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Motor learning in animal models of Parkinson's Disease: Aberrant synaptic plasticity in the motor cortex

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Abstract

In Parkinson's disease (PD), dopamine depletion causes dramatic changes in the brain resulting in debilitating cognitive and motor deficits. PD neuropathology has been restricted to postmortem examinations, which are limited to only a single time point of PD progression. Models of PD where dopamine tone in the brain are chemically or physically disrupted are valuable tools in understanding the mechanisms of the disease. The basal ganglia have been well studied in the context of PD, and circuit changes in response to dopamine loss have been linked to the motor dysfunctions in PD. However, the etiology of the cognitive dysfunctions that are comorbid in PD patients has remained unclear until now. In this paper, we review recent studies exploring how dopamine depletion affects the motor cortex at the synaptic level. In particular, we highlight our recent findings on abnormal spine dynamics in the motor cortex of PD mouse models through *in vivo*, time-lapse imaging and motor-skill behavior assays. In combination with previous studies, a role of the motor cortex in skill-learning, and the impairment of this ability with the loss of dopamine, is becoming more apparent. Taken together, we conclude with a discussion on the potential role for the motor cortex in the motor-skill learning and cognitive impairments of PD, with the possibility of targeting the motor cortex for future PD therapeutics.

Parkinson disease (PD) is a chronic, disabling neurological disease that affected over 4 million people worldwide over the age of 50 in 2005, and is expected double by 2030^{1,2,3}. In addition to motor deficits, cognitive deficits, including the impairment of motor skill-learning, are frequent comorbidities in PD: nearly 80% of PD patients eventually develop

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cognitive impairment or dementia^{4,5}. Progressive degeneration of nigrostriatal dopaminergic neurons is the pathophysiological hallmark of PD, resulting in dramatically reduced dopamine tone in the brains of PD patients^{6,7,8}.

The most well documented disruption of neural circuitry in PD occurs in the basal ganglia, a composite of several brain structures densely innervated by the dopaminergic system⁹. It is widely accepted that dysfunction of basal ganglia circuitry via the basal ganglia-thalamo-cortical pathway is responsible for the development of the motor movement disorders observed in PD: the loss of dopaminergic neurons results in excessive activation of the basal ganglia output nuclei and subsequent inhibition of thalamocortical and brainstem motor systems. Therefore, the loss of nigrostriatal dopamine tone is what is thought to ultimately result in the motor dysfunctions observed in PD^{10,11}.

The neuropathology of PD has been documented principally and extensively through postmortem examination, providing a detailed snapshot of a PD brain at a single time point^{12,13}. While much has been discovered regarding the cause of movement disorders in PD, there is little information about the cognitive and skill-learning deficits also present in PD patients. Recent studies have confirmed a critical role of the motor cortex in motor learning, suggesting that abnormal rewiring of the motor cortex neural circuit as a result of dopamine depletion may be involved in the skill-learning and cognitive deficits in PD.

In this review, we will first summarize previous studies on the roles of the motor cortex in skill acquisition and motor learning, and dopaminergic modulation in the mammalian motor cortex. Next, we will detail recent developments in our understanding of abnormal spine dynamics through our *in vivo*, time-lapse study of the motor cortex of PD mouse models. We will conclude with a discussion on the synaptic mechanisms of motor learning deficits after DA depletion, and the potential of targeting the motor cortex as a therapeutic avenue to treat PD symptoms.

Integration of Motor Cortex is Critical to Acquisition of Motor Skills

Motor skill acquisition is understood to be the culmination of task-specific modifications of specific muscle activities, ultimately allowing for a smooth and precise movement sequence¹⁴. The motor cortex plays a central role in motor skill learning, and several studies have demonstrated that motor training can induce changes in motor map organization: motor skill training causes an expansion of movement representations within trained limb areas in the motor cortex of rodents, primates and humans^{15–18}. Furthermore, this map reorganization is required for successful skill learning. Studies clearly show that motor cortex structure and function must be intact in order for successful motor learning to occur. For example, motor cortex lesions prior to training induce severe learning deficits in acquiring motor skills, but do not result in major deficits in motivation and baseline control¹⁹. Motor learning depends on protein synthesis in the motor cortex: injecting Anisomycin, a protein synthesis inhibitor, into the specific cortical area representing a trained forelimb immediately after daily training impairs motor learning, and learning is reinstated after restoring protein synthesis²⁰. Removing acetylcholinergic inputs to the motor cortex before skill training either prevented learning-induced map reorganization in the

motor cortex or impaired motor learning²¹. Interestingly, motor map reorganization is not simply caused by increased use, and reorganization is not considered to be a physical corollary of motor skill consolidation.

Synapse plasticity in Motor Cortex Responds to Motor Learning

It is well established that motor skill learning can induce both functional and structural synaptic plasticity within the motor cortex. A synapse is a structure for electrical or chemical signaling in the central nervous system, and it is believed that synaptic plasticity provides an underlying mechanism for learning and memory. Most excitatory synapses in the mammalian brain are composed of presynaptic axonal en passant boutons and postsynaptic dendritic spines, which are small protrusions extending from dendritic shafts.

Determining synapse dynamics is essential for understanding the structural plasticity of neural circuits. It is expected that motor training promotes synaptogenesis and increased dendritic arborization in the motor cortex, but different experimental paradigms and methods generate diverse and even conflicting conclusions. For instance, studies show significant increases in synapse number in layer II/III or layer V pyramidal neurons within the motor cortex immediately after acquiring a new skill, but not during training^{22,23}. On the contrary, a study reported a decrease in spine density of layer III neurons, but no change in layer V pyramidal neurons, in the motor cortex after motor skill training²⁴. Yet another study showed that motor training increased spine size but did not affect spine number in layer I cortical neurons²⁵. All of the above data regarding synapse/spine structural changes are the result of single time-point observations of fixed or *in vitro* preparations. Given the complexity of neural circuits, it is necessary to explore the cellular and circuit mechanisms of motor learning by examining synapse plasticity in the living, intact brain over extended periods of time.

Developments of both imaging technology and molecular labeling tools enable the visualization of synapses in living animals. Specifically, two-photon microscopy has permitted live, repeated imaging of fluorescence-labeled synapses in the living cortex to a depth of several hundred micrometers from the pial surface^{26,27}. Using two-photon imaging in fluorescence-expressing transgenic animals, researchers studied turnover (formation and elimination) and morphological changes of synaptic structures. Previous studies have also investigated spine dynamics, understood to be good indicators of synaptic plasticity^{28,29}, during and after motor learning, demonstrating a correlation and causal link between physical synaptic changes in the motor cortex and motor learning. They found that the novel motor skill learning, but not simple exercise or recall of previously learned skills, triggered a rapid formation of new spines in layer V motor cortex pyramidal neurons, and the degree of spine formation correlated with the animals' performance^{30,31}. Furthermore, learning-induced, newly formed spines were preferentially stabilized and retained with skill memory, providing a long-lasting structural basis for the enhancement of synaptic strength and persistence of a learned motor skill^{30,31}. These studies also found that longer training caused increased spine elimination^{30,31}, suggesting that removal of inappropriate connections may be the basis for skill refinement. In addition, training pre-trained animals with a novel skill induced further spinogenesis in the motor cortex, suggesting that different motor skill

memories are stored in different neural circuits^{30,31}. A recent study from Haruo Kasai's lab has provided strong evidence for the causal relationship of synapse dynamics and motor skill acquisition. Using an elegantly designed synaptic optoprobe called AS-PaRac1, researchers manipulated potentiated spines and found the motor skill learning was significantly disrupted by undoing the changes of synaptic dynamics that accompany skill learning³², confirming that the acquisition of new motor skill depends on the formation of learning-specific synaptic connectivity. Together, these studies suggest a critical role of durable circuit rewiring in the motor cortex during motor learning.

Functional plasticity, such as long-term potentiation and long-term depression of synaptic efficacy in the motor cortex, are proposed as candidate mechanisms for the acquisition of motor skills. Reaching task training increases the baseline amplitudes of field potentials in either layer I or layer II/III in motor cortex contralateral to the trained limb, suggesting a strengthening of connections between primary motor cortex neurons to mediate initial learning^{25,33}. Interestingly, in both animals and humans, it has been found that long-term potentiation is reduced while long-term depression is enhanced following acquisition of novel motor skills^{33,34}. Moreover, the skill training-triggered enhancement of synaptic strength persists long after initial learning acquisition and parallels with the retention of the skill memory, while both long-term potentiation and long-term depression thresholds shift upward³⁵. This study suggests that the persistent synaptic strengthening reflects permanent storage of the skill memory, and the range shift ensures the possibility of further synaptic strengthening. All of these findings provide evidence for the role of long-term potentiation/depression in the motor cortex as a mechanism of skill learning.

Dopaminergic Modulation of Primary Motor Cortex and Motor Functions

Dopamine exerts its functions by binding to and activating receptors on the cell surface. Dopamine receptors are a class of G protein-coupled receptors and exert their effects via a complex second messenger system. There are two main classes of dopamine receptors³⁶: the D1 class and the D2 class. D1 receptors are coupled to Gs signaling, which subsequently activates adenylyl cyclase, increasing the intracellular concentration of the second messenger cyclic adenosine monophosphate. Conversely, D2 receptors are coupled to Gi/o signaling, which inhibits the formation of cyclic adenosine monophosphate by inhibiting the enzyme adenylyl cyclase. Pyramidal neurons in primary motor cortex express both D1 and D2 receptors^{37,38}. Inhibition of either D1 or D2 receptors in primary motor cortex reduced long-term potentiation within primary motor cortex and impaired skill acquisition³⁹.

Two anatomically and functionally distinct pathways for dopaminergic modulation of primary motor cortex have been determined: mesocortical projections and nigrostriatal projections. Mesocortical afferents directly project to and richly innervate primary motor cortex dendritic processes in either superficial or deep layers of the rodent and primate cortex^{40,41}. Primary motor cortex receives direct dopaminergic projections from both the ventral tegmental area and the substantia nigra pars compacta via the mesocortical pathway⁴². Therefore, activation of this pathway could modulate primary motor cortex cortical activity. Through determining activity-dependent *Fos* expression or by using voltage-sensitive dye imaging, neuronal activity in primary motor cortex region can be

evoked by activation of this pathway^{43,44}. Moreover, it has been shown that mesocortical pathways can modulate the dynamics of horizontal, intracortical connections within primary motor cortex to optimize motor skill learning³⁹. On the other hand, nigrostriatal projections indirectly modulate primary motor cortex activity by activating a series of basal ganglia nuclei to regulate movement execution^{45,46}. As the output nucleus of the basal ganglia, the substantia nigra reticulata inhibits activity of thalamus, which excites the cortex. In this way, nigrostriatal projections can indirectly modulate circuit rewiring of motor cortex through feedback of the cortex–basal ganglia–thalamus closed-loop.

Pathological changes in Motor cortex in PD

The past few decades have seen important developments in understanding the role of the motor cortex in the pathophysiology of PD, and while the etiology of this disease is still unclear, these studies strongly suggest a critical role of the motor cortex in the development of PD. Nearly 80% of patients with PD progress to dementia⁴⁷, and one of the defining pathological characteristics of both Parkinson's disease and dementia^{48–51} are Lewy bodies accompanied by neurodegeneration. Frederick Lewy first described Lewy bodies in 1912, which were later proven to be α -synuclein-containing cytoplasmic inclusions⁴⁸ in the substantia nigra of PD patients⁴⁹. Furthermore, the appearance of Lewy bodies in PD motor cortex was demonstrated at later neuropathological stages⁵². Gray matter atrophy was also found in the motor-related regions of the cortex of PD patients, and this was more extensive in the postural instability gait difficulty-subtype of PD^{53–55}. As postural instability gait difficulty relates to an increased risk for developing cognitive deterioration^{56,57} and dementia^{4,58}, gray matter atrophy may underlie the neural basis for cognitive decline observed in postural instability gait difficulty. Moreover, postmortem immunohistochemical analyses demonstrated a loss of motor cortex dopamine and noradrenaline⁵⁹. In addition, severe disruption of catecholaminergic cortical innervation was reported in the motor and premotor cortical regions in patients with PD⁵⁹. It has been suggested that catecholaminergic denervation of these cortical areas may play a role in the motor malfunctions of PD, including deficits in motor planning⁶⁰. On the other hand, neuroimaging studies showed hyperactivation in the motor cortex of PD patients: the blood oxygenation level-dependent activation in motor cortex was positively correlated with severity of upper limb rigidity⁶¹. The lower threshold of motor cortical stimulation on the side contralateral to the rigid limb was reported in PD patients⁶² despite other studies finding no change in motor threshold in PD patients^{63–68}. Thus it has been proposed that hyperactivation could be related to specific symptoms of the disease, such as rigidity^{61,67–69}. It is also hypothesized that cortical hyperactivation in PD may be due to compensations involving cerebral circuits outside of the basal ganglia⁷⁰. Furthermore, brain-imaging studies in PD patients demonstrated the performance of a variety of motor tasks was accompanied with hyperactivation in the primary motor cortex^{71–73}, and the primary motor cortex was hyperactive during either automatic or cognitively controlled movements⁶¹. These findings provide evidence that supports the correlation between abnormal motor cortex activity and the motor deficits of PD.

Given that the substantial correlations between the motor cortex and PD, some questions remain: if and how does dopamine depletion in PD induce synaptic adaptations in the motor

cortex? What is the relationship between structural and functional plasticity in the primary motor cortex of PD patients? Is there a specific synaptic mechanism in the motor cortex for the skill deficits seen in PD? The motor cortex has become a hot topic of study in PD pathogenesis and therapy over the years, and several advances have been made to further our understanding of the role of dopamine in the motor cortex of PD patients.

Dopamine Regulates Synaptic Plasticity in Motor Cortex

Synaptic plasticity is the ability of synapses to change their strength in response to alterations in activity⁷⁴. This adaptation of neurons to their changing environment plays vital roles in the formation and maintenance of newly established neural circuitry⁷⁵ and is believed to be one of the crucial foundations of learning and memory⁷⁶. The synaptic plasticity in specific brain areas is targeted when studying PD pathology, and the alteration of plasticity in the striatum following dopaminergic denervation has been proven to be a critical event during the development of PD⁷⁴. For instance, in animal models of PD, dopamine depletion induced a rapid and significant loss of spines and glutamatergic synapses on striatopallidal medium spiny neurons^{77,78}. Furthermore, DA plays an important role in ensuring bidirectional plasticity in medium spiny neurons in physiological conditions, and this plasticity is thrown out of balance in PD models⁷⁹. Most PD research focuses on synaptic adaptations in the striatum, because the striatum receives the highest density of dopaminergic innervations⁸⁰. It has been repeatedly demonstrated that spine density is significantly reduced in striatal medium spiny neurons in conditions of dopamine depletion via a 6-hydroxydopamine lesion of the medial forebrain bundle⁸¹. More recent works show that the density of spines in Striatum-GPe but not Striatum-GPi neurons decreases in PD models, which may be related to the development of parkinsonian symptoms⁸². In PD animal models, both long-term potentiation and long-term depression in medium spiny neurons were absent^{83–86}, and the expression of long-term potentiation could be restored by treatment with L-DOPA⁸⁷. Furthermore, D1 signaling promotes long-term potentiation^{3,7} whereas D2 signaling promotes long-term depression^{85,88}. Changes in striatal plasticity are now believed to underlie the network pathology and motor symptoms in PD⁸⁹. On the other hand, the motor cortex, which is the control center for precise fine motor movements and receives rich afferents from midbrain dopaminergic neurons⁹⁰, has received little attention until recent years.

Using traditional morphological methodology, a recent study showed enlargement of spine size, but not spine density, in PD animal models⁹¹. However, postmortem studies can only capture end stages of the process, overlooking the intermediate processes. Thus, sensitive *in vivo* methods are required to investigate the process of synaptic remodeling in PD motor cortex to provide a more complete understand of the pathological progression. Using two-photon *in vivo* imaging microscopy the Ding lab and Xu lab uncovered abnormal remodeling of neuronal circuits in the motor cortex in various mouse models of PD⁹². The researchers used transcranial, two-photon laser scanning microscopy to study the synaptic remodeling of layer V pyramidal neurons in the motor cortex (Fig 1). In this study, the researchers primarily used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mouse model of PD to investigate the changes of structural plasticity in motor cortex in detail. MPTP is a neurotoxin that causes the selective loss of dopaminergic neurons in the

midbrain area of both humans and animals^{93,94}. The MPTP-treated mouse is a common animal model to study the pathogenesis and therapy for PD⁹⁵. Their first finding was that successive MPTP treatment induced significant increase of both spine elimination and formation of the apical dendrites of layer V pyramidal neurons in both adolescent and adult mice motor cortex. The net effect was a modest decrease in total spine number. These results were reproduced in reserpine-treated mice, another commonly used PD animal model, and not observed in the neighboring barrel cortex of adult mice. The systemic administration with L-DOPA, the endogenous precursor of dopamine and the most widely used drug for treating PD, partially rescued this enhanced spine turnover, confirming that the aberrant spine dynamics observed in the motor cortex of PD mice is dependent on dopamine depletion. Through repeated imaging, the authors traced the fates of individual spines over 16 days and observed that pre-existing spines in PD mouse models became unstable. These data suggest that dopamine depletion causes marked enhancement of spine remodeling and increased instability of pre-existing synaptic connections in the motor cortex, despite the mild decrease of total spine number. Moreover, treatment with dopamine receptor antagonists demonstrated that D1 receptors uniquely modulated spine elimination and D2 receptors specifically controlled spine formation, suggesting that the two main classes of dopamine receptors have distinct roles in regulating synaptic plasticity. Finally, through focal lesions of dopaminergic terminals, the authors confirmed that dopamine depletion promoted spine turnover in the motor cortex by primarily local mechanisms that depend specifically on direct mesocortical dopaminergic projections.

In addition to studying changes in structural plasticity, researchers have also investigated potential alterations in functional dynamics of synapses in PD models. Many lines of evidence show that induction of long-term potentiation/depression regulate spine turnover, suggesting that structural plasticity is associated with long-term, functional changes in synaptic efficacy^{96–100}. In PD patients, both long-term potentiation and long-term depression -like plasticity induced by various methods, such as paired associative stimulation or repetitive transcranial magnetic stimulation, in motor cortex were reportedly reduced^{101–105}. In rats, blockade of dopamine receptors reduces long-term potentiation within motor cortex³⁹. The *in vivo* study from the Ding and Xu labs showed that the dopamine system finely modulates structural plasticity of the layer V pyramidal neurons in motor cortex⁹². The scientists further examine changes in synaptic functional plasticity following dopamine depletion using whole-cell patch clamp recordings⁹². They found that long-term potentiation induction in motor cortex, and not in barrel cortex, was impaired in PD mice models. Moreover, long-term potentiation was specifically blocked by the D1 receptor antagonist, but was not affected by the D2 receptor antagonist, showing that D1, but not D2, receptor activation is required for long-term potentiation. Moreover, long-term depression could not be elicited by the pairing protocol in motor cortex of both control adult and PD adult mice, suggesting long-term depression may not directly contribute to changes in spine dynamics in adult mice, including in PD mouse models. The changes of cortical synaptic plasticity in the various experimental models of PD are summarized in Table 1.

Effects of Dopamine Depletion on Neural Circuit Rewiring Triggered by Skill Training

Dopamine depletion causes impairments in skill learning and memory retention in both humans and in animals^{39,106}. A clinical research study showed that while L-DOPA administration in PD patients did relieve motor symptoms, it did not improve functional plasticity in the motor cortex. Because impairments in motor cortex plasticity are not associated with motor signs of PD⁶¹, DA in the motor cortex may instead be specifically influencing motor learning and memory¹⁰⁷. The following question then remains: is it true that the impairments of motor skill acquisition result from aberrant synaptic plasticity in the motor cortex? To address this question, the Ding and Xu labs determined the relationship between performance in a food-reaching task and structural plasticity in the motor cortex of MPTP-injected PD mouse models⁹². The PD mice exhibited impairments in both motor learning and memory. More importantly, motor skill training failed to elicit dendritic structural plasticity in the motor cortex of MPTP-injected mice, again showing that proper reorganization of the neural circuit in motor cortex is the prerequisite for successful acquisition of motor skills. In addition, most newly formed, spines formed during motor training in PD mice were unable to become stable synapses and were then eliminated, showing that stabilization of these spines in PD mice was impaired, and providing a synaptic mechanism for the deficits of skill motor memory seen in PD.

New Model for Dopamine Regulation of Synaptic Plasticity in Motor Cortex

Given that pathological activity in the motor cortex may translate into the motor symptoms observed in PD, the synaptic adaptations and neuronal activities involved in the PD motor cortex have begun to attract more and more attention in recent years^{39,108–112}. The study detailed above in which researchers examined the remodeling of the motor cortex neural circuits in a PD model through combining *in vivo* imaging of spine dynamics, electrophysiological analyses of synaptic functional plasticity, and behavioral investigation, provides evidence for abnormal remodeling in PD motor cortex and allows us to better understand the mechanisms underlying motor skill learning and memory deficits in PD⁹². The main advancements are as follows: First, synaptic plasticity and neural circuit rewiring in the motor cortex is mainly regulated by the mesocortical dopaminergic direct projections. Second, the rewiring in the motor cortex is distinctively regulated by D1 and D2 dopamine receptors in motor cortex. Third, compromised learning-induced spine dynamics and selective stabilization in the motor cortex may contribute to deficits of motor learning and memory retaining observed in PD.

Intriguingly, these findings also elucidate a new relationship between structural and functional plasticity of synapses in the motor cortex. Many lines of evidence have shown that functional changes are involved in synaptic structural changes in neural circuitry. Furthermore, many studies support that induction of long-term potentiation enhances spine formation while induction of long-term depression promotes spine elimination^{96–100,113}. However, in the motor cortex of dopamine-denervated adult mice, elimination of long-term potentiation is accompanied with an increased rate of spine elimination, which is mimicked

by D1 antagonism. And D2 antagonism did not influence long-term potentiation, but did increase the rate of new spine formation. These data demonstrate that depletion of endogenous dopamine or D1 antagonism results in the lack of long-term potentiation, destabilizing dendritic spines and increasing spine elimination. Together, this suggests that the presence of long-term potentiation can stabilize spines. In fact, long-term potentiation promoting the transition from nascent spines to stable, mature spines has been reported before¹¹⁴. Moreover, in the absence of long-term depression, the rate of elimination of dendritic spines is maintained at a certain degree in the motor cortex, but at a higher degree in a PD mouse, indicating a dissociation between long-term depression and spine elimination. Whether this distinct relationship between long-term synaptic structural and functional plasticity is restricted to the motor cortex under these specific conditions requires further investigation.

More importantly, these new findings give us a chance to revisit the fundamentals of how the dopaminergic system regulates synaptic plasticity and the rewiring of the neural circuit in the motor cortex, and to better understand the synaptic mechanisms of the impairments of motor learning and memory. Under physiological conditions, normal dopaminergic tone originating from the midbrain stabilizes synaptic connections through D1 receptor–dependent long-term potentiation, and inhibits aberrant synapse information through the D2 receptors, keeping the neuronal circuits in the motor cortex in balance (Fig 1I). This balance provides a homeostatic mechanism by which layer V neurons integrate converging, motor training related inputs, into superficial cortical layers. This then allows dynamic adaptations in synaptic plasticity resulting in acquiring and retaining motor skills. Conversely, in PD models, due to concurrent loss of both D1 and D2 receptor activation, both spine elimination and spine formation are dramatically enhanced. This is the direct result of the failure of D1-dependent long-term potentiation induction and the loss of D2-dependent synaptogenesis. These aberrant changes in synaptic plasticity lead to abnormal remodeling of neural circuits in the motor cortex, which then disrupts learning-induced synaptic reorganization and stabilization of learning-induced, newly formed spines. Taken together, the above interpretation for dopaminergic regulation of structural and functional plasticity suggests that the pathologically enhanced dynamics of the motor cortex neural circuit in response to dopamine depletion, combined with the destabilization of both pre-existing and newly formed spines, may collectively contribute to deficits in motor learning observed in PD.

Therapeutic Implications and Perspectives

Deep brain stimulation (DBS) has been established as the gold standard for surgical treatment in patients with PD¹¹⁵. Unfortunately DBS is not fully effective in controlling all motor symptoms, and adverse effects and well-documented side effects, such as deterioration of speech and gait^{116–118}, are common. Furthermore, the therapeutic mechanisms of DBS are not well understood¹¹⁹. On the other hand, one of the most cost-effective medications is levodopa, a precursor of dopamine, but long-term administration of levodopa often causes hyperkinetic motor symptoms, termed levodopa-induced dyskinesia^{120–122}. The search for a more safe and effective therapy is a critical area of PD research. Promisingly, and a limited number of pilot studies have demonstrated that the motor cortex may be the potential candidate for novel therapeutic target for PD¹²³.

In fact, many human and animals studies suggest that DBS modulates cortical activity, which is believed to aid in PD remission in the clinic^{124–128}. Optogenetic experiments have shown that direct cortical stimulation was more effective than manipulation of subthalamic nucleus neuronal activity in producing therapeutic effects in PD model mice¹²⁶. In addition, some clinical studies have shown that both repetitive, transcranial magnetic stimulation and subdural cortical stimulation improve motor performances in PD^{129–131}. Furthermore, subdural cortical stimulation on the side contralateral to the worst clinical side can significantly reduce levodopa-induced dyskinesia in PD patients¹³². In recent years, repetitive transcranial magnetic stimulation (rTMS) has been explored by several groups as a possible treatment for PD^{133–135}. As a noninvasive neuromodulation technique, the clear advantage of repetitive transcranial magnetic stimulation is that such approach does not require either anesthesia or surgery. In addition, repetitive transcranial magnetic stimulation targeting the primary motor cortex and other frontal regions can produce persistent changes in neural activity. Chou et al. recently demonstrated that repetitive transcranial magnetic stimulation may improve motor symptoms for PD patients¹³⁶, although some other clinical attempts such as unilateral subdural motor cortex stimulation¹²³ and intermittent theta-burst transcranial magnetic stimulation¹³⁷ did not improve motor symptoms in PD patients. It is important to note that the efficacy of the treatment may be impacted by a combination of many factors, such as, site of stimulation, stimulation parameters (frequency and pulses)¹³⁶, etc. Taken together, these studies point to the motor cortex as a locus for dopamine-related motor activity. The novel contributions of the recent study regarding dynamic changes of synapses in motor cortex has strong implications for treatment strategies for PD: rescue of abnormal synaptic plasticity and neuronal activity in the motor cortex may be a potential, and precise, therapeutic target for treating patients with PD.

There is growing evidence to support that exercise may improve not only the motor symptoms of PD, but is also improves the cognitive impairments seen in PD¹³⁸. This is also seen in rodent models of PD: when PD mice were exercised by treadmill, they experienced improvements in motor learning on the rotarod task¹³⁹. Some studies have suggested that physical activity is associated with lower risk in development of PD^{140,141} and delay of the symptoms onset in PD patients¹⁴². Furthermore, it was reported that the physical exercise was effective in improving some symptoms of PD such as co-morbidities, disuse and limitations^{143–145}. Therefore, exercise has received widespread attention as a therapeutic avenue for patients with PD^{146,147}. However, much remains to be known regarding the mechanisms of action involved in exercise-mediated alleviation of Parkinsonian symptoms. There are many types of exercise which can be grouped into either “physical” exercises, such as running or lifting weights, or “motor-skill” exercises, such as ballroom dancing or Tai Chi. There are clear benefits to physical exercises, including the increase of endurance, strength and stability. Based on the findings that skill training causes synaptic reorganization and enhances the stability of newly formed connections in the corresponding motor cortex^{30,31}, it is plausible that more sustained “motor-skill” related exercises, which require continued learning and training of novel movements, may be more beneficial for PD patients (Fig 1J). Further studies implementing *in vivo* imaging of spine dynamics combined with electrophysiology to analyze synaptic plasticity in animals undergoing different exercise protocols are needed to confirm this hypothesis and elucidate involved synaptic mechanisms.

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References

1. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006; 5:525–535. [PubMed: 16713924]
2. Dorsey ER, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007; 68:384–386. [PubMed: 17082464]
3. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008; 79:368–376. [PubMed: 18344392]
4. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol*. 2003; 60:387–392. [PubMed: 12633150]
5. Doyon J. Motor sequence learning and movement disorders. *Curr Opin Neurol*. 2008; 21:478–483. [PubMed: 18607210]
6. Lang AE, Lozano AM. Parkinson's disease. First of two parts. *N Engl J Med*. 1998; 339:1044–1053. [PubMed: 9761807]
7. Lang AE, Lozano AM. Parkinson's disease. Second of two parts. *N Engl J Med*. 1998; 339:1130–1143. [PubMed: 9770561]
8. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci*. 1973; 20:415–455. [PubMed: 4272516]
9. Obeso JA, et al. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. *Mov Disord*. 2008; 23(Suppl 3):S548–559. [PubMed: 18781672]
10. Gerfen CR, Keefe KA, Gauda EB. D1 and D2 dopamine receptor function in the striatum: coactivation of D1- and D2-dopamine receptors on separate populations of neurons results in potentiated immediate early gene response in D1-containing neurons. *J Neurosci*. 1995; 15:8167–8176. [PubMed: 8613751]
11. Bartels AL, Leenders KL. Parkinson's disease: the syndrome, the pathogenesis and pathophysiology. *Cortex*. 2009; 45:915–921. [PubMed: 19095226]
12. Braak H, Braak E. Pathoanatomy of Parkinson's disease. *J Neurol*. 2000; 247(Suppl 2):II3–10. [PubMed: 10991663]
13. Jellinger KA. The pathology of Parkinson's disease. *Adv Neurol*. 2001; 86:55–72. [PubMed: 11554010]
14. Hammond G. Correlates of human handedness in primary motor cortex: a review and hypothesis. *Neurosci Biobehav Rev*. 2002; 26:285–292. [PubMed: 12034131]
15. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci*. 1996; 16:785–807. [PubMed: 8551360]
16. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J Neurophysiol*. 1998; 80:3321–3325. [PubMed: 9862925]
17. Kleim JA, Cooper NR, VandenBerg PM. Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Res*. 2002; 934:1–6. [PubMed: 11937064]
18. Pearce AJ, Thickbroom GW, Byrnes ML, Mastaglia FL. Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. *Exp Brain Res*. 2000; 130:238–243. [PubMed: 10672477]

19. Kawai R, et al. Motor cortex is required for learning but not for executing a motor skill. *Neuron*. 2015; 86:800–812. [PubMed: 25892304]
20. Luft AR, Buitrago MM, Ringer T, Dichgans J, Schulz JB. Motor skill learning depends on protein synthesis in motor cortex after training. *J Neurosci*. 2004; 24:6515–6520. [PubMed: 15269262]
21. Conner JM, Culberson A, Packowski C, Chiba AA, Tuszynski MH. Lesions of the Basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. *Neuron*. 2003; 38:819–829. [PubMed: 12797965]
22. Kleim JA, Lussnig E, Schwarz ER, Comery TA, Greenough WT. Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. *J Neurosci*. 1996; 16:4529–4535. [PubMed: 8699262]
23. Kleim JA, et al. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *J Neurosci*. 2004; 24:628–633. [PubMed: 14736848]
24. Kolb B, Cioe J, Comeau W. Contrasting effects of motor and visual spatial learning tasks on dendritic arborization and spine density in rats. *Neurobiol Learn Mem*. 2008; 90:295–300. [PubMed: 18547826]
25. Harms KJ, Rioult-Pedotti MS, Carter DR, Dunaevsky A. Transient spine expansion and learning-induced plasticity in layer 1 primary motor cortex. *J Neurosci*. 2008; 28:5686–5690. [PubMed: 18509029]
26. Denk W, Strickler JH, Webb WW. Two-photon laser scanning fluorescence microscopy. *Science*. 1990; 248:73–76. [PubMed: 2321027]
27. Theer P, Hasan MT, Denk W. Two-photon imaging to a depth of 1000 microm in living brains by use of a Ti:Al₂O₃ regenerative amplifier. *Opt Lett*. 2003; 28:1022–1024. [PubMed: 12836766]
28. Gray EG. Electron microscopy of synaptic contacts on dendrite spines of the cerebral cortex. *Nature*. 1959; 183:1592–1593. [PubMed: 13666826]
29. Yuste R, Bonhoeffer T. Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annual review of neuroscience*. 2001; 24:1071–1089.
30. Xu T, et al. Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature*. 2009; 462:915–919. [PubMed: 19946267]
31. Yang G, Pan F, Gan WB. Stably maintained dendritic spines are associated with lifelong memories. *Nature*. 2009; 462:920–924. [PubMed: 19946265]
32. Hayashi-Takagi A, et al. Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature*. 2015; 525:333–338. [PubMed: 26352471]
33. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. *Science*. 2000; 290:533–536. [PubMed: 11039938]
34. Ziemann U, Ilic TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci*. 2004; 24:1666–1672. [PubMed: 14973238]
35. Rioult-Pedotti MS, Donoghue JP, Dunaevsky A. Plasticity of the synaptic modification range. *J Neurophysiol*. 2007; 98:3688–3695. [PubMed: 17913995]
36. Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci*. 2007; 30:228–235. [PubMed: 17408758]
37. Dawson TM, Barone P, Sidhu A, Wamsley JK, Chase TN. Quantitative autoradiographic localization of D-1 dopamine receptors in the rat brain: use of the iodinated ligand [125I]SCH 23982. *Neurosci Lett*. 1986; 68:261–266. [PubMed: 2944035]
38. Lidow MS, Goldman-Rakic PS, Rakic P, Innis RB. Dopamine D2 receptors in the cerebral cortex: distribution and pharmacological characterization with [3H]raclopride. *Proc Natl Acad Sci U S A*. 1989; 86:6412–6416. [PubMed: 2548214]
39. Molina-Luna K, et al. Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PLoS One*. 2009; 4:e7082. [PubMed: 19759902]
40. Descarries L, Lemay B, Doucet G, Berger B. Regional and laminar density of the dopamine innervation in adult rat cerebral cortex. *Neuroscience*. 1987; 21:807–824. [PubMed: 3627435]

41. Lewis DA, Campbell MJ, Foote SL, Goldstein M, Morrison JH. The distribution of tyrosine hydroxylase-immunoreactive fibers in primate neocortex is widespread but regionally specific. *J Neurosci.* 1987; 7:279–290. [PubMed: 2879896]
42. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol.* 2004; 74:1–58. [PubMed: 15381316]
43. Hosp JA, Pekanovic A, Rioult-Pedotti MS, Luft AR. Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *J Neurosci.* 2011; 31:2481–2487. [PubMed: 21325515]
44. Kunori N, Kajiwarra R, Takashima I. Voltage-sensitive dye imaging of primary motor cortex activity produced by ventral tegmental area stimulation. *J Neurosci.* 2014; 34:8894–8903. [PubMed: 24966388]
45. Fuxe K, Manger P, Genedani S, Agnati L. The nigrostriatal DA pathway and Parkinson's disease. *J Neural Transm Suppl.* 2006;71–83. [PubMed: 17017512]
46. Gerfen CR, Surmeier DJ. Modulation of striatal projection systems by dopamine. *Annu Rev Neurosci.* 2011; 34:441–466. [PubMed: 21469956]
47. Emre M, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord.* 2007; 22:1689–1707. quiz 1837. [PubMed: 17542011]
48. Spillantini MG, et al. Alpha-synuclein in Lewy bodies. *Nature.* 1997; 388:839–840. [PubMed: 9278044]
49. FHL. 3 Band: Spez Neurologie II. 1912. Pathologische Anatomie. Lewandowsky's Handbuch der Neurologie, 3 Band.
50. Okazaki H, Lipkin LE, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriplegia in flexion. *J Neuropathol Exp Neurol.* 1961; 20:237–244. [PubMed: 13730588]
51. Kosaka K, Oyanagi S, Matsushita M, Hori A. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. *Acta Neuropathol.* 1976; 36:221–233. [PubMed: 188300]
52. Braak H, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003; 24:197–211. [PubMed: 12498954]
53. Jankovic J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology.* 1990; 40:1529–1534. [PubMed: 2215943]
54. Shao N, Yang J, Li J, Shang HF. Voxelwise meta-analysis of gray matter anomalies in progressive supranuclear palsy and Parkinson's disease using anatomic likelihood estimation. *Front Hum Neurosci.* 2014; 8:63. [PubMed: 24600372]
55. Rosenberg-Katz K, et al. Gray matter atrophy distinguishes between Parkinson disease motor subtypes. *Neurology.* 2013; 80:1476–1484. [PubMed: 23516323]
56. Lewis SJ, et al. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *J Neurol Neurosurg Psychiatry.* 2005; 76:343–348. [PubMed: 15716523]
57. Burn DJ, et al. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry.* 2006; 77:585–589. [PubMed: 16614017]
58. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain.* 2007; 130:1787–1798. [PubMed: 17535834]
59. Gaspar P, Duyckaerts C, Alvarez C, Javoy-Agid F, Berger B. Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. *Ann Neurol.* 1991; 30:365–374. [PubMed: 1683212]
60. Rogers MW, Chan CW. Motor planning is impaired in Parkinson's disease. *Brain Res.* 1988; 438:271–276. [PubMed: 3345432]
61. Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage.* 2007; 35:222–233. [PubMed: 17223579]
62. Cantello R, et al. Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. *Neurology.* 1991; 41:1449–1456. [PubMed: 1891097]

63. Bares M, Kanovský P, Klajblová H, Rektor I. Intracortical inhibition and facilitation are impaired in patients with early Parkinson's disease: a paired TMS study. *European Journal of Neurology*. 2003; 10:385–389. [PubMed: 12823490]
64. Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. *Brain*. 1994; 117(Pt 2):317–323. [PubMed: 8186958]
65. Berardelli A, Rona S, Inghilleri M, Manfredi M. Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. *Brain A Journal of Neurology*. 1996; 119(Pt 1):71–77. [PubMed: 8624695]
66. Strafella AP, et al. Effects of chronic levodopa and pergolide treatment on cortical excitability in patients with Parkinson's disease: a transcranial magnetic stimulation study. *Clinical Neurophysiology*. 2000; 111:1198–1202. [PubMed: 10880793]
67. Pierantozzi M, et al. Effect of apomorphine on cortical inhibition in Parkinson's disease patients: a transcranial magnetic stimulation study. *Exp Brain Res*. 2001; 141:52–62. [PubMed: 11685410]
68. Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. *Ann Neurol*. 1995; 37:181–188. [PubMed: 7847860]
69. Kleine BU, Praamstra P, Stegeman DF, Zwarts MJ. Impaired motor cortical inhibition in Parkinson's disease: motor unit responses to transcranial magnetic stimulation. *Experimental Brain Research*. 2001; 138:477–483. [PubMed: 11465746]
70. Obeso JA, Rodriguez-Oroz MC, Lanciego JL, Diaz MR. How does Parkinson's disease begin? The role of compensatory mechanisms. *Trends in Neurosciences*. 2004; 27:125–127. [PubMed: 15036875]
71. Sabatini U, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. *Brain*. 2000; 123(Pt 2):394–403. [PubMed: 10648446]
72. Thobois S, et al. Overactivation of primary motor cortex is asymmetrical in hemiparkinsonian patients. *Neuroreport*. 2000; 11:785–789. [PubMed: 10757520]
73. Haslinger B, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain*. 2001; 124:558–570. [PubMed: 11222456]
74. Hughes JR. Post-tetanic potentiation. *Physiol Rev*. 1958; 38:91–113. [PubMed: 13505117]
75. Yu X, Zuo Y. Spine plasticity in the motor cortex. *Curr Opin Neurobiol*. 2011; 21:169–174. [PubMed: 20728341]
76. Hebb, DO. *The Organization of Behavior*. New York: Wiley & Sons; 1949.
77. Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Direct and indirect pathways of basal ganglia: a critical reappraisal. *Nat Neurosci*. 2014; 17:1022–1030. [PubMed: 25065439]
78. Day M, et al. Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. *Nat Neurosci*. 2006; 9:251–259. [PubMed: 16415865]
79. Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science*. 2008; 321:848–851. [PubMed: 18687967]
80. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci*. 1990; 13:244–254. [PubMed: 1695398]
81. Ingham CA, Hood SH, Arbuthnott GW. Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age. *Brain Res*. 1989; 503:334–338. [PubMed: 2514009]
82. Nishijima H, et al. Morphologic changes of dendritic spines of striatal neurons in the levodopa-induced dyskinesia model. *Mov Disord*. 2014; 29:336–343. [PubMed: 24573720]
83. Centonze D, et al. Unilateral dopamine denervation blocks corticostriatal LTP. *J Neurophysiol*. 1999; 82:3575–3579. [PubMed: 10601483]
84. Calabresi P, Picconi B, Tozzi A, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci*. 2007; 30:211–219. [PubMed: 17367873]
85. Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. *Nature*. 2007; 445:643–647. [PubMed: 17287809]

86. Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J Neurosci.* 1992; 12:4224–4233. [PubMed: 1359031]
87. Picconi B, et al. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. *Nat Neurosci.* 2003; 6:501–506. [PubMed: 12665799]
88. Gerdeman GL, Ronesi J, Lovinger DM. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nat Neurosci.* 2002; 5:446–451. [PubMed: 11976704]
89. Calabresi P, Mercuri NB, Di Filippo M. Synaptic plasticity, dopamine and Parkinson's disease: one step ahead. *Brain.* 2009; 132:285–287. [PubMed: 19168452]
90. Hosp JA, Molina-Luna K, Hertler B, Atiemo CO, Luft AR. Dopaminergic modulation of motor maps in rat motor cortex: an in vivo study. *Neuroscience.* 2009; 159:692–700. [PubMed: 19162136]
91. Ueno T, et al. Morphological and electrophysiological changes in intratelencephalic-type pyramidal neurons in the motor cortex of a rat model of levodopa-induced dyskinesia. *Neurobiol Dis.* 2014; 64:142–149. [PubMed: 24398173]
92. Guo L, et al. Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. *Nat Neurosci.* 2015; 18:1299–1309. [PubMed: 26237365]
93. Heikkilä RE, Hess A, Duvoisin RC. Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine in mice. *Science.* 1984; 224:1451–1453. [PubMed: 6610213]
94. Langston JW, Langston EB, Irwin I. MPTP-induced parkinsonism in human and non-human primates--clinical and experimental aspects. *Acta Neurol Scand Suppl.* 1984; 100:49–54. [PubMed: 6333134]
95. Meredith GE, Totterdell S, Potashkin JA, Surmeier DJ. Modeling PD pathogenesis in mice: advantages of a chronic MPTP protocol. *Parkinsonism Relat Disord.* 2008; 14(Suppl 2):S112–115. [PubMed: 18585085]
96. Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature.* 1999; 399:66–70. [PubMed: 10331391]
97. Kwon HB, Sabatini BL. Glutamate induces de novo growth of functional spines in developing cortex. *Nature.* 2011; 474:100–104. [PubMed: 21552280]
98. Harvey CD, Svoboda K. Locally dynamic synaptic learning rules in pyramidal neuron dendrites. *Nature.* 2007; 450:1195–1200. [PubMed: 18097401]
99. Wiegert JS, Oertner TG. Long-term depression triggers the selective elimination of weakly integrated synapses. *Proc Natl Acad Sci U S A.* 2013; 110:E4510–4519. [PubMed: 24191047]
100. Hayama T, et al. GABA promotes the competitive selection of dendritic spines by controlling local Ca²⁺ signaling. *Nat Neurosci.* 2013; 16:1409–1416. [PubMed: 23974706]
101. Ueki Y, et al. Altered plasticity of the human motor cortex in Parkinson's disease. *Ann Neurol.* 2006; 59:60–71. [PubMed: 16240372]
102. Morgante F, Espay AJ, Gunraj C, Lang AE, Chen R. Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. *Brain.* 2006; 129:1059–1069. [PubMed: 16476674]
103. Gilio F, et al. Repetitive magnetic stimulation of cortical motor areas in Parkinson's disease: implications for the pathophysiology of cortical function. *Mov Disord.* 2002; 17:467–473. [PubMed: 12112192]
104. Eggers C, Fink GR, Nowak DA. Theta burst stimulation over the primary motor cortex does not induce cortical plasticity in Parkinson's disease. *J Neurol.* 2010; 257:1669–1674. [PubMed: 20496035]
105. Suppa A, et al. Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. *Exp Neurol.* 2011; 227:296–301. [PubMed: 21145888]
106. Frith CD, Bloxham CA, Carpenter KN. Impairments in the learning and performance of a new manual skill in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1986; 49:661–668. [PubMed: 3734823]
107. Kishore A, Joseph T, Velayudhan B, Popa T, Meunier S. Early, severe and bilateral loss of LTP and LTD-like plasticity in motor cortex (M1) in de novo Parkinson's disease. *Clin Neurophysiol.* 2012; 123:822–828. [PubMed: 21945457]

108. Goldberg JA, et al. Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. *J Neurosci.* 2002; 22:4639–4653. [PubMed: 12040070]
109. Pasquereau B, DeLong MR, Turner RS. Primary motor cortex of the parkinsonian monkey: altered encoding of active movement. *Brain.* 2016; 139:127–143. [PubMed: 26490335]
110. Pasquereau B, Turner RS. Primary motor cortex of the parkinsonian monkey: altered neuronal responses to muscle stretch. *Front Syst Neurosci.* 2013; 7:98. [PubMed: 24324412]
111. Pasquereau B, Turner RS. Primary motor cortex of the parkinsonian monkey: differential effects on the spontaneous activity of pyramidal tract-type neurons. *Cereb Cortex.* 2011; 21:1362–1378. [PubMed: 21045003]
112. Li Q, et al. Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex. *Neuron.* 2012; 76:1030–1041. [PubMed: 23217750]
113. Steiner P, et al. Destabilization of the postsynaptic density by PSD-95 serine 73 phosphorylation inhibits spine growth and synaptic plasticity. *Neuron.* 2008; 60:788–802. [PubMed: 19081375]
114. Hill TC, Zito K. LTP-induced long-term stabilization of individual nascent dendritic spines. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2013; 33:678–686. [PubMed: 23303946]
115. Hariz M, Blomstedt P, Zrinzo L. Future of brain stimulation: new targets, new indications, new technology. *Mov Disord.* 2013; 28:1784–1792. [PubMed: 24123327]
116. Hariz MI, et al. Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. *Mov Disord.* 2008; 23:416–421. [PubMed: 18067188]
117. Eklund E, et al. Perceived articulatory precision in patients with Parkinson's disease after deep brain stimulation of subthalamic nucleus and caudal zona incerta. *Clin Linguist Phon.* 2015; 29:150–166. [PubMed: 25333411]
118. Wertheimer J, et al. The impact of STN deep brain stimulation on speech in individuals with Parkinson's disease: the patient's perspective. *Parkinsonism Relat Disord.* 2014; 20:1065–1070. [PubMed: 25048615]
119. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol.* 2004; 115:1239–1248. [PubMed: 15134690]
120. Fahn S, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004; 351:2498–2508. [PubMed: 15590952]
121. Parkinson Study Group. A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of the CALM-PD Study. *Clin Neuropharmacol.* 2000; 23:34–44. [PubMed: 10682229]
122. Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord.* 2005; 20:190–199. [PubMed: 15551331]
123. Moro E, et al. Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson's disease. *Brain.* 2011; 134:2096–2105. [PubMed: 21646329]
124. Fraix V, Pollak P, Vercueil L, Benabid AL, Maudouli F. Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. *Clin Neurophysiol.* 2008; 119:2513–2518. [PubMed: 18783985]
125. Dejean C, Hyland B, Arbuthnott G. Cortical effects of subthalamic stimulation correlate with behavioral recovery from dopamine antagonist induced akinesia. *Cereb Cortex.* 2009; 19:1055–1063. [PubMed: 18787234]
126. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science.* 2009; 324:354–359. [PubMed: 19299587]
127. Lehmkuhle MJ, Bhangoo SS, Kipke DR. The electrocorticogram signal can be modulated with deep brain stimulation of the subthalamic nucleus in the hemiparkinsonian rat. *J Neurophysiol.* 2009; 102:1811–1820. [PubMed: 19625533]
128. Kuriakose R, et al. The nature and time course of cortical activation following subthalamic stimulation in Parkinson's disease. *Cereb Cortex.* 2010; 20:1926–1936. [PubMed: 20019146]

129. Ikeguchi M, et al. Effects of successive repetitive transcranial magnetic stimulation on motor performances and brain perfusion in idiopathic Parkinson's disease. *J Neurol Sci.* 2003; 209:41–46. [PubMed: 12686400]
130. Khedr, E. Non invasive stimulation for treatment of movement disorders. In: Canavero, S., editor. *Textbook of Therapeutic Cortical Stimulation.* Nova Science; New York, NY, USA: 2009. p. 183-200.
131. Canavero, S. Invasive cortical stimulation for Parkinson's disease (PD): why, where and how. In: Canavero, S., editor. *Textbook of Therapeutic Cortical Stimulation.* Nova Science; New York, NY, USA: 2009. p. 217-227.
132. Cioni CDS, Tufo T, Meglio M. "Motor stimulation for movement disorders," in *Handbook of Stereotactic and Functional Neurosurgery.* Minerva Medica. 2011:85–96.
133. Pascualleone A, et al. Akinesia in Parkinson's disease. II. Effects of subthreshold repetitive transcranial motor cortex stimulation. *Neurology.* 1994; 44:892–898. [PubMed: 8190293]
134. Elahi B, Elahi B, Chen R. Effect of transcranial magnetic stimulation on Parkinson motor function--systematic review of controlled clinical trials. *Movement Disorders.* 2009; 24:357–363. [PubMed: 18972549]
135. Fregni F, Simon D, Wu A, Pascualleone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J Neurol Neurosurg Psychiatry.* 2005; 76:1614–1623. [PubMed: 16291882]
136. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson Disease: A Systematic Review and Meta-analysis. *Jama Neurology.* 2015; 72:432–440. [PubMed: 25686212]
137. Benninger DH, et al. Intermittent theta-burst transcranial magnetic stimulation for treatment of Parkinson disease. *Neurology.* 2011; 76:601–609. [PubMed: 21321333]
138. Murray DK, Sacheli MA, Eng JJ, Stoessl AJ. The effects of exercise on cognition in Parkinson's disease: a systematic review. *Translational Neurodegeneration.* 2014; 3:1–13. [PubMed: 24398160]
139. Gorton LM, et al. Exercise effects on motor and affective behavior and catecholamine neurochemistry in the MPTP-lesioned mouse. *Behavioural Brain Research.* 2010; 213(2):253–262. [PubMed: 20472000]
140. Chen H, Zhang SM, Schwarzschild MA, Hernán MA, Ascherio A. Physical activity and the risk of Parkinson disease. *Digest of the World Latest Medical Information.* 2005; 64:664–669.
141. Saso AJ, Paffenbarger RS, Gendre I, Wing AL. The role of physical exercise in the occurrence of Parkinson's disease. *Archives of Neurology.* 1992; 49:360–365. [PubMed: 1558515]
142. Tsai CH, et al. Environmental risk factors of young onset Parkinson's disease: a case-control study. *Clinical Neurology & Neurosurgery.* 2002; 104:328–333. [PubMed: 12140099]
143. Ellis T, et al. Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. *Archives of Physical Medicine & Rehabilitation.* 2005; 86:626–632. [PubMed: 15827910]
144. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabilitation & Neural Repair.* 2009; 23:600–608. [PubMed: 19131578]
145. Informationexchange, C.F.I.R. *Physical Therapy - Exercise and Parkinsons Disease.* 2010.
146. Speelman AD, et al. How might physical activity benefit patients with Parkinson disease? *Nat Rev Neurol.* 2011; 7:528–534. [PubMed: 21750523]
147. Zigmond MJ, Cameron JL, Hoffer BJ, Smeyne RJ. Neurorestoration by physical exercise: moving forward. *Parkinsonism Relat Disord.* 2012; 18(Suppl 1):S147–150. [PubMed: 22166417]

FIG. 1.

Dendritic spine dynamics in the mouse motor cortex in motor learning and Parkinson's disease. **(A)** Illustration of an anesthetized animal under a two-photon microscope. **(B)** The targeted area of the skull is marked with circle for *in vivo* imaging. **(C)** The blood vasculature under the chronic window was imaged using a charge-coupled device camera and was used as a landmark for relocating the same region during repeated imaging. **(D)** *In vivo* 2-photon imaging dendritic spines of Layer V pyramidal neurons using Thy1-YFP transgenic mice. Two-photon image with a low-magnification of dendritic branches in the region indicated in the white box in (C). **(E–H)** Repeated imaging for the same dendritic branch segment with a high-magnification indicated in the white rectangle in (D) at day 0, 4, 8 and 16. Arrow and arrowheads indicate spine elimination and formation, respectively. Scale bars represent 200 μ m (C), 20 μ m (D) or 2 μ m (H). **(I)** Schematic of changes in spine formation and elimination in motor-skill training and following dopamine depletion. Spine formation is modulated by the activation of D2 receptor, and spine stabilization is regulated by the D1 receptor activation. Motor learning induces activity-dependent spine formation

and stabilization. Stabilization of newly formed spines has been proposed to be one of the neural substrates for encoding long-lasting motor memory. In conditions where dopamine tone is lost (i.e., Parkinson's disease), the lack of dopamine receptor activation leads to increased rates of spine elimination. **(I)** Skill-training achieved through a reaching task (on day 0, inset) leads to enhanced spine survival in the motor cortex that persists for many months. Interestingly, spine survival is only transiently enhanced after skill training in MPTP-injected mice. We hypothesize that continued skill-training (red dashed line) will be beneficial for synaptic plasticity and maintenance of newly formed spines in mouse models of dopamine depletion. (Adapted from Guo et. al., 2015, with permission)

Table 1

The changes of cortical synaptic plasticity in the various experimental models of PD.

Reference	Species	Models	Methods	Cortical synaptic plasticity
1. Molina-Luna et al. (2009)	Rat	6-OHDA lesioned	Immunofluorescence & Electrophysiology	Dopaminergic terminals in M1 reduced in 6-OHDA model. Blocking dopaminergic transmission interferes optimal expression of LTP in M1.
2. Hosp et al. (2011)	Rat	6-OHDA lesioned	Immunofluorescence	Destroying dopaminergic neurons in VTA depletes dopaminergic terminals in M1.
3. Li et al. (2013)	Rat	6-OHDA lesioned	Electrophysiology	Dopamine depletion confined to the M1 could lead to impairment in cortical LTP.
4. Matheus et al. (2016)	Rat	6-OHDA lesioned	Immunohistochemical staining & Electrophysiology	6-OHDA decreased the optical density of tyrosine hydroxylase (TH) in PFC. The lower dose of 6-OHDA selectively impairs long-term potentiation (LTP) in the mPFC.
5. Guo et al. (2015)	Mice	6-OHDA lesioned & reserpine injections	<i>in vivo</i> two-photon imaging & Electrophysiology	Dopamine depletion resulted in structural changes in the motor cortex. LTP induction in M1 was impaired in dopamine-depleted mice by both reserpine injections and 6-OHDA lesions.
6. Ueno et al. (2014)	Rat	6-OHDA lesioned	Retrograde tracer	The size of dendritic spines in IT-type neurons of right M1 increased in the PD model.
7. Huang et al. (2011)	Humans	PD patients	Evoked potential recording	PD patients with LID exhibit a lack of depotentiation-like cortical plasticity.
8. Gaspar et al. (1991)	Humans	PD patients	Postmortem	Dopaminergic and noradrenergic innervations reduced in motor cortex in parkinson's disease.
9. Yu et al. (2007)	Humans	PD patients	fMRI	The primary motor cortex was hyperactive during either automatic or cognitively controlled movements in parkinson's disease.
10. Cantello et al. (1991)	Humans	PD patients	Evoked potential recording	The threshold of motor cortical stimulation was significantly lowered in the side contralateral to the rigid limb in PD patients.