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Review

Dopaminergic modulation of primary motor cortex: From cellular and synaptic mechanisms underlying motor learning to cognitive symptoms in Parkinson's disease

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ABSTRACT

The primary motor cortex (M1) is crucial for movement execution, especially dexterous ones, but also for cognitive functions like motor learning. The acquisition of motor skills to execute dexterous movements requires dopamine-dependent and -independent plasticity mechanisms within M1. In addition to the basal ganglia, M1 is disturbed in Parkinson's disease (PD). However, little is known about how the lack of dopamine (DA), characteristic of PD, directly or indirectly impacts M1 circuitry. Here we review data from studies of PD patients and the substantial research in non-human primate and rodent models of DA depletion. These models enable us to understand the importance of DA in M1 physiology at the behavioral, network, cellular, and synaptic levels. We first summarize M1 functions and neuronal populations in mammals. We then look at the origin of M1 DA and the cellular location of its receptors and explore the impact of DA loss on M1 physiology, motor, and executive functions. Finally, we discuss how PD treatments impact M1 functions.

1. Introduction

The primary motor cortex (M1) is one of the major brain areas responsible for planning and execution of motor commands (Ebbesen and Brecht, 2017; L. Guo et al., 2015a, 2015b; Whishaw et al., 1986). Coordinated movements necessitate constant adjustments to adapt to an ever-changing environment and require plasticity mechanisms within M1 that are crucial for the acquisition and maintenance of motor skills. Numerous alterations of cortical functions have been observed in neurodegenerative diseases and particularly in Parkinson's disease (PD; Swann et al., 2016). This disease, first described in 1817 by James Parkinson, is characterized by progressive degeneration of the dopaminergic (DAergic) neurons in the *substantia nigra pars compacta* (SNc), inducing dramatically reduced levels of dopamine (DA) in the brain of PD patients. The loss of DA results in dysfunction in neuronal circuits controlling motor execution, mainly in the basal ganglia, a brain region highly innervated by DAergic afferents and involved in motor function. This leads to the typical motor impairment observed in PD: resting tremor, akinesia, rigidity, and postural instability (Nambu et al., 2015). Interestingly, M1, which integrates information from the sensory and premotor cortices and transmits appropriate motor commands to the spinal cord and basal ganglia, also receives DAergic innervation. Disturbances in the function of M1 have also been identified in PD, leading to cognitive dysfunctions such as deficits in motor skill learning (Burciu and Vaillancourt, 2018; Marinelli et al., 2017). In this review, we will first describe M1 microcircuit organization and M1 function in motor execution and motor learning, based on studies in rodents and humans. Then, we will show the importance of M1 DA in physiological conditions and the consequences of its depletion in experimental models of PD and in PD patients. Finally, we will give a non-exhaustive review of the impact of current PD therapy on M1 functions and discuss the possibility of targeting M1 to treat cognitive symptoms in PD.

Abbreviations: 6-OHDA, 6-hydroxydopamine; CStr, cortico-striatal; CThNs, cortico-thalamic neurons; DA, dopamine; DAergic, dopaminergic; DBS, deep brain stimulation; EMCS, extradural motor cortex stimulation; GABA, γ-aminobutyric acid; ITNs, intratelencephalic neurons; LID, levodopa-induced dyskinesia; LIPUS, low-frequency low-intensity pulsed ultrasound; LTP, long-term plasticity; M1, primary motor cortex; MPTP, 1-méthyl-4-phényl-1,2,3,6-tétrahydropyridine; PD, Parkinson's disease; PKA, protein kinase A; PLC, phospholipase C; PNs, pyramidal neurons; PT, pyramidal tract; PV, parvalbumin; SNc, *substantia nigra pars compacta*; SST, somatostatin; STN, subthalamic nucleus; UPRDS, unified Parkinson's disease rating scale; VTA, ventral tegmental area..

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2. Cellular organization of the M1 microcircuit

2.1. Organization of M1 into 6 layers

Like other cortices, M1 is organized into 6 layers of interconnected neurons. It is composed of two main neuronal populations: approximately 75% glutamatergic excitatory pyramidal neurons (PNs) and 25% GABAergic (GABA, γ-aminobutyric acid) inhibitory neurons (Shipp, 2007; Callaway et al., 2021). Interestingly, a species-specific adaptation in the proportion of GABAergic neurons is observed: they represent 16% of M1 neurons in mice, 23% in marmosets and 33% in humans (Bakken et al., 2021). It should be noted that the existence of layer 4 (L4) in M1 is debated (Barbas and García-Cabezas, 2015; Donoghue and Wise, 1982), though recent functional investigations suggest that M1 contains a circuit-level equivalent of L4 in the mouse, i.e., with the same synaptic organization as L4 neurons in the sensory cortex (Yamawaki et al., 2014; Yao et al., 2021).

2.2. Cell types in M1

2.2.1. PNs

The PNs are the main projection neurons of the structure and are divided into 3 different subtypes, depending on the location of the soma in the cortical layers and on their projection targets: the pyramidal tract neurons (PTNs), the intratelencephalic neurons (ITNs), and the corticothalamic neurons (CThNs; Hooks et al., 2013). PTNs are found in L5 and project to the brainstem and spinal cord and can also project to the thalamus and striatum (Cowan and Wilson, 1994; Donoghue and Kitai, 1981; Kita and Kita, 2012; Parent and Parent, 2006). They respond to somatosensory stimulation, mainly proprioceptive stimuli. Moreover, PTNs fire just before the onset (~200 ms before) and during flexion movements and stop firing during extension movements (Beloozerova et al., 2006; Economo et al., 2018; Li et al., 2016; Li et al., 2015; Turner and DeLong, 2000). These PTNs are topographically organized in M1 in a logical manner to coordinate multi-joint forelimb muscle contraction during performance of motor skills (Wang et al., 2017). ITNs can be found in L2 to L6. Those in L2/3 project to other cortices (ipsi- or contralaterally) and are called cortico-cortical ITNs (CC). ITNs in deeper layers project to the striatum and are therefore called cortico-striatal (CStr) ITNs. CStr ITNs are not as responsive to somatosensory stimuli compared to PTNs, and they are selectively activated depending on the direction of the movement to ensure the proper transmission of cortical states to specific spiny projection neurons of the striatum for subcortical processing (Turner and DeLong, 2000). Finally, M1 CThNs project mainly to the posterior and ventro-medial thalamic nuclei and these CT pathways are believed to re-enforce sensorimotor integration and motor control (Shepherd and Yamawaki, 2021).

2.2.2. GABAergic cortical neurons

The GABAergic cortical neurons can be classified into different classes depending on their morphology, intrinsic properties, and expression of specific transcription and molecular factors (Bouzas et al., 2008; Scala et al., 2021). Three major classes stand out regarding the latter criteria, which together account for nearly 100% of cortical GABAergic neurons: the parvalbumin-expressing (PV) neurons, the somatostatin-expressing (SST) neurons, and the $5HT_{3A}$ receptor-expressing neurons (Rudy et al., 2011). PV neurons, representing around 40% of the population, are the major group of cortical GABAergic and comprise basket cells and chandelier cells. They exhibit a unique electrical profile, clearly distinct from the other cortical neurons. Their short action potential duration and high spiking frequency has seen them classified as fast-spiking neurons. In the neocortex, PV neurons can massively project onto the somata and proximal dendrites of PN (for the basket cells) and onto the axon initial segment (for the chandelier cells), enabling the control of the output of these cells (Hu et al., 2014). Interestingly, PV neurons are the only neocortical GABAergic neurons making autapses. These synapses made on themselves enable a decrease of their firing frequency, but most importantly, facilitate precise spike timing (Bacci and Huguenard, 2006). PV neurons also have the particularity in the neocortex of being the major population surrounded by mesh-like structures composed of hierarchical assemblies of extracellular matrix molecules called perineuronal nets, which limit plasticity in adulthood (Sorg et al., 2016; Van't Spijker and Kwok, 2017 for reviews). SST neurons, also classified as low-threshold spiking or regular-spiking non-pyramidal neurons, are the neocortex's second main GABAergic population (Urban-Ciecko and Barth, 2016). They project mainly to the apical and distal dendrites of PNs, enabling the control of the excitatory inputs received. PV and SST neurons are often referred to as 'interneurons'. However, a non-negligible proportion of them are long-range neurons and can project to the contralateral homotypic cortex (Rock et al., 2016; Zurita et al., 2018) or to the striatum (Melzer et al., 2017). Up to a third of the direct pathway's spiny projection neurons respond to optogenetic stimulation of these long-range cortical GABAergic neurons (Melzer et al., 2017). While long-range PV neuron stimulation decreases locomotion, long-range SST neuron stimulation promotes locomotion. Finally, $5HT_{3A}R$ neurons represent the third-largest class of GABAergic cortical neurons. It is a very heterogeneous group that can be divided into two sub-classes: one expressing the neuropeptide VIP and the other non-VIP, also called the neurogliaform. Such VIP-positive neurons preferentially target other GABAergic neurons in the motor cortex (Bohannon and Hablitz, 2018), such as PV neurons (Donato et al., 2013), while neurogliaform cells preferentially target PNs (Schuman et al., 2019).

3. M1, a key structure in motor function and motor learning of dexterous movements

3.1. Role of M1 in movement execution

The involvement of M1 in motor function was first demonstrated in 1870 by Fritsch and Hitzig, when they showed that electrical stimulation of specific regions of the cerebral cortex of a non-anesthetized dog induces discrete movements (Fritsch and Hitzig, 2009; republished and translated to English, 2009). Later, Penfield and Boldrey described the motor homunculus in a locally anesthetized human by electrically stimulating various cortical regions (Penfield and Boldrey, 1937). This functional somatotopy consists of the representation of the different body parts along the M1 region. The size of the representation of the body part depends on the complexity of movements that can be achieved; the more complex the movements, the larger the region. Such M1 mapping has been described across many other animal species, like non-human primates, rodents, or cats (Woolsey et al., 1952; Brown and Teskey, 2014). However, defining M1 boundaries in some species is difficult as M1 may overlap with the somatosensory cortex (Hall and Lindholm, 1974). Interestingly, a complete overlap between those two cortices has been reported in a marsupial opossum considered to be a 'primitive' species (Frost et al., 2000). This tends to suggest that the segregation between M1 and the sensory cortex might be linked to the appearance of more dexterous movements and may underlie a specification of pure motor M1 areas that are highly involved in dexterous abilities.

Lesion approaches have also contributed to dissecting the role of M1 in movement execution and motor skill learning. Unilateral lesions of the M1 forelimb area in rodents induce deficits in contralateral forelimb movements, and the larger the lesion, the larger the impairments (Touvykine et al., 2016; Whishaw, 2000). Thus, the largest and longest-lasting effects of M1 lesions are seen in movements requiring dexterity and finer control of the digits. These lesion approaches primarily show differences among species in M1 rehabilitation. In humans, lesions of M1 or the pyramidal tract (PT) lead to paralysis that may be partially recovered if the lesion is superficial (Darling et al., 2011; Kwakkel et al., 2003).Furthermore, lesions in humans induce deficits in movements

and, more specifically, considerable deficits in dexterous movements. If the lesion is too large, it can lead to total paralysis with no possible recovery (Kwakkel et al., 2003). In non-human primates, M1 lesions especially affect dexterous movements, like grasping (Savidan et al., 2017). In other primates, M1 lesions can be recovered entirely, presumably through compensation by subcortical areas, including reticulospinal pathways (Darling et al., 2011; Lashley, 1924; Leyton and Sherrington, 1917; Zaaimi et al., 2012). After M1 lesions, non-primate mammals and rodents can recover rapidly and can still perform most of their behavioral repertoire, which is already learned and mainly non-dexterous (Kawai et al., 2015). Overall, lesion approaches support the hypothesis that M1 plays an essential role in dexterous movements, which take a prominent place in the human behavioral repertoire. More recently, using an optogenetic approach in rodents, Galiñanes et al. showed that the selective silencing of M1 is able to block movement initiation and to stop already-initiated movements in a forelimb reaching and grasping task (Galiñanes et al., 2018). This work emphasizes once again the prominent role of M1 in dexterous motor sequences. Interestingly, it has been shown in monkeys that a short electrical stimulation of the motor cortex is able to elicit muscle contraction, while an electrical stimulation lasting for a behaviorally-relevant duration (0.5 seconds) is sufficient to create complex and multi-joint movements (Graziano et al., 2002, 2005). These movements belong to the natural behavioral repertoire of the studied species and are arranged across the cortex, depending on the target location in space to which the movement is directed. Such arrangement of movement can be found at the cellular level in rodents: L2/3 PNs are activated for specific movement directions and target positions for reaching movements (Galiñanes et al., 2018).

3.2. Role of M1 in motor skill learning

Besides its prominent role in motor execution, M1 is also crucial for cognitive functions such as learning new motor skills (Bachtiar et al., 2018; Dupont-Hadwen et al., 2019; Kida et al., 2016; Smyth et al., 2010). Complex motor skills and habits are not innate; they must be learned through trial and error. Motor skill learning consists of improving the speed, accuracy, and consistency of a specific movement throughout training that lasts over time. Once learned, the stereotyped movement sequence is executed automatically in response to its specific cue. M1 is instrumental for both the acquisition (Hosp et al., 2011) and maintenance (Ohbayashi, 2020) of motor sequences. During motor training and learning, the M1 corticomotor map is reorganized with, for instance, an increase in the area corresponding to the body part involved in the trained task (Monfils et al., 2005). However, the role of M1 in the maintenance of motor sequences is not as clear across different species. Rodents that have learned a task in which they have to pull a lever are still able to do it after M1 lesion (Kawai et al., 2015). The blockade of protein synthesis is also not sufficient to impair a learned motor sequence in rodents, while it is sufficient to impair the learning of this same task (Hosp et al., 2011). However, protein synthesis blockade in M1 of primates is sufficient to alter learned motor sequences without altering motor execution (Ohbayashi, 2020). Those concordant data may underlie, once again, the fact that M1 may play a critical role for dexterous skill learning and that subcortical areas may not be able to compensate in species with a more dexterous behavioral repertoire.

The development of a forelimb prehensive task in rodents (Guo et al., 2015a; Guo et al., 2015b; Metz and Whishaw, 2000; Fig. 1A) combined with cell type-specific manipulations and monitoring (Guo et al., 2015a; Levy et al., 2020; Li et al., 2017b) have been instrumental for the in-depth dissection of the role played by different M1 neuronal subtypes in motor skill learning. The single pellet reaching task (Chen et al., 2014) is classically used in rodents, as this task is highly relevant to study motor dexterity. The movement is composed of different phases, which are very similar in rodents and humans (Klein et al., 2012), making results easily transposable from rodents to humans. Recordings of neurons in all layers of M1 during single pellet reaching task have revealed that L5 PNs and fast-spiking GABAergic interneurons are primarily recruited during movement execution (Huber et al., 2012; Isomura et al., 2009; Levy et al., 2020; Li et al., 2017b), while L2/3 neuronal activity is primarily outcome-related (Levy et al., 2020; Fig. 1B) in the murine forelimb area. This suggests there is a cell type- and layer-specific separation of monitoring and control of motor function during motor skill learning. Furthermore, reporting of motor outcome by L2/3 neurons seems to emerge from the learning process, as the number of indicative neurons increases during learning (Levy et al., 2020).

At the cellular level, several plasticity mechanisms take place during motor skill learning. It has been shown that following motor skill training, cortico-spinal neurons that control distal forelimb musculature express increased excitability (Biane et al., 2019) and that local L5 recurrent excitation between these neurons is also increased (Biane et al., 2019), as is that of thalamo-cortical projections (Biane et al., 2016). During the learning process, a substantial proportion of L5b

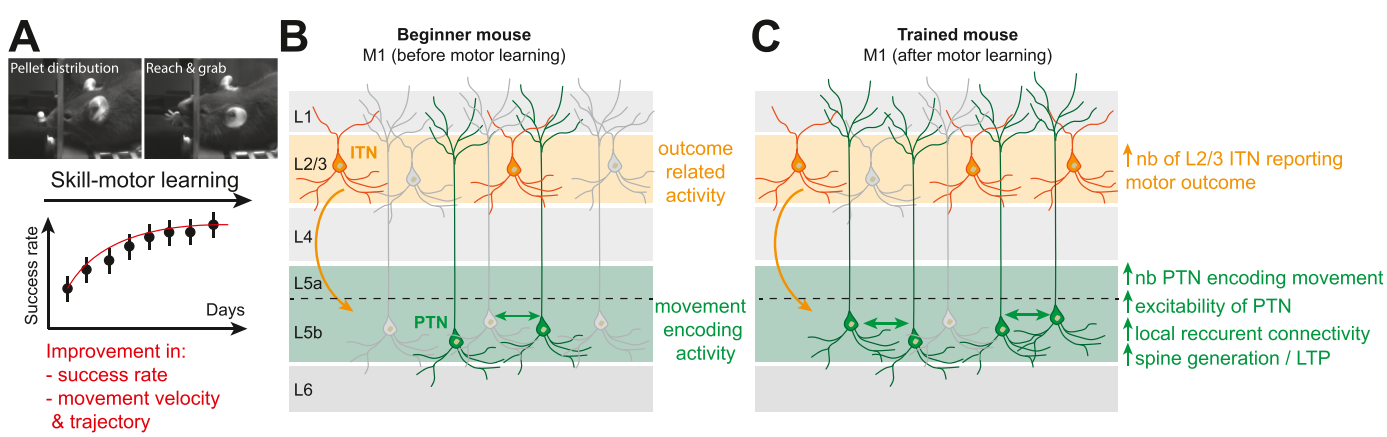

Fig. 1. Intrinsic and synaptic plasticity in M1 induced by motor skill learning.
A: A mouse performing pellet prehension in a reaching skill task. Over several days of training, the mouse improves its skills, which can be monitored by an increase in the success rate of prehension, an increase in movement velocity and the acquisition of stereotyped movements. B: Simplified diagram of M1 before training, in which L2/3 and L5b PN are represented. Only a subset of neurons (colored neurons) is involved in movement encoding (L5b neurons) and monitoring of motor performance (L2/3 neurons). C: After motor skill learning, the numbers of L2/3 neurons reporting motor outcomes and movement-encoding L5b neurons are increased. Intrinsic and synaptic plasticity is observed in L5b neurons. IT neurons, which are present in all layers, are shown only in L2/3. CThN, which are present in L6, are not represented for the sake of simplicity of the diagram.
CThN: cortico-thalamic neurons; IT-CC: intra-telencephalic cortico-cortical neurons; PTN: pyramidal track neurons.

neurons progressively change, from being non-informative about forelimb velocity and trajectory to possessing similar information about motor behavioral outputs to neurons that exhibit clear movement-encoding firing at the beginning of training (Li et al., 2017b). Several studies also report the induction of long-term plasticity (LTP) during motor skill learning (Guo et al., 2015b; Li et al., 2017b). These intrinsic and synaptic plasticities are thought to stabilize the activity patterns in M1 which accompany motor learning (Li et al., 2017b; Peters et al., 2014) and certainly contribute to the augmentation of movement-encoding L5 neurons in trained animals. It has also been shown that new spines in the dendrites of L5 PN are generated when motor skills are learned (Guo et al., 2015b; Harms et al., 2008; Xu et al., 2009; Fig. 1C). A recent study provides an insight about the mechanism underlying spinogenesis during motor skill learning (Albarran et al., 2021). Using mice lacking paired immunoglobulin receptor B (PirB$^{-/-}$), Albarran and colleagues demonstrate that NMDA-dependent LTP, whose expression is under the control of PirB, promotes M1 PN stabilization of newly-formed dendritic spines that are associated with enhanced acquisition and maintenance of motor skills (Albarran et al., 2021). These findings are consistent with previous studies showing that impairing intrinsic or/and synaptic plasticity in M1 is sufficient to impair motor skill learning (Biane et al., 2019; Hayashi-Takagi et al., 2015).

4. Dopaminergic innervation, dopamine receptor expression and function in M1

4.1. Origins of DA within M1

The first evidence of the presence of DA in the cortex, not as a precursor of norepinephrine, dates from the 1970s (Thierry et al., 1974). A decade later, DAergic terminals were clearly described in the frontal cortex, coming from the ventral tegmental area (VTA) and the substantia nigra *pars compacta* (SNc; Fallon, 1981; Swanson, 1982). These DAergic terminals were then identified in M1 with tyrosine hydroxylase (TH) immunocytochemistry after NE terminal depletion (Berger et al., 1985). In rodents, they are mainly located in the deepest layers of the motor cortex, while in primates, they are widespread in all layers (Berger et al., 1991; Descarries et al., 1987; Lewis et al., 1987). Labeling of the DA transporter in rats also reveals that DAergic terminals innervate deep layers of M1, especially those targeting the forelimb representation area (Hosp et al., 2015; Vitrac et al., 2014). Using retrograde tracing in rats, it has been shown that those DAergic projections in M1 come from the VTA and to a lesser extent, from the SNc (Hosp et al., 2011; Molina-Luna et al., 2009), in a similar fashion as in the frontal cortex (Ott and Nieder, 2019). This finding supports the conclusion that the meso-cortical pathway is preserved across species and thus is a functionally important pathway for M1 computations. In humans, it has also been shown that VTA DAergic neurons project to motor areas (Hosp et al., 2019). More importantly, both D1-like and D2-like DAergic receptors are expressed in M1 of many mammalian species (Camps et al., 1990; Gaspar et al., 1995; Huntley et al., 1992; Mansour et al., 1990). Notably, PTNs in rodents express D1, D2, and D5 DAergic receptors (Awenowicz and Porter, 2002; Fig. 2). In addition, taking advantage of the *Drd2-Cre: Ribotag* mouse line, it has also been shown that D2 receptor-expressing cells are distributed in all cortical layers and in a wide variety of M1 GABAergic neurons, in particular PV neurons (Cousineau et al., 2020).

Apart from the DA release from midbrain neurons, it has also been shown thanks to voltage sensitive dye imaging in rat M1 that glutamate can also be released by midbrain neurons, underlying a potential role of excitatory transmission from the midbrain to M1 in motor processes (Kunori et al., 2014). These findings are not surprising as similar mechanisms have already been observed in the PFC (Mercuri et al., 1985; Watanabe et al., 2009). Interestingly, the release of glutamate by midbrain neurons is thought to enable the fast transmission of reward information (Lapish et al., 2007; Lavin et al., 2005). The role of release of glutamate by midbrain neurons in M1 could be similar, as glutamate

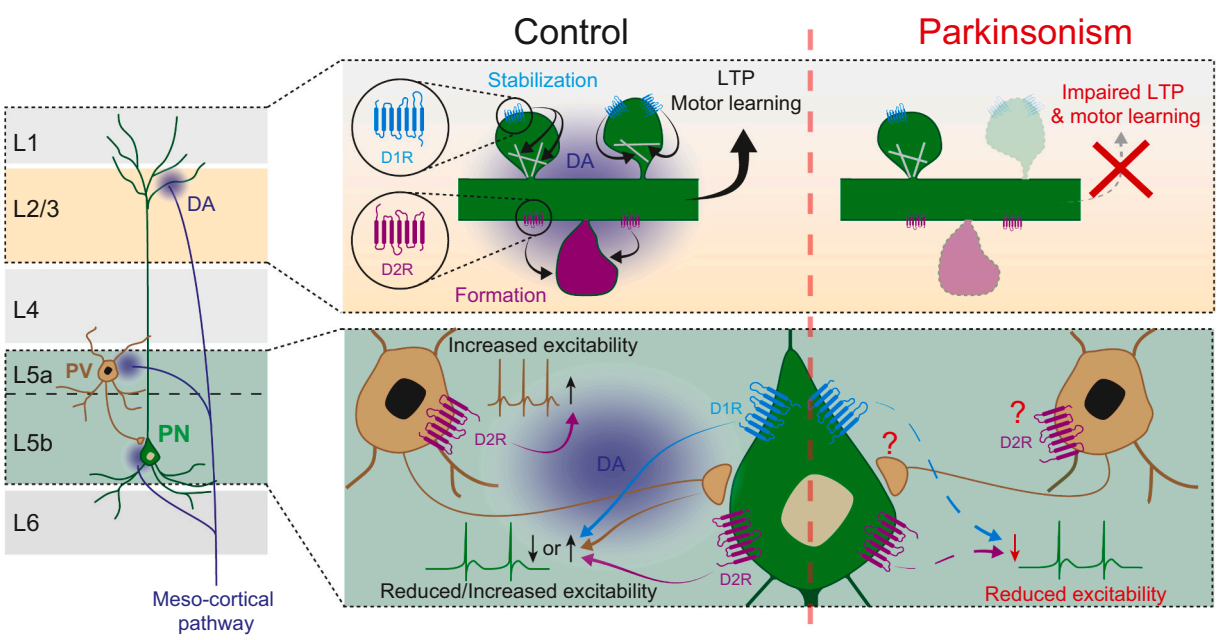

Fig. 2. DA-dependent plasticity in M1.
Schematic depicting an L5 PN and an L5 PV neuron and dopaminergic meso-cortical inputs.
The top dashed rectangle shows a dendritic branch of an L5 PN receiving DAergic innervation. On the left is the D2 receptor-dependent spine formation (in magenta) and the D1 receptor-dependent stabilization of spines (grey lines inside the spines). This form of DA-dependent structural plasticity underlies long term plasticity (LTP) at glutamatergic synapses and motor learning. In Parkinson's disease, the levels of DA progressively decrease in the brain (including M1) and DA-dependent plasticity is lost. Spine turnover is increased, leading to impaired LTP at glutamatergic synapses and impairment of motor performance.
The bottom dashed rectangle represents a magnification of the cell body of an L5b PN and PV neurons. On the left is the effect of DA (shown as the purple cloud) on D1- and D2-like receptors on the excitability of the neurons. On the right part of the rectangle, the reduced tone of DA in the brain (including M1) during the progression of PD leads to direct and indirect (circuit mediated) alterations of L5b PN excitability.

could signal the reward and DA could induce M1 plasticity in order to refine the movement to get the reward.

4.2. Effect of DA receptor stimulation on M1 neuron excitability

Intracellular cascades induced by DAergic receptor activation are complex and vary with the cell types and the brain region. In M1, little is known about the signaling pathways used by DA-receptors to modulate neuronal excitability. Traditionally, activation of D1-like or D2-like receptors have opposite physiological effects via different G proteins, stimulating or inhibiting, respectively, the protein kinase A (PKA) signaling cascade (Mishra et al., 2018). However, in M1, it has been shown that DAergic receptors may work differently. As a matter of fact, phospholipase C (PLC) inhibitors and PKA inhibitors impair LTP in M1 neurons (Rioult-Pedotti et al., 2015). Further, D1 or D2 blockade in M1 induces impaired motor skill learning and M1 LTP, but PLC agonist injection is sufficient to prevent this impairment. Therefore, these data suggest a similar effect of both types of receptors in M1. At the cellular level, the modulations exerted by DA on the excitability of the different M1 neuronal populations are multiple (Table 1). It is clear in the literature that a discrepancy of the effect of DA on PNs is observed. In this review, we tried to summarize what has been discovered so far, being careful to separate what has been done *in vivo* or *ex vivo*. An *ex vivo* study in mice showed changes in intrinsic properties (input resistance, action potential half width) and an increase in the excitability of PNs following D1R and/or D2R receptor blockade (Swanson et al., 2020). Another one, still *ex vivo* in mice, reported however no modulation of L5 PNs by bath application of a D2R agonist (Cousineau et al., 2020). In other species, *in vivo* recordings showed a decrease in excitability of PNs following DA local microinjection in rats (Awenowicz and Porter, 2002), as well as in cats (Huda et al., 1999). However, D2R agonist quinpirole local injections in rats induced an increase in the spike firing rate of PNs (Vitrac et al., 2014), and systemic injection of D2R antagonist haloperidol in rats induced the opposite effect, *i.e.* a reduced spike firing rate (Parr-Brownlie and Hyland, 2005). The divergence of these *in vivo* studies' results could be due to the drug used and its application method (local microinjection vs systemic injection); nevertheless, the impact of DA on PNs is still unclear. There is a need of studies using the same experimental design in order to decipher the impact of DA receptors activation or blockade on PNs. It is also crucial to take into account the diversity of PNs to better understand the action of DA on M1 PNs. Overall it seems that activation of D1 or D2 receptors globally decrease excitability of some PNs (Awenowicz and Porter, 2002; Huda et al., 2001, Huda et al., 1999; Fig. 2). It has also been shown that activation of D2-like receptors *ex vivo* induces an increase in PV neurons' excitability and their synaptic transmission onto L5 PNs in M1 (Cousineau et al., 2020; Fig. 2), corroborating the fact that D2-like receptor activation can have an excitatory effect on M1 neurons. Moreover, activation of D2 receptors via quinpirole infusion in M1 increases the firing frequency of PN in a dose-dependent manner *in vivo* (Vitrac et al., 2014), which is reminiscent of the quinpirole-mediated increased excitability of prefrontal cortex L5 PNs (Gee et al., 2012). This mono-directional effect of both types of DAergic receptors is not surprising in M1, as it is also found in the prefrontal cortex. Regarding synaptic transmission, numerous pieces of evidence highlight the effect of DA on both glutamatergic and GABAergic transmission and neuronal properties in the prefrontal cortex (Trantham-Davidson, 2004). The downstream β-arrestin2 signaling pathway (Urs et al., 2016) or the release of neurotensin via activation of D2 autoreceptors of M1 DAergic neuron terminals could explain the D2 excitatory effect (Petrie et al., 2005), as is the case in the prefrontal cortex. Nonetheless, it has been shown that *in vivo* DA infusion in the forepaw representation of the cat motor cortex decreases the activity of PTNs and their evoked response to callosal and thalamic inputs (Huda et al., 2001; Huda et al., 1999); those effects are rescued by the application of DAergic antagonists, for either D1 or D2 (Awenowicz and Porter, 2002; Huda et al., 2001). This decrease in PTN activity could be

Table 1
Effect of dopaminergic pharmacology and dopamine-depletion on M1 neuronal subtype activity.

Type of manipulation	Neuronal subtype		Recording conditions	References
	Pyramidal neurons	GABAergic interneurons		
DA	↓ in response of PN to callosal & thalamic excitatory inputs	N/D	*In vivo* anesthetized Local microinjections	Huda et al., 1999, 2001
	↓ in firing rate of PTN		*In vivo* anesthetized Local microinjections	Awenowicz and Porter, 2002
D1 agonist	N/D	N/D		
D2 agonist	No effect on L5 PN excitability	↑ in L5 PV-IN excitability	*Ex vivo*	Cousineau et al., 2020
		↑ in PV-IN to PN GABAergic transmission	*Ex vivo*	Cousineau et al., 2020
	↑ in firing rate of L5 PN		*In vivo* anesthetized Systemic i.p. injections	Vitrac et al., 2014
D1 antagonist	↑ in L5 PN excitability	N/D	*Ex vivo*	Swanson et al., 2020
D2 antagonist	↓ in firing rate of PN	N/D	*In vivo* freely-moving Systemic i.p. injections	Parr-Brownlie and Hyland, 2005
	↑ in L5 PN excitability		*Ex vivo*	Swanson et al., 2020
DA-depletion in the midbrain	↓ in excitability of L2/3 PN and ↑ in excitability in L5 PN		*Ex vivo*	Swanson et al., 2020
	↓ in excitability of L5 PTN / No effect on ITN		*Ex vivo*	Chen et al., 2021
	↓ in firing rate of PN	No effect on the firing activity of putative PV-IN	*In vivo* freely-moving Unilateral MFB 6-OHDA injection	Li et al., 2021
		↓ in firing rate of SST-IN	*In vivo* head-fixed Systemic i.p. MPTP injections, also local cortical MPTP injections	Chen et al., 2019
	↓ in firing rate of PTN during freezing and grasp ↓ in late phase firing rate of L2/3 ITN		*In vivo* head-fixed Striatal 6-OHDA injection	Aeed et al., 2021*

(*continued on next page*)

Table 1 (*continued*)

Type of manipulation	Neuronal subtype		Recording conditions	References
	Pyramidal neurons	GABAergic interneurons		
DA-depletion in M1	↓ in L2/3 PN excitability	N/D	*Ex vivo*	Swanson et al., 2020
	No effect on L5 PN excitability			

i.p.: intraperitoneal; ITN: intratelencephalic neurons; MFB: medial forebrain bundle; PN: pyramidal neurons; PTN: pyramidal track neurons; PV-IN: parvalbumin interneurons; SST-IN: somatostatin interneurons

* Unilateral striatal DA-depletion

due to the DA-mediated increased excitability of PV interneurons as neurons from the VTA, the main source of DA for M1, project directly to M1 GABAergic neurons (Duan et al., 2020). As PV interneurons are powerful regulators of cortical activity (Ferguson and Gao, 2018), they would be well-placed to select the inputs coming to the motor cortex to refine its outputs.

4.3. Role of DA in M1 plasticity

M1 undergoes learning-dependent plasticity during motor skill learning (Karni et al., 1995), and motor performance is correlated to DA metabolite levels in the cerebrospinal fluid (McEntee et al., 1987). Furthermore, the *in vivo* pharmacological blockade of D1 or D2 DAergic receptors in M1 both induces a decrease of LTP in L2/3 of rats and is sufficient to alter skill learning (Molina-Luna et al., 2009). In addition, the selective blockade of D2 receptors in M1 induces a decrease of M1 neurons' activity, leading to the increase in movement time, *i.e.* bradykinesia, during a skilled reaching task in rats (Parr-Brownlie and Hyland, 2005). Moreover, spine turnover in M1 L5 PNs is under the control of DA: while the stabilization/elimination of spines involves D1 receptors, spine formation involves D2 receptors (Guo et al., 2015a; Fig. 2). However, the selective blockade of DAergic receptors has no effect on skill performance once the skill is learned. These data emphasize the role of the meso-cortical pathway and hence cortical DA in the acquisition of motor skills, but not in their maintenance, by selecting and potentiating the newly-formed spines necessary for the execution of the movement in the learning process while depressing the unnecessary ones.

5. M1 disturbances in Parkinson's disease

5.1. M1 disturbances in animal models of PD

In addition to the cardinal motor symptoms (tremor, rigidity bradykinesia and postural instability), PD patients also experience significant disability in executing fine motor tasks (Dan et al., 2019; Proud and Morris, 2010; Vanbellingen et al., 2011), like tying shoelaces or handwriting (Pohar and Allyson Jones, 2009). These fine motor symptoms respond to DA replacement therapy (Gebhardt et al., 2008; Lee et al., 2018) suggesting that DA plays an important role in dexterous skills. Indeed, a substantial loss of DA innervation in M1 has been reported in PD patients (Gaspar et al., 1991). Although VTA DAergic neurons, the main source of DA for M1, are not as sensitive to oxidative stress occurring during PD as SNc DAergic neurons (Surmeier et al., 2011), they still degenerate (Alberico et al., 2015) and this degeneration takes place later than SNc DAergic neurons (Harrison et al., 2016).

To look further at the role of DA in the pathophysiology of M1 during PD, animal models are essential. Many neurotoxins have been used to model PD, especially 6-hydroxydopamine (6-OHDA) and MPTP, which selectively destroy DAergic neurons (Betarbet et al., 2002; Schober, 2004). These two neurotoxins mimic different aspects of the pathophysiology of PD. MPTP and 6-OHDA do not use the same cellular pathway to kill catecholaminergic neurons. Moreover as MPTP can cross the blood brain barrier but the 6-OHDA not, the administration mode and the effect are different. Classically, systemic injection of MPTP mimics well the early stages of PD as it induces less degeneration of DAergic neurons and less loss of cell body compared to unilateral 6-OHDA injection, which is a good model for a dramatic loss of DA as observed in late stages of PD (Schober, 2004; Ferro et al., 2005). Treatment with rotenone, another neurotoxin, also reproduces most features of PD (Radad et al., 2019), by entering in DAergic neurons thanks to its lipophilic properties and mediating cell death through oxidative stress, α-synuclein phosphorylation and aggregation. Recently, non-neurotoxin models based on injections of Lewy bodies extracted from the brain of PD patients or α-synuclein fibrils (Chu et al., 2019), which are closer to the pathophysiology of PD, have been developed. These different compounds reproduce more or less the features of PD at the behavioral, network, cellular, and molecular levels, but also the chronic and progressive aspects of PD (Chia et al., 2020; Gerlach and Riederer, 1996; Lorigados et al., 1996), as some of them are more relevant than others depending on the aspect of PD studied and their ability to induce PD symptoms in the animal model used (rats' resistance to MPTP toxicity for example). Among the studies done on M1, it is important to distinguish those in which DA-depletion has been achieved by toxin injections in the midbrain (in the medial forebrain bundle or the SNc) to dramatically reduce DA tone in the brain, as occurs in late stages of PD (Chen et al., 2019, 2021; Li et al., 2021) with those that directly manipulate M1 to investigate the role of cortical DA (Guo et al., 2015a, 2015b. Here, we give a non-exhaustive review of the pathophysiology of M1 in PD models.

The midbrain 6-OHDA model has been widely used to investigate the changes observed in M1 during PD, especially in rats (Campos et al., 2021; Hosp et al., 2011; Molina-Luna et al., 2009). Proteomic analysis of M1 in 6-OHDA rats showed alterations in the expression of proteins involved in autophagy, mRNA processing, ATP binding, and maintaining the balance of neurotransmitters (Li et al., 2017a). DA-depletion also induces a loss in excitability of L2/3 and L5 PNs in M1 *ex vivo* (Chen et al., 2021; Swanson et al., 2020; Table 1; Fig. 2). PET functional imaging of 6-OHDA rats also reveals significant glucose hypometabolism in M1 and the *substantia nigra*, suggesting an impairment of the cortico-subcortical network as observed in PD patients (Jang et al., 2012). Moreover, striatal DA depletion also disrupts the forelimb representation map in M1 (Plowman et al., 2011; Viaro et al., 2010). In 6-OHDA rats, it has been shown that M1 activity is disturbed during the grasping phase of the movement after DA depletion (Hyland et al., 2019), and PN firing frequency is decreased during a reaching movement compared to control rodents (Aeed et al., 2021; Li et al., 2021). Additionally, 6-OHDA rats display an abnormal local field potential power at beta frequencies in the cortex at rest (Mallet et al., 2008) and during a reaching movement (Li et al., 2021). Two recent studies also report that the excitation of M1 or M2 PNs with optogenetics can partially restore motor performance in mice (Aeed et al., 2021; Magno et al., 2019). This may underline that the dexterity disturbance observed in PD patients could be due to alteration of M1 activity following DA loss, highlighting the need for cortical treatment to target those fine motor issues. Moreover, projections from M1 to subcortical structures are also disturbed in 6-OHDA rats. In addition to cortico-striatal dysfunctions which have been extensively studied (Zhai et al., 2018), direct glutamatergic inputs from M1 to the subthalamic nucleus, known as the hyperdirect pathway, are highly reduced in 6-OHDA rats (Wang et al., 2018), mice (Chu et al., 2017) and MPTP-treated monkeys (Mathai et al., 2015). The activation of the hyperdirect pathway leads to an inhibition of movements, and together with the direct and indirect pathways, enables proper control of motor behaviors. In addition to their decreased number, inputs from M1 to STN are also weaker in 6-OHDA mice, as both amplitude and frequency of cortico-STN excitatory post-synaptic currents are diminished after DA depletion (Chu et al., 2017). This

weakening of synaptic transmission of cortico-STN axon terminals could be due to the decreased amount of vesicular glutamate transporter 1 in the subthalamic nucleus (Wang et al., 2018; Chu et al., 2017; Mathai et al., 2015), thus leading to the abnormal activity of this pathway observed in PD patients.

5.2. Comparison between animal models of PD and PD patient symptoms

In addition to motor deficits, PD patients also exhibit cognitive impairments such as impairments in long-term memory, visual information processing, motor learning and executive function (Watson and Leverenz, 2010). Electroencephalographic recordings in PD patients also revealed a reduced functional connectivity within the primary motor cortex (Formaggio et al., 2021). Moreover, functional MRI studies in PD patients have shown a decreased functional connectivity between parietal and motor cortical areas (Palomar et al., 2013), as well as the functional connectivity between sensory and motor cortex (Wang et al., 2021). The isolation of motor areas from these other areas certainly contributes to difficulties of PD patients to learn and perform day life movements. Furthermore, the functional connectivity between M1 and the rostral supplementary area is increased in PD patients (Wu et al., 2011), while the functional connectivity between the rostral supplementary area and structures involved in motor preparation and initiation (*i.e.* left putamen, right premotor cortex) are decreased (Wu et al., 2011). This suggests that cognitive processes necessary to learn, prepare and initiate the movement are at least as disturbed as processes needed for movement execution during PD. As for humans, motor skill learning is also altered and well-documented in animal models of DA loss (Molina-Luna et al., 2009; Hosp et al., 2011; L. Guo et al., 2015a, 2015b). Using the single pellet reaching task, it has been shown that selective depletion of DAergic fibers that project to the M1 and correspond to the trained limb alters the acquisition of this skill in rats (6-OHDA) and mice (MPTP; Molina-Luna et al., 2009; L. Guo et al., 2015a, 2015b). However, the same M1 DA depletion did not affect performance once the skill had been learned, indicating a role for M1 DA in skill acquisition but not in its maintenance. Furthermore, 6-OHDA injection directly in the VTA highlighted the importance of M1 DA coming from this region in motor learning. Indeed, the VTA is the main source of DA in M1, and the destruction of these DAergic neurons leads to a suppression of skill learning that can be partially re-established with levodopa infusion in M1 (Hosp et al., 2011). VTA DAergic neurons projecting onto M1 are specifically activated during successful food-rewarded skill acquisition and not by the reward alone (Leemburg et al., 2018). Interestingly, those VTA to M1 DAergic neurons are no longer recruited once the task is learned or in individuals unable to learn the motor sequence. This emphasizes that M1 DA is crucial for skill learning but no longer necessary for skills already learned. The structural and functional plasticity of dendritic spines is important for learning and memory. In mice, Guo and colleagues showed the impact of DA loss following MPTP treatment on M1 dendritic spines in the context of skill learning (Guo et al., 2015a). Throughout the training of a new motor skill, the survivability of these spines increases and is still increased 30 days after the last training session. This increased spine survivability is only present during the first training session in M1 MPTP-treated mice and is no longer present 8 days after the last training session. Furthermore, this increase in spine turnover is accompanied by impaired LTP (Fig. 2), suggesting that this phenomenon may contribute to the observed learning deficiency in these DA-depleted mice (Guo et al., 2015a). These different studies laid the foundations of the significance of M1 DA for the accurate learning of dexterous movements, and the potential implication of its depletion in PD.

GABAergic neurons play a crucial role in M1 network activity and the balance of excitation/inhibition is crucial for proper neocortex function. It is not surprising that GABAergic inhibition in M1 is disturbed in PD patients (Chu et al., 2009; Ni et al., 2013; Sailer et al., 2003). A decrease in the activity of SST interneurons has been observed after MPTP infusion in the rat cortex, which is associated with a destabilization of dendritic spines in PN as well as impairments in motor learning (Chen et al., 2019). Interestingly, re-establishing activity in SST neurons with a chemogenetic approach rescues dendritic spine loss and motor deficits. In addition, parvalbumin levels are increased in PD model rats (Capper-Loup et al., 2005), suggesting a putative dysfunction of this neuronal cell type in this model, since electrical properties of PV neurons are strongly linked to their parvalbumin levels (Chard et al., 1993; Donato et al., 2013). In monkeys, carotid artery injection of MPTP has been used to induce a Parkinson-like syndrome, leading to several effects relative to the different M1 neuronal populations (Pasquereau and Turner, 2011). M1 activity related to movement is decreased, mainly in PTN but not in CStr ITNs (Pasquereau and Turner, 2015). Timing of M1 activation is also disturbed in this model. Indeed, the movement-related activity of PTN is impaired, with earlier onset activation and a longer activation. PTN excitability has been shown to be decreased in M1 L5 of 6-OHDA mice, while ITNs remain unaffected (Chen et al., 2021), which may explain this timing alteration and also lead to lesser M1 outputs. Moreover, the firing pattern of M1 neurons is dramatically modified in MPTP-treated monkeys, with an increase in burst discharge and an abnormal level of synchrony at beta frequencies (Goldberg et al., 2002). This excessive level of M1 synchronization may be at the origin of the rigidity observed in PD, by causing the simultaneous contraction of antagonistic muscles (Goldberg et al., 2002).

6. M1 as a potential target for treatment of motor and cognitive impairments in PD

6.1. Impact of PD treatments on M1 activity and function

Levodopa medication has been the first-line treatment for PD since 1967, when it was discovered that high doses of this DA precursor were highly efficient against PD (Cotzias et al., 1967). Levodopa presents the advantage of crossing the blood-brain barrier, while DA cannot. It is then converted into DA by the action of the DOPA-decarboxylase enzyme, thus leading to a DA concentration increase (Fahn, 2008). Levodopa treatment is often combined with an inhibitor of the peripheral DOPA decarboxylase, like carbidopa, to specifically increase DA concentration within the central nervous system (Fahn, 2006). Besides the effects of this DA replacement therapy in the basal ganglia, levodopa also has an impact on M1. As previously mentioned, inhibition in M1 is disturbed in PD patients (Chu et al., 2009; Ni et al., 2013; Sailer et al., 2003). This inhibition shapes oscillatory activity within M1, since blocking GABA receptors or GABA transporter with specific antagonists abolish beta and gamma oscillations (Yamawaki et al., 2008). In addition, DA also plays a role in M1 oscillatory activity, given that both D1-like and D2-like receptor agonists promote both beta and gamma oscillations within M1 (Özkan et al., 2017), the same oscillations that are shaped by interneurons. Thus, it is not surprising that levodopa treatment increases the power of beta oscillations within M1 in PD patients (Cao et al., 2020), putting into question the contribution of these oscillations in M1 to causing PD symptoms.

Deep Brain Stimulation of the subthalamic nucleus (STN-DBS) is another symptomatic PD treatment, but due to inter-individual differences in the spectrum of symptoms of the patients and its surgical invasiveness, it only benefits a minority of PD patients. It is thus essential to determine the precise mechanism of how DBS suppresses PD symptoms, in order to make it accessible to a broader population. Several hypotheses have been proposed to explain the beneficial effects of STN-DBS (Deniau et al., 2010; Eusebio et al., 2011; Hammond et al., 2008), including a growing body of evidence on a cortical effect of STN-DBS in both experimental models of PD (Degos et al., 2013; Gradinaru et al., 2009; Li et al., 2007) and PD patients (Cunic et al., 2002; Fraix et al., 2008; Payoux et al., 2004). Further, an interesting study investigated the role of M1 neurons forming the hyperdirect pathway in STN-DBS in 6-OHDA rats (Li et al., 2012). STN-DBS antidromically activates

M1 passing fibers with several consequences for M1 microcircuit activity. Firstly, the STN-DBS restored the basal activity of M1 neurons in 6-OHDA rats. Secondly, the new M1 basal activity is correlated with the most beneficial DBS frequency, e.g. 125 Hz (Li et al., 2014; Li et al., 2012). Finally, the most beneficial stimulation frequency induces the biggest reduction of abnormal beta oscillations (de Hemptinne et al., 2015), M1 neuronal synchrony, and burst discharge occurrence (Li et al., 2014; Li et al., 2012). Together, these results indicate that STN-DBS directly influences M1 neuronal activity at the single-cell and network levels, thus contributing to the alleviation of PD symptoms. The mechanism underlying the regularization of M1 PN activity by STN-DBS has been investigated recently in hemiparkinsonian rodents (Valverde et al., 2020). In this study, the authors reported that the excitability of PNs was reduced following STN-DBS stimulation. Surprisingly, STN-DBS has opposite effects on cortical GABAergic neurons, as it decreases the firing rate of PV neurons while increasing that of SST neurons. In addition, specifically increasing SST neuronal activity *via* an optogenetics approach alleviates motor symptoms in PD model rodents (Valverde et al., 2020). The optogenetic activation of M1 PV neurons leads to motor improvement to a lesser extent. These data suggest that the disturbance of M1 circuitry may come from the integration and treatment of PN excitatory inputs, and not from their electrical properties. Indeed, SST neurons project to the apical dendrites of PNs, thus controlling the excitatory inputs they receive. Opto-activation of SST neurons in PD model rodents can then lead to improved processing of the information in M1. PV neurons are known to control the spiking activity of PNs; their opto-activation may only shut down PN activity, not helping the processing of disturbed excitatory inputs to M1. It may explain the lesser impact on motor symptoms when stimulating PVs rather than SSTs. Together, this evidence suggests that M1 GABAergic neurons could be a putative target for a more precise alternative to STN DBS.

Physical activity has been shown to improve motor symptoms in early PD patients (Emig et al., 2021; Gilat et al., 2021; Tiihonen et al., 2021) suggesting that exercise could partially balance the effects of DA loss within M1. As mentioned before, M1 activity impairments during PD are characterized by a decrease in PTN spontaneous firing rate, but also by exaggerated synchrony of these neurons at beta frequencies (Goldberg et al., 2002; Pasquereau and Turner, 2011). 6-OHDA rats that undergo treadmill exercise have a significantly increased firing rate of PTN and decreased power spectrum of β oscillations. These rats also made fewer foot faults during a ladder test (Shi et al., 2021), thereby exhibiting improved PD symptoms at the network and behavioral levels. Even if the beneficial effects of physical activity on PD symptoms are well-acknowledged, there is still a gap in our understanding of its mode of action. This is the case with M1, as the causal link between changes in M1 neurons' activity and improvement of PD symptoms has not yet been made. However, it could be possible that exercising increases M1 DA levels in PD patients, leading to improved motor and cognitive symptoms, since DA levels are increased during exercise in healthy people (Singh and Staines, 2015). Also, as serotonin, norepinephrine and brain derived neurotrophic factor levels are also increased in healthy people during physical activity (Singh and Staines, 2015) the levels of these compounds could be increased in PD patients during exercise and compensate for the DAergic depletion in M1 as well as in sub-cortical systems.

6.2. Targeting M1 to improve symptoms of PD

Apart from its beneficial effects on motor symptoms, levodopa is well-known to induce major side effects, the most frequent and debilitating being levodopa-induced dyskinesia (LID). Interestingly, it has recently been shown in 6-OHDA rats that LID is strongly correlated with an augmented GABA efflux in M1, leading to increased inhibition within M1. This phenomenon has been identified as a compensatory mechanism for LID, as exogenously increasing this already-increased inhibition within M1 with a $GABA_A$ receptor agonist reduces the severity of LID (Lindenbach et al., 2015). This is consistent with the fact that the emergence of LID in PD patients has been associated with abnormal synaptic plasticity within M1 (Morgante et al., 2006). Furthermore, levodopa administration in 6-OHDA rats induces an increase in c-Fos and activity-regulated cytoskeletal-associated protein expression in M1, which are early genes involved in plasticity phenomena. This suggests that hyperactivity of M1 occurs during dyskinesia (Lindenbach et al., 2015), explaining the need to increase inhibition within M1. Thus, restoring more physiological synaptic plasticity could potentiate inhibition within M1, and could consequently be a potential therapeutic target to reduce severity of LID.

It has been shown that high-frequency motor cortex stimulation in MPTP-treated baboons significantly reduced PD symptoms (Drouot et al., 2004). More recently, low-frequency low-intensity pulsed ultrasound (LIPUS) targeting M1 has also been found to have beneficial effects on PD models. In MPTP-treated mice, M1-targeted LIPUS increases rearing in the open field test after 4 days of treatment, and locomotor activity during a pole test after 5 days of treatment. Furthermore, LIPUS increases superoxide dismutase and glutathione peroxidase levels in MPTP-treated mice (Zhou et al., 2019); the levels of these two enzymes are diminished in PD patients, leading to oxidative stress (Nikam et al., 2009; Surendran and Rajasankar, 2010). Furthermore, overexpression of superoxide dismutase has been found to improve DAergic neuron survival over time (Botella et al., 2008). Even if the entire mechanism of action of M1-targeted LIPUS remains unclear, the re-establishment of more physiological levels of antioxidants could partially explain its effect, making M1-targeted LIPUS a good treatment for oxidative stress during PD.

In addition to motor impairments, persistent pain is another feature of PD, contributing to the decreased quality of life of people affected by the disease. M1 has been identified as a good target for chronic pain treatment (Canavero and Bonicalzi, 1995; Tsubokawa et al., 1991), and Canavero and Paolotti used it for the first time to treat chronic pain during PD. They showed improvements in pain symptoms, separate from the motor improvement (Canavero and Paolotti, 2000). Campos and colleagues showed evidence of how M1-targeted stimulation may alleviate these symptoms during PD (Campos et al., 2021). While DA depletion in rats induces pain hypersensitivity, M1 stimulation was able to reverse it. Furthermore, M1 stimulation was able to restore the descending serotonergic pathway to the spinal cord, crucial for analgesia control. For the spinal cord network, motor cortex stimulation also restores proper neuronal and astrocytic activity (Campos et al., 2021). Finally, M1 stimulation induces a release of endogenous opioids (Maarrawi et al., 2007), which could contribute to the alleviation of chronic pain during PD.

Extradural motor cortex stimulation (EMCS) was identified primarily as a treatment for chronic pain (Canavero and Bonicalzi, 1995; Tsubokawa et al., 1991). EMCS has been performed on PD patients, and a first case of motor symptom improvement was observed in the early 2000s (Canavero and Paolotti, 2000). Several similar cases of motor improvements with EMCS were reported a few years later (Canavero et al., 2002; Pagni et al., 2003; Pagni et al., 2005). PD patients treated with EMCS exhibit long-lasting improved scores on the unified PD rating scale (UPRDS) with no complications observed due to the surgical procedure after several years (Bentivoglio et al., 2012; De Rose et al., 2012; Piano et al., 2021). Notably, patients exhibit improvements in axial symptoms, *i.e.* decreased bradykinesia, rigidity, tremor and akinesia, and also decreased LID when off medication, thus increasing their quality of life. Furthermore, symptoms like postural instability, gait freezing, dysphonia, and dysphagia are improved, while STN-DBS has no effect on these symptoms and can have side effects, especially on dysphonia and dysphagia (Cioni, 2005; Lavano et al., 2016). These improvements are noticeable especially when off levodopa medication, but also when on medication, meaning that it is possible to decrease the drug treatment (Cioni, 2005). While the mechanism of action of EMCS is not fully

understood, it is now known that EMCS enhances the activity of M1-related cortical areas, such as the supplementary motor area, whose activity is decreased during PD (Fasano et al., 2008; Piano et al., 2021). A modeling study carried out in 2012 showed that EMCS activates the axons of either basket cells or PTN (Zwartjes et al., 2012). This is consistent with the fact that both PNs (Vitrac et al., 2014) and PV interneurons (hence basket cells; Cousineau et al., 2020) are excited by D2-like receptor activation, and therefore their activity may decrease during PD. Stimulating the axons of these two neuronal populations should restore more physiological levels of activity and information transmission, and so improve PD symptoms. To conclude, even if the motor improvements are smaller compared to STN-DBS, EMCS treatment offers an alternative choice to treat some symptoms that are not improved by DBS, especially for patients who are not eligible for DBS, notably older patients, thanks to the less invasive nature of EMCS.

6.3. Levodopa-induced dyskinesia as drug-induced side effect on M1 function

Apart from its beneficial effects on motor symptoms, levodopa is well-known to induce major side effects, the most frequent and debilitating being levodopa-induced dyskinesia (LID). Interestingly, it has recently been shown in 6-OHDA rats that LID is strongly correlated with an augmented GABA efflux in M1, leading to increased inhibition within M1. This phenomenon has been identified as a compensatory mechanism for LID, as exogenously increasing this already-increased inhibition within M1 with a $GABA_A$ receptor agonist reduces the severity of LID (Lindenbach et al., 2015). This is consistent with the fact that the emergence of LID in PD patients has been associated with abnormal synaptic plasticity within M1 (Morgante et al., 2006). Furthermore, levodopa administration in 6-OHDA rats induces an increase in c-Fos and activity-regulated cytoskeletal-associated protein expression in M1, which are early genes involved in plasticity phenomena. This suggests that hyperactivity of M1 occurs during dyskinesia (Lindenbach et al., 2015), explaining the need to increase inhibition within M1. Thus, restoring more physiological synaptic plasticity could potentiate inhibition within M1, and could consequently be a potential therapeutic target to reduce severity of LID.

7. Conclusion & perspectives

It is now well-established that M1 is instrumental both in motor execution and motor learning. By ensuring proper synaptic plasticity within M1, DA appears to be a key neuromodulator for motor learning and execution of dexterous movements. Hence, DA loss during PD dramatically affects M1 functions, as seen in the different animal models of PD, but especially in PD patients. Notably, DA manages the inhibitory network within M1, which plays an important role in shaping PN activity, ensuring both the execution and learning of dexterous movements. It is not surprising to find the excitation/inhibition balance is disturbed in PD, resulting in an overall decreased inhibition within M1, and that both DA replacement therapies and stimulation approaches enhance it, highlighting a potential target for more precise DBS. Therefore, the precise mechanism of action of DA on M1 GABAergic neurons should be explored more in detail. It would be significant to investigate whether their electrical properties or activity are affected in absence of DA. In addition, studying their activity with *in vivo* calcium imaging throughout the acquisition of a new motor sequence could unravel their precise role together with their dysfunction in physiological and pathophysiological conditions. Moreover, increasing research indicates that M1 is a good target to alleviate some symptoms of PD, motor and non-motor, making it a good alternative for people no longer responsive to first-line treatments, not eligible for DBS, or as a complementary treatment.

While our understanding of the role of M1 in motor learning has greatly progressed in recent years, several questions remain open. What is the contribution of the different types of GABAergic interneurons to motor learning? What is the net impact of DA on M1 L5 PNs? What is the dynamic of DA release during the acquisition of new motor skills? Which cell types and synapses are specifically modulated by DA during motor skill learning and thus preferentially affected after the loss of DA in PD? The field now has new tools and techniques at its disposal to address these questions. For instance, fluorescent DA sensors (Labouesse et al., 2020; Patriarchi et al., 2018; Sun et al., 2018 for review) coupled with a miniaturized microscope (Aharoni and Hoogland, 2019; de Groot et al., 2020; Gulati et al., 2017; Kondo et al., 2018; Rynes et al., 2021) could help us investigate how M1 DA is released *in vivo* in freely-moving rodents or non-human primates, enabling us to better understand i) the kinematics of DA release, especially throughout the different steps of motor skill acquisition, and ii) the M1 cognitive impairments displayed in PD patients. More generally, identifying key cellular and synaptic mechanisms including DA-dependent structural and functional plasticity involved in motor-related cognitive symptoms of PD would enable development of new treatment that could improve the quality of life of PD patients.

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