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Consensus paper: Use of transcranial magnetic stimulation to probe motor cortex plasticity in dystonia and levodopa-induced dyskinesia

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Plasticity includes the ability of the nervous system to optimize neuronal activity at a cellular and system level according to the needs imposed by the environment. Neuroplasticity phenomena within sensorimotor cortex are crucial to enhance function to increase skillfulness. Such plasticity may be termed "adaptive" to indicate its ecologically beneficial role. In professional musicians, enhanced adaptive plasticity is associated with one of the highest level of motor skill a human being can achieve and the amount of these changes is even dependent on the age at which instrumental playing was started. In addition, adaptive neuroplastic changes occur when nervous system try to repair itself thus compensating dysfunctions. However, when these adaptive phenomena are pushed to an extreme, they can produce a maladaptive sensorimotor reorganization that interferes with motor performance rather than improving it. The model we discuss here is focal hand dystonia I which an intrinsic abnormality of neural plasticity, in some predisposed individuals, may lead to abnormal sensorimotor integration and to the appearance of a characteristic movement disorder. Deficient homeostatic control might be an important mechanism triggering this maladaptive reorganization, and future behavioral studies are needed to confirm this hypothesis.

In the second part of this consensus paper, we will critically discuss as a second model, the hypothesis that levodopa-induced dyskinesia correlate with an aberrant form of plasticity in the human primary motor cortex, possibly because of abnormal oscillations within the basal ganglia loop. Disorders of cortical plasticity have not in the past been considered as possible causes of human clinical states. The recognition that this can occur, together with a speculative mechanism, generates an important and provocative hypothesis for future research at the clinical-scientific interface.

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The acquisition of new motor skills relies on the ability of synapses, within motor areas, to undergo changes in synaptic efficiency,[1-3] which are driven by efferent demand and afferent input. For instance, several studies wth string players[4] and piano learners[5] have shown that skillful playing of music require extensive procedural and motor learning that results in plastic reorganization of the human brain. However, a system capable of such flexible reorganization harbors the risk of unwanted changes. The question we would like to address in this consensus paper is whether it is possible to envisage that plasticity phenomena could be affected in diseases and give rise to identifiable clinical states. The model we propose here is focal hand dystonia (FHD), in which patients have involuntary muscle contractions at rest or during the performance of highly skilled fine motor tasks, resulting in impaired motor performance. We argue that normal mechanisms of neural plasticity that are recruited after injury or during practice are abnormal in some individuals. This leads to inappropriate associations between sensory input and motor output and the appearance of a characteristic movement disorder. In the second part of this paper, we will show how patients with Parkinson's disease (PD) and with levodopa-induced dyskinesia (LID) may exhibit a very different type of plasticity alterations within sensorimotor cortex, compared with dystonia, which may be secondary to an altered pattern of oscillations within the basal ganglia loop.

Enhanced gain of plasticity in focal dystonia

Dystonia is a motor disorder characterized by sustained involuntary muscular contractions resulting from cocontraction of antagonistic muscles and overflow into extraneous muscles.[6] One fascinating and intriguing feature of dystonia is the task specificity. For instance, in simple writer's cramp, the mere act of handwriting induces the classic dystonic posture, whereas the same patient can use the hand normally in other motor tasks.[7] Indeed the occurrence of dystonia in these high-skilled stereotypical movements suggests a breakdown within motor memories that may result from abnormal plasticity. In some circumstances, dystonic movements can be the consequence of periods of intensive training of a particular movement.[8] This is the case of musician's dystonia in which patients spend many hours per day with their attention focused on instrumental practice. It has been proposed that synchronous and convergent afferent input arising from repetitive motor tasks may play an important role in driving the abnormal cortical plasticity seen in FHD (discussed later in the text). This hypothesis arises from work conducted in both animal and human subjects. In an animal model of dystonia, Byl et al[9] demonstrated that primates who were trained to make a particular highly specific hand movement (while receiving a synchronous vibration of the whole hand) can develop a clinical condition very similar to FHD. What it is interesting to note is that the finger map within somatosensory cortex was distorted with larger receptive fields and overlapping representations of the individual digits.[9] Therefore, in keeping with these studies, it can be postulated that if motor training is pushed to an extreme, it can produce a maladaptive sensorimotor reorganization that interferes with task performance rather than improving it.[10] In addition, it has been demonstrated that surgical joining of the skin of adjacent digits, which increases synchronous afferent inputs, produces changes similar to over-training.[11] Likewise, in healthy humans, Hebbian-like pairing of tactile stimuli to digits induce a distortion of somatosensory maps.[12] Finally, synchronous stimulation of peripheral muscles induces organizational changes in motor representations, characterized by an increase in map size of stimulated muscles and a reduction in map separation, as assessed b using transcranial magnetic stimulation (TMS).[13] Even if none of these subjects had an overt dystonia develop, motor map disorganization was similar to that observed in both motor[14] and sensory representation[15] in FHD. Although the results of these studies are very obvious, on the other hand, they only show that some types of repetitive activity can lead to an abnormal reorganization of the sensorimotor cortex and dystonia but does not give any clues as to why only in humans, some subjects do have dystonia develop after excessive training, whereas others are completely healthy.

It could be hypothesized that subtle abnormalities of plasticity may render some individuals susceptible to dystonia if plastic changes are driven to their extreme by frequent repetition. Given the low penetrance of dystonia in familial cases,[16] identification of genetic mutations or polymorphisms determining increased susceptibility is challenging. Indeed, there is now evidence suggesting that mechanisms of neural plasticity that are recruited after injury or during practice may be subtly abnormal in dystonic patients.[17-20] A number of noninvasive neurophysiologic methods have recently been developed to study plasticity at a system level in the human brain looking at long-term potentation (LTP) and long-term depression (LTD)-like phenomena. The paired associative-stimulation (PAS) protocol consists of repetitive TMS (rTMS) over the motor cortex with each magnetic stimulus paired with contralateral peripheral nerve stimulation.[21] This protocol resembles experimental procedures producing Hebbian LTP/LTD- plasticity in animal experimentation. By using PAS, it was demonstrated that the LTP-like facilitatory

effects on TMS-evoked motor evoked potentials (MEPs) recorded from the target muscle were enhanced in writer's cramp patients.[17,18] Because PAS-induced effects in some studies[22] were shown to be partly mediated by changes in spinal cord excitability, it remains a possibility that abnormal PAS-induced plasticity is related to abnormalities in the spinal cord. In addition, abnormal plasticity has also been found within the blink reflex circuits of the brainstem in patients with blepharospasm, a focal dystonia affecting the eyelid closing muscles.[23]

The magnitude of the after effects induced by plasticity-driving protocols is strongly influenced by the activation history of the targeted neuronal circuit[1,20,24] (faulty regulation of homeostatic-like plasticity in humans is described later in this text). Indeed, LTP-like plasticity is occluded or even reversed in healthy subjects immediately after a short period of learning a simple motor task.[1,24] Consequently, one might suggest that reduced activity in targeted neuronal circuits induces the opposite effect and enhances LTP-like plasticity. It could be hypothesized that the enhanced PAS-induced facilitation in dystonia patients is due to a reduced use of the affected hand, thus simply indicating a phenomenon secondary to the development of dystonic symptoms. If this is the case, then the enhancement of facilitatory PAS-induced plasticity could be simply caused by an activity-dependent lateral shift of the synaptic modification threshold[25-27] between enhancing and suppressing induction conditions. In keeping with this notion, the efficacy of PAS10 to induce LTD-like excitability changes should be decreased, because the formation of LTD is decreased by prior synaptic inactivity.[28] However, this was not the case in patients with FHD in whom PAS10-induced depression of cortical excitability exceeded that obtained in healthy controls.[18]

Accordingly, 1 Hz rTMS applied to the premotor cortex was previously shown to suppress metabolic activity at the site of stimulation as well as at the primary motor cortex and supplementary motor area.[29] Siebner et al[29] found that changes in activity were more pronounced in patients than in nondystonic subjects. It seemed that the premotor cortex and connected motor areas were reacting more strongly than normal to rTMS conditioning. Indeed, both enhanced PAS10-induced suppression of corticospinal excitability[18] and enhanced metabolic depression by 1 Hz rTMS[29] suggested that dystonia is not only characterized by too much facilitatory plasticity, but may also exhibit enhanced inhibitory plasticity just as well.

In addition there are at least three other different lines of research that seem to be in agreement with the hypothesis of aberrant plasticity in dystonia. First, Quartarone et al[30] have recently demonstrated that this excessive motor cortex plasticity is not restricted to the circuits clinically affected by dystonia, but generalizes across the entire sensorimotor system, which was suggested to possibly represent an endophenotypic trait of the disease. Largely similar observations were made by Schramm et al.[31]

Second, Edwards et al[19] reported that the suppressive effect of theta burst stimulation (TBS) was enhanced in patients with primary dystonia, whether because of the DYT1 gene or other causes. Nonaffected DYT1 gene carriers also differed from the controls but in the opposite direction, with no effect of such an intervention. In other words, the lack of TBS after effects in nonaffected DYT1 gene carriers may protect them from having dystonia develop.[19]

Third, in a population of patients with psychogenic dystonia sensorimotor plasticity was normal.[32] These findings led to the suggestion that the enhanced LTP-like after effects are not just a mere consequence of the abnormal dystonic posture. On the opposite, the experimental data show stronger effects of LTP/LTD-like plasticity inducing protocols in dystonia that suggest the presence of an increased gain of synaptic motor cortical plasticity in dystonia relating to the formation of both LTP- and LTD-like phenomena.

Spatial disorganization of LTP/LTD-like plasticity in writer's cramp

One of the most important feature of associative plasticity in healthy controls is the input specificity because PAS after effects are largely confined to the cortical target representation receiving a dual congruent input.[17,21,33] Instead in writer's cramp patients, PAS tended to enhance excitability also of nearby muscle representations.[17,18] The loss of spatial specificity was more prominent for LTD-like PAS10 protocol.[18] As reported previously, in healthy controls MEP amplitudes were reduced in the homotopically conditioned APB muscle, whereas MEP responses recorded from the heterotopically conditioned ADM were even enhanced. By contrast, in patients, PAS10 suppressed cortical excitability in both homotopically and heterotopically conditioned muscles.[18]

Faulty regulation of sensorimotor plasticity in humans: when plasticity becomes detrimental

What drives the abnormal gain of plasticity and what underlies somatosensory and motor cortical dedifferentiation? Plasticity is controlled by several physiologic mechanisms of which GABAergic inhibition is particularly noteworthy.[34] Abnormalities of intracortical inhibition have been identified previously both in the motor and somatosensory system in dystonic patients.[35,36] Evidence from animal studies suggests that GABA-mediated inhibition plays a pivotal role in spatially focusing LTD-dependent plasticity.[34] Therefore, the loss of spatial specificity of PAS10 after effect may well be explained by a failure of

neuronal surround inhibition. On the other hand, GABAergic inhibition controls LTP induction in somatosensory[37] and motor cortex.[38] A deficient striatal GABAergic inhibition associated with enhanced LTP-formation was found in an animal model of dystonia.[39] In line with this work, it has been demonstrated that the GABA-B receptor agonist baclofen decreases PAS-induced LTP-like plasticity in human motor cortex.[40] What is interesting to note is that the facilitatory effect of associative stimulation on intracortical inhibition, evaluated with cortical silent period (CSP) duration, was attenuated in patients with FHD.[17] In healthy controls, the CSP recorded from the APB muscle was significantly prolonged after associative stimulation,[17,21] whereas in patients with FHD there was only a subtle increase in the duration of the CSP.[17] Because the duration of the CSP is thought to reflect the excitability of cortical (presumably GABA-B) interneurons,[41,42] this finding indicates that these intracortical inhibitory circuits were less responsive to the conditioning effects of associative stimulation in patients with FHD.

Taken together, these data suggest a failure of GABAergic mechanisms that are recruited during LTP-LTD like phenomena within sensory motor cortex and it may be speculated that these could underlie the loss of spatial specificity of PAS-induced after effects. Future studies are needed to further elucidate this point.

However, other mechanisms may serve to constrain the spatial organization and gain of plasticity. For example, neural plasticity is strictly regulated within cerebral cortex by the level of activity in the postsynaptic neuron, which, in turn, depends on the past activity of that neuron: the greater the ongoing activity, the less effective are processes leading to LTP, whereas processes leading to LTD are enhanced. Conversely, the lower the activity of the postsynaptic neurons, the more effective are processes that lead to LTP. These principles are described in the model originally theorized by Bienenstocket al.[25] Given that modifications of synaptic strength must be carefully controlled, it is possible that deficiencies in synaptic scaling may compromise regulation of either magnitude or spatial organization of induced plasticity.[43] Homeostatic-like plasticity in human motor cortex may be probed noninvasively by using several neurophysiologic approaches.[44] In one of these paradigms, transcranial direct current stimulation (tDCS) is used to precondition the response of the motor cortex to a subsequent period of rTMS. Preconditioning of the primary motor cortex with a facilitating protocol (10 minutes of anodal tDCS) leads to an increase in the inhibitory effect that is induced by subsequent 1 Hz rTMS. On the contrary, preconditioning with a suppressing protocol (10 minutes of cathodal tDCS), causes subsequent 1 Hz rTMS to facilitate corticospinal excitability instead of the usual inhibition. Quartarone et al[45] applied this protocol of homeostatic-like plasticity in patients with FHD to see whether the after-effects of 1 Hz rTMS can be modulated to the same extent as in controls. Anodal tDCS produced a facilitatory effect on corticospinal excitability in FHD comparable with controls subjects; however, unlike in the controls, 1 Hz rTMS failed to completely counteract the increase in cortical excitability induced by anodal tDCS.[45] This finding might suggest that dystonia patients have a reduced efficiency of mechanisms that reverse plasticity in motor cortex. In other words, their nervous system does not have the usual arsenal of adaptive mechanisms that limit the allowed level of synaptic potentiation. It can be hypothesized that a fine regulation of synaptic strength reduces behavioral interference between overlapping motor tasks, thus avoiding the consolidation of abnormal movement combinations. Although there is no direct evidence on the pathogenic role of a homeostatic plasticity dysfunction on motor behaviors, we believe that when this process goes wrong, it leads to interference between tasks possibly causing dystonic postures.[10] Future behavioral studies are needed to further clarify this issue.

On the other side, cathodal tDCS failed to produce any inhibitory effect on motor cortex excitability of patients affected by dystonia.[45] This may be because tDCS does not only act via synaptic mechanisms, but is also mediated by changes in membrane polarization.[46] We can speculate that this failure to induce inhibition might reflect hyperpolarization of cell membrane potentials at rest in FHD. Again, 1 Hz rTMS did not shape cortical excitability after cathodal tDCS. However, because of the lack of cathodal priming effects, it is not possible to make firm conclusions about the response of homeostatic mechanisms to inhibitory preconditioning.

Abnormal sensorimotor plasticity and abnormal motor learning in FHD

Although the deficits in sensorimotor plasticity are clear, we cannot immediately assert that they have a role in producing dystonic symptoms unless we can show that these artificial paradigms interact with motor behaviors in some way. Two recent studies suggest that this is indeed the case. In healthy volunteers, changes in motor cortex plasticity induced by TMS paradigms interact with learning of simple motor tasks in a manner expected of homeostatic plasticity. Wycislo and Classen,[47] Ziemann et al,[1] and Stefan et al[24] tested how a short period of behavioral motor learning changed the amount of plasticity induced by a standard PAS protocol. They found that the amount of facilitatory PAS was reduced after learning, whereas the amount of inhibitory PAS was increased or remained unchanged. The data suggest that PAS probably shares similar circuits engaged in motor learning. If this is the case, then we can infer that patients with FHD may have abnormalities of motor learning.

This assumption is in line with studies of motor learning either in human and animal models of dystonia. A mutation in the gene coding for torsin A (DYT1 mutation) leads to

dystonia in about 30% of mutation carriers. Ghilardi et al[48] showed that clinically unaffected human carriers of the mutation acquired a novel motor task less rapidly than non-mutation carriers. Because motor function was apparently normal in the nonaffected mutation carriers, impairment of skill acquisition in this cohort cannot be attributed to faulty motor performance itself during the learning, and suggests instead that plasticity processes underlying motor learning may be abnormal. In keeping with these findings, motor learning was impaired in nondystonic mice expressing torsin A with DYT1 dystonia mutation.[49] Although these studies suggest an abnormality of plasticity, at least behaviorally in some models of dystonia, they also suggest that perhaps abnormal plasticity alone may not be sufficient to generate a dystonic phenotype.

In conclusion, even if there is plenty of evidence that abnormal plasticity is involved in the pathogenesis of dystonia, there is no direct evidence that is the primary cause of the dystonic symptoms.

Can clinical features of dystonia be matched to abnormalities of cortical plasticity?

As noted previously, previous work[1,24] has demonstrated that the type of plasticity that is probed by PAS may be closely related to neuronal mechanisms involved in motor learning by repeated practice. PAS involves activity in somatosensory afferents along with activation of intracortical circuits. This is important because dystonia, as pointed out previously, may develop after alterations of somatosensory inputs, such as after sensory nerve lesions and painful trauma. Therefore, it can be postulated that in dystonic patients during skilled motor practice, there is an excessive tendency to form associations between sensory inputs and motor outputs that may lead to dedifferentiation of motor representations. Abnormalities of spatial properties may be tightly related to overflow of muscular activity to extraneous muscles. In addition, loss of spatial differentiation may be relevant for progression of dystonia toward adjacent body segments. The loss of spatial specificity of PAS10-induced depressant effects is also very important in disrupting motor organization as LTD is fundamental in reducing cortical responsiveness to behaviorally irrelevant or unused sensory stimuli.[50] In conclusion, taken together, the current findings suggest that alterations of sensorimotor plasticity may account for some peculiar clinical features of dystonia.

Is enhanced plasticity always pathologic? Evidence from professional musicians

Opposed to the findings outlined previously, recent studies have also shown that enhanced PAS-induced LTP/LTD-like plasticity is not necessarily and exclusively associated with a loss of hand motor control. On the contrary, it is associated with one of the highest level of motor skill a human being can achieve, that of professional musicians. These persons show enhanced LTP/LTD-like plasticity and also steeper recruitment of corticospinal and intracortical inhibitory excitability, as measured with the input-output curves (IO curves)[51] and short-intracortical inhibition curves (SICI curves).[52] Furthermore, the amount of these changes is even dependent on the age at which instrumental playing was started: the earlier they started, the wider is their range of PAS-induced synaptic modifiability and the steeper is their recruitment of corticospinal and intracortical inhibitory projections.[53] Imaging studies have shown that musicians have structural alterations in their brains.[54-58] Indeed, the increase in grey matter volume in the sensorimotor cortex is larger in musicians who started to play their instrument at an earlier age,55 and it reflects the choice of instrument,58 consistent with a causal connection between presumed synaptic growth and the duration and pattern of training. If so, then it may be that increased synaptic connectivity is one factor that leads to increased recruitment of corticospinal and intracortical inhibitory connections in musicians.

These findings in healthy musicians highlight one important point. The interpretation of any differences in the effect of plasticity-inducing protocols, such as PAS, between groups of individuals depends on whether the slopes of the IO curves before the intervention are equal in the groups. For example, using the known effect of increasing TMS intensity on the MEP size as a model for the PAS effect, then an increase in the test pulse by 20% would increase MEP by, for example, 50% in groups with "standard" IO slope. However, if the IO slope were twice as steep, then the increase in MEP would be twice as much, 100%. In many studies, the IO properties of the corticospinal system are described by responses at just 2 stimulation intensities: one eliciting a threshold response and the other one eliciting an MEP response of a certain amplitude, such as 1 mV. However, the IO curve may not be linear at higher intensities. Because in musicians and nonmusicians, the slopes of the baseline IO curve were indeed different, it was important to test the effect of PAS over the entire range of input intensities by measuring the IO curve and its slope. Rosenkranz et al[53] found that in musicians, PAS increased the slope of the IO curve significantly more and therefore that PAS had a greater effect than in nonmusicians. If the steeper baseline IO curve in musicians reflects an increased number of interneuronal connections caused by adaptation to long-term musical training, a proportionally stronger PAS effect suggests that these (additional) synapses are also associated with a higher propensity of the target circuit to undergo changes in synaptic efficacy.[53]

These considerations are pertinent to the interpretation of the findings in dystonia. The PAS effects in healthy subjects and in dystonia patients have only been measured as amplitude change of MEPs evoked by a standard test

pulse or by looking at changes in the duration of cortical silent period.[1,17,18,21,59,60] However, differences in corticospinal recruitment (IO curves) have been described in dystonia patients[61,62] showing that they, too, have a steeper recruitment of corticospinal projections. The changes of MEP amplitudes after LTP/LTD-like plasticity inducing protocols (for example, PAS25) do represent a change in excitability. However, to better distinguish whether this change in excitability is due to changed efficacy within a given pool of synapses (synaptic plasticity) or to a quicker recruitment of synapses within a more densely connected or even overlapping network, the IO curve would have been needed as a more comprehensive measures of excitability recruitment. The latter option could also explain the "loss of spatial specificity" in the target versus nontarget muscles (discussed in previous text), which has been reported in dystonia patients.[17,63] Indeed, a recent study comparing PAS-induced LTP/LTD-like plasticity in healthy musicians and musician's dystonia patients, whose IO curves were similar at baseline, showed no significant differences in the amount of slope change, indicating that synaptic plasticity in healthy and dystonic musicians operates within a similar range (Rosenkranz et al, unpublished data) . However, it should be also considered that parameters of sensorimotor organization are differently altered in musician's hand dystonia and writer's cramp patients, suggesting pathophysiologic differences.[64]

The model for homeostatic plasticity that forms our understanding of shifts of LTP/LTD-like plasticity is mainly based on findings in healthy subjects after short-term exposure to either experimentally induced LTP/LTD-like plasticity or behavioral interventions that engage LTP, such as short-term motor learning.[1,24] However, changes in neuroplasticity that are associated with dystonia, irrespective of whether they might either precede the symptom manifestation or develop secondary to it, are more likely to resemble longer-term adaptations similar to those seen in long-term learning. Animal studies and recent studies on healthy subjects have shown that mechanisms of short- and long-term motor learning are different.[65-69]

Whereas short-term learning engages LTP, long-term motor learning does not. In fact, if motor training is continued for several days and skill level increases continuously, the recruitment of corticospinal projections and of intracortical inhibition, as well as in the sensorimotor organization of the hand motor area, are changed, whereas the susceptibility to induction of experimental LTP/LTD-like plasticity is restored.[69] Thus, long-term motor learning is likely to rely on motor cortex reorganization, probably by forming new synaptic connections as similarly described in animal studies of long-term learning.[68] In the extreme model of excessive motor learning, such as in professional musicians, there might be an additional shift and increase of the synaptic modification range in addition to this persistent synaptic connectivity that ensures the availability for new synaptic strengthening.[67,69]

Conceptual implications

In addition to the methodologic considerations mentioned previously, these findings have several conceptual implications for the understanding and interpretation of experimental findings on neuroplasticity in dystonia.

1. The neuroplastic changes associated with dystonia are likely to be complex and involve several areas of the brain and different mechanisms of plasticity. Thus, changes in single components have to be set into context to be comprehensively understood. For instance, in professional musicians, the enhanced LTP/LTD-like plasticity is associated with a quicker recruitment of intracortical inhibition that might represent two systems that outbalance each other.[53] One tentative hypothesis, which lacks experimental proof at the moment, could be that in dystonia other factors determine whether enhanced plasticity turns out to be "maladaptive." Several studies on dystonia described a reduced intracortical inhibition[35,36] that might drive the system into decompensation; however, this finding is not a specific trait of organic dystonia.[70-72]
2. Once the symptoms of dystonia are manifest, it is difficult if not impossible to distinguish whether the experimental findings in dystonia represent primary abnormalities and thus might have preceded or even triggered the symptom manifestation, or whether they are an adaptation and developed secondary to the occurrence of symptoms. The dystonic symptoms are characterized by muscle overactivation and also, consequently, by overflow of sensory movement-induced feedback, and surely represent a strong reorganizational force per se. Neurophysiologic abnormalities in measures of motor cortical excitability have been described in organic, psychogenic, and fixed dystonia syndromes,[72,73] thus it is possible that these changes develop as a consequence rather than a cause of dystonia. Similarly, aberrant LTP/LTD-like plasticity might not have an early and primary pathogenic role, but evolve secondarily, a consequence rather than a cause of the disease.[18,53]
3. The interpretation of experimental findings is often influenced by the circumstances or conditions in which they occur. For example, because enhanced plasticity has been described in dystonia, this finding has been interpreted as a "maladaptation," thus a development that either triggers dystonia or interferes with the recovery. However, when put in a different context, for example, in professional musicians, the same experimental finding might get a completely different label and is interpreted as "beneficial" adaptation to increased learning demands. In an attempt to make the findings in dystonia and musicians fit into one comprehensive picture, (a) one might say that enhanced plasticity in professional musicians might increase the propensity for musicians to develop dystonia, thus has a strong tendency to

become "bad," but (b) one might also say that the increased plasticity seen in dystonia patients might indicate that their motor system has switched into the "learning mode" that enables motor programs affected by dystonia to become flexible and adaptable, and thus in principle represent a "good" adaptation. It needs be remembered that both versions are hypothetical interpretations at the moment and any qualitative interpretation of the experimental findings should thus be approached with care.

Cortical plasticity in LID

Chronic dopaminergic treatment of PD is complicated by the development of LID in about 40% of patients after 4-6 years of levodopa therapy.[74] Although several hypotheses have been formulated to explain these motor complications, the underlying mechanism of LID remains unclear. Recently, it was suggested that corticostriatal projections to the basal ganglia[75] may be involved in the pathophysiology of LID. Studies conducted in vitro[76] in animal models of parkinsonism[77] and in PD patients[78] have suggested that the glutamatergic corticostriatal projection to medium spiny neurons in the striatum may play an important role in the priming and development of LID. Medium spiny neurons represent 95% of total striatal cells and receive glutamatergic inputs from all areas of the cortex, activating postsynaptic metabotropic and ionotropic receptors of glutamate. In the central nervous system, ionotropic glutamate receptors, NMDA and AMPA receptors, play a key role in the induction of long-lasting changes in strength of synaptic transmission. Just as in cortical regions, LTP and LTD are needed in the striatum for the production and storage of motor skills. A peculiar feature of synaptic plasticity in the striatum is its relationship with dopaminergic transmission. In fact, dopamine (DA) is essential for induction of striatal LTD and LTP.[79,80] Dopamine inhibits glutamate release,[81] modulating opening, distribution, and anchoring to plasma membranes of AMPA and NMDA receptors.[82] An alteration of striatal LTP and LTD has been found in experimental models of parkinsonism[79,80] when they were subjected to high-frequency cortical stimulation. Moreover, a study conducted in corticostriatal slices from rats experiencing LID has shown that dyskinesia is associated with the inability to down-regulate LTP in the striatum.[83] The studies previously reported suggest that a pathologic form of striatal synaptic plasticity, related to abnormal function of NMDA receptors, could cause the development of atypical motor patterns leading to LID. In late stages of PD, chronic nonphysiologic stimulation of DA receptors on striatal neurons,[84] can induce modifications in NMDA channel firing and thus development of aberrant motor patterns leading to motor complications. This hypothesis is strongly supported by evidence that NMDA receptor antagonists improve motor complications in parkinsonian rats,[85] MPTP primates,[86] and in PD patients.[78] Moreover, a study performed postmortem on brains of PD patients has shown higher levels of NMDA and AMPA receptors in the lateral putamen of those patients experiencing motor complication compared with patients without motor complications and controls.[87]

Synaptic plasticity in PD and LID

Because experimental models of PD are characterized by an abnormal plasticity in corticostriatal system and these findings strictly correlate with the development of dyskinesia, Morgante et al[88] hypothesized that synaptic plasticity might also be abnormal in M1 and that LID in PD might be correlated with it. LTP-like plasticity was tested in the motor cortex by means of PAS25 in two groups of patients with moderate PD with and without peak-dose dyskinesia, matched for disease severity and duration and levodopa equivalents.[88] When tested with the facilitatory PAS protocol during their practically defined OFF state, neither nondyskinetic nor dyskinetic PD patients exhibited any change in MEP amplitude. Levodopa administration restored MEP facilitation induced by PAS in the nondyskinetic only, but not in the dyskinetic PD. Similar findings were reported by Ueki et al[89] in a group of PD patients without dyskinesia characterized by a loss of LTP-like plasticity in M1 off medication. Again, when evaluated after dopaminergic treatment, nondyskinetic PD patients had an increase of MEP amplitude after PAS.[89] These data demonstrate that dopaminergic deficiency may prevent the motor cortex from changing the strength of synaptic connection when applying a repetitive, low-frequency stimulation, similar to the effects of dopaminergic denervation on striatal plasticity described in experimental models of parkinsonism. Whether an altered pattern of neuronal discharge in the basal ganglia may lead to abnormal plasticity in the M1 or this finding rather reflects a reduction of dopaminergic innervations in upper layers of motor and prefrontal cortices,[90] still remains to be established. Whatever the mechanism, the lack of LTP-like plasticity in M1 may account for the disordered motor learning in PD.[91]

A main finding of study by Morgante et al[88] was that dyskinetic PD patients are characterized by deficient synaptic plasticity in the motor cortex even when on medication. This is unlikely to be correlated to the presence of involuntary movements themselves. In fact, the finding that patients with cranial and cervical dystonia,[30] who presented involuntary movements during the recording, exhibit an opposite pattern after PAS, with an excessive increase in cortical excitability and a lack of topographical specificity, makes this explanation unlikely.[17] Moreover, the background electromyographic area was measured in both dyskinetic and nondyskinetic PD patients, without differences between the two groups.[88] The lack of LTP-like plasticity in the M1 might be secondary to the altered patterns of

firing within the basal ganglia loop associated with LID or, alternatively, it could itself play a role in inducing aberrant plasticity in the striatum. If so, the lack of LTP in M1, despite levodopa treatment, could represent an endophenotypic trait predisposing to the development of LID. Alternatively, it may be that deficient LTP-like sensorimotor plasticity reflects an alteration of sensorimotor integration induced by dopaminergic treatment. Indeed, short-afferent inhibition (SAI), a technique which assesses sensorimotor processing, is reduced in PD on medication, possibly reflecting an adverse effect of dopaminergic medications.[92] More interestingly, deep brain stimulation of the subthalamic nucleus (STN-DBS), which has been shown to be effective for LID, improves short latency afferent inhibition.[93] In conclusion, deficient synaptic plasticity in the motor cortex could be correlated to the reduction of SAI induced by dopaminergic medications, thus contributing to the development of dyskinesia.

Methodologic limitations and future directions of research

The data of the current article have shown a substantial progress in the field; however, as was outlined previously, it has become clear that a lot a work remains to be done in the future. Although the presented data seem to be concordant in demonstrating a pathogenetic role of maladaptive plasticity in dystonia and LID, several methodologic factors associated to the TMS procedure must be taken in account before drawing definitive conclusions. It should be considered that the magnitude of PAS after effects in normal subjects are dependent on age,[94] resting motor threshold,[95] and by the time of the day, being stronger when assessed in the evening.[96] Moreover, another significant methodologic factor that needs to be considered in plasticity TMS studies is attention,[47] which can itself decrease, or even reverse, PAS after effects. This is crucial for PD patients in whom an executive dysfunction with lack of attention is a feature of the disease itself. This point was considered in the study by Ueki et al,[89] assessing motor cortex plasticity in PD without dyskinesia; the frontal assessment battery score administered to all patients was in the normal range. Thus, PD patients studied with the PAS protocol had normal executive function and level of attention was kept high during all the TMS recordings. Another factor that might invalidate the data is previous treatment with botulinum toxin (BTX) in FHD patients. In the study by Quartarone et al,[17] only 4 of 10 patients were never treated with BTX and in Weise et al,[18] 6 of 10 patients with FHD had never received BTX.

In addition there are some unclear points that still need to be addressed:

1. The role of the dopaminergic system on sensorimotor plasticity remains to be further explored.
2. The majority of studies on sensorimotor plasticity have been carried out in writer's cramp. However, the motor cortex of patients with writer's cramp is less sensitive than normal to afferent input from the hand, whereas the opposite is true for patients with musician's dystonia.[64] Thus, it might emerge in the future that particular mechanisms of plasticity are affected in different subgroups of individuals.
3. The role of GABAergic circuits deserve further study as a potential source of the abnormal sensorimotor plasticity in patients affected by dystonia. According to this hypothesis, reduced inhibition may not itself lead to a dystonic phenotype but only by virtue of its effects on synaptic plasticity. Although this assumption is obvious from animal studies this has not been demonstrated in vivo in humans.

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