

# Maladaptive plasticity in levodopa-induced dyskinesias and tardive dyskinesias: old and new insights on the effects of dopamine receptor pharmacology

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Maladaptive plasticity can be defined as behavioral loss or even development of disease symptoms resulting from aberrant plasticity changes in the human brain. Hyperkinetic movement disorders, in the neurological or psychiatric realms, have been associated with maladaptive neural plasticity that can be expressed by functional changes such as an increase in transmitter release, receptor regulation, and synaptic plasticity or anatomical modifications such as axonal regeneration, sprouting, synaptogenesis, and neurogenesis. Recent evidence from human and animal models provided support to the hypothesis that these phenomena likely depend on altered dopamine turnover induced by long-term drug treatment. However, it is still unclear how and where these altered mechanisms of cortical plasticity may be localized. This study provides an up-to-date overview of these issues together with some reflections on future studies in the field, particularly focusing on two specific disorders (levodopa-induced dyskinesias in Parkinson's disease patients and tardive dyskinesias in schizophrenic patients) where the modern neuroimaging approaches have recently provided new fundamental insights.

**Keywords:** levodopa-induced dyskinesias, tardive dyskinesias, hyperkinetic movement disorders, inferior frontal cortex, dopaminergic treatment

## INTRODUCTION

Plasticity refers to the ability of the nervous system to change the effectiveness of transmission in neural circuits. This can involve changes at several levels (neuronal, synaptic, protein, or genomic structure) and modulates both the structure and function of neuronal networks. Several human and animal studies demonstrated that exercise and/or behavioral enrichment can increase neuronal survival and resistance to brain insult, promote brain vascularization, stimulate neurogenesis, and enhance learning [for review, see Ref. (1)].

Although neural plasticity is generally viewed as an adaptive process, there is considerable evidence that plasticity can also be maladaptive [for review, see Ref. (2)]. For instance, sensory deprivation, chronic stress, and excessive exercise would reduce variability and impair adaptability. In particular, chronic stress is associated with a loss of neurons and synapses. Furthermore, stress may increase activity in certain brain regions, such as the amygdala and the mesolimbic dopaminergic system, leading to hypertrophy of these structures (3). Again, Byl et al. (4) showed that monkeys that were over-trained to make a particular highly specific hand movement sometimes developed difficulties in moving their hands in a similar manner to focal hand dystonia. The somatosensory cortex of these animals was less organized than that of healthy monkeys, with larger receptive fields and overlapping representations of the individual digits. A change in the pattern

of connectivity in the sensory and motor cortices was thought to lead to inappropriate associations between inputs and outputs of the motor areas and cause errors in selecting muscles used in voluntary movement.

However, maladaptive neural plasticity may be triggered not only by exercise and/or behavioral deprivation, but also by other factors, such as chronic drug therapy. In the last few years, several influential authors (5–7) proposed that some hyperkinetic movement disorders [levodopa-induced dyskinesias (LIDs), primary dystonia, Huntington's disease, and tardive dyskinesias (TDs)] are caused by maladaptive synaptic plasticity. The scope of this study is to summarize evidence on the role of dopaminergic replacement in inducing maladaptive neural changes in these hyperkinetic disorders, delineating the presence of shared neural mechanisms. Particular attention will be paid to recent evidence coming from molecular and neuroimaging studies that allow *in vivo* evaluation of neural plasticity.

## PARKINSON'S DISEASE WITH LEVODOPA-INDUCED DYSKINESIAS

The classical clinical picture of Parkinson's disease (PD) consists of motor deficits, such as akinesia, rigidity, tremor, and postural dysfunction. These motor symptoms are greatly improved by treatments with dopamine (DA) replacement therapy or DA agonists, but after 4–6 years, the therapeutic window becomes narrow

and patients start to experience very disabling motor symptoms, such as motor fluctuations and LIDs. LIDs in PD has been thought to originate from an imbalance between “direct” and “indirect” pathways regulating neural activity in the striato-frontal network (8, 9). The neurons of the direct pathway project to the globus pallidus pars interna (GPI) and onward to the thalamus. The neurons comprise the indirect pathway project to the globus pallidus pars externa (GPe), where they synapse with more GABAergic projection neurons. In turn, these neurons project to the subthalamic nuclei (STN) and form synapses with the glutamatergic neurons that provide output to the GPI and the substantia nigra pars reticulata (SNr). The essential pathophysiological characteristic of the LIDs state is the presence of under-activity of the indirect pathway and overactivity of the direct pathway. In the last few years, this model has been reinforced and modified to extend knowledge about the interplay between striatal nuclei and the frontal cortex. Indeed, LIDs have also been demonstrated to be associated with a sequence of events that includes pre-synaptic (i.e., increased synaptic level of DA) and post-synaptic modifications (i.e., downstream changes in proteins and genes), and abnormalities in non-DA transmitter systems (9). Overall, all these events combine to produce alterations in the firing patterns and the coherence between the basal ganglia and the cortex, leading to excessive disinhibition of thalamocortical neurons and overactivation of frontal areas, with specific involvement of motor, premotor, and prefrontal cortices (10, 11). The presence of altered cortical excitability in the motor and prefrontal cortex has also been demonstrated by electrophysiological studies employing transcranial magnetic stimulation (TMS) in patients with PD (12, 13). Moreover, as repetitive TMS applied over the supplementary motor area (SMA), the primary motor cortex (M1) was able to induce a transient reduction of LIDs severity (14, 15). Despite the traditional striato-thalamo-cortical pathways, in the last few years, advances in the neurophysiological field provide alternative scenarios highlighting the involvement of other circuits involved in the pathophysiological mechanisms of LIDs. In particular, reduction of peak-dose dyskinesia for up to 4 weeks was described following repeated sessions of continuous theta burst stimulation (cTBS) delivered bilaterally to the lateral cerebellum (16). This later finding would seem to support the hypothesis that alterations in cerebellar sensory processing function, occurring secondary to abnormal basal ganglia signals reaching it, may be an important element contributing to the maladaptive sensorimotor plasticity of motor cortex and the emergence of abnormal involuntary movements (17).

### TARDIVE DYSKINESIAS IN PSYCHIATRIC DISORDERS

Chronic blockage of DA receptors by anti-psychotic drugs in patients with psychiatric disorders has been known to produce another well-known hyperkinetic movement disorder named TDs. Originally, the term TDs referred to abnormal movements produced by long-term DA receptor antagonist therapy, mainly characterized by rapid, repetitive, stereotypic movements affecting mainly the oral, buccal, and lingual areas, and less movements affecting the limb and the trunk; however, other phenomenologies have been described in TDs, such as dystonia and akathisia (18). More than half of TDs cases may persist, even after

conventional antipsychotics are switched to atypical ones (19), or anti-psychotics are discontinued (20). The most popular pathophysiological model for TD is based on DA receptor hypersensitivity triggered by anti-psychotic drugs (7, 21, 22). According to this theory, chronic use of DA antagonists, particularly at high levels of antagonism (i.e., haloperidol), results in gradual hypersensitization of DA receptors. Indeed, chronic administration of neuroleptics might cause adaptive changes in DA receptors, causing an increase in the number of D2 receptors (23). D2 receptors being expressed on indirect pathway medium-spiny neurons and being inhibitory, the consequence of D2 hypersensitivity might determine disinhibition of the GPI and the subthalamic nucleus (7). Support for hypersensitivity of DA receptors in TDs mainly comes from rodent models (24). Moreover, further support comes from clinical observations that increasing anti-psychotic dosage temporarily suppresses TD (25) whereas withdrawing anti-psychotics or administering DA agonists exacerbates dyskinesic symptoms in the short term (21). However, although chronic anti-psychotic use is associated with D2 hypersensitivity, the evidence supporting a direct role on TDs generation are not consistent; indeed, DA receptors binding in PET studies was not correlated with severity of dyskinesias and post-mortem studies did not disclose any difference in number of D2 receptors between patients with and without TDs (26).

### SHARED MALADAPTIVE NEURAL PLASTICITY IN LIDs AND TDs PATIENTS

Although LIDs and TDs are underlined by drugs acting on the DA receptor in an opposite way and associated with different diseases, there is evidence for shared neurodegenerative mechanisms, likely depending on aberrant neural plasticity in the prefrontal cortex.

The development of LIDs has been attributed in cell studies to dysfunctional cortico-striatal plasticity triggered by the combined effects of DA denervation and chronic pharmacological DA replacement (27) and has also been demonstrated *in vivo* in PD patients with LIDs (12, 13). Chronic non-physiologic stimulation of DA receptors on striatal neurons (23) can induce modifications in NMDA receptors firing and thus the development of aberrant motor patterns leading to motor complications. This has provided the rationale for the use of NMDA receptor antagonists such as amantadine for treating PD patients with LIDs (28). Despite the recent evidence on the efficacious effects of amantadine in ameliorating LIDs [improved motor symptoms in 60–70% of patients; (29)], the restoring of deficient DA with its precursor L-3,4-dihydroxyphenylalanine (levodopa) is again the most effective treatment for PD. In the last decades, concern has been raised that levodopa could have toxic effects on the brain of patients with PD (30). Although some *in vitro* studies support this hypothesis (31), this concern remains uncertain in human studies (32). Recent evidence coming from neuroimaging studies has provided new impetus to unravel the potential effects of levodopa on brain morphometry. Indeed, our group has recently demonstrated that specific morphological alterations are associated with the development of LIDs in PD patients (33). Using unbiased voxel-based morphometry to compare gray matter volume in dyskinesic and non-dyskinesic patients, closely matched for age, duration of medication and age of onset, we observed

significant increases of gray matter volume within the inferior frontal cortex (IFC), the degree of which increased with the severity of motor fluctuations. The IFC is an associative area specifically involved, together with motor and premotor cortices, basal ganglia and STN, in the regulation of motor inhibition (34). The presence of “increased” gray matter volume was in accordance with other neuroimaging studies investigating the neurobiological effects of levodopa treatment in healthy individuals. Indeed, Salgado-Pineda et al. (35) demonstrated an increased gray matter volume in healthy controls 1 week after levodopa administration. All this evidence suggested that levodopa applied in a pulsatile and non-physiological manner can perturb the normal physiological mechanisms that mediate motor control and eventually result in the remodeling of neuronal contacts and pathways, producing long-lasting changes and aberrant neural plasticity (i.e., increased neuronal arborization). The presence of altered anatomy of the IFC has been confirmed using different populations (36) and neuroimaging metrics [i.e., cortical thickness; Ref. (37)] and has raised an interesting scientific debate on the potential effects of levodopa on brain morphometry (38, 39). In particular, the main notion proposed by Vernon and Modo (38) concerned the key role that animal models of PD would play in providing new insight about the hypothesis proposed above. Indeed, although several models of basal ganglia dysfunctions have been proposed to understand the pathophysiological mechanisms underlying motor manifestations in patients with PD (8), these changes cannot completely explain the overall motor symptoms of LIDs in patients. Indeed, a large body of *in vitro* and *in vivo* studies in animal models of parkinsonism have suggested an alternative “glutamatergic” hypothesis for LIDs. Several authors demonstrated that the glutamatergic cortico-striatal projection to medium-spiny neurons might play an important role in the priming and development of LIDs, by induction of abnormal synaptic plasticity at the cortico-striatal level (40–42). The alteration of glutamatergic transmission as causative of LIDs has also been demonstrated *in vivo* by Ahmed et al. (43), who described abnormalities in glutamate transmission in striatal and frontal regions in dyskinetic compared to non-dyskinetic patients with PD. Despite the plethora of studies supporting the glutamatergic contribution to LIDs, there is also a vast consensus that dysfunctions of the serotonergic system are implicated in the development of LIDs and other complications of levodopa therapy. Indeed, serotonin neurons have the ability to synthesize, store, and release DA, formed from exogenous levodopa, but due to the lack of any autoregulatory feedback control, the DA released from serotonin terminals generally show excessive swings in the patients in response to repetitive, intermittent levodopa treatment (44). Such dysregulated release of levodopa-derived DA is likely to be the main trigger of dyskinesia in levodopa-primed animals (44), and may also play a role in PD patients undergoing long-term levodopa therapy (45, 46). Using animal models, Rylander et al. (47) provided the first evidence that levodopa treatment induces sprouting of serotonin axon terminals, with an increased incidence of synaptic contacts and a larger activity-dependent potentiation of DA release in the DA-denervated striatum. This latter finding is of great interest since our reported morphological abnormalities in patients with LIDs (33, 36) highlighted the role of the IFC,

a region strongly innervated and regulated by the serotonergic system (48, 49).

Interestingly, similar evidence, highlighting the presence of neural abnormalities in the IFC driven by chronic DA therapy, has also been provided in the psychiatric realm. In particular, chronic psychotropic treatment might cause either adaptive changes in DA receptors (increase in the number of D2 receptors and supersensitivity of D1 receptors) (50) or determine structural remodeling of the brain. Post-mortem studies investigating brains of schizophrenic patients with long duration of anti-psychotic exposure (i.e., haloperidol) showed significant structural abnormalities (51–54), with evidence for slight shrinkage (5%) of the brain in terms of weight, length, and cortical volume and for enlarged (15%) ventricles. Animal studies have confirmed this evidence, demonstrating that chronic (8 weeks) exposure to both haloperidol and olanzapine resulted in significant decreases in whole-brain volume (6–8%) driven mainly by a decrease in frontal cerebral cortex volume (8–12%) (55). Finally, a recent *in vivo* neuroimaging study investigating the neuroanatomical differences between schizophrenic patients with TDs with respect to patients without TDs (closely matched for age at onset of illness, duration of illness, or anti-psychotic chlorpromazine equivalent dose) demonstrated, for the first time, the presence of volumetric abnormalities in the same prefrontal region described in patients with LIDs: the IFC. The merit of this work (56) was to provide evidence on the presence of maladaptive neural rearrangements in the IFC driven by chronic psychotropic treatment.

## CONCLUSION

Although all these findings are pieces of a very difficult puzzle to assemble, what clearly emerged is that all these disorders have been associated with altered DA turnover induced by long-term drug treatment that might ultimately induce maladaptive synaptic plasticity. We believe that further advances in the understanding of the maladaptive mechanisms of synaptic plasticity in other hyperkinetic movement disorders (Tourette syndrome, dystonia, and Huntington’s disease) will lead in the next few years to defining the exact biological impact of chronic DA therapy on the neurological and psychiatric brain, which might ultimately stimulate development for new treatments. For instance, in a recent neuroimaging study, Ganos et al. (57) described the presence of gray matter abnormalities of the IFC in patients affected by Tics in Gilles de la Tourette syndrome. So far, evidence emerging from recent molecular and neuroimaging studies would seem to suggest an intriguing hypothesis that some important hyperkinetic movement disorders might share similar pathophysiological mechanisms (7). In particular, part of these shared mechanisms would seem to be localized outside the classical motor pathway (cerebellum-striato-thalamic-motor network), involving a critical region (IFC) taking part in the hyperdirect pathway, a neural circuit playing a critical role in motor control (58), which might become a new potential therapeutic target for future studies (59).

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