Hyperkinetic disorders and loss of synaptic down-scaling: from basic science to clinical neurophysiology

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Abstract

Recent clinical and preclinical studies have shown that different hyperkinetic disorders such as Huntington's disease, dystonia and L-DOPA-induced dyskinesia in Parkinson's disease are all characterized by loss of the ability to reverse synaptic plasticity and an associated increase in excitability of excitatory neuronal inputs to a range of cortical and subcortical brain areas. Moreover, these changes have been detected in patients either *via* direct recordings from implanted deep brain electrodes, or non-invasively using techniques of transcranial magnetic stimulation. Here we discuss the mechanisms underlying the loss of bidirectional plasticity and the possibility that future interventions could be devised to reverse these changes in patients with hyperkinetic movement disorders.

Introduction

The ability to adjust movements to fit task requirements employs plastic mechanisms operating at the level of cortex and striatum[1]. These mechanisms regulate the excitability of output structures and limit excessive neuronal activity without compromising the stability and integrity of the underlying circuits that drive behavior. This ability ~~is often referred to as "homeostatic" plasticity, a mechanism that~~ allows neurons to sense their functional state and to adjust their properties to maintain stable function[2].

Physiological adaptations related to motor learning require neural networks able to detect correlations between environmental events and to store this information as changes in synaptic strength. Classical examples of brain activity-dependent adaptations are long-term potentiation (LTP) and long-term depression (LTD)[3]. However, excessive expression of these forms of plasticity can be detrimental for behavior and motor activity. ~~For example, failure of homeostatic mechanisms to control expression of LTP in the basal ganglia could result in abnormal potentiation of all synaptic inputs leading to excessive excitability as well as abnormal changes in neuronal morphology and synapse number.~~ In the present perspective, we propose that the loss of synaptic down-scaling would lead to a loss of control of LTP in the basal ganglia, as well as in the cortex, and to hyperkinetic motor manifestations, such as those observed in Huntington's disease (HD), dystonia, and L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia (LID) in Parkinson's disease (PD).

HD, dystonia, and LID can all be classified as hyperkinetic disorders although they differ in their mixture of dyskinetic, choreic, and dystonic movements[4]. Recent advances in genetic, molecular, and imaging studies have allowed a better understanding of the similarities and differences between them. It has been suggested that LID, dystonia, and HD share several molecular and synaptic abnormalities which seems surprising since distinct neuronal subtypes are affected by the different

pathologies. Yet, as we show below, all can lead to changes in control of synaptic plasticity.

HD is a progressive neurodegenerative disorder, causing movement, mood and cognition alterations, which profoundly impairs processing of corticostriatal information[5]. While late stage pathology in HD involves cell death, the appearance of early motor manifestations is associated with subtle functional alterations in the excitatory synaptic activity and in the formation of aberrant cortical and subcortical plasticity[6]. In the early stage of HD, neuronal death is rare. Similarly, most primary forms of dystonia do not cause neurodegeneration either early or late in the disease; instead they are associated with an imbalance of transmitters and other biochemical abnormalities[7,8]. From the pathophysiological point of view, the pathogenesis of LID in PD is more complex. The loss of the majority of nigral dopaminergic neurons, leading to a dramatic striatal dopamine (DA) denervation, is an essential precondition for the expression of LID[9,10]. However, hyperkinesias only occur if associated with subtle alterations of the dendritic spines of cortical and striatal neurons[11,12].

~~In the past, the difficulties in modeling pathology together with the complexity of the corticostriatal network allowed only a partial understanding of the mechanisms driving these specific hyperkinetic conditions. Recently, advances in building appropriate experimental models and new experimental tools such as optogenetics and novel techniques of functional imaging and clinical neurophysiology have permitted a more accurate analysis of the circuit-specific deficits. This has allowed a redefinition of the models of neurologic hyperkinetic disorders.~~

Cortical and striatal pathological synaptic potentiation of excitatory transmission in experimental models of Huntington's disease

HD ~~is a genetic neurodegenerative condition causing disorders of movement, mood and cognition that~~ is induced by a polyglutamine expansion in the huntingtin (Htt) protein[6]. Genetic mouse models of HD~~, in association with improved imaging techniques both in HD patients and subjects at risk of the disease,~~ have contributed to a better knowledge of the cellular and molecular

mechanisms underlying the pathogenesis of HD. The neurodegenerative process starts earlier in the striatum than in other brain areas, and abnormal activity of glutamatergic corticostriatal synapses contributes to an imbalance in survival- versus death-signaling pathways within the striatum[5,13]. Striatal projection neurons (SPNs) of the indirect pathway seem more vulnerable than those of the direct pathway and their dysfunction contributes to motor symptoms during early stages of the disease[14]. Since the striatum is the primary location of the neurodegenerative process, it has been hypothesized that down-scaling of the plasticity of striatal glutamatergic synapses on striatal neurons is impaired, and that this leads to early cognitive and motor symptoms. In support of this hypothesis, alterations in the induction and reversal of synaptic plasticity have been demonstrated in a genetic (R6/2 mice) model of the disease. ~~Striatal~~ SPNs in this model have been shown to express normal LTP, but to be unable to depotentiate their synapses after a low-frequency stimulation (LFS) protocol (Figure 1A)[15]. The inability of SPNs to reverse synaptic strength to pre-LTP levels disrupts ~~homeostatic~~ regulatory processes that destabilize neuronal circuits during information storage and could contribute to the impaired behavioral flexibility described in early-stage HD patients[15].

It has been proposed that reduced brain-derived neurotrophic factor (BDNF) transcription, transport and signaling contribute to striatal neuronal dysfunction and degeneration in HD[6]. However, this view has recently been challenged, since in mouse models of early symptomatic HD, BDNF delivery to the striatum and its activation of tyrosine-related kinase B (TrkB) receptors were found to be normal, while TrkB receptor activation resulted in an aberrant postsynaptic control of induction of potentiation at corticostriatal synapses[16]. It seems likely that the consequence of the expression of mutant Htt is a change in striatal excitatory synaptic activity, triggered by a decrease of glutamate uptake and by increased signaling at NMDA receptors[17].

Striatal DA signaling is also altered in HD and progresses through the course of the disease[18]. Alterations of the A2A adenosine receptors (A2AR) mirror changes of the DA system since both DA and A2AR converge on the regulation of the cAMP/PKA/DARPP-32 pathway that, in turn,

regulates the efficacy of glutamatergic transmission and striatal plasticity (Figure 2)[19,20]. Up-regulation of PKA activity and increased function of A2AR are also seen in HD patients[20-23]. Accordingly, genetic inactivation or pharmacological manipulation of A2AR prevent or reverse working memory deficits in early HD, respectively[24].

Based on clinical and experimental findings, it has been hypothesized that some of the behavioral alterations in HD, including reduced behavioral flexibility, may be caused by altered DA modulatory function[25]. Interestingly, aberrant synaptic plasticity and dopaminergic dysfunction has been shown not only in the striatum, but also in the cortex of a mouse model of HD[26].

Altered spine and synaptic plasticity could underlie the motor as well as cognitive symptoms in HD. Recently, the kinetics of spine alterations and plasticity in HD has been investigated using long-term two-photon imaging to track individual dendritic spines in the R6/2 genetic model[27]. In R6/2 mice the probability that newly formed spines are stabilized and transformed into persistent spines was greatly reduced compared to controls, and in R6/2 mice, aggregates of mutant htt were localized in dendritic spines. The evidence that alterations in dendritic spine dynamics, survival, and density in R6/2 mice appear before the onset of motor symptoms indicates that decreased stability of the cortical synaptic circuitry underlies the early symptoms in HD.

Experimental models of HD suggest that striatal grafts might rescue motor deficits and learning of complex motor skills in experimental models of HD. Embryonic striatal grafts create functional connections with the host striatal circuitry, and restore synaptic transmission facilitating the recovery of bidirectional synaptic plasticity[28].

Aberrant synaptic plasticity in experimental models of dystonia

Dystonia comprises a heterogeneous group of "hyperkinetic" movement disorders characterized by sustained muscle contractions, causing twisting repetitive movements and abnormal postures. Dystonia can be classified by age at onset, by distribution (focal, segmental, generalized, or

hemidystonia) or by aetiology (isolated or combined)[29]. ~~Gross and light microscopic examination fail to reveal relevant neuropathological changes in the brain[8], consisting with the idea that the pathophysiology of dystonia is determined by abnormalities in neural processing and synaptic plasticity~~. The discovery of various genes implicated in dystonia as well as the experimental use of new genetic models has provided information about the mechanisms of the disease[30]. Unfortunately, most of these rodent models do not exhibit overt dystonia, although they show subtle motor abnormalities with peculiar neurochemical and neurophysiological alterations. Among the various synaptic and electrophysiological alterations described in these models, a major common characteristic seems to be abnormal corticostriatal synaptic plasticity. Early-onset ~~primary~~ DYT1 dystonia ~~(DYT1 dystonia)~~, the most common and severe form of inherited dystonia, is caused by a 3bp deletion on a glutamic acid residue in the C-terminal coding region of the protein torsinA[31]. In transgenic mice overexpressing mutant torsinA, no corticostriatal LTD could be elicited, whereas LTP was greater than in control animals. Moreover, while LFS reverted potentiated synapses to resting levels (depotentiation) in control mice, this phenomen ~~form of homeostatic plasticity~~ was absent in mutant mice (Figure 1B)[32]. Of note, these abnormalities in synaptic plasticity were reproducible across species and distinct mouse lines, as they were found both in transgenic rats overexpressing mutant torsinA[33], as well as in knock-in mice heterozygous for Δ-torsinA (Tor1a+/Δgag)[34]. Collectively, these findings confirm the existence of a specific endophenotype linked to DYT1 mutation and indicate that the "loss of down-scaling" is a distinctive feature in multiple models of DYT1 dystonia.

A major contributor to the aberrant control of synaptic plasticity in the DYT1 model appears to be a breakdown of the usual reciprocal relationship between striatal DA and acetylcholine[35,36], due a change in D2 receptor (D2R)-regulation of cholinergic activity. Data collected from different ~~mouse and rat~~ rodent models of DYT1 dystonia show that the D2 receptor agonist quinpirole produces a paradoxical excitation of cholinergic interneurons, rather than inhibition[37,38]. The consequent

imbalance in neurotransmitter content impairs bidirectional corticostriatal synaptic plasticity, which can then be restored by anticholinergic drugs. This is consistent with the clinical use of anticholinergic agents in dystonia, and offers a rationale for the development of improved antimuscarinic therapies. Moreover, a relevant link has been demonstrated between torsinA mutation and D2 receptor: A2A receptor antagonism counteracts the ~~deficit in~~ D2 receptor deficit observed in mutant mice, suggesting that modulation of PKA is a critical pathophysiological factor (Figure 2)[39].

~~Targeting the intrinsic cholinergic system with~~ Anticholinergic drugs reverses the deficit in motor control and restores striatal LTD in DYT1 ΔGAG knock-in heterozygous mice[40]. In a novel model, showing conditional deletion of torsinA in embryonic progenitors of forebrain cholinergic and GABAergic neurons it has been observed that the onset of dystonic movements correlates with degeneration of striatal cholinergic interneurons, while remaining interneurons show morphological and electrophysiological alterations. More importantly, abnormal movements were significantly reduced with an antimuscarinic drug[41].

~~It has been proposed that excessive plasticity, particularly in the developing motor system, could lead to the formation of extra connections between inputs and outputs that lead to expression of excessive muscular activity and unwanted movements of dystonia. This is exacerbated by the failure of depotentiation, which could normally be involved in reversing such changes, but which become permanent in dystonia.~~ Altogether these findings ~~taken together further~~ support the hypothesis that impaired balance among glutamatergic inputs, cholinergic interneurons, responses to dopaminergic signal, and activity of SPNs are involved in the ~~striatal~~ motor abnormalities in DYT1 dystonia[42].

Synaptic dysfunctions in experimental models of L-DOPA-induced dyskinesia in Parkinson's disease

L-DOPA initially revolutionized the symptomatic treatment of PD[43]. Unfortunately, treatment becomes complicated in most patients after 5–10 years with increasingly frequent motor fluctuations and hyperkinetic involuntary movements[9].

It has been hypothesised that the development of LID is linked to impaired synaptic plasticity at corticostriatal synapses and in particular with the loss of synaptic depotentiation[44]. Indeed, DA-denervation in rats using the toxin 6-hydroxy-dopamine (6-OHDA) causes loss of corticostriatal LTP that can be restored by chronic treatment with L-DOPA (Figure 1C)[44]. Interestingly, ~~it has been demonstrated that~~ depotentiation is selectively lost only in dyskinetic animals, whereas it is expressed in animals that do not develop involuntary movements (Figure 1C)[44]. This suggests that loss of synaptic depotentiation might destabilize neuronal circuits in the basal ganglia, resulting in dyskinesias.

Abnormalities of synaptic plasticity in dyskinetic animals are related to changes in the D1/PKA/DARPP-32 signaling pathway that inhibit protein phosphatase (PP)-1 activity (Figure 2), a molecule that is involved in depotentiation at corticostriatal synapses. Activation of D1 receptors results in PKA-catalyzed phosphorylation of DARPP-32 on Thr34, which, in turn, converts DARPP-32 into a potent inhibitor of PP-1. Interestingly, dyskinetic animals express higher levels of Thr34-phosphorylated DARPP-32 than non-dyskinetic rats and drug-naïve controls[44]. Accordingly, striatal synaptic depotentiation is prevented by pretreatment with PP-1 and PP-2A inhibitors, D1-like-receptor agonists, and adenylyl cyclase activators[44].

The Ras-extracellular signal-regulated kinase (Ras-ERK) pathway ~~a signal transduction cascade involved in synaptic plasticity,~~ controls synaptic activity in SPNs and represents a critical signaling pathway downstream of the D1 receptor[45]. Notably, a recent study has shown that the Ras-ERK pathway regulates both activity-dependent striatal LTP and synaptic depotentiation. Genetic

inactivation of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1), a neuronal activator of Ras proteins, causes loss of LTP in SPNs in the direct pathway without affecting LTP in the indirect pathway. Interestingly, characterization of LTP in 6-OHDA-lesioned animals showing LID after chronic L-DOPA treatment has shown a complex Ras-GRF1- and pathway-independent, involvement of ERK[45].

A possible way to reduce LID involves targeting striatal phosphodiesterases, which regulate intracellular levels of cGMP[46]. The phosphodiesterase inhibitors zaprinast and UK-343664 rescue the loss of LTD at corticostriatal synapses *via* a mechanism requiring the modulation of intracellular cGMP levels. Intrastriatal injection of these drugs is also associated with reduced LID, thus supporting the idea that targeting phosphodiesterases can ameliorate LID by facilitating the re-emergence of striatal LTD[46]. Moreover, it has been recently shown a complex serotonergic regulation on striatal bidirectional synaptic plasticity underlying the antidyskinetic effect of serotonergic agonists[47].

The molecular mechanisms of LID have also been investigated using spike-timing dependent plasticity (STDP) at corticostriatal synapses in slices from 6-OHDA-lesioned mouse models of parkinsonism and LID, generated in BAC transgenic mice with eGFP labeling the direct or indirect output pathways[48]. In control mice, bidirectional synaptic plasticity (LTP, LTD and depotentiation) can be observed in both striatal output pathways. In parkinsonian mice both pathways exhibit only unidirectional plasticity, irrespective of stimulation paradigm. A symptomatic dose of L-DOPA restores bidirectional plasticity in both pathways to levels comparable with control animals. In animals with LID, treatment with L-DOPA leads to LTD in the indirect pathway, whereas only LTP can be induced in the direct pathway. Thus, this study confirms the concept that while normal motor control requires bidirectional plasticity of both striatal outputs, dyskinetic movements are caused by a switch from bidirectional to unidirectional plasticity.

Another recent study suggests that STDP in the PD state and in LID is cell-type specific. In fact, the intrinsic excitability and corticostriatal synaptic connectivity of SPNs of the indirect pathway are lower in PD models than in healthy condition. Conversely, these properties of SPNs in the direct pathway are enhanced in tissues from PD models and suppressed in LID models[49].

Transcranial magnetic stimulation (TMS) and dysfunctional plasticity in the cortex of patients with hyperkinetic disorders

TMS is a non-invasive method of stimulating the brain in conscious humans. Because it is not possible to stimulate deep brain structures such as basal ganglia reliably, the target in most studies of hyperkinetic movement disorders has been the motor cortex. TMS has the advantage that the response is easily quantified by measuring the size of the movement it evokes in contralateral muscles. The choice of motor cortex is supported by the fact that (1) it shows early degenerative changes (e.g. in HD[50]); (2) it receives dopaminergic innervation that influences synaptic plasticity[51]; and (3) it is a primary output target of basal-ganglia-thalamo-cortical circuits. Thus, it might be expected to reflect some of the changes described in striatal connections.

A number of common TMS methods have been used in hyperkinetic movement disorders to probe:

1. the excitability of cortico-spinal connections (motor thresholds),
2. GABAa cortical inhibition (SICI, short interval intracortical inhibition),
3. GABAb inhibition (silent period),
4. a cholinergic-sensitive form of inhibition (SAI, short latency afferent inhibition)
5. the initial stages of synaptic plasticity leading to LTP and LTD (rTMS, repetitive TMS; TBS, theta burst stimulation; PAS, paired associative stimulation, a form of STDP) (for summary see[52]).

The response to these methods varies considerably between individuals, so that none is diagnostic. However, group differences are reliable given sufficiently large sample sizes.

Huntington's disease

Initial work on HD focused on measures of excitability and inhibition in clinically manifesting individuals. They appeared to suggest that the excitability of GABAa systems (SICI method) were reduced[53] whereas GABAb (silent period) seemed elevated[54,55]. However, later studies sometimes failed to replicate the findings[56] suggesting that the effects are small, if present. One report found reduced cholinergic-sensitive inhibition (SAI), which was even present in preclinical cases but this has not been replicated[56].

The effects of HD on plasticity are clearer. Three studies using different forms of plasticity-probing methods (rTMS, TBS and PAS) have all reported a smaller response than normal[57-59], which would be consistent with the idea that plasticity at cortical synapses is reduced. Notably, between them these methods probed both facilitatory (LTP-like) and inhibitory (LTD-like) effects, and occurred even in non-symptomatic carriers suggesting early cortical involvement in HD before the appearance of clinical signs[59].

Dystonia

As in HD, initial studies concentrated on measures of cortical excitability and GABA function. The majority of studies reported reduced GABAa excitability (SICI) in many types of focal dystonia (e.g.[60-62]). As usual, the effects are probably smaller than in the initial reports[63,64]. Similarly GABAb (silent period) has also been found to be reduced in most reports[60,65,66], but not always (e.g.[67]). Other forms of inhibition have also been reported as reduced in patients with dystonia, such as "surround inhibition" (suppression of excitability in uninvolved hand muscles when people try to produce a focal contraction of just one muscle[68]) and inhibition from premotor to motor cortex[69]. All these studies are compatible with the notion that disordered control of inhibitory systems in motor cortex might contribute to the excess muscle activity that is characteristic of dystonia. However, in patients with focal dystonia these changes can often be observed in clinically unaffected parts of the body;

they can also be seen in patients with "psychogenic" dystonia, suggesting that some other factor determines whether dystonia occurs.

Building on the work in experimental animals, there have been a large number of studies of cortical plasticity in dystonia. Initial work[70,71] found a pronounced increase in the responsiveness to tests of both LTP-like and LTD-like plasticity (PAS protocol). Although this has been replicated in several later studies (e.g.[72-75]), it is not a universal finding (e.g.[76]), probably because of the inter-individual variation in the effect size. Notably it is easier to demonstrate increased plasticity in patients with organic dystonia than in "psychogenic" cases, suggesting that it is an important contributor to clinical symptoms[77]. Finally, within individuals, there is reduced ~~homeostatic regulation~~ control of plasticity in dystonia[78,79]. ~~All of these changes have been regarded as consistent with the notion that excessive muscle contractions in dystonia arise because of formation of unwanted associations between activity in remote muscles and a prime mover.~~

Parkinson's disease and LID

Most of the work examining differences between patients with and without dyskinesia has focused on measures of cortical plasticity. The initial study of Morgante et al[80] found absent LTP-like plasticity (PAS protocol) in patients when off treatment that was restored after administration of L-DOPA. Importantly, this effect was not seen in patients who had LID, consistent with a lack of dopaminergic modulation of synaptic plasticity in these cases. More recently, a TMS method for probing depotentiation of LTP-like plasticity has been introduced by Huang et al[61]. Consistent with the animal models, patients with LID were unresponsive to the depotentiation protocol (Figure 3A)[81] suggesting that depotentiation is abnormal in the motor cortex of patients with LID.

Deep brain stimulation and aberrant plasticity in the basal ganglia of patients with hyperkinetic disorders

Deep brain stimulation (DBS), utilizing high-frequency electrical stimulation of deep brain structures, is an effective therapeutic option for treatment of a variety of neurological and psychiatric disorders[82]. DBS targeting the internal segment of the globus pallidus (GP), subthalamic nucleus (STN), and thalamus is used to treat symptoms of movement disorders, such as PD associated with LID and dystonia (Figure 4A).

The first study that characterized synaptic plasticity in PD patients with DBS electrodes implanted in the STN measured field potentials (fEPs) in substantia nigra pars reticulata (SNr) that were evoked by stimulation through a nearby microelectrode[83]. HFS in the SNr failed to induce a lasting change in test fEPs in patients OFF medication whereas after oral L-DOPA administration, it potentiated fEP amplitudes, indicating that DA medication restores LTP-like changes in the human basal ganglia. In a more recent study, the same group has analyzed whether LFS in the GPi and SNr could depotentiate synapses that had already undergone HFS-induced potentiation[84]. GPi and SNr synapses in PD patients with less severe LID underwent greater depotentiation following LFS than in patients with more severe LID (Figure 4B). This demonstration of impaired depotentiation in basal ganglia output nuclei in PD patients with dyskinesia is an important validation of animal models of LID. Indeed, the ability of a synapse to reverse previous potentiation may be crucial to the normal function of the basal ganglia, avoiding storage of non-essential motor information.

DBS of GPi is an excellent treatment for primary generalized or segmental dystonia. It is less effective for dystonia secondary to structural brain damage[85]. It has been hypothesized that DBS suppresses abnormally enhanced synchronized oscillatory activity within the motor cortico-basal ganglia network. Accordingly, pallidal DBS suppresses pathologically enhanced low frequency activity in patients with dystonia[86].

Electrophysiological features of dystonia in patients prior to and in the early treatment period following pallidal DBS have been assessed longitudinally[87]. Following DBS, short-latency intracortical inhibition increased toward normal levels with the same time course as the patients'

clinical benefit[88]. In contrast, synaptic plasticity changed rapidly, following a different time course. Clinical benefit may be delayed because engrams of abnormal movement persist and take time to normalize suggesting that plasticity may be a driver of long-term therapeutic effects of DBS in dystonia.

The use of DBS in the treatment of HD is in an exploratory phase and the optimal brain structure to be targeted has to be determined. The number of patients treated with DBS for HD is small, however, preliminary studies show benefit following internal and external GP stimulation. The thalamus, STN, and substantia nigra pars compacta could also be potential targets. Further clinical studies are necessary to validate the efficacy of neuromodulation and to determine the optimal target for HD[89].

Abnormal excitability as a target for therapeutic interventions in hyperkinetic movement disorders

In the last decade rTMS has been widely used as a possible treatment for both PD and hyperkinetic movement disorders. Although studies on the efficacy of rTMS in treating movement produced variable results, mostly owing to the variety in individual rTMS protocols, evidence suggests that rTMS improves motor symptoms for these patients. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of rTMS effects[90,91]. Most of these studies have been focused on the treatment of PD with LID and on dystonia, while only a few reports have reported data on HD patients. In most of these therapeutic trials the driving hypothesis has been the attempt to restore the physiological bidirectional plasticity that in hyperkinetic disorders might be lost at cortical and subcortical levels.

The most complete set of data is for rTMS treatment of PD where there have been more than one hundred studies. The results of the most robust of these trials are summarized in the review by Lefaucheur et al[92]. The consensus is that rTMS over M1, premotor or supplementary motor areas

may have some potential clinical benefit but that the effects so far reported are too small to be of useful in clinical practice.

There has also been interest in using rTMS to reduce LID. Interestingly, rTMS at 1-Hz but not 5-Hz over the supplementary motor area (SMA) in a group of patients with advanced PD reduced dyskinesias induced by continuous apomorphine infusion (Figure 3B)[93]. This observation indicates that the most effective therapeutic protocol is similar to the one producing depotentiation in animal studies. The existence of residual beneficial clinical after effects of consecutive daily applications of low-frequency rTMS on LID in PD has been also demonstrated in a placebo-controlled, single-blinded, crossover study[94].

Some studies have explored the possibility that LID can be reduced by targeting brain structures that are not included in the "classical" basal ganglia circuits. Continuous theta burst stimulation of the cerebellum may have anti-dyskinetic effects, possibly *via* the modulation of cerebello-thalamocortical pathways[95]. A study combining resting state functional magnetic resonance imaging with rTMS has shown that the inferior frontal cortex is implicated in LID and could be a potential therapeutic target[96].

In dystonia, increased cortical excitability of the motor cortex and the brain stem[97] could be a target for rTMS modulation. Again, the consensus at the present time[92] from the small number of studies that have been completed is that any effects are small and at present are not of clinical relevance.

There have been case studies reporting improvement in choreiform movements with administration of low-frequency rTMS lasting for a brief period rTMS[98]. However, other case series using bilateral low-frequency rTMS in patients with severe HD failed to replicate the findings[99].

Conclusions

Both experimental and clinical findings suggest that in hyperkinetic disorders distinct but also common mechanisms interact at both cellular and network levels to influence synaptic scaling and synaptic plasticity.

In physiological conditions, the compartmentalization of synaptic plasticity to specific connections and neuronal populations facilitates appropriate information storage of motor-related signals. In hyperkinetic disorders, the specificity of cellular and network related plasticity is lost, with the results that cortex and basal ganglia store ~~non-essential~~ redundant information. This loss of specificity in hyperkinetic disorders can occur at different levels and is linked to the genetic and/or molecular bases underlying the disease: (1) abnormalities of activity-dependent post-translational modifications of synaptic proteins at the activated synapses; (2) paradoxical local protein synthesis and degradation at synapses and (3) disruption of the molecular mechanisms contributing to depotentiation.

Clinical electrophysiological studies using TMS and DBS (Figures 3 and 4) have confirmed the role of maladaptive plasticity in patients with hyperkinetic disorders. More importantly, ~~clinician scientists have begun to use~~ these methods are now commonly utilized to target this pathological plasticity and ameliorate some of the symptoms associated with these disorders. ~~The challenge for the future will be to harness new techniques such as optogenetics to take advantage of existing promising results obtained in experimental animal models and apply them to patients with hyperkinetic movement disorders (Figure 5)[100,101].~~

At present, however, there is still a gap in the knowledge on the reciprocal links between plastic changes occurring in the basal ganglia and aberrant plasticity observed in the cortex. In fact, while most electrophysiological studies on animal models of hyperkinetic disorders focus on basal ganglia circuits, clinical electrophysiological studies using TMS mostly target cortical circuits (motor cortex). Although this gap should be filled in future studies, loss of down-scaling in both cortical

and subcortical structures might represent a common synaptic mechanism occurring in distinct hyperkinetic disorders, as detected using neurophysiological approaches (Figure 5).

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Figure legends

Figure 1. Alterations of striatal synaptic plasticity in three experimental models of hyperkinetic disorders. **(A)** The graph shows the time course of excitatory postsynaptic potential (EPSP) amplitude in response to high frequency stimulation (HFS) and subsequent low frequency stimulation (LFS), recorded in striatal spiny neurons from R6/2 mice (dark green), modelling Huntington's disease (HD) and wild type controls (WT mice, light green) (modified from[15]). Note that LTP is equally expressed in both WT and HD mice while this latter group do not show depotentiation after LFS. **(B)** The graph shows the time course of EPSP responses to HFS and synaptic depotentiation protocol in a dystonia model, obtained through intracellular recordings carried in corticostriatal slices from transgenic mice overexpressing human mutant (hMT, dark red) and wild type TorsinA controls (hWT, orange) (modified from[32]). Note that the genetic model of dystonia shows an increased LTP and a loss of depotentiation in comparison with the controls. **(C)** The plot illustrates the changes in mean EPSP amplitudes following HFS and LFS in 6-OHDA-lesioned rats chronically treated with L-DOPA. Animals responding to L-DOPA treatment with dyskinesia fail to display synaptic depotentiation following LFS (dark blue), while animals showing therapeutic effects of L-DOPA (light blue) display a full recovery of bidirectional synaptic plasticity (modified from[44]). On the right the electrophysiological traces represent examples of EPSP recorded in the various experimental conditions. Vertical and horizontal scale bars measure 10 mV and 20 ms, respectively.

Figure 2. Schematic representation of the common abnormalities in cAMP/PKA pathway downstream dopamine D1 and adenosine A2A receptors in striatal spiny neurons in experimental models of hyperkinetic disorders. Synaptic alterations in Huntington's disease, dystonia and L-DOPA-induced dyskinesia are associated with abnormal functioning of dopamine D1 and adenosine A2A receptors, expressed in striatonigral (D1-positive, left) and striatopallidal (D2-positive, right)

spiny neurons. Aberrant stimulation of D1 receptors induce abnormal activation of PKA and increased phosphorylation of DARPP-32, associated with reduction of protein phosphatase 1 action on NMDA receptors. A similar pattern of alteration is hypothesized downstream hyperactive A2A receptors.

Figure 3. Effects of TMS on motor cortex plasticity in PD patients with L-DOPA-induced dyskinesia (LID). **(A)** Continuous theta burst stimulation (10 seconds train) followed by 1-min of voluntary contraction (cTBSc0) was used as protocol to induce LTP of motor evoked potentials (MEP). To depotentiate (Depo, dotted lines) this previously induced LTP a 10 seconds train of continuous TBS (cTBS150) was given at 1 min after cTBSc0. In healthy subjects (left) synaptic depotentiation is observed, while PD patients with LID, who had received a half dose of L-DOPA (right) were not able to show reversal of LTP following the application of the two protocols (modified from[81]). **(B)** The graph shows the time course of mean Abnormal Involuntary Movement Scale (AIMS) scores in PD patients with disabling LID before and after two different repetitive transcranial magnetic stimulation (rTMS) protocols. While 5-Hz protocol (blue dotted lines) failed to produce therapeutic benefit, low frequency 1-Hz stimulation (light blue continuous lines), mimicking the depotentiation protocol applied in experimental animal models, was able to decrease AIMS score in most of the patients (modified from[93]).

Figure 4. Effects of deep brain stimulation (DBS) on subcortical synaptic plasticity in dystonic and PD patients with LID. **(A)** The graph shows paired pulse response curves of field potentials recorded in the substantia nigra pars reticulata (SNr) of PD patients (left) and dystonic subjects (right) before and after high frequency stimulation across a range of interstimulus intervals (ISI). In the SNr of PD patients on dopaminergic medication paired stimulation before HFS evoked a paired-pulse depression (dark blue) that was further increased following HFS (light blue). Conversely, in

the SNr of dystonic patients, no measurable paired pulse depression was observed at any ISI before HFS (dark red). Following HFS in these patients, a paired pulse depression was observed (orange) (modified from[88]). **(B)** This diagram, showing the amplitude of field potentials recorded from SNr during DBS procedure, reveals the relationship between the response to LFS-induced change with the dyskinesia score. The selection of population by dyskinesia severity and duration reveals 2 groups within the ON data; one group, with low level of dyskinesia that responded to LFS and underwent depotentiation (light blue), and one group, with high level of dyskinesia that did not respond to LFS and fails to show depotentiation (dark blue) (modified from[84]).

Figure 5. Translating synaptic plasticity in humans from in vitro models. Both stimulation of motor cortex by transcranial magnetic stimulation (TMS, upper left) and high-frequency activation of either subthalamic nucleus (STN) or globus pallidus (GPi) by deep brain stimulation (DBS, upper right) converge to subcortical regions to rewire the basal ganglia circuit. Such a rearrangement involves, at synaptic level, long-term changes of the efficiency of corticostriatal synapses (left inset). Following high-frequency stimulation (HFS) of cortical fibers, these synapses can exhibit either LTD or LTP and then synaptic depotentiation (SD).

~~**Figure 5.** Schematic diagram of possible effects of cell-type specific optogenetic stimulation in the motor cortex. Expression of channelrhodopsin-2 (ChR2) in cortical pyramidal neurons might allow targeted activation of corticostriatal pathways and induction of postsynaptic down-scaling in striatal spiny neurons by low frequency stimulation (left). Selective expression of ChR2 in cortical GABAergic interneurons would generate, upon high frequency optical stimulation, a strong intracortical GABAergic inhibition that could reduce the glutamatergic excitatory inputs to striatal spiny neurons (right). Both these approaches could modulate the output signals from the striatum and ameliorate hyperkinetic movement disorders.~~