Deep brain stimulation and dystonia: mechanisms of efficacy and advances in our understanding of dystonia pathogenesis

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Introduction

The term 'dystonia' was first used in 1911 by Hermann Oppenheim to describe a movement disorder characterised by involuntary sustained muscle contractions, abnormal postures and repetitive, twisting movements. The nature of the disorders grouped under this heading is heterogeneous, and the term may refer to a syndrome or a secondary symptom of another condition. Three methods of classification are used: by age of onset; by body part affected; and by aetiology (1).

Despite the discovery of hereditary forms of dystonia (with genetic mutations identified in 19 loci of 10 genes so far - see (2) for an up-to-date discussion), the pathogenesis of primary idiopathic dystonia is not fully understood. Numerous studies suggest that a loss of inhibition at all levels of the CNS is a key feature (3). Maladaptive CNS plasticity (4) and disordered basal ganglia somatotopy (5) have also been demonstrated. Moreover, patients with dystonia also exhibit abnormalities of sensory processing (6–8), including raised temporal discrimination thresholds (TDTs); conceptually, the link between sensory and motor abnormalities may be one of decreased surround inhibition, leading to both an inability to execute targeted movements and reduced sensory saliency in discrimination tasks (9). Dysfunctional reorganization of synaptic connectivity in response to sensory input (in particular repetitive input, in the case of musician's dystonia or writer's cramp) could manifest in an abnormal motor output, with excessive activation of motor regions, overflow of movement and co-contraction of agonist and antagonist muscles. Excess plasticity could enhance the process of feedback reinforcement in these patients and lead to formation and storage of aberrant motor patterns.

There are several treatment options, depending on the type of dystonia, although their success is variable (1). Botulinum toxin injections are very effective in some focal dystonias, and anticholinergic drugs are the most commonly prescribed pharmacological agent. Surgical treatment of dystonia used to consist of pallidotomy or thalamotomy, radiofrequency-induced lesions of the posteroventral globus pallidus internal (GPi) segment or thalamus; since the late 1990s, however, this has been almost entirely replaced by deep brain stimulation (DBS) of these structures, usually of the pallidum. Patient improvement has been reported to be as high as 80-90% in primary dystonia and is sustained at long-term follow up. The surgery is most effective in patients with mobile generalized, segmental or refractory cervical dystonia, much less so in degenerative dystonias or those due to structural brain damage.

The mechanism by which pallidal stimulation mediates its effects is unclear. Traditional 'rate' models of dystonia considered the basal ganglia to be hypoactive in their output, with decreased pallidal inhibition of the thalamus leading to unwanted movement (dyskinesia or hyperkinesia). The beneficial effects of pallidotomy meant that this model was no longer tenable: instead of worsening the dystonia (as one would expect following an even greater reduction of GPi activity), it led to a dramatic improvement.

Neuronal activity in the basal ganglia in dystonia

In healthy subjects, pallidal neurons are tonically active in the absence of inhibitory striatal input and fire at steady high rates (10). The development of DBS has allowed for the unique opportunity of obtaining electrophysiological recordings from the brains of patients with dystonia. These revealed reduced mean GPi neuronal firing rates in dystonia (11), which was consistent with models of hypoactive GPi output. Additionally, GPi neurons were shown to exhibit irregular patterns of activity, with erratically clustered discharges separated by long pauses, and these have been linked to dystonic muscle contractions (12).

Yet low firing rates are not a consistent finding (13) and it is probable that data discrepancies might be due to different pathogenic mechanisms underpinning different forms of dystonia.

Local field potential (LFP) recordings from the basal ganglia of patients with Parkinson's or dystonia who have undergone functional neurosurgery have revealed oscillatory LFP activity that can broadly be divided, according to frequency, into three bands: <8, 8-30, >60 Hz (14). It has been demonstrated that, compared with PD patients, temporal patterns of synchronized neuronal activity in dystonia are characterised by increased power in 4-10 Hz band and decreased activity in the 13-30 Hz band (15). Dystonic electromyographic activity has been shown to be coherent with pallidal LFP in the 3-10 Hz range (12), and the intensity of dystonic contraction found to correlate with the amplitude of 3-10 Hz LFP activity (16,17).

The noisy signal hypothesis posits that these uncontrolled increases in synchronization of low-frequency oscillations might 'limit the coding abilities of neuronal populations' and prevent the transmission of information via neuronal firing rates, thus interfering with voluntary movement (14). Assuming that the LFPs recorded represent synchronised activity of neurons that is focally generated, and that what is observed is pathological or at least some amplification of the normal physiological response, it would appear that LFP recordings point to the importance of abnormal patterns, as well as firing rate, of basal ganglia activity.

Interestingly, the geste antagoniste (a sensory trick involving a particular movement/position that can alleviate dystonic symptoms in some patients) has been shown to induce desynchronization in 6-8 and 13-30 Hz bands, lending support to the theory that synchronized low-frequency oscillatory activity is closely associated with dystonic movement, since disruption of this synchronized activity (mediated by sensory input) results in temporary relief (16).

Perhaps, however, it is too simplistic to focus on increased synchronization in one frequency band - dystonic contractions might reflect more subtle changes in the balance between akinetic beta (13-30 Hz) and prokinetic gamma (30-100 Hz) activity (18). Animal models suggest a link between low levels of beta LFP activity and dyskinesias; perhaps 'disproportionate attenuation in the beta band' leads to 'inadequate suppression of unwanted motor programs' (18). The significance of finely-tuned gamma activity in the basal ganglia and thalamus is now being explored in a number of movement disorders, including dystonia; although beyond the scope of this essay, the potential link between gamma LFPs and attention is fascinating in the context of recent theories related to the role of excessive internal attention in generating dystonic movements (19).

Yet the question of whether recorded LFPs reflect activity intrinsic to the basal ganglia or are the result of activity elsewhere in the brain remains to be elucidated. Recently it was found that recorded LFP oscillations in the 8-20 Hz band in dystonia only correlate with ~ 10% GPi neuronal firing, and most of these neurons failed to display significant beta oscillations (20). The authors hypothesise that increases in power in these LFP spectra could represent the manifestation of dystonic symptoms rather than being a pathogenic mechanism per se.

Mechanism of DBS

DBS is only an effective treatment at high frequency, usually >100 Hz, and is delivered in continuous trains of short duration cathodic stimuli. It is assumed that DBS mainly affects large axons of projection neurons and GPi efferents; antidromic activation of afferent terminals should also be considered (21). Because of the similar effects of DBS to pallidal lesions, it was initially argued that DBS works by inhibiting GPi output, eliminating the disruptive 'noisy signal'. Several means by which this inhibition might occur were suggested, including membrane hyperpolarisation; activation of GABA-ergic axon terminals

of GPe and striatal afferents that terminate on GPi neurons; and synaptic depression due to transmitter depletion (22).

Yet another study found thalamic firing reduced by approximately 50-70%, suggesting an increase in GPi efferent output (23). Likewise, when Liu and colleagues recorded 4 subthalamic nucleus (STN) neurons in a dystonia patient during implantation of DBS electrodes, it was notable that the cells' firing rate was profoundly inhibited at clinically effective settings, but not so at lower intensity, ineffective settings (24). The authors argue that one of the mechanisms of DBS might be the 'driving of fibres of passage from GPe to STN' and that this could contribute to its therapeutic effects. These papers raise the question of whether, as well as somatic inhibition, orthodromic or antidromic activation of axons in the GPi occurs, leading to axonal collateral-mediated effects elsewhere in the basal ganglia and CNS.

A possible explanation for the contradiction in data observed in these studies was provided via an integrated model used to simulate the effects of extracellular DBS on thalamic relay neurons (21). According to this study somatic activity might not be an accurate representation of efferent output in the GPi. The authors present evidence that a neuron can simultaneously exhibit somatic inhibition and axonal excitation, the latter being independent of stimulation-induced trans-synaptic inputs. Modulation of pathological network activity is two-fold - the activity of pallidal neurons surrounding the electrode is masked via stimulating inhibitory trans-synaptic inputs and efferent output is 'locked' into high-frequency firing patterns.

Recent findings by Liu and colleagues support this model (24). Using dual-microelectrode mapping, they recorded neurons from the GPi of dystonia patients. The 2 main parameters they looked at were the firing rate and the recorded positive fEP amplitudes, the latter being a measure of electrical activity that corresponds to the inhibitory postsynaptic potential generated by a GABAa receptor-activated current, which

equates to striatal GABA release on GPi neurons. GP neurons showed frequency-dependent decreases in firing rate and preceding high frequency stimulation increased the average silent period following stimulation. The fEP amplitude increased with frequency until about 20 Hz then decreased significantly above 30 Hz. The authors argued that DBS initially activates GABA-ergic afferent terminals and inhibits GPi neuron firing, with the reduced fEP with longer periods of stimulation at high frequency indicating synaptic fatigue - meaning that the pathological transmission of information (via inhibition) in the GPi is blocked.

Yet fiber volleys (representing action potentials in axons including those of GPi neurons) were recorded after every stimulus pulse, meaning that it is possible for DBS to bring about 'focal inhibition of neuronal spiking while exciting axonal fibers' (24). It would seem that GPi output is 'replaced by intrinsic activity and stimulation-evoked activity in the axons' and it is probable that the large number of neurons affected by a DBS electrode would result in a 'regular synchronized high frequency output to premotor structures' (24).

Interestingly, since both fEP amplitude and the silent period were potentiated by high frequency stimulation (HFS), it was proposed that clinically effective DBS involves mechanisms of short term plasticity at inhibitory synapses in the GPi. One of the main electrophysiological abnormalities recorded in dystonia patients is their enhanced response to plasticity protocols. Perhaps effective DBS relies on this very characteristic. Paired-associative stimulation (PAS) response has been correlated with increased retention of clinical benefit post-DBS arrest, indicating that patients with highest plasticity are more capable of storing new patterns of motor activity (25).

Another conundrum is the gradual improvement in clinical condition seen in dystonia patients post-DBS, which reaches a maximum at ~6 months post surgery and then stabilizes, as opposed to the immediate results observed in Parkinsonian patients. Might this reflect a gradual reorganization of neural wiring, with neural networks becoming more 'normal' and abnormal patterns being 'unlearned'? It has in fact been demonstrated that

this progressive improvement is paralleled by changes in several electrophysiological measures of motor inhibition that are classically abnormal in those with dystonia. Spinal reciprocal inhibition, blink reflex inhibition and short-latency intracortical inhibition (SICI) all exhibit a monotonic time course of improvement, with patient values reaching those of healthy volunteers at ~6 months, mirroring the time course of clinical improvement.

The long-term effects of DBS on PAS response were also studied. Of note is the non-monotonic time course of change in this electrophysiological measure; the authors found that DBS resulted in a PAS effect that was 'dramatically reduced/absent 1 month post-surgery' afterwards slowly increasing towards normal levels (26). Moreover, elsewhere it is reported that PAS values in dystonia patients post-DBS are not only decreased in comparison to values observed in DBS-naïve patients, but are lower than those found in normal subjects (25). It is argued that the progressive time course of clinical improvement can in part be explained by the role excess plasticity is thought to play in the pathogenesis of dystonia. If excess plasticity is responsible for the gradual formation of inappropriate connections in the motor system, one can predict that DBS would initially have little effect on dystonic movements, since it takes time to establish new motor patterns or relearn a movement.

My colleagues and I sought to identify what effect, if any, GPi-DBS had on TDT abnormalities in dystonia patients. We measured the TDTs of 10 patients who all exhibited marked clinical improvement of dystonic symptoms post DBS (although the optimum design would have been to test TDT before and after). Nevertheless, our study identified persistent abnormalities in TDT, despite previous findings that excessive response to plasticity protocols is reversed following DBS. One conclusion is that GPi-DBS corrects dysfunction in the dystonic network downstream of the basal ganglia but not upstream. Another is that abnormalities in sensory processing such as the raised TDT do indeed fulfill the criteria of an endophenotype in dystonia i.e. a measurement that reflects disease susceptibility and is not

altered by clinical disease severity. It is in this context that TDT has been explored in families of patients with cervical dystonia where TDT abnormalities have been found in approximately 50% of relatives, including many without clinical symptoms of dystonia. This fits with the pattern of low penetrance of clinical symptoms in genetic dystonia, where many gene carriers are unaffected (e.g. in patients with the DYT1 mutation).

Several studies have demonstrated that when DBS is turned off, dystonic symptoms reappear rapidly, sometimes within a few hours (27). The severity of relapse is widely variable between individuals, however, and some report movement scores worse than those taken pre-operatively. This would suggest that DBS mediates its effects solely via blockage of pathological signals rather than producing long-term change. Yet a recent study looking at the effects of turning stimulation off in dystonia patients who had had DBS for 5 years or more found that none of the patients returned to baseline severity (25). Moreover, three patients reported no significant alteration in clinical condition, pointing to permanent change possibly secondary to neural reorganization. The occasional case of retained clinical benefit despite DBS arrest has been reported in the literature (28) and these might become more numerous as the number of patients receiving this treatment increases. One possible explanation for the discrepancy in results between different groups might be that some of the effects of DBS change from being reversible in the first few years to being non-reversible after 5 years or more, although this is hard to square with the observed plateau in clinical improvement at 6 months.

DBS and functional imaging data

The discovery of genetic mutations causing primary dystonia has led to much work on the characteristics of gene carriers and what determines penetrance. Using magnetic resonance diffusion tensor imaging, reduced integrity of cerebello-thalamo-cortical fibers in both DYT1 manifesting and non-manifesting carriers has been demonstrated; it remains to

be seen whether similar microstructural defects are present in cases of sporadic dystonia (29). Characteristic alterations in metabolic activity at rest have been described, with several trait-related and penetrance-relate patterns of metabolic activity documented. The normal motor-related activation pattern (NMRP) upon performing a specific movement task is found to be elevated in manifesting DYT1 carriers compared with controls and non-manifesting carriers, and could be a consequence of reduced cortical inhibition.

Imaging studies have shown that GPi-DBS is associated with reduced PET activation in a number of brain regions, including primary and secondary mortor cortices, thalamus, putamen and prefrontal regions (30). Moreover, clinically effective DBS was associated with a reduction of NMRP expression, which was abnormally elevated when stimulation was turned off. This points to both direct and indirect effects of pallidal DBS, resulting in global alterations in activity that lead to normalization of the 'baseline overactivity of sensorimotor networks' (29).

Conclusion

Data collected from dystonia patients who have undergone DBS indicates that dystonia is the result of subtle changes in sensorimotor network function rather than the result of basal ganglia abnormality per se. Evidence from functional and electrophysiological studies showing widespread dysfunction in a number of brain regions supports this. In such a model, dystonia might arise from a discrete lesion in one node in the network, or from malfunction at several points in the circuit, or because of altered communication between nodes. This broad spectrum of pathogenic mechanisms is consistent with the heterogeneous nature of the disorders grouped under the heading 'dystonia'. Functional, electrophysiological and neurochemical changes in secondary dystonia might be different from those in primary idiopathic dystonia, which in turn might be subtly different from hereditary forms (31); this could explain the variation in response to DBS.

An integrated model of dystonia's constellation of features, incorporating electrophysiological abnormalities, neurochemical alterations (namely, levels of the neurotransmitters dopamine, acetylcholine and GABA) and microstructural and metabolic changes, has yet to be achieved. None of the electrophysiological abnormalities alone are sufficient to cause disease, as shown by their presence in non-dystonic limbs of patients and in unaffected relatives. This means that these findings are unlikely to be a consequence of or compensatory reaction to dystonic movement. It is difficult to deduce whether neurochemical imbalances and altered patterns of basal ganglia activity are pathogenic in themselves or the result of pathology elsewhere. It seems probable that the presence of these features together constitutes an individual's underlying vulnerability to developing dystonia, and that some as yet unknown environmental factor is required for full penetrance.

In order to fully understand dystonia, and develop more effective treatments, we must broaden our scope to explore other brain areas in this disease; the cerebellum, and its communication with the basal ganglia, has emerged as a promising focus of enquiry, with emphasis placed on the role compensatory cerebellar changes play in disease pathogenesis (32). Taken together with findings of reduced cerebello-thalamo-cortical tract integrity in hereditary forms of dystonia, future approaches could focus on the interplay between these two areas of the brain.

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