blepharospasm and oromandibular dystonia (Berardelli et al. 1985). Also, the recovery cycle of the blink reflex, which assesses brainstem excitability, was found to be abnormal, due to reduced inhibition of the R2 component, mainly in patients affected by blepharospasm (Berardelli et al. 1985; Schwingenschuh et al. 2011), but also in segmental/generalized dystonia or torticollis, and not in those with focal arm dystonia; this suggested that the extent of dystonia and its proximity to the cranial muscles might be important in determining abnormal interneuronal function (Nakashima et al. 1990).

Basal ganglia

Although interneuronal abnormalities were observed at the spinal cord and brainstem level, the primary cause of dystonia was still thought to reside in the BG (Marsden and Rothwell 1987). This hypothesis came from the observation that secondary dystonia is most often due to lesions of the BG or thalamus and that it is frequently part of syndromes which entail BG pathology (Marsden and Rothwell 1987). According to the first model proposed to explain the involvement of BG in dystonia, the direct pathway is hyperfunctional, while the indirect one is hypofunctional, as a consequence of reduced activity along putamen-external globus pallidus (GPe) connections and increased inhibition of the subthalamic nucleus (STN) and internal globus pallidus (GPi) by the GPe; this abnormalities would result in reduced inhibition of the thalamus and increased excitation of the cortex (DeLong 1990; Mitchell et al. 1990). Invasive human studies have shed some light on the neuronal activity of BG in dystonia. Single-cell recording in patients undergoing functional neurosurgery demonstrated several abnormalities in the activity of GPe and GPi neurons, consisting in a decreased discharge rate (Vitek 2002; Starr et al. 2005) and overall irregular firing (Vitek et al. 1999; Hutchison et al. 2003; Starr et al. 2005; Vitek et al. 2011). These changes contribute to dystonia, as confirmed by the fact that deep brain stimulation (DBS) improves dystonia by restoring more physiological firing patterns in the GPi (Barow et al. 2014). Another electrophysiological abnormality in the BG of dystonic patients is represented by an excess of synchronized low-frequency (4-10Hz) activity (Silberstein et al. 2003). The finding of high coherence between this abnormal oscillations and involuntary EMG activity in dystonic muscles suggested that excessive low-frequency oscillatory activity in BG is causally involved in

dystonia (Chen et al. 2006; Neumann et al. 2015). Abnormal bursting and oscillatory activity might not be specific for dystonia, as similarities have been observed with Parkinson's disease (PD); however, these would be superimposed on a low background discharge rate in dystonia, whereas the latter would be higher in PD (Starr et al. 2005). It is to note that a decrease in BG output in dystonia has not always been confirmed (Hutchison et al. 2003), likely due to different dystonia phenotypes studied; it has been proposed that the final common pathway linking the different forms of dystonia needs to be found in cortical processing (Wichmann and Dostrovsky 2011).

Motor cortex

The BG are part of a group of parallel closed circuits that originate in the cerebral cortex, traverse the thalamus, and then project back to the cortical areas of origin (DeLong 1990). Cortical motor areas are one of the primary projection target of the BG (i.e. the motor loop) and the concept of a possible involvement of the inhibitory circuits within the primary motor cortex in dystonia was thought to be reasonable. Moreover, the introduction of transcranial magnetic stimulation (TMS) encouraged researchers to non-invasively explore cortical excitability in humans.

In the pioneering study of Ridding et al. (1995), paired-pulse TMS, consisting of a subthreshold conditioning stimulus preceding a suprathreshold test stimulus, at an interstimulus interval (ISI) of 1-6 ms, was applied over the primary motor cortex (M1) of patients with focal task specific dystonia, to investigate M1 inhibitory intracortical circuits (Ridding et al. 1995b). Dystonic patients showed significant less inhibition compared to healthy controls. This paradigm is now known to be mediated by GABAa receptors and is called short-interval intracortical inhibition (SICI) (Chen et al. 2008). Later studies strengthened this result and showed that reduced intracortical inhibition not only contributes to dystonia, but also predispose its development. For instance, both manifesting and non-manifesting gene carriers of the most common form of generalised dystonia (DYT1 gene mutation) had reduced SICI and shortened cortical silent period (SP)(Edwards et al. 2003), which is another TMS measure of intracortical inhibition likely mediated by GABAb receptors (Chen et al. 2008). SICI was found to be reduced also in patients with functional dystonia; this abnormality was considered to be secondary to the prolonged abnormal posture of the affected body part (Espay et al. 2006). However, this would not explain the presence of reduced SICI in non-manifesting DYT1 carries (Edwards et al. 2003) and in unaffected body parts of suspected functional patients with fixed dystonia (Avanzino et al. 2008). Therefore, the role of SICI in dystonia is still not completely clear, but it is possible that it predisposes to the development of a dystonic phenotype and that additional factors (for instance genetic or psychological) are needed to develop the symptoms (Edwards et al. 2003; Latorre et al. 2019). Long-interval intracortical inhibition, a measure believed to involve GABAb receptor neurotransmission, can

be normal in dystonia at rest (Meunier et al. 2012), but reduced during movements (Chen et al. 1997). Another measure of inhibition, namely interhemispheric inhibition (IHI), was found to be reduced in dystonia, especially in those with mirror phenomenon (Beck et al. 2009; Nelson et al. 2010; Sattler et al. 2014). IHI refers to the inhibitory control of one brain hemisphere over the other, mediated by transcallosal fibres, and represent a marker of bimanual control; in dystonia the abnormal IHI may contribute to the overflow of muscle activities and mirror dystonia.

One of the distinguished features of dystonia is that it can affect highly skilled individuals (such as musicians) as a possible result of maladaptive reorganisation of neuronal structures caused by overtraining. It is therefore possible that plastic cortical changes may reinforce an intrinsic deficit and trigger symptoms onset in predisposed subjects (Rothwell and Huang 2003). In fact, dystonia caused by excess practice does not occur in everyone, but it has been proposed to occur only in individuals with possible pre-existing abnormalities in cortical function (Quartarone et al. 2006). This is supported, for instance, by the evidence that patients with focal hand dystonia, despite unilateral symptoms, show bilateral abnormalities in the somatosensory and motor systems (as demonstrated in behavioural (Fiorio et al. 2003), magnetoencephalography (Meunier et al. 2001), MRI (Garraux et al. 2004) and TMS (Ridding et al. 1995a) studies); since these dysfunctions occur in body areas not affected by dystonia, they are likely to reflect a primary brain dysfunction. Sensorimotor cortical plasticity was found abnormally increased in writer's cramp using paired associative stimulation (PAS), a TMS technique able to induce long-term potentiation (LTP)-like phenomena (Quartarone et al. 2003). The cause of this dysfunction was assumed to be related to the mechanisms that counteract the destabilizing influence of synaptic plasticity and, hence, stabilize neural activity within a physiologically meaningful range, i.e. homeostatic plasticity. To confirm this hypothesis a method to probe homeostatic plasticity was used in writer's cramp patients (Quartarone et al. 2005). It consisted of applying transcranial direct current stimulation (tDCS), which can facilitate or inhibit motor excitability according to its direction (i.e. anodal and cathodal), to precondition the response of the motor cortex to a subsequent period of inhibitory low-frequency repetitive transcranial magnetic stimulation (rTMS). Differently from healthy subjects, rTMS induced no consistent changes in corticospinal excitability after preconditioning by either form of tDCS in patients, indicating a loss of the normal homeostatic response pattern.

Abnormal synaptic plasticity was therefore proposed to be the key mechanism that underlies the development of the symptoms. As a matter of fact, while other electrophysiological measures (like intracortical inhibition and sensory abnormalities) are similarly abnormal in manifesting and non-manifesting individuals with inherited primary dystonia (DYT1 gene mutation), susceptibility to plastic change in response to TMS stimuli appears to differentiate such individuals (Edwards et al. 2006). Also,

abnormal plasticity distinguishes organic from functional dystonia (Quartarone et al. 2009). Accordingly, although reduced inhibition and possibly sensory abnormalities predispose to the development of dystonia, maladaptive plasticity seems to be more closely linked to the clinical emergence (Edwards et al. 2006).

A direct consequence of these observations is that synaptic plasticity modulation could be potentially used to treat dystonia. For instance, it has been shown that reducing cortical excitability in patients with dystonia using rTMS can produce corresponding changes in abnormal spinal motor output (Huang et al. 2004). Interestingly, DBS to the GPi, an effective treatment for primary dystonia, has its maximum clinical effect weeks or months after surgery, differently from PD, in which it takes only hours. This slowly progressive change might be due to a process of neural reorganization. In fact, while after DBS, SICI, reciprocal inhibition and blink reflex inhibition progressively normalize, in parallel to the clinical improvement, synaptic plasticity has a different course: it is virtually abolished at one month and then increases towards normal values over the following months (Ruge et al. 2011b). This implies that, when DBS is turned on, it rapidly removes abnormal BG signals (resulting in absent response to plasticity-inducing paradigms), but it takes time to cancel the persisting ''memory'' of abnormal movement pattern and to restore more normal patterns of activity. This observation suggests that plasticity determines the long-term therapeutic effects of DBS in dystonia. Accordingly, it was demonstrated that DBS induces long-term neural reorganization in the motor system, with a significant variation among patients depending on the plastic response (Ruge et al. 2011a). A good plastic response reflects a longer-term retention of normal movement patterns after treatment.

Somatosensory cortex

Since dystonia was recognized as a motor disease, clinicians and researchers have always been fascinated by a peculiar phenomenon: the relief of dystonic activity by touching the body segment affected by it. This phenomenon is known as "sensory trick" or "geste antagoniste". Such observation suggests that dystonia is influenced by tactile and proprioceptive sensory inputs and, if so, that abnormal muscle activity might be controlled by modulating afferent information. In one of the early studies on writer's cramp it was shown that increasing and decreasing muscle spindle activity by means of vibration or intramuscular injection of lidocaine, resulted respectively in dystonic movements of the limbs and dystonia suppression (Kaji et al. 1995). Despite the results confirmed that muscle afferents may contribute in producing dystonic posture, to understand the role of proprioceptive input additional data is required. Conversely, more attention has been given to the mechanisms that underlie sensory information processing and sensorimotor integration in dystonia. For instance, it was found that patients with writer's cramp lack the normal gating of afferent

information due to a disordered central control of afferent inputs (Murase et al. 2000). Moreover, an abnormal somatotopic digital representation in the primary somatosensory cortex (S1) has been demonstrated in focal hand dystonia(Bara-Jimenez et al. 1998; Elbert et al. 1998; Bara-Jimenez et al. 2000; Meunier et al. 2001), but it is still not clear whether this finding represents a primary pathological process of dystonia or is a consequence of other phenomena, such as abnormal sensory inputs/dedifferentiation of sensory feedback from the affected body part, or repetitive dystonic movements .

The principal evidence of the sensory involvement in dystonia is that of abnormal tactile information processing in both the spatial and temporal domains (Tinazzi et al. 2006; Conte et al. 2019). Indeed, at a behavioural level, the most consistent sensory abnormality of dystonia is increased somatosensory temporal discrimination threshold (STDT), a measure of the acuity of temporal processing of sensory information defined as the shortest interval at which two tactile stimuli delivered to the same body part can be recognized as temporally separated (Conte et al. 2019). Increased STDT in dystonia is related to reduced activity of inhibitory circuits within S1 (as demonstrated by the correlation between high STDT and reduced suppression of somatosensory evoked potentials recovery cycle and reduced area of high-frequency oscillations), and assumed to be the result of specific abnormalities within circuits processing the temporal aspects of afferent inputs (Antelmi et al. 2017). STDT is not ameliorated by GPi DBS (Sadnicka et al. 2013), supporting the hypothesis that sensory abnormalities in dystonia might reflect the functional derangement of a network involving BG-thalamus-sensorimotor cortex.

The idea of reversing dystonia's pathophysiological abnormalities by inducing plastic changes was also applied to the somatosensory cortex. With the intent of enhancing the defective inhibitory mechanisms in the sensorimotor cortex, and therefore normalise the processing of the somatosensory input and possibly improve symptoms, a peripheral non-invasive stimulation, known as high-frequency repetitive somatosensory stimulation (HF-RSS), was applied in dystonic patients (Erro et al. 2018). HF-RSS is a patterned electric stimulation applied to the skin through surface electrodes, which has been demonstrated to enhance intracortical inhibitory mechanisms within S1 and M1 (Erro et al. 2016; Rocchi et al. 2017). These effects are a considered a form of short-lasting synaptic plasticity. Patients with cervical dystonia, however, showed a paradoxical response to HF-RSS, as it reduced, instead of increasing, inhibition within the sensorimotor cortex. According to the authors, this reverse plastic response was likely due to abnormal homeostatic inhibitory plasticity within the sensorimotor cortex (Erro et al. 2018).

Cerebellum

Reports of cerebellar lesions causing dystonia have raised the question of a cerebellar involvement in its pathophysiology and encouraged researcher to investigate it further. The two principal cerebellar functions studied in dystonia are associative motor learning and motor adaptation.

Eyeblink classic conditioning (EBCC) is an associative learning protocol in which a sound is conditioned to provoke an eyeblink in the absence of the unconditioned stimulus, that is an electric shock to the supraorbital nerve. The EBCC is related to the integrity of the olivo-cerebellar circuit and relies on integration of afferent information at the level of Purkinje cells and deep cerebellar nuclei (Monaco et al. 2018). EBCC is impaired in patients with primary focal dystonia (Teo et al. 2009; Kojovic et al. 2013), but it is normal in patients with generalised and segmental inherited dystonia caused respectively by DYT1 and DYT6 gene mutation (Sadnicka et al. 2015). This discrepancy might suggest that the cerebellar contributions differs according to the form of dystonia. However, Antelmi and coworkers pointed out that these conflicting results might be due to the fact that focal forms of dystonia are often associated with tremor, which could have been overlooked in early studies (Antelmi et al. 2016). The authors demonstrated, in fact, that EBCC segregate with tremulous dystonia, whereas dystonic patients without tremor show normal conditioning. In conclusion, it is possible that tremor in dystonia may be linked to dysfunction in cerebellar circuits mediating EBCC.

The ability to overcome movement perturbations caused by novel environment or altered sensory feedback, when performing a motor task, is called motor adaption and depends on cerebellar function. Motor adaptation is not impaired in patients with cervical dystonia, when assessed by visual and proprioceptive sensorimotor integration tasks, regardless the presence of tremor (Sadnicka et al. 2014b). Associative learning and motor adaptation are distinct functions of the cerebellum, expressive two different forms of motor learning. This might explain the different results obtained, however, to clarify their involvement in dystonia pathophysiology more data are needed.

Finally, minor evidence on functional impairment of cerebellar modulation on the motor cortex in dystonia comes from the observation of absent cerebellar-brain-inhibition, measured by TMS, in dystonic patients (Brighina et al. 2009).

Conclusion: the network model

Thanks to the combination of careful clinical observation and detailed electrophysiological investigations, in about 3 decades, our concept of dystonia has radically changed, and its pathophysiological features have been delineated (Table 1). Initially, dystonia was thought to be a psychiatric disorder, but evidence of reduced inhibition at different levels of the central nervous system, increased sensorimotor synaptic plasticity and abnormalities in BG neuronal firing have supported the idea of dystonia being a BG disorder. Surprisingly, later studies have highlighted that

systems other than motor, like somatosensory pathways and cerebellum, are involved in its pathophysiology. This body of evidence suggests that dystonia does not result from dysfunction of a single brain region, but most likely from the dysfunction of a network (Jinnah et al. 2017; Balint et al. 2018). This explains why it is so difficult to identify a single pathological locus in dystonia and is in line with evidence that secondary dystonia can be caused by lesions in BG, as well as other structures, in particular the thalamus, brainstem and cerebellum. The network model posits that all subtypes of dystonia result from a network disorder that includes the BG, cerebellum, thalamus, and sensorimotor cortex (Figure 1); however, the precise role and the relevance of each component and the distribution of brain changes have not yet been elucidated. According to the model, dystonia can be produced by a single or multiple nodes dysfunction, in addition to an abnormal interplay among the nodes (Jinnah et al. 2017). The cerebellum seems to have a major role in this regard, as confirmed by animal studies (Quartarone et al. 2019). Indeed, the cerebellum relays proprioceptive information to M1 and contributes to analysis of its spatial and temporal aspects; this processing is deranged in dystonia (Quartarone et al. 2019). Despite this notion being established, electrophysiological data on cerebellar dysfunction in dystonia are still inconclusive, likely because of technical limitations and difficulty of obtaining direct evidence of cerebellar activity in humans.

Considering the network model, it is plausible that the various forms of dystonia (e.g. focal, generalised, and task-specific) reflect derangement at different levels of the network. This might explain the incongruent results among studies investigating patients with different clinical manifestations. Another explanation of this inconsistency may reside in a more complex matter. In recent studies, the "canonical" findings of dystonia, such as reduced inhibition and increased plasticity, have been questioned, giving therefore further importance to the network model. For instance, in some studies SICI has been found to be normal (Kojovic et al. 2013; Ganos et al. 2017; Govert et al. 2020) and others have shown a variable response to plasticity protocols in patients with dystonia (Sadnicka et al. 2014a). The lack of reproducibility of some results can be attributed to the different reliability of the TMS measures, but the interindividual variability to plasticity-inducing paradigm needs also to be taken into account (Latorre et al. 2019). Nevertheless, while to consider some of the most common electrophysiological abnormalities found in dystonia simply as disease "tags" would be overly simplistic, there is no doubt they can help us to draw inferences on the mechanisms causing dystonia (Latorre et al. 2019). In the light of the data and speculations offered here, a unifying theory for dystonia, supported by the network model theory, might be tempted (Conte et al. 2019). Reduced inhibition, as demonstrated by reliable measures such as spinal reciprocal inhibition and blink reflex inhibition, could destabilise circuits' control and therefore cause excess activity, that induces dystonic muscle contraction. This is reinforced by deranged processing of the

somatosensory input, as supported by reduced somatosensory intracortical inhibition, that may contribute to scarce spatial and temporal discrimination and abnormal sensorimotor integration. In an otherwise normal system, these changes might be compensated; however, the instability of the plasticity control mechanisms might fail in their intent to counteract the excitability imbalance, eventually leading to the expression of dystonia (Figure 1). Although the cerebellum is certainly involved in this network dysfunction, it is still not completely clear what its role in humans is.

In conclusion, with electrophysiology we have been able to establish the pathophysiological basis of this fascinating disorder; not only to fulfil our genuine curiosity on its underlying mechanisms but also with the intent to open very promising treatment scenarios.

Table 1. Electrophysiological characteristics of dystonia

BRC: blink recovery cycle, CBI: cerebellar-brain-inhibition EBCC: eyeblink classic conditioning, GPi/e: internal/external globus pallidus, HF-RSS: high-frequency repetitive somatosensory stimulation, HFO: high-frequency oscillations, IHI: interhemispheric inhibition, RI: reciprocal inhibition, rTMS: repetitive transcranial magnetic stimulation, S1: primary somatosensory cortex, SEP: somatosensory evoked potentials, SICI: short-interval intracortical inhibition, SP: silent period, STDT: somatosensory temporal discrimination threshold, tDCS: transcranial direct current stimulation, TVR: tonic vibration reflex.

Figure 1. Representation of the pathophysiology of dystonia according to the network model

The nodes of the network are highlighted with blue ovals and connected by blue arrows (which represent functional, rather than anatomical, connections). A schematic explanation of a unifying theory for dystonia, as discussed in the text, is offered in the boxes.

M1: primary motor cortex, S1: primary somatosensory cortex

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