Aberrant plasticity and “learned” motor inhibition in Parkinson’s disease

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Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative movement disorder characterized by severe loss of substantia nigra dopamine (DA) neurons. The target region of substantia nigra DA neurons is the dorsal striatum. According to the classic model, activation of DA receptors on striatal medium spiny neurons (MSNs) modulates their intrinsic excitability. Activation of D1 receptors makes MSNs in the direct “Go” pathway more excitable, whereas activation of D2 receptors makes MSNs in the indirect “NoGo” pathway less excitable. Therefore increased DA increases the responsiveness of the Go pathway while decreases the responsiveness of the NoGo pathway. Both mechanisms increase motor output. Conversely, diminished DA will favor the inhibitory NoGo pathway. Therefore, DA has direct, “on-line” effect on motor performance. However, in addition to modulating the intrinsic excitability of MSNs “on-line”, DA also modulates corticostriatal plasticity, therefore could potentially produce cumulative and long-lasting changes in corticostriatal throughput. Studies in my lab suggest that DA blockade leads to both direct motor performance impairment and D2 receptor dependent NoGo learning (“learned” motor inhibition) that gradually deteriorates motor performance. NoGo learning is experience dependent and task specific. It is different from blocked learning since NoGo learning impairs future performance even after DA is restored. More recent data from my lab suggest that NoGo learning in the absence of DA arises from increased LTP at the indirect pathway corticostriatal synapses and contributes significantly to PD-like motor symptoms. Our data and hypotheses suggest a novel therapeutic strategy for PD that targets directly signaling molecules for corticostriatal plasticity (e.g. the cAMP pathway and downstream signaling molecules) and prevents aberrant plasticity under conditions of DA denervation.

Key words: Parkinson’s disease; dopamine; striatum; medium spiny neurons; basal ganglia; corticostriatal plasticity; motor learning; learning and performance; cAMP pathway; aberrant plasticity

帕金森氏病中的异常可塑性和习得性动作抑制

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摘要：帕金森氏病是一种进行性的神经系统运动障碍疾病，其主要病理特征是黑质多巴胺能神经元的严重丢失。黑质多巴胺能元的投射区域为背侧纹状体（多巴胺能神经元发出上行纤维到达纹状体）。根据经典模型，激活纹状体中型多棘神经元（medium spiny neurons, MSNs）上的多巴胺受体调节它们内在的兴奋性。在Go/NoGo调控中，激活D1受体可增强“Go”直接通路的MSNs的兴奋性，而激活D2受体则可降低“NoGo”间接通路的MSNs兴奋性。因此，多巴胺升高既可增强Go通路的反应性，同时又可降低NoGo通路的反应性。这两种机制均可导致运动输出的增强。相反，减少多巴胺则更倾向于增强抑制性的“NoGo”通路。因此，多巴胺对于运动表现首先具有直接的、即时的调控作用。然而，除了即时调控MSNs的内在兴奋性外，多巴胺尚具有调控皮层-纹状体可塑性的功能，进而对皮层-纹状体通路产生潜在的、累积性的、持久的改变。我们的研究显示，阻断多巴胺在直接损害运动表现的同时，也介导了NoGo学习（一种习得性动作抑制），从而使得运动能力逐渐恶化。这种恶化是潜在的、累积性的和持久的。NoGo学习是D2受体依赖的，它是一种经验依赖性及任务特异性的学习。NoGo学习与“学习过程被阻断”不同，因为NoGo学习对未来运动的损害甚至在多巴胺水平恢复后仍然存在。最近，我们的研
Parkinson’s disease (PD) is a progressive neurodegenerative movement disorder characterized by severe loss of substantia nigra dopamine (DA) neurons. The most important PD motor symptoms include tremor at rest, rigidity, slowness of voluntary movement, postural instability, and freezing [1]. Cognitive and other behavioral impairments often occur in advanced stage PD with degeneration spread to brain regions other than the substantia nigra DA neurons.

1 The classic model of basal ganglia organization and functions

The main target region of substantia nigra DA neurons is the dorsal striatum via the nigrostriatal dopaminergic pathway. The striatum is the main entry point for cortical glutamatergic inputs to the basal ganglia that eventually form the corticostriatal loops. According to the classic model [2–5], activities in corticostriatal loops are modulated by DA through two parallel pathways. Activity in the D1-expressing direct, striatonigral “Go” pathway favors excitation of cortical activity and facilitates motor output. Activity in the D2-expressing, indirect striatopallidal “NoGo” pathway, in contrast, favors inhibition of cortical activity and inhibits motor output [6].

At cellular level, activation of DA receptors on striatal medium spiny neurons (MSNs) has been demonstrated to modulate gating of ion channels, therefore modulate the intrinsic excitability of MSNs acutely [7–9]. Activation of D1 receptors makes MSNs in the direct pathway more excitable whereas activation of D2 receptors makes MSNs in the indirect pathway less excitable. Therefore DA shifts the balance between these two pathways such that increased DA increases the responsiveness of the direct “Go” pathway via D1 activation while simultaneously decreases the influence of the “NoGo” pathway via D2 activation. Both mechanisms increase motor output when there is increased DA release. Conversely, diminished DA will favor the inhibitory indirect “NoGo” pathway due to greater activity in D2-expressing MSNs as a consequence of less activation of D2. Therefore, DA can differentially modulate the excitability of MSNs in both the direct and indirect pathways. Moreover, DA also modulates corticostriatal glutamate release [10, 11]. In summary, by increasing and decreasing corticostriatal throughput in the direct and indirect pathways, DA has a direct, “on-line” modulatory effect on motor performance.

2 Dopamine and corticostriatal plasticity

In addition to modulating the intrinsic excitability of MSNs “on-line”, DA also modulates corticostriatal plasticity in both the direct “Go” and indirect “NoGo” pathways, therefore produces cumulative and long-lasting changes in corticostriatal throughput. The interplay between DA and glutamate input to MSNs of the striatum and DA dependent plasticity at corticostriatal synapses have provided the basis for models of reinforcement learning [12–17]. Corticostriatal plasticity can enhance or diminish the responsiveness of either pathway to cortical input, presumably selectively facilitating or inhibiting specific responses. In brain slices, long-term depression (LTD) is the predominant form of synaptic plasticity at corticostriatal synapses [14]. There is general agreement that corticostriatal LTD in the dorsal striatum requires D2 receptor activation and retrograde signaling via endocannabinoids that depress glutamate release via presynaptic CB1 receptors. Under certain conditions in brain slices and in vivo preparations, corticostriatal long-term potentiation (LTP) can be induced [12, 15, 18, 19].

There has been suggestive evidence that the role of DA in corticostriatal synaptic plasticity may contribute to motor learning [20–23] and motor deficits in PD models. For example, Ogura and colleagues [24] found that partial lesions did not significantly impair motor performance immediately whereas impaired motor learning, suggesting that learning deficits precede performance deficits. More recently, a direct connection
between the lack of corticostriatal LTD and PD symptoms was suggested. DA denervation leads to corticostriatal LTD deficit. Moreover, rescuing LTD also rescued PD-like symptoms \[25\]. However, it is not clear how rescued LTD may benefit motor learning that may in turn contribute to the rescued motor performance.

Theoretically, both DA dependent corticostriatal LTD and LTP in both the direct and indirect pathways could have profound effects on MSN activity and therefore play central roles in motor learning and as a consequence motor performance. However, overall, the role of corticostriatal plasticity plays in the symptoms, progression and treatment of PD has not been well established.

### 3 Aberrant plasticity and “learned” motor inhibition in Parkinson’s disease

Technically, the relative contribution of DA’s direct effects on performance and its indirect effects on performance mediated through learning have been difficult to disentangle and controversial. One inherent difficulty in studying the role of DA in motor learning versus motor performance is that changes in motor learning will inevitably lead to changes in motor performance; and learning can only be discerned by changes in performance.

To overcome the aforementioned difficulties, studies in my laboratory have modified the simple accelerating rotarod task to a multi-phase task in order to dissociate DA mediated motor learning and motor performance. We have detailed the role of DA in motor learning in Pitx3 deficient mice and demonstrated how the role of DA in motor learning contributes significantly to PD symptoms and PD therapy \[26\]. The Pitx3-deficient mice have selective nigrostriatal neuron loss, resulting in a 90% reduction in dorsal striatal DA \[27–30\]. These mice do not have severe motor impairments in the open field, but they display severe deficits in motor functions that require more skills. Precisely because they have preserved gross motor function, they are excellent models for investigation of the role of DA in motor learning in great details. We have found that the Pitx3 deficient mice display severe motor learning deficits that can be rescued by L-DOPA treatment \[26\]. The most interesting and striking finding of the study is that cessation of L-DOPA treatment after acquisition of motor skills does not result in immediate drop in performance. Instead, there is a gradual decline of performance, which is not related to L-DOPA’s pharmacokinetics and not due to passive “forgetting”. Instead, it is dependent on the re-testing experience, i.e., these animals will go through an active “NoGo learning” (or “learned” motor inhibition) process after cessation of L-DOPA treatment and during the re-testing experience \[26\].

Our data on wild-type mice using D1 and D2 antagonists further support the above model and indicate that “NoGo” learning is D2 but not D1 dependent \[26\]. We used wild-type mice and trained them on the rotarod motor learning task. After training without any drugs, mice were either treated with the D2 antagonist eticlopride or D1 antagonist SCH23390. With eticlopride, mice exhibited a gradual decline in performance (“NoGo” learning). In contrast, SCH23390 resulted in an immediate decrement in performance without causing gradual further decline (i.e. without “NoGo” learning). In a more recent study (manuscript under revision), DA antagonists were administered during learning. Although the apparent effects of SCH23390 and eticlopride seem to be similar and both seem to block learning, but they are very different as revealed by the relearning curve after cessation of drug treatments. After SCH23390 treatment ended, wild-type mice were able to learn quickly just like naïve mice. In contrast, after eticlopride treatment ended, wild-type mice learned much slower than naïve mice would. These data suggest that D1 antagonist blocks learning. In contrast, D2 antagonist causes “NoGo” learning, which significantly retards future learning even after cessation of drug treatment.

Our data, collectively, suggest that DA blockade causes both a direct performance impairment and “NoGo” learning. In the absence of DA, there is DA D2 receptor dependent “NoGo” learning that gradually deteriorates motor performance. “NoGo” learning is different from blocked learning since “NoGo” learning impairs future performance even after DA is restored. Importantly, such “NoGo” learning is experience dependent and task specific. The “NoGo” learning phenomena implies the functional significance of bidirectional corticostriatal plasticity and further emphasize that abnormal corticostriatal plasticity may underlie motor symptoms in PD.

### 4 Computational models explaining the contribution of aberrant plasticity to “learned”
motor inhibition

The above hypothesis is in agreement with published computational models suggesting an interaction between DA's effects on MSN activity and corticostriatal synaptic plasticity, to affect motor learning and performance. Wiecki and Frank et al. \cite{51} elaborated on how the direct pathway (“Go” pathway) and the indirect pathway (“NoGo” pathway) may undergo plasticity (and therefore motor “Go” learning and “NoGo” learning). When DA is elevated, the direct “Go” pathway is more active, increasing the probability of Hebbian synaptic plasticity there and therefore facilitates motor learning. At the same time, elevated DA makes the indirect “NoGo” pathway less active, decreasing the probability of synaptic plasticity there and therefore does not affect “NoGo” learning. Conversely, when DA decreases, the indirect “NoGo” pathway is more active, increasing the probability of synaptic plasticity there and therefore facilitates “NoGo” learning and leads to “learned motor inhibition”. At the same time, reduced DA makes the direct “Go” pathway less active, decreasing the probability of synaptic plasticity there and therefore does not affect motor learning. Taken together, such a model suggests that elevated DA release will cause “Go” learning which is D1 receptor dependent whereas reduced DA release will cause “NoGo” learning which is D2 receptor dependent.

5 The cAMP pathway in corticostriatal plasticity

Both the DA D1 and D2 receptors are mainly coupled to the cAMP pathway \cite{32, 33}. DA mainly stimulates cAMP production in D1 neurons and inhibits cAMP production in D2 neurons. Although much is known about the role of DA in corticostriatal plasticity, the coupling of DA receptors to the cAMP pathway, the role of the cAMP pathway in synaptic plasticity elsewhere in the brain (e.g. in the hippocampus) \cite{34-38}, and the role of cAMP in corticostriatal plasticity have not been sufficiently explored. The striatum is very unique in its cAMP pathway compared to other brain regions such as the hippocampus and cortex. The main adenylyl cyclase (AC) isoform in the brain is AC1 that is mainly activated by calcium-calmodulin (Ca-CaM). Stimulation of cAMP production via AC1 is the main mechanism of NMDA receptor and calcium dependent synaptic plasticity \cite{37, 38}. However, AC1 is highly expressed in all brain regions but not in the striatum. In contrast, the Ca-CaM-insensitive isoform AC5 is highly expressed in the adult striatum \cite{39-41}. Therefore, cAMP production in adult striatum is mainly modulated by G-protein coupled receptors rather than by calcium. This may explain why DA signaling plays such a dominating role in the induction and directionality of corticostriatal plasticity \cite{14, 17, 19}. Published work from my laboratory has demonstrated that mice lacking AC5 show the loss of corticostriatal LTD \cite{42}. More interestingly, postsynaptic administration of intracellular cAMP in MSNs induces LTP of glutamatergic transmission at corticostriatal synapses in wild-type MSNs \cite{42}, suggesting that cAMP regulation may play a pivotal role in the directionality of corticostriatal plasticity.

The above notion is also supported indirectly by a seminal paper published a few years ago by Shen and colleagues \cite{19}. That study elegantly showed that activation of different receptors on MSNs can determine the type of plasticity that is induced under physiological conditions, thereby, allowing bi-directional plasticity at corticostriatal synapses formed on both subpopulations of MSNs. For D1 expressing MSNs, LTP requires activation of D1 receptors. However, for D2 expressing MSNs, LTP requires activation of adenosine A2A receptors, which stimulates cAMP production in D2 MSNs, but is not expressed on D1 MSNs. The above findings are also supported by independent studies from other groups. In mice lacking D2 receptors, the same high-frequency stimulation protocol (HFS) that induces LTD instead induces LTP \cite{43}. In 6-OHDA-lesioned mice, a model of PD, HFS-induced LTD is impaired \cite{29}.

More recent data from my lab suggest that NoGo learning in the absence of DA arises from increased LTP at the indirect pathway corticostriatal synapses and contributes significantly to PD-like motor symptoms (manuscript under revision). Therefore, I therefore hypothesize that dynamic changes in the cAMP pathway in the different subpopulations of MSNs contribute to the directionality of plasticity. More specifically, increases in cAMP levels in both subtypes of MSNs will result in LTP, whereas decreases in cAMP levels will induce LTD of glutamate transmission at corticostriatal synapses. Since DA causes opposite changes in cAMP levels in MSNs that express D1 or D2 receptors, DA regulates plasticity in these two cell types in opposite ways. How may DA mediated changes in corticostriatal plasticity in D1 versus D2 neurons contribute to PD motor symptoms? I propose that altered plasticity, namely in-
increased LTP in striatopallidal MSNs in the absence of DA, gives rise to the “NoGo” learning (“learned” motor inhibition) process that contributes significantly to PD motor symptoms.

6 Preventing aberrant plasticity as a new approach for Parkinson’s disease therapy

From a clinical perspective, preventing aberrant plasticity and aberrant learning therefore may represent a promising but unrecognized approach in PD therapies. For example, published data from my laboratory suggest that the poorly understood long-duration response (LDR) to L-DOPA arises as a correction of aberrant learning [26]. In PD therapy, LDR is a sustained motor improvement response that is acquired through chronic L-DOPA treatment and lasts for days and even weeks after L-DOPA treatment cessation, and represents the most important component of therapeutic efficacy [44, 45]. The underlying mechanisms involved in LDR are not due to continued peripheral circulation of L-DOPA, or prolonged DA release after L-DOPA treatment. I propose that LDR is caused by retained motor performance due to previous DA dependent motor learning and that the gradual decline in LDR is due to experience dependent gradual “NoGo” learning in the absence of DA. More specifically, DA denervation induces both the direct motor performance impairment and the cumulative and long-lasting “learned” motor inhibition through aberrant corticostriatal plasticity in the indirect “NoGo” pathway. The short-duration response (SDR) of L-DOPA reflects the correction of direct motor performance deficits caused by DA depletion and lasts only as long as L-DOPA is present. In contrast, by correcting underlying abnormal corticostriatal plasticity, L-DOPA also prevents aberrant motor learning, which is responsible for LDR. This LRD aspect of L-DOPA treatment is cumulative and retained even on discontinuation of treatment.

The above example demonstrates the potential role of corticostriatal plasticity in existing DA replacement therapy for PD. It remains to be demonstrated if non-DA replacement therapy that directly targets signaling molecules for corticostriatal plasticity (e.g. the cAMP pathway and downstream signaling molecules) could be used to prolong LDR or completely prevent aberrant plasticity, and therefore be used as a novel therapeutic strategy for PD.

The hypothesis presented here has implications for rehabilitative approaches to treating PD as well. Since DA depletion leads to experience-dependent aberrant learning that impedes performance, any skill practice occurring during states of no or low DA (i.e., medication troughs) might actually lead to deterioration of skills. In contrast, practice occurring during peak medication would maximize motor learning benefits.

In summary, DA denervation is traditionally hypothesized to cause an imbalance between the direct and indirect pathways; symptoms are believed to result primarily from over-activity of the inhibitory, D2-expressing indirect pathway. Here I propose an aberrant learning process in parallel with the imbalance between inhibitory and facilitatory motor control. Specifically, I hypothesize that increased activity in the D2-expressing inhibitory pathway due to increased LTP in the absence of DA results in “learned” inhibition of motor actions. This new framework suggests a novel therapeutic strategy for PD: prevention of aberrant plasticity.

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