The role of neuroplasticity in dopaminergic therapy for Parkinson disease

Xiaoxi Zhuang, Pietro Mazzoni and Un Jung Kang

Abstract | Dopamine replacement is a mainstay of therapeutic strategies for Parkinson disease (PD). The motor response to therapy involves an immediate improvement in motor function, known as the short-duration response (SDR), followed by a long-duration response (LDR) that develops more slowly, over weeks. Here, we review evidence in patients and animal models suggesting that dopamine-dependent corticostriatal plasticity, and retention of such plasticity in the absence of dopamine, are the mechanisms underlying the LDR. Conversely, experience-dependent aberrant plasticity that develops slowly under reduced dopamine levels could contribute substantially to PD motor symptoms before initiation of dopamine replacement therapy. We place these findings in the context of the role of dopamine in basal ganglia function and corticostriatal plasticity, and provide a new framework suggesting that therapies that enhance the LDR could be more effective than those targeting the SDR. We further propose that changes in neuroplasticity constitute a form of disease modification that is distinct from prevention of degeneration, and could be responsible for some of the unexplained disease-modifying effects of certain therapies. Understanding such plasticity could provide novel therapeutic approaches that combine rehabilitation and pharmacotherapy for treatment of neurological and psychiatric disorders involving basal ganglia dysfunction.

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Introduction

Neurodegenerative disorders such as Parkinson disease (PD) are generally considered to be progressive conditions that involve gradual degeneration of specific neuronal subgroups, and their symptoms are viewed as deficits that are passive manifestations of neuronal loss. As such, treatment of PD with dopaminergic agents would be expected to restore the missing neurotransmitter and ameliorate clinical deficits in a consistent and predictable way. Indeed, dopaminergic agents elicit a well-established immediate and dramatic response, consisting of improved mobility.[1,2] In about 50% of patients, however, the motor response to dopaminergic agents begins to fluctuate after ~4–6 years of treatment and becomes shorter in duration, with parkinsonian symptoms re-emerging at the end of dosing intervals ('wearing off').[3,4] In addition, abnormal involuntary movements, termed levodopa-induced dyskinesias, appear with a similar time course following initiation of dopamine replacement therapy.[4–6]

The above observations are not easily explained by a static model in which deficits result from loss of dopamine, and restorative effects of therapy are solely due to direct neurotransmitter replacement. Conversely, neural plasticity as evidenced by physiological and biochemical measurements has been noted in response to the loss of dopaminergic input and to long-term dopaminergic therapy.[7–9] Some researchers have suggested that these responses represent compensatory changes that reduce and delay the symptomatic motor deficit from dopamine loss,[10,11] but the functional significance of these changes has yet to be delineated.

This Review focuses primarily on neuroplasticity mechanisms that underlie fluctuations in the motor response to dopamine replacement therapy, because recent research enables us to make specific, testable hypotheses that link clinical phenomena to behaviours in animal models and electrophysiological and molecular mechanisms of synaptic plasticity. We review the evidence that a specific component of the response to dopaminergic therapy—namely, the long-duration response (LDR)—is the key driver of motor response fluctuations, and propose the hypothesis that the LDR represents motor learning mediated by the basal ganglia. To elaborate on this hypothesis, we review the literature on the role of dopamine in modulation of cell excitability and synaptic plasticity, and discuss whether the above proposed processes are plausible potential mechanisms for the LDR. We then discuss empirical evidence from animal and human studies that support the hypothesis. Although we focus on the LDR in PD, our hypothesis has broader implications for many disorders involving abnormal function of the basal ganglia.

Motor response to levodopa

Short-duration response

Improvement in motor function produced by dopaminergic medication is one of the most dramatic and

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Key points

- Dopaminergic loss and therapy in Parkinson disease (PD) leads to changes in synaptic plasticity, particularly at cortiostriatal synapses
- The motor response to dopamine therapy involves acute improvement in motor performance (short-duration response [SDR]) and a more gradual improvement in motor function (long-duration response [LDR]) that develops over weeks
- Clinical evidence shows that the LDR is a critical component of motor response fluctuations and may be a more effective target of therapy than the SDR
- Motor learning mediated by synaptic plasticity in the basal ganglia circuitry results in the LDR in an animal model of PD
- Synergistic interaction between effects of physical activity and dopamine signalling contributes to the LDR
- Enhancement of motor learning and prevention of aberrant plasticity and learned inhibitory behaviour could be a novel approach to disease modification in PD

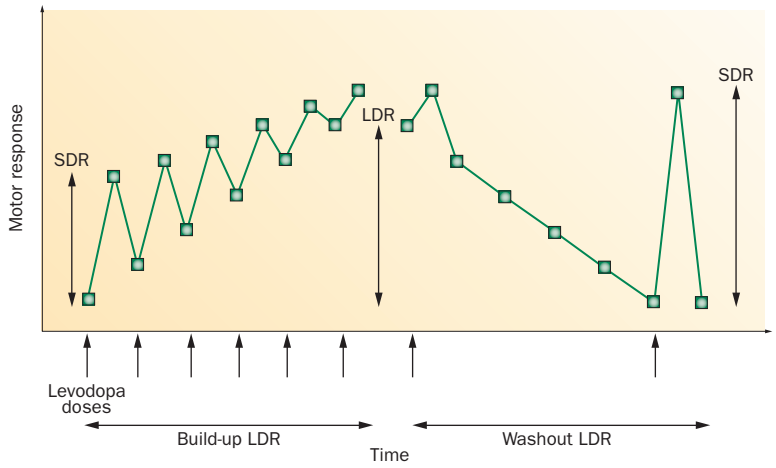

Figure 1 | The long-duration response and short-duration response to levodopa. In patients with PD, each dose of levodopa (vertical arrow) produces an SDR. Both the peak and trough levels of motor response build up slowly with repeated treatment. In early stages of PD, the LDR component can be greater in magnitude than the SDR. Daily testing of motor performance after withdrawal from levodopa treatment reveals a gradual decline to baseline. When a single dose of levodopa is given after a washout period, the SDR appears to be greater in magnitude than the SDR observed before the washout. This apparent increase in SDR is due to the loss of the LDR, which mainly affects the trough levels, but not the peak levels, of the motor response.[14–16] Abbreviations: LDR, long-duration response; PD, Parkinson disease; SDR, short-duration response.

well-established effects of therapies for PD. The immediate response to acute levodopa challenge is sometimes used as a diagnostic test for PD, because such a response indicates a presynaptic dopaminergic deficit.[12,13] This type of response is, therefore, often referred to as the short-duration response (SDR) although such a definition is not entirely accurate, as discussed below. Levodopa therapy administered several times a day initially has sustained benefit for the patient, with little variation in motor function from dose to dose. In advanced-stage PD, however, the effect of each levodopa dose wears off after a few hours and is restored shortly after another dose of medication. This 'wearing off' occurs despite the fact that the peripheral pharmacokinetic properties of drug handling and metabolism have not changed over time.[14]

Wearing off has often been attributed to shortening of the duration of the SDR and, therefore, the SDR has been the focus of efforts to understand the mechanism underlying motor fluctuations and to develop new therapeutic approaches. To achieve a sustained SDR to dopaminergic stimulation, substantial efforts have gone into development of long-acting synthetic dopamine agonists, drugs that block levodopa or dopamine metabolism, and slow-release preparations of levodopa. However, modification of the pharmacokinetic properties of these therapeutic agents has produced only partial improvement in clinical outcome.[6] Consistent with this result, pharmacodynamic characterization in a cohort of patients with PD demonstrated that the SDR to dopaminergic therapy increased in magnitude and showed decreased latency of onset over 4 years, but was largely unchanged in duration.[15,16] In addition, a rodent model of SDR involving improvement of akinesia as the primary measure, rather than the commonly used drug-induced rotational behaviour, showed a similar pattern of SDR changes over time.[17] These studies suggest that changes in the SDR are not sufficient to account for the wearing-off phenomenon.

Long-duration response

The stable therapeutic response to dopamine replacement in early-stage PD cannot be completely predicted by pharmacological properties of the drugs, suggesting involvement of mechanisms beyond acute responses to individual drug doses.[18] Although less studied than the SDR, the LDR has been hypothesized to contribute to the response to therapy that develops over days to weeks of chronic use of dopaminergic medications,[19,20] and continues to gradually accumulate over a few months (Figure 1).[21] As both the SDR and LDR are components of the observed responses to PD therapy and often cannot be clearly distinguished from each other, in this Review we use these terms to refer to the hypothetical underlying processes rather than the observed responses.

Observed responses are regarded as the combination of the SDR and the LDR. Nevertheless, the SDR can be unambiguously observed when dopamine therapy is given acutely without prior treatment, and the LDR after multiple doses can be inferred on the basis of the observed response and known SDR. In early PD, the magnitude of the LDR is as large as or greater than that of the SDR,[21,22] often obscuring the true extent of the SDR magnitude.[23] This contribution of the LDR accounts for the lack of apparent motor response fluctuation to dopaminergic drugs. On the other hand, the loss of the LDR allows more-severe parkinsonian symptoms to appear at the end of the dose intervals, making the motor fluctuations in advanced PD more noticeable.[15,16] As such, the LDR rather than the SDR determines the trough level of wearing off.

Just as the LDR builds up slowly after initiation of dopamine replacement therapy, it also dissipates slowly in the absence of dopaminergic therapy or with inadequate therapy.[16] The duration of the LDR has been estimated to be several days to weeks after discontinuation of either levodopa or dopamine agonists.[14,21,24,25] On the basis of total Unified Parkinson Disease Rating Scale scores, one study estimated the half-life of both

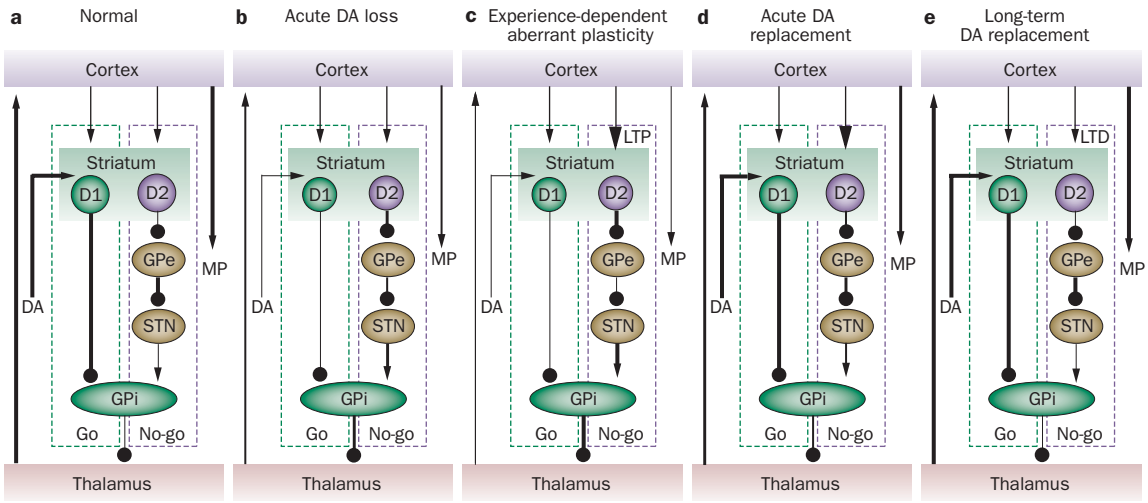

Figure 2 | Dopaminergic modulation of striatal cell excitability and corticostriatal plasticity. Arrowheads represent excitatory synaptic connections and bulbheads represent inhibitory synaptic connections; line thickness corresponds to level of neuronal activity and head size corresponds to synaptic strength. **a** | Activity in corticostriatal loops is modulated by DAergic input from the substantia nigra. The D1-expressing 'go' pathway increases cortical activity and facilitates movement. The D2-expressing, indirect, striatopallidal 'no-go' pathway reduces cortical activity and inhibits movement. DA increases the responsiveness of the go pathway and decreases the influence of the no-go pathway. **b** | Reduction in DA levels favours the inhibitory no-go pathway. **c** | With reduced DA and experience-dependent cortical input to striatal neurons, aberrant LTP develops at corticostriatal synapses in the no-go pathway, leading to 'learned' motor inhibition. **d** | DA replacement therapy has immediate therapeutic effects (the SDR) due to D1–D2 activation, although aberrant LTP is not reversed. DA only partially overcomes the indirect pathway abnormality. **e** | Repeated DA replacement therapy and experience-dependent cortical input to striatal neurons facilitates normal LTD at corticostriatal synapses in the no-go pathway, which restores normal activity (the LDR). Abbreviations: DA, dopamine; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; LDR, long-duration response; LTP; long-term potentiation; MP, motor performance; SDR, short-duration response; STN, subthalamic nucleus.

levodopa and bromocriptine-mediated LDR to be about 8 days.[25] In a recent study of chronic levodopa treatment in patients with early-stage PD, the LDR declined by only 15% over a 2-week withdrawal period,[21] suggesting a slower rate of dissipation of the beneficial effect of the LDR than was previously realized.

The rate of LDR loss is faster in more advanced PD than in early PD, and in the more affected side of the body than in the less affected side.[15,16] The effect of disease severity on the magnitude of the LDR is less clear,[15,22,26,27] in part because a long withdrawal period would be required to assess the magnitude of the LDR. Preservation of presynaptic storage of dopamine in early PD, compared with in advanced PD, was initially suggested to underlie the slower loss of the LDR in early PD. The presence of the LDR following administration of dopamine agonists, however, suggests involvement of postsynaptic rather than presynaptic mechanisms, as such agonists do not rely on presynaptic storage.[14,24,25] Changes in peptide expression in postsynaptic striatal neurons depend on the extent of loss of dopaminergic afferents,[28,29] and such differential postsynaptic changes could mediate the variability in the degree and time course of the LDR with disease progression.

Dopamine and basal ganglia function

To understand the biological basis of the SDR and LDR, it is important to review the role of dopamine in basal ganglia function. The striatum is the main entry point for cortical glutamatergic inputs to the basal ganglia, which contribute to corticostriatal loops. According to the classic model of basal ganglia function,[30–33] corticostriatal loops are divided into two parallel pathways, and activity in these pathways is modulated by dopaminergic input from the substantia nigra (Figure 2a). Activity in the D1-expressing, direct, striatonigral 'go' pathway increases excitation of cortical activity and facilitates movement. By contrast, activity in the D2-expressing, indirect, striatopallidal 'no-go' pathway increases inhibition of cortical activity and inhibits movement.[33,34]

At the cellular level, activation of dopamine receptors on striatal medium spiny neurons (MSNs) modulates gating of ion channels and, therefore, acutely alters the intrinsic excitability of these neurons.[35–37] Activation of D1 receptors increases the excitability of MSNs in the direct pathway, whereas activation of D2 receptors decreases the excitability of MSNs in the indirect pathway (Figure 2a). Both mechanisms increase motor output when dopamine release is increased. Conversely, a reduction in dopamine favours the inhibitory no-go pathway, which reduces motor output (Figure 2b). Dopamine can, therefore, differentially modulate the excitability of MSNs in both the direct and indirect pathways, with a net effect of facilitating movement. Moreover, dopamine also modulates glutamate release from corticostriatal terminals via D2 receptors localized on the terminal.[38,39] In summary, through regulation of corticostriatal throughput in the direct and indirect pathways, dopamine has a direct modulatory effect on immediate motor performance, which is the mechanism suggested to underlie the SDR.

Box 1 | Basal ganglia-mediated motor learning: evidence from human studies

The basal ganglia play a key part in motor learning, and can be considered to have a unified role as a 'selection machine'[94,95] in motor sequence (selection of what movement to make) and skill learning (selection of optimal movement parameters). Patients with basal ganglia disorders, such as Parkinson disease (PD) and Huntington disease (HD), are impaired in some motor learning tasks but not in others. This variation might relate to differences in types of motor learning, which include adaptation, sequence learning, and motor skill learning.[96]

Adaptation

Adaptation is the gradual return to normal performance after introduction of a perturbation,[97] as occurs after we change the sensitivity of our computer mouse. In the brain, adaptation is associated with cerebellar activation,[98,99] and is impaired by cerebellar disease.[100–102] In most studies, adaptation is normal in patients with PD and HD.[102–105]

Sequence learning

Sequence learning refers to learning a series of movements, such as hitting a series of keys[106] or targets.[107] It results in learning what movements to perform (action selection), and is normally accompanied by basal ganglia activation[108] and release of striatal dopamine.[109,110] Patients with PD and HD are impaired in sequence learning.[111]

Motor skill learning

Motor skill learning emphasizes improvement of performance over baseline level and results in acquisition of a new ability or improved movement reliability.[112,113] The motor cortex is involved in motor skill learning,[114–116] and the basal ganglia probably also contribute. Patients with HD and PD are impaired in learning to track a moving target at increasing speeds[117–119] and to fasten buttons in an automatic fashion.[120]

Dopamine and corticostriatal plasticity

Whereas the SDR can be viewed as the direct modulatory effect of dopamine on motor performance, the LDR can be better understood in terms of changes in synaptic strength in corticostriatal connections. In addition to modulating the intrinsic excitability of MSNs acutely (Figure 2a,b,d), dopamine also influences corticostriatal plasticity and, thereby, produces cumulative and long-lasting changes in corticostriatal throughput (Figure 2c,e). The temporal relationships between dopaminergic and glutamatergic input to MSNs of the striatum and dopamine-dependent plasticity at corticostriatal synapses have provided the basis for models of reinforcement learning.[40–45] Corticostriatal plasticity can enhance or diminish the responsiveness of go and no-go pathways to cortical input. Studies using brain slices demonstrate that long-term depression (LTD) is the predominant form of synaptic plasticity at corticostriatal synapses.[42] Corticostriatal LTD in the dorsal striatum is thought to require D2 receptor activation and retrograde endocannabinoid signalling that depresses glutamate release via presynaptic CB1 receptors. Under certain conditions in brain slices and in *in vivo* preparations, dopamine-dependent corticostriatal long-term potentiation can be induced.[40,43,46,47]

The central role of dopamine in modulating the excitability of MSNs and in corticostriatal plasticity suggests that dopamine could have a role in motor skill learning, in addition to its role in motor performance. Studies in rats and mice have suggested that dopamine-dependent corticostriatal synaptic plasticity might contribute to motor learning.[48–51] Moreover, in rat models of PD, denervation of dopaminergic neurons seemed to be responsible for motor learning deficits that preceded motor performance deficits.[52,53] Various types of motor learning exist, and are thought to involve different brain structures (Box 1). In this Review, we focus on motor skill learning, in which the basal ganglia probably have a major role.

LDR and 'learned' motor inhibition

The above discussions are limited to the role of dopamine in modulating corticostriatal plasticity and promoting motor learning. Recent studies, however, have also emphasized that the presence and absence of dopamine can have opposing effects on synaptic strength, suggesting that aberrant plasticity in the absence of dopamine could play a part in PD symptoms.[46] Moreover, studies in mouse brain tissue found evidence to suggest that lack of corticostriatal LTD might contribute to PD symptoms.[54] Dopamine denervation leads to a deficit in corticostriatal LTD, and biochemical interventions that rescue LTD improve PD-like symptoms in animal models.[54] However, how rescued LTD and, presumably, rescued motor learning could ultimately improve motor performance and alleviate PD motor symptoms is not clear from these studies. In addition, the relative contribution of dopamine's direct effects on performance versus indirect effects through learning has been controversial and difficult to determine.

Studies in dopamine-deficient mice

To dissociate dopamine-mediated motor learning from dopamine-mediated, acute enhancement of motor performance, we used transgenic mice lacking the transcription factor Pitx3. Such mice have selective nigrostriatal neuron loss, resulting in a 90% reduction in dorsal striatal dopamine.[55–58] We found that the mice displayed severe deficits in motor learning that could be rescued by levodopa treatment.[59] Such learning occurred slowly over days in a cumulative fashion (Figure 3a,b),[59] similar to the slow build up of the LDR by dopaminergic therapy in patients with PD. A striking aspect of the findings was that cessation of levodopa treatment after acquisition of motor skills resulted in a gradual, rather than immediate and rapid, decline in performance (Figure 3c,d). This reduction in perfomance was not related to the pharmacokinetics of levodopa and was not due to passive forgetting of learned motor skills over time. The extent of performance decline increased as the animals were retested repeatedly. As impairment of motor performance was evident only when treatment discontinuation was combined with retesting, our data suggest that the mice went through an active no-go learning (or 'learned' motor inhibition) process (Figure 2c) after cessation of levodopa treatment and during retesting.[59]

The temporal pattern of motor performance in the above model recapitulates the LDR, which dissipates over days to weeks. These results suggest that dissipation of the LDR might constitute an aberrant form of experience-dependent plasticity—that is, a form of aberrant learning. The implication is that some motor symptoms in PD, such as akinesia, might be 'learned' over time, through aberrant reinforcement owing to reduced dopaminergic transmission.

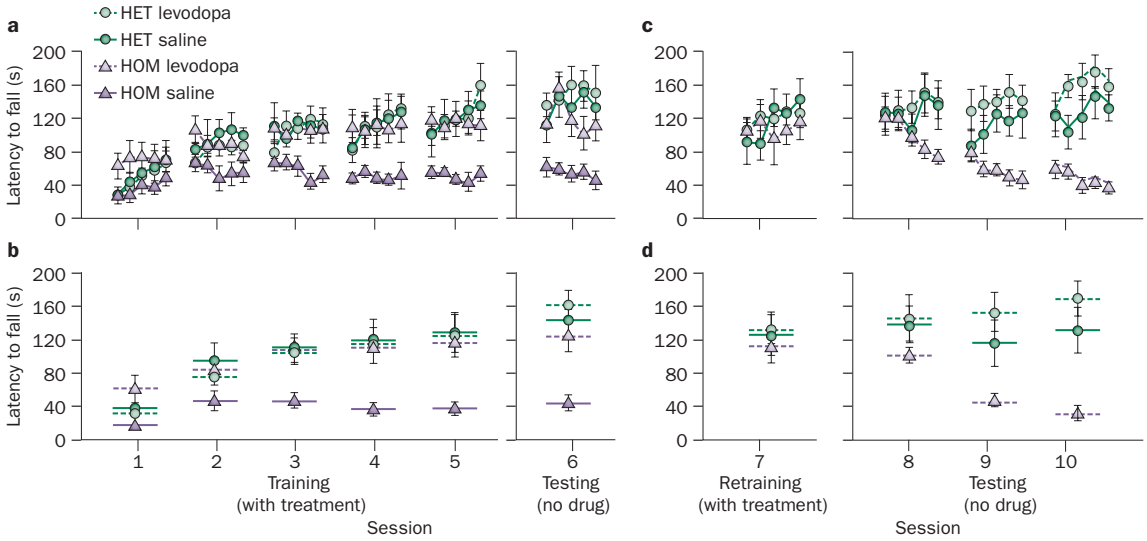

Figure 3 | Rotarod performance during and after levodopa treatment. **a**,**b** | Control Pitx3-heterozygous mice and Pitx3-deficient homozygous mice, which lack striatal dopamine, were trained on the rotarod motor learning test after administration of either saline or levodopa for five sessions (sessions 1–5). After a 3-day treatment break, the mice were tested without treatment (session 6). **c**,**d** | The same mice were retrained on the rotarod with either saline or levodopa for one session (session 7). After a 5-day treatment break, mice were run for three sessions without any treatment (sessions 8–10). The experience-dependent rather than immediate decline in performance after cessation of levodopa treatment suggests that mice went through an active 'no-go' learning process. Parts a and c show latency to fall in each trial. Parts b and d show average latency to fall during each session. $n = 6$ per genotype per treatment. Abbreviations: HET, Pitx3 heterozygous; HOM, Pitx3-deficient homozygous. Permission obtained from John Wiley and Sons © Beeler, J. A. *et al. Ann. Neurol.* **67**, 639–647 (2010).

Studies in wild-type mice

Results from our studies using D1 and D2 antagonists in wild-type mice further support the above model and indicate that no-go learning is dependent on D2 but not D1 receptors.[59,60] In one study,[59] mice were trained on the rotarod motor-learning task without any drugs, and were then treated with either the D2 antagonist eticlopride or the D1 antagonist SCH23390. Mice exposed to the D2 antagonist exhibited a gradual decline in performance (no-go learning), whereas exposure to the D1 antagonist resulted in an immediate decrement in performance without causing gradual further decline (lack of no-go learning). In another study,[60] dopamine antagonists were administered during learning. Although the D1 and D2 antagonists seem to have similar effects and both appear to block learning, they have different effects on relearning after cessation of treatments. After cessation of SCH23390 treatment, wild-type mice were able to learn as quickly as were naive mice. By contrast, learning was significantly slower in eticlopride-treated mice than in naive mice, even after cessation of treatment. These data suggest that the D1 antagonist blocked learning, whereas the D2 antagonist caused no-go learning, which significantly retarded future learning even after cessation of drug treatment.[60]

Dual effects of dopamine on motor performance

Collectively, our data suggest that dopamine blockade causes both direct performance impairment and no-go learning. In the absence of dopamine, D2-dependent no-go learning gradually degrades motor performance (Figure 2c). Importantly, such learning is experience-dependent and task-specific. The no-go learning phenomenon implies a functional importance for bidirectional corticostriatal plasticity[46] and further emphasizes the potential contribution of abnormal corticostriatal plasticity to motor symptoms in PD. The above hypothesis is in agreement with published computational models that suggest an interaction between the effect of dopamine on MSN activity and corticostriatal synaptic plasticity, which affects both motor learning and performance.[61]

The above hypothesis was further explored through a retrospective review of a clinical trial that examined the response of patients with PD to levodopa and placebo.[21] The magnitude of the LDR was estimated as the change in patients' finger tapping speed from before the treatment regimen to before administration of the first morning dose of the study drug at each visit (practically defined as 'off state' as withdrawal of medication overnight minimizes any residual SDR). If the LDR represents activity-dependent motor learning facilitated by dopamine, it should be greater in the more frequently used hand than in the nondominant hand in patients treated with levodopa, but not in patients in the placebo group. The clinical data were largely consistent with this hypothesis. Conversely, hand dominance did not influence the SDR magnitude in the levodopa or placebo groups, suggesting that the effect of increased activity of finger movements in the dominant hand is reflected in long-term motor-task learning but not in an immediate response to dopaminergic drugs.

Clinical applications

Enhancement of the LDR

If the loss of the LDR rather than changes in the SDR accounts for the wearing-off phenomenon, a more effective approach to improve pharmacological therapy for

PD could be to enhance and maintain the LDR rather than focusing on prolonging the SDR.[62,63] A retrospective analysis of a clinical study that examined the response to levodopa found that the LDR is dose-dependent.[21] The LDR magnitude reached a plateau after 9 weeks of 50 mg levodopa thrice daily, whereas a 200-mg thrice-daily regimen produced a greater magnitude of LDR at 9 weeks than did lower doses, and continued to increase the LDR magnitude beyond 24 weeks.[21] Development of the LDR in early-stage PD requires a minimum threshold dose of dopaminergic therapy, and has a maximum dose above which no greater magnitude of LDR is generated, although the precise doses vary between individuals.[64] Furthermore, the LDR is produced more effectively with a larger dose given once a day than smaller doses given three times a day, even when the total daily dose is higher with the latter dose schedule.[64] The LDR can be lost over time despite continuing dopaminergic therapy, but can be restored by increasing the total daily dose through more-frequent dosing.[16] The magnitude of the SDR at the time of first levodopa exposure correlates with the magnitude of the LDR measured 6–12 months later.[22]

The above studies provide evidence that the SDR might be a necessary precursor to LDR development.[14] Moreover, repeated treatment of hemiparkinsonian rats with the D1–D2 receptor agonist apomorphine leads to development of increasing rotational behaviours, but this priming effect is prevented if the rats are restrained to prevent rotational behaviours, underscoring the contribution of motor learning to the therapeutic reponse.[65] As such, improvement of motor symptoms is probably needed to turn the SDR into the LDR, in agreement with our hypothesis that the LDR represents activity-dependent motor learning facilitated by dopamine.

The hypothesis presented in this Review also has potential implications for rehabilitative approaches to patients with PD. If dopamine depletion leads to experience-dependent plasticity and 'learned' motor inhibition, any practice of motor skills that occurs under conditions of inadequate or no medication might lead to deterioration of skills. By contrast, practice during optimal dopamine replacement would maximize the benefits of dopamine-dependent plasticity, motor learning and the LDR.

Prevention of aberrant plasticity

Most of the literature on reinforcement-driven motor learning focuses on improvement of motor skills in the presence of dopamine. Here, we highlight the role of such learning in deterioration of motor skills (no-go learning) in the absence of dopamine, and its contribution to impairments in motor performance in PD, which is best illustrated by the descending phase of the LDR during cessation of drug treatment (Figure 2c). We hypothesize that the same aberrant corticostriatal plasticity mechanism is responsible for the motor symptoms of PD before initiation of dopamine replacement therapy. This process can be difficult to discern in PD owing to the gradual nature of dopaminergic neuron degeneration. Neuroleptic-induced parkinsonism, on the other hand, could be a suitable model to test this hypothesis, because the onset of drug treatment and of parkinsonian symptoms can, in theory, be established.

From a clinical perspective, prevention of aberrant plasticity and aberrant learning represents a promising but unexplored approach to treatment of PD and other movement disorders. Results of previously published trials of symptomatic treatments could potentially be reinterpreted, however, as the effects of prevention of aberrant plasticity.[2,66] Trials of dopaminergic agents have shown long-lasting benefits after withdrawal of medications, which raised controversy over whether such effects represented disease modification or insufficient washout of symptomatic effects.[2,66] Disease modification could involve slowing of the degenerative process, but evidence to support such an effect of dopamine replacement therapy is lacking. Other researchers suggested that early treatment of PD could limit and delay the circuitry changes that evolve as PD progresses.[11] Changes in presynaptic dopamine turnover,[7] gene expression in striatal neurons,[8] and basal ganglia neuronal activity pattern downstream from striatal neurons[9] have been demonstrated after dopaminergic loss. Some investigators have proposed that these changes help to maintain apparently normal motor function until compensation fails in the face of ongoing degeneration,[10] but functional evidence for such compensation is not yet available. We propose that aberrant plasticity contributes to disease progression, and further suggest that an alternative form of disease modification is prevention or reversal of aberrant plasticity produced by therapeutic agents, as discussed above.

Whether therapy that directly targets signalling molecules involved in corticostriatal plasticity, such as the cAMP pathway, could be used to prolong the LDR or to prevent aberrant plasticity remains to be demonstrated. Data from animal studies have shown that adenosine A2A receptor antagonists can attenuate no-go inhibitory learning via cAMP signalling in MSNs,[60] bypassing of the lack of D2 receptor activation by dopamine. We propose that the association between consumption of caffeine, which activates adenosine A2A receptors, and decreased risk of PD[67] could, therefore, be mediated by the effect of caffeine on basal ganglia plasticity rather than neuronal cell survival. Whether such effects can be seen with other agents that are hypothesized to have disease-modifying effects—such as monoamine oxidase B inhibitors and nicotine—remains to be examined.

Other types of aberrant plasticity

The above discussion focused on aberrant plasticity in the indirect pathway and its contribution to akinesia and to the LDR following dopamine replacement therapy. Additional processes are, however, likely to be affected by corticostriatal plasticity. For example, bidirectional corticostriatal synaptic plasticity also occurs in the direct pathway,[46] which may contribute to motor skill learning (Box 1), and to levodopa-induced dyskinesia, as discussed below.[68]

Some of the consequences of plasticity could be adaptive. For example, increased dopamine receptor sensitivity

could be beneficial in the setting of reduced dopamine production and release. In the early stages of PD, changes in cortical plasticity could have a compensatory role.[69] However, mechanisms governing synaptic plasticity under a physiological range of regulated dopamine release and clearance could become maladaptive under conditions of severe dopamine loss and dopamine replacement therapy, when dopamine release may no longer be regulated in response to environmental challenges. Such maladaptive mechanisms might underlie levodopa-induced dyskinesia. Experimentally, aberrant plasticity in the form of an inability to reverse established long-term plasticity has been noted in rodent models of dyskinesia.[70,71]

Direct investigation of corticostriatal plasticity in humans is not currently possible. Abnormal neuroplasticity in patients with PD has, however, been identified at the level of the motor cortex—a structure that receives indirect input from the basal ganglia and in which plasticity can be measured using transcranial magnetic stimulation (TMS).[72] Such changes include reduced short-term[73] and long-term[68,74–77] plasticity within the primary motor cortex, as well as altered connectivity between the premotor and primary motor cortex.[78,79] These abnormalities are reduced by administration of levodopa in some[78,79] but not all[74,76] cases. This variation in the effect of levodopa might relate to differences in the type of plasticity probed by different stimulation protocols. Such abnormalities in motor cortex plasticity in patients with PD could be an indirect consequence of changes in corticostriatal plasticity that results in altered basal ganglia output to the motor cortex.[72] Abnormal motor cortex plasticity could also arise from loss of dopaminergic terminals in the motor cortex.[80]

In the context of levodopa-induced dyskinesia, and in agreement with findings in rodent studies, patients with PD experiencing this adverse effect of therapy showed a lack of depotentiation of cortical plasticity.[81] Levodopa failed to effectively normalize excitability of inhibitory systems, as measured by single and paired TMS,[82] and did not restore motor cortex plasticity[75] in patients with dyskinesia, in contrast to its effect in patients without dyskinesia.

Despite prominent abnormalities in cortical excitability and plasticity in patients with PD, attempts to improve motor symptoms through modulation of cortical excitability using TMS have yielded mixed results.[83,84] The use of more-recent theta-burst stimulation protocols, which induce cortical plasticity in healthy individuals, did not produce motor benefits in patients with PD,[85,86] despite comparable increases in cortical excitability in patients and controls.[87] A possible explanation is that abnormalities in the motor cortex seen in PD reflect secondary changes in corticostriatal plasticity, such that manipulation of cortical excitability does not affect primary changes in corticostriatal synapses in the basal ganglia. Considerable gaps remain to be bridged in treatment of clinical phenomena and cortical plasticity abnormalities in PD, and in linking them to corticostriatal plasticity observed in experimental models.

Conclusions and future directions

In this Review, we propose a hypothesis for the contribution of synaptic plasticity in specific corticostriatal pathways to PD symptoms and the therapeutic effects of dopamine replacement therapy. Denervation of dopaminergic neurons is traditionally hypothesized to cause an imbalance between the direct and indirect pathways, which has a direct modulatory effect on immediate motor performance. In addition, we propose that task-specific aberrant corticostriatal plasticity in the absence of dopamine contributes to the gradual deterioration of motor performance, representing a parallel mechanism for akinesia. This new framework suggests a novel therapeutic strategy for PD that consists of maintenance of normal plasticity and prevention of aberrant plasticity.

More broadly, aberrant synaptic plasticity has been implicated in a number of neurological and psychiatric disorders such as levodopa-induced dyskinesia,[70,71] tardive dyskinesia,[88] fragile X syndrome,[89,90] obsessive–compulsive disorder[91,92] and Tourette syndrome.[93] These studies represent an exciting new trend in translational neuroscience and promising new directions for therapy development. The example that we discussed here—namely, corticostriatal plasticity mechanisms underlying PD motor symptoms and response to therapy—allows us to make specific hypotheses about the direction of synaptic strength change at specific synapses. We hypothesize that both development of akinesia through learned inhibition in the absence of dopamine and restoration by LDR in the presence of dopamine are mediated by synaptic strength changes at the corticostriatal connection (Figure 2). This hypothesis allows us to make specific predictions about behavioural changes following dopamine therapy. Elaboration of the proposed aberrant plasticity mechanisms in various other conditions, and formulation of more-specific predictions about behavioural changes, will conceivably be the next step in efforts to harness the power of synaptic plasticity for treatment of neurological and psychiatric disorders.

Review criteria

The PubMed database was searched for articles published in the past 10 years, using search terms "motor learning" AND "Parkinson" OR "basal ganglia"; "corticostriatal plasticity" AND "humans"; and "Parkinson" AND "plasticity". Full-text papers in English were included. Reference lists of identified papers were searched for further leads.

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Author contributions

All authors contributed to researching data for the article, discussion of the article content, writing of the article and to review and/or editing of the manuscript before submission.