Rewiring of motor cortex neural circuits in a mouse model of Parkinson’s disease

Background to this study

Parkinson’s disease (PD) is a neurodegenerative condition characterized by disruptions in both fine movement control and motor learning. Pathologically, these disruptions are attributed to the loss of dopamine neurons in the midbrain (a region of the brainstem). While it is known that changes in synaptic plasticity are important for learning new motor skills and maintaining memory throughout life, little research has focused on the deficits in motor learning that are seen in PD.

The primary motor cortex (M1) is a region of the brain that functions in planning and executing motor movements. Neurons in M1 receive direct dopamine innervation from two regions within the brainstem – the ventral tegmental area and the substantia nigra pars compacta – via the mesocortical pathway, which is one of the four major dopamine pathways in the brain. Since there is a strong dopamine input to M1 from the mesocortical pathway, it is believed that activation of this pathway could directly affect M1 cortical activity. Furthermore, it has been shown that dopamine signaling within M1 modulates the synaptic plasticity of connections between neurons in M1 and is important for optimizing motor skill learning. Therefore, since proper M1 processing is essential for motor learning, alterations in this processing pathway may contribute to the severe motor learning difficulties seen in PD.

Memory formation and maintenance involves long-term synaptic structural and functional plasticity. While the former relates to the creation/remodeling of dendritic spines, the latter relates to the properties of enhancement (long-term potentiation aka LTP) and reduction (long-term depression aka LTD). In M1, synaptic structural changes are associated with functional synaptic plasticity such that LTP-producing methods lead to spine formation, increased spine volume, and therefore increased strength of synaptic connections between neurons and LTD-producing methods lead to spine shrinkage and elimination. Naturally, spine creation and remodeling can be triggered by the learning of new motor skills. When these newly-learned motor skills are repeated, these newly created/remodeled spines undergo stabilization, ensuring long-term memory storage. There is strong evidence that blocking dopamine receptors in M1 can abolish LTP induction in M1 superficial layers and thus impair the ability to learn motor tasks.
**What the researchers were trying to do**

The researchers wanted to investigate how the loss of dopamine innervation affects the motor cortex in a mouse model of PD. Specifically, they wanted to see how dendritic spine dynamics and synaptic functional plasticity are impacted and if any relationship exists between them.

**What they did**

The investigators injected adult and adolescent mice with different chemicals that affect aspects of the neural circuitry involved in PD. They then imaged the dendrites of and recorded the connections between specific neurons (layer V pyramidal neurons) in the forelimb area of M1 before and after injection.

**What they found**

*Dopamine depletion enhances spine dynamics in M1*

In the first part of their experiment, the investigators injected mice with MPTP and reserpine, two drugs which are used in animal-models of PD because they lead to the specific destruction of dopaminergic neurons. Images captured by the investigators showed that dendritic spine turnover (elimination and formation) in M1 of both adult and adolescent mice were significantly increased with treatment. Furthermore, the investigators also imaged the neighboring sensory cortex in these mice and found no change in spine turnover. This further supported their conclusion that dopamine depletion causes enhancement of spine turnover in M1.

*Dopamine depletion leads to unstable circuits in M1*

As stated in the above finding, the investigators were able to show that dopamine depletion enhances spine turnover in M1. Since spine turnover reflects the rewiring of neuronal circuits, the investigators then wanted to compare the spine turnover in PD models to control models. The images that the investigators captured showed that in PD models (MPTP-treated mice) fewer pre-existing spines remained after prolonged MPTP treatment, whereas in control models most pre-existing spines remained stable. These findings indicate that dopamine depletion, like that seen in PD, triggers constant remodeling of the neural circuits in M1 and destabilizes pre-existing synaptic connections.
**L-DOPA can partially impact rates of spine turnover**

L-DOPA is the most widely used drug for treating PD because it is the endogenous precursor of dopamine. To determine the effects of L-DOPA on spine turnover, the investigators treated mice with MPTP for 4 days and then followed that with 4 days of L-DOPA treatment. They found that L-DOPA could partially reverse the enhancement of spine turnover caused by MPTP when compared to MPTP injection alone. This finding confirmed that the spine turnover of M1 in MPTP-injected mice is a result of dopamine depletion.

**Dopamine receptors play a key role in spine dynamics in M1**

The investigators wanted to understand how the two dopamine receptors – D1 and D2 – impact spine dynamics in M1. They did this by treating mice with antagonists at both of these receptors. Their experiments showed that D1 receptors were specifically involved in spine elimination and D2 receptors were specifically involved in spine formation. Together, these findings show that the D1 and D2 receptors are critical to maintaining proper spine turnover dynamics in M1.

**The mesocortical pathway directly regulates M1 spine turnover**

As stated in the background section, neurons in M1 receive direct dopamine innervation from the brainstem via the mesocortical pathway. To investigate how this pathway impacts spine turnover, the investigators carefully destroyed dopamine terminals in the forelimb area of M1 by injecting the neurotoxin 6-OHDA. Before and after images of the dendrites in this area of M1 showed that spine turnover was significantly increased following this injection. This data indicates that the loss of dopamine promotes spine turnover primarily through local mechanisms involving the mesocortical pathway.

**D1 receptor activation is required for LTP; dopamine depletion weakens LTP induction**

Since the investigators showed that dopamine depletion enhances spine turnover and that the D1/D2 dopamine receptors play a key role in this turnover, they next wanted to investigate how dopamine receptor signaling can impact LTP and LTD induction. Using a technique called whole-cell patch clamp, the investigators were able to record inputs on layer V pyramidal neurons in M1. These recordings showed that LTP induction was impaired in dopamine-depleted mice. After further experiments, the investigators were able to conclude that D1, and not D2, receptor activation is required for LTP.
Dopamine depletion impairs learning of new motor skills by preventing stabilization by LTP

The investigators wanted to determine the relationship between spine plasticity in M1 and performance on motor skill tasks following dopamine depletion. They trained two groups of mice to perform a food-reaching task: a control group and an MPTP injected group. Their results showed that performance on a newly learned motor skill is impaired by dopamine depletion.

The investigators then imaged the dendritic regions of control and MPTP injected mice to see how the neural circuits in M1 are remodeled by learning a new motor skill. They found that learning-induced spines were significantly more stable in control mice than learning-induced spines in MPTP-injected mice. The investigators related these findings to the fact that the learning-induced spine formation in MPTP-injected mice was unable to stabilize because of impairments in LTP caused by dopamine depletion.

Conclusions

The investigators concluded that:

- Structural and functional plasticity in M1 is mainly influenced by the activity of the mesocortical dopamine pathway
- Spine formation and elimination in M1 are directly linked to D1 and D2 receptor signaling, respectively
- Dopamine signaling through D1 receptor activation is required for LTP
- Dopamine depletion impairs performance of newly learned motor skills and burdens learning-induced spine stabilization in M1

What this means for the reader

Despite its crucial role in fine motor control and its rich input of dopaminergic innervation, the motor cortex (M1) has received very little attention in PD research. Through their elaborate and intricate experiments, the investigators hoped to provide a glimpse into the biomolecular events involved in the restructuring of the local neural circuitry in a mouse model of PD. By establishing the relationship between dopamine depletion, D1/D2 receptor activation, spine turnover, and LTP, the investigators were able to formulate a new model for dopamine depletion-induced synaptic structural and functional plasticity in M1. This new model effectively relates chronic dopamine depletion to both a net loss of stable spines in layer V pyramidal neurons and a failure to stabilize learning-induced spines in a motor-learning task. Taken together, these findings highlight the role of M1 in the impairments observed in motor
performance and motor memory in a mouse model of PD. This study also establishes M1 as a promising research target for future PD studies.

**Original paper**

*Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease*  
*(Guo et al., 2015)*

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