Submission to European Journal of Neuroscience

Journal section: Trailblazers of Neuroscience – Review article

Title: Dopaminergic reinforcement in the motor system: Implications for Parkinson's disease and deep brain stimulation

Authors: Alessia Cavallo[1] & Wolf-Julian Neumann[1]

Affiliations: [1]Movement Disorder and Neuromodulation Unit, Department of Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Chariteplatz 1, 10117 Berlin, Germany

Corresponding author:
Prof. Dr. med. Wolf-Julian Neumann
Assistant Professor for Interventional and Cognitive Neuromodulation
Movement Disorders and Neuromodulation Unit, Department of Neurology, Charité – Universitätsmedizin Berlin, Campus Charité Mitte | Chariteplatz 1 | 10117 Berlin | Germany
julian.neumann@charite.de

Running title: Dopaminergic reinforcement

Count: 13 pages, 4 figures, 3 text boxes

Word count: Main text: 3293, Abstract: 245

Keywords: dopamine, basal ganglia, neural reinforcement, Parkinson's disease, closed-loop deep brain stimulation

Abstract

Millions of people suffer from dopamine-related disorders spanning disturbances in movement, cognition and emotion, often attributed to changes in striatal dopamine function. Understanding how dopamine signaling in the striatum and basal ganglia shapes human behavior is fundamental to advancing the treatment of affected patients. Dopaminergic neurons innervate large scale brain networks and many different roles for dopamine signals have been proposed, such as invigoration of movement and tracking of reward contingencies. The canonical circuit architecture of cortico-striatal loops sparks the question, whether dopamine signals in the basal ganglia serve an overarching computational principle which could provide new insights into symptom generation in psychiatry to neurology. Here, we review the perspective that dopamine could bidirectionally control neural population dynamics, increasing, or decreasing their strength and likelihood to reoccur in the future, a process previously termed *neural reinforcement*. We outline how the basal ganglia pathways could drive strengthening and weakening of circuit dynamics and discuss the implication of this hypothesis on the understanding of motor signs of Parkinson's disease (PD), the most frequent dopaminergic disorder. We propose that loss of dopamine in PD may lead to a pathological brain state where repetition of neural activity leads to weakening and instability, possibly explanatory for the fact that movement in PD deteriorates with repetition, as defined by the sequence effect or decrement of movement. Finally, we speculate on how therapeutic interventions such as deep brain stimulation (DBS) may be able to reinstate reinforcement signals and thereby improve treatment strategies of PD in the future.

BOX 1: Glossary.

Basal ganglia - The basal ganglia are a group of gray matter nuclei located deep within the forebrain.

Deep brain stimulation - a neurosurgical procedure that involves implanting electrodes into specific regions deep within the brain that are connected to a device similar to a pacemaker, which delivers controlled electrical impulses to modulate the activity of targeted brain areas.

Direct/Indirect pathway - Originating at D1/D2 expressing spiny projection neurons in the striatum, which are excited/inhibited by dopamine release and lead to increased/decreased cortical excitability.

Neural activity patterns – A measurable correlate of neural ensemble activity, either recorded directly as spatiotemporal patterns of spiking, or indirectly as sum potentials in local field potentials or potentially through changes in blood oxygenation observable with functional magnetic resonance imaging.

Neural population dynamics – Activity of a group of neurons represented as a neural trajectory in a low-dimensional space.

Neural reinforcement – Concept describing the brain's ability to adaptively strengthen or weaken neural population dynamics to aid neural learning, which can lead to behavioral reinforcement and adaptation.

Parkinson's disease - Progressive neurological disorder that is characterized by the degeneration of dopamine-producing neurons in the brain, particularly in the substantia nigra.

Reinforcement homeostasis – Equilibrium between the strengthening and weakening of neural population dynamics that is required to maintain stability of neural population dynamics.

Spiny projection neuron – Abbreviated SPN, also called medium spiny neuron (MSN) is a GABAergic inhibitory cell-type representing the majority of neurons within the human striatum, the major input of the basal ganglia.

Subthalamic nucleus – The STN is the only glutamatergic nucleus of the basal ganglia and receives input from cortex and globus pallidus externus. It is part of the indirect basal ganglia pathway and the primary target for deep brain stimulation in Parkinson's disease

Introduction

Dopamine and the basal ganglia (for a glossary see Box 1) have been conserved for over 500 million years of evolution with fundamental impact on the development of human and animal behavior (Stephenson-Jones *et al.*, 2011). Severe brain disorders can arise from dysregulation of dopamine release and innervation. Millions of people globally suffer from dopaminergic disorders that can include neurological and neuropsychiatric disease entities, such as Parkinson's disease, obsessive compulsive

disorder and Schizophrenia. Despite the pressing need to understand the pathophysiology of these disorders, a fundamental understanding of dopamine function that can integrate the multifaceted symptoms of these disorders is missing. This represents a significant roadblock to the development of new treatment strategies and a better understanding of brain function.

Over 60 years of research, many different roles have been attributed to dopamine release in the striatum, the main input nucleus of the basal ganglia (Box 2). Accordingly, parallel basal ganglia loops have been described that pass through anatomically different regions and subserve different functions (Alexander *et al.*, 1986). Nevertheless, the neuronal populations and synaptic projections are highly stereotypical. Across all functional loops direct and indirect basal ganglia pathways exist, which are modulated by dopamine release in an opposing manner. These parallel but stereotypically structured loops, and their similar modulation by dopamine release keeps sparking the question whether the computational process performed by the basal ganglia and its modulation by dopamine can be generalized across functional domains (Figure 1).

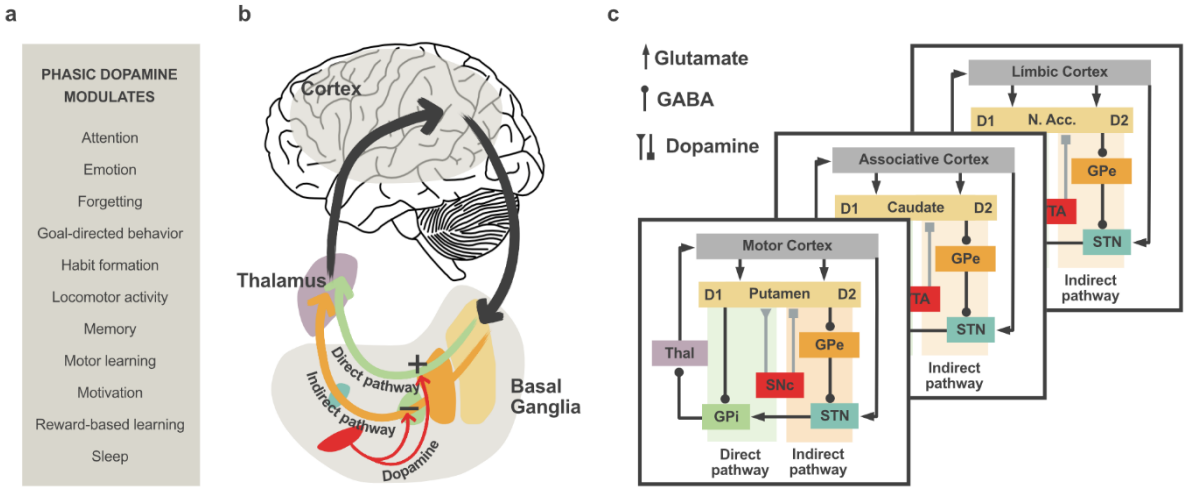

FIGURE 1: Dopamine and the basal ganglia. a Phasic dopamine signaling has been reported in relation to variety of functions, among which goal-directed behavior (Grace *et al.*, 2007), reward-based learning (Daniel & Pollmann, 2014), motor learning (Wood, 2021), habit formation (Amaya & Smith, 2018), motivation (Phillips *et al.*, 2008), emotion (Salgado-Pineda *et al.*, 2005), locomotor activity (Fishman *et al.*, 1983), memory (Shohamy & Adcock, 2010) and forgetting (Sabandal *et al.*, 2021), attention (Nieoullon, 2002) and sleep (Oishi & Lazarus, 2017). **b** Dopaminergic neurons originate in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) and innervate the cortical and subcortical brain regions, among which the densest projections reach the striatum, the main input nucleus of the basal ganglia (Smith & Kieval, 2000). Within the striatum, dopaminergic neurons target two different populations of so-called spiny projection neurons, that either express D1 receptors and are upregulated by dopamine release or express D2 receptors and are downregulated by dopamine release through opposing G-Protein coupled cyclic adenylyl cyclase signal cascades (Smith & Kieval, 2000). These spiny projection neurons and their opposing modulatory effects are the origin of the direct (D1) and indirect (D2) basal ganglia pathways, which form segregated projections through the basal ganglia nuclei and have bidirectional control over basal ganglia processing and excitability of thalamocortical projections. **c** This canonical architecture is mirrored across motoric, associative and limbic domains, explaining the diverse functions attributed to dopamine. The neuronal populations and synaptic projections are highly stereotypical, raising the question whether dopamine signaling might drive the same fundamental computation across functional domains.

In this article, we propose and review the perspective that a fundamental computational function of dopamine is neural reinforcement, the bidirectional orchestration of neural population dynamics, strengthening and weakening neural activity patterns and modulating their likelihood to reoccur. Moreover, we translate this concept into a new understanding of the pathophysiology of Parkinson's disease, the most prominent dopaminergic disorder. Finally, we give an outlook how this concept could inspire new individualized precision medicine approaches such as invasive brain computer interface neuroprosthetics.

BOX 2: Back to the future: Dopamine and basal ganglia function from movement to reward and back. Early studies reporting less movement in animals in a dopamine depleted and more movement in animals in a dopamine enhanced state have suggested a role of dopamine in controlling locomotor activity (Beninger, 1983). The complexity of effects of dopamine depletion in animal models and human patients with Parkinson's disease (PD), however, has cast doubt on a purely motor centered view of dopamine (Marshall *et al.*, 1976; Beninger, 1983). Instead, it was suggested that tonic dopaminergic activity might be necessary to maintain an appropriate level of behavioral alertness, thus enabling adaptation in response to external stimuli (Schultz, 1994; Baunez *et al.*, 1995). While early descriptions of phasic dopaminergic firing were also related to motor activity, later research shifted the focus to the encoding of reward contingencies from sensory stimuli. Here, the observation that dopamine neurons respond to the presence of unexpected and the absence of expected rewards has led to the interpretation of phasic dopamine as a so-called reward prediction error (RPE) (Schultz *et al.*, 1997) signal. By signaling the discrepancy between expected and received reward, the RPE is thought to drive reward-based learning and consequently goal directed behavior. Beyond that, it has been argued that dopamine may encode the incentive salience ('wanting') attributed to reward stimuli instead of a teaching signal per se (Berridge, 2007). Further, studies reporting the modulation of dopaminergic firing not only in response to rewarding but also to aversive events have inspired a more general role of dopamine in motivational control (Bromberg-Martin *et al.*, 2010). Despite substantial differences in the suggested computations, the aforementioned theories share the general understanding that phasic dopamine encodes information about sensory stimuli, be it rewarding, salient or aversive. This shift in attention from motor to sensory and reward based functions has also resulted in a shift of focus from motor to limbic brain circuits. Thus, the dominant narrative of dopamine function, both in neuroscience and pop-science literature, is that dopamine signals reward or pleasure, often neglecting that reward related signals may be anatomically specific to dopamine neurons originating in the VTA and innervating limbic circuits. Similar to the original non-human primate studies, a new series of rodent studies found significant modulation of transient dopamine signals time-locked to the onset of movement (Dodson *et al.*, 2016; Coddington & Dudman, 2019), even in the absence of sensory events, inspiring a renaissance in the quest to elucidate the role of dopamine in motor control. Most of the neural and behavioral consequences of dopamine release can be conceptualized within the so-called "vigorous tutor" paradigm, meaning that they reflect a combination of motor vigor and learning effects (Turner & Desmurget, 2010). Examples for the former are correlations of dopaminergic firing and movement speed (Wang & Tsien, 2011; Barter *et al.*, 2015) or changes in movement speed through direct activation of D1/D2 neurons (Kravitz *et al.*, 2012; Yttri & Dudman, 2016). The latter effect is observed through lasting alterations in the probability of motor output. Here, optogenetic activation of dopamine neurons or D1/D2 receptors has been reported to increase the likelihood of movement initiation in rodents (Cui *et al.*, 2013; Tecuapetla *et al.*, 2016) and dopaminergic firing during a specific movement has been shown to signal a higher likelihood of the occurrence of the same movement in the future (Markowitz *et al.*, 2023).

Neural reinforcement as a fundamental circuit computation of dopamine and the basal ganglia

An increasing number of studies set out to decipher the computational principles of dopaminergic function. A recent report suggested that mesolimbic dopamine may adapt the rate of learning from action as a fundamental mechanism (Coddington *et al.*, 2023). Another paper has suggested that dopamine release in the tail of the striatum signals a reward independent "action prediction error" which drives habit formation and mirrors the reward-prediction error (see Box 2) logic encoded by dopaminergic activity in more ventral areas of the striatum (Greenstreet *et al.*, 2022). While there is no doubt that dopamine and the basal ganglia shape human behavior in many ways, the approximation of a fundamental computational role could inspire advances both in basic research as well as therapeutic interventions. Neurotechnology such as deep brain stimulation (DBS) can provide an unprecedented spatiotemporal precision for the therapeutic alteration of brain activity. To leverage this potential, detailed knowledge about the targeted brain circuits, pathophysiological mechanisms and intervention effects are required. Hence, there is a pressing need to develop integrative models of brain circuit computations.

Adaptation of behavior, be it related to movement or cognition, requires adaptation of neural activity patterns over time. Recently, in the domain of reward based learning, a concept termed *neural reinforcement* was used to describe how dopamine and the basal ganglia can refine neural population dynamics at the cortical level, and modulate their likelihood to re-enter the circuit (Athalye *et al.*, 2020).

In brief, a fast reinforcement mechanism was proposed to select inputs that permit the re-entrance of cortical dynamics which produced a desired behavior, while a slower mechanism was proposed to lead to refinement of the cortical dynamics to improve the reliability of the neural trajectories. Thus, the cortico-basal ganglia circuits and their organization in canonical re-entrant loops (Alexander *et al.*, 1986) with the basal ganglia projecting back to the same cortical populations could orchestrate the re-entrance and refinement of cortical patterns through modulation of excitability and plasticity at cortico-striatal synapses (Athalye *et al.*, 2020). Unfavorable dynamics in turn could become dispersed and less likely to reoccur. In the original description, this plasticity is based on reward related dopaminergic input from the VTA to the striatum. However, we are sure that the authors agree that this mechanism can be extended to unrewarded behavior. In this regard, a recent optogenetic study employing photometric recordings as well as optogenetic manipulations has shown that behavioral states in mice could be selectively strengthened, thus entered more frequently, by increased levels of dopamine release in the dorsolateral striatum during the targeted behavioral state (Markowitz *et al.*, 2023). In addition, optogenetic manipulation studies in mice have reported that movement kinematics could be either strengthened by increasing direct pathway or suppressed by increasing indirect pathway activity (Yttri & Dudman, 2016), independent to reward manipulations.

Thus, the fundamental role of dopamine could be conceptualized as controlling neural reinforcement, the strengthening and weakening of neural and behavioral states through the orchestration of direct and indirect basal ganglia pathways. Importantly, both direct and indirect pathways are required to act in parallel to shape the neural trajectory and its underlying dynamics. Here, tonic levels of dopamine reflect the reinforcement homeostasis or equilibrium between these pathways, for which transient increases and decreases in synaptic dopamine release may facilitate the selective strengthening or weakening of ongoing neural dynamics and competing activity by shifting the balance between the two pathways. As a consequence, this shift could induce long-term potentiation and long-term depression related plasticity at cortico-striatal, thalamostriatal, thalamocortical and cortico-cortical synapses that govern stability and strength of population dynamics (Shen *et al.*, 2008). Importantly, this hypothesized process could be generalized across cognitive, emotional as well as motor states. Ultimately, this function could be rephrased to state that dopamine facilitates neural learning and thus dopamine release coincides with the necessity for the neural circuit to learn, be it to reach the intended motor trajectory or to optimize reward prediction from sensory cues. This general idea is not new, but it remains central, as it could be the key to understanding and reinstating the most powerful feature of the most complex object in the universe, the human brain's ability to learn. Even though direct evidence supporting the specific mechanisms above is scarce, it may provide a powerful framework that allows the integration of diverse findings associated neural learning through dopamine and the basal ganglia in health and disease.

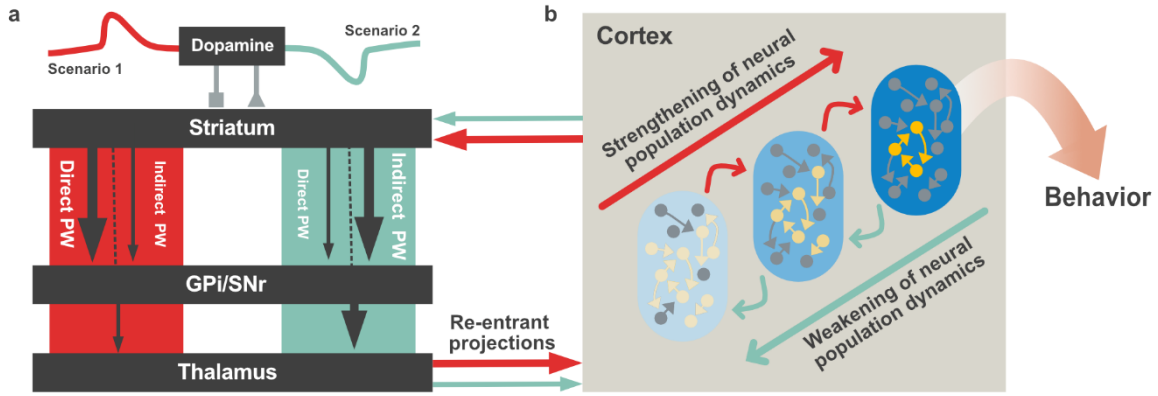

FIGURE 2 Dopamine-driven neural reinforcement. Firing of dopaminergic neurons could comprise the fundamental computational function of enabling neural reinforcement through the orchestration of direct and indirect basal ganglia pathways. While tonic dopamine may maintain the reinforcement homeostasis, phasic

increase and decreases in dopamine release may enable strengthening and weakening of neural population dynamics, respectively. **a Scenario 1** Phasic increases in dopamine release result in a shift towards the direct pathway and consequently in an increased excitation of the cortical population from which the cortico-striatal input originated. **b Scenario 1** This may strengthen and refine the neural population dynamics through plasticity at cortico-striatal, thalamostriatal, thalamocortical and cortico-cortical synapses. **a Scenario 2** Phasic decreases in dopaminergic activity, on the other hand, lead to a shift towards the indirect pathway and consequently to a decreased excitation of the original cortical population dynamics. **b Scenario 2** This may result in gradual weakening and dispersion of the neural population dynamics associated with the behavioral state.

Understanding Parkinson's disease as a disorder of neural reinforcement

Parkinson's disease (PD) is one of the fastest growing diseases and the most common dopaminergic disorder, now affecting more than six million people worldwide (Dorsey *et al.*, 2018). Symptoms span slowness of movement, emotion and cognition (Poewe *et al.*, 2017). Degeneration of dopaminergic neurons in the substantia nigra pars compacta leads to a loss of dopaminergic innervation to the motor striatum. Consequently, the loss of upregulation on direct pathway spiny projection neurons and the loss of downregulation on indirect pathway spiny projection neurons leads to a chronic disbalance with excessive activation of the indirect pathway. Based on the observation that PD is a hypokinetic disorder, the traditional box and arrow models (Albin *et al.*, 1995) propose that the indirect pathway is antikinetic, while the direct pathway is prokinetic. Recent optogenetic experiments, however, challenge this view as they found that both pathways can elicit and interfere with movement and are intrinsically active during movement initiation (Yttri & Dudman, 2016; Coddington & Dudman, 2019). Similarly, clinical observations can provide grounds for disbelief in this concept, most prominently the so-called paradox of stereotaxic neurosurgery, which describes the fact that both hyperkinetic and hypokinetic disorders can be treated with basal ganglia lesions (Marsden & Obeso, 1994). In addition to the wealth and complexity of motor and non-motor symptoms of PD, paradoxical kinesia is a well-known phenomenon that contradicts the pro- vs. antikinetic dogma. It describes the observation that PD patients can develop normal levels of motor output, e.g. under threat, or when exhibiting previously learned but rarely used movement patterns, such as riding the bicycle. If movement would be globally suppressed through indirect pathway hyperactivity, this would not be expected to change from one situation or movement pattern to the next.

We argue that a neural reinforcement centered framework could provide an explanation for both the optogenetic and clinical observations: in the hypodopaminergic state the homeostasis required for maintenance of stability in neural dynamics could be lost through the excessive activity of the indirect pathway. In the absence of dopamine induced strengthening, a neural activity pattern that reverberates through the cortex – basal ganglia loop, could become weaker, more dispersed and less likely to reoccur with every repetition. On the behavioral level, this could result in a sequential degradation of motor output. This concept provides a striking explanation for a disease defining feature of PD, the so-called sequence effect, where movement speed and amplitude decrease with repetition (Ling *et al.*, 2012). Importantly, the weakening of activity patterns through the potentiation of the indirect pathway does not have to result in a purely antikinetic state.

The most convincing evidence for the reinforcement centered viewpoint on Parkinson's disease, stems from a recent rodent study that addressed the hypothesis whether motor decline is a consequence of repetition (summarized in Figure 3b) (Cheung *et al.*, 2023). The study trained mice on two separable motor tasks before lesioning their dopamine neurons with 6-hydroxydopamine (6-OHDA). After the lesion, in the PD state, motor output rapidly declined upon performance of the task that the mice performed but was preserved over days for the second task that the mice did not perform. Only after performance of the task did the motor output decline, at a similar rate to the first task directly after the lesion. This is consistent with the concept that not the circuit state per se or the time spent without dopamine is antikinetic, but instead the behavior that is exhibited in the hypodopaminergic state gets

weakened through repetition, likely alongside the neural dynamics. Interestingly, the authors report that medication induced long-term rescue of motor performance was also experience-dependent and task-specific, with an increase in motor performance in a specific task observed only when dopaminergic medication was paired with the same task performance. Again, this observation is in line with the gradual strengthening of task related neural population dynamics while dynamics not associated with the task performance are not affected by the increased dopaminergic state. This concept could be extended to explain hyperkinetic symptoms in PD, such as dyskinesia and other movement disorders like dystonia and Tourette's Syndrome, where increased direct pathway activation could strengthen noisy activity patterns leading to involuntary movement execution (Simonyan *et al.*, 2017).

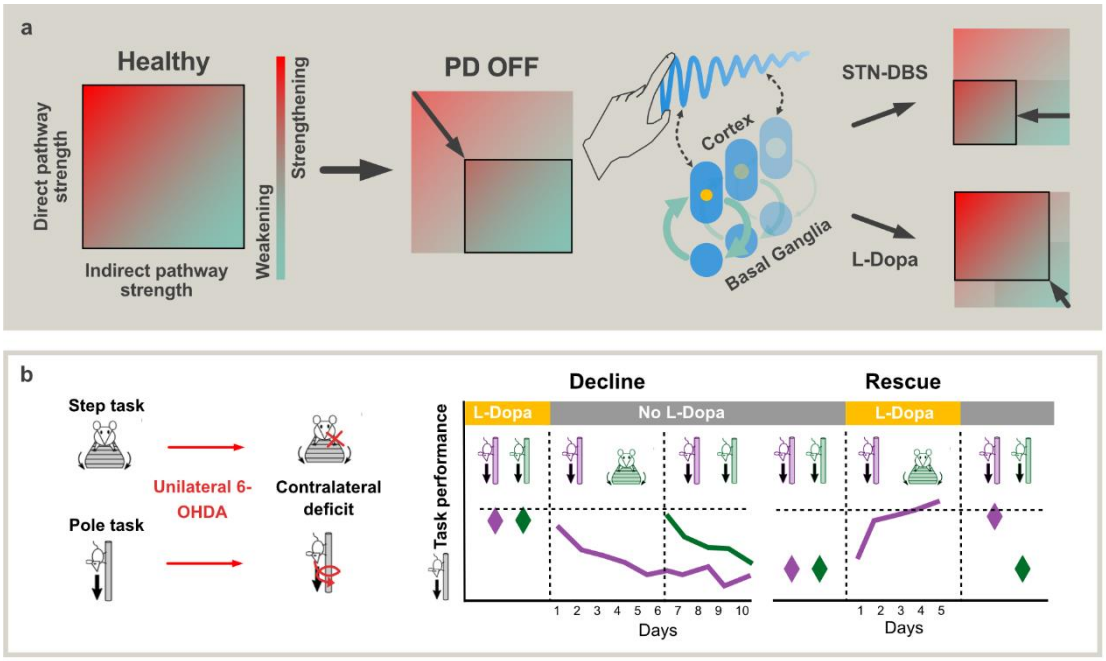

FIGURE 3 Parkinsons's disease as a disbalance of neural reinforcement. a In the healthy state direct and indirect basal ganglia pathway activity are balanced by tonic dopamine release, with phasic increases and decreases shifting the balance towards the direct and indirect pathway. In Parkinson's disease (PD), the equilibrium between the pathways is shifted chronically towards the indirect pathway as dopaminergic innervation to the striatum is gradually lost. This PD OFF state might be characterized by chronic weakening of neural population dynamics present in the circuit. This is consistent with the gradual decrement of movement amplitude observed in Parkinson's disease. Levodopa (L-Dopa) and subthalamic deep brain stimulation (STN-DBS) shift the balance towards the direct pathway and thereby counteract the chronic weakening present in the PD OFF state. **b** In line with a reinforcement centered framework, a recent rodent study(Cheung *et al.*, 2023) has shown that parkinsonian motor decline and medication induced rescue are task dependent. Mice were trained on two tasks (step/pole task) before unilaterally lesioning dopamine neuron with 6-hydroxydopamine (6-OHDA), which induced a contralateral motor deficit (less steps with the contralateral paw). Interestingly, if mice performed the step task in the dopaminergic OFF state (No -L-Dopa), with a gradual decline in motor task performance, and were subsequently tested on the pole task, they were initially not impaired in the pole task. Similarly, pole task performance in the dopaminergic ON state (L-Dopa) only improved when the pole task and not the step task was performed. These results are in accordance with the notion that neural population dynamics present in the circuit are selectively strengthened and weakened through neural reinforcement, while other activity patterns remain unaffected.

Taken together, the loss of dopamine in Parkinson's disease may be associated with a chronic disbalance in the homeostasis of neural reinforcement. In the hypodopaminergic state, exhibited movement could be weakened with every repetition. This can explain the sequence effect, the decrement in amplitude and velocity of movement and could also shed light on preserved movement e.g. for riding the bicycle. Finally, it can explain why the first affected hemibody side is the side of the dominant hand (van der Hoorn *et al.*, 2012) and the most affected movements are typically activities of constant use, including mimic expression, speech, gait, writing and other hand movements. Importantly, a recent perspective has suggested that even the spreading of neuropathology in form of lewy bodies could be reliant on activation and glutamatergic excitotoxicity through activation of cortico-striatal projections (Foffani &

Obeso, 2018). Dopamine replacement therapy with levodopa may counteract the disbalance of neural reinforcement (see Box 3) but may come too late to keep neural dynamics unaffected by the long-term chronic degradation from dopaminergic cell loss in PD.

BOX 3 Modulation of neural reinforcement with dopaminergic medication

The most common treatment strategy for PD is the administration of levodopa, a precursor to dopamine that is metabolized by dopaminergic neurons and can be released on demand (Tambasco *et al.*, 2018). Following the rationale outlined in this review, levodopa could partly and temporarily restore reinforcement, by normalizing synaptic levels of dopamine leading to upregulation of the direct and the downregulation of the indirect BG pathway. Some key problems, however, arise, that can make the stabilization of purposeful neural population dynamics more complex than in the healthy state. Most importantly, dopamine treatment is started after symptoms are already prevalent, often after more than 80% of dopaminergic neurons are degenerated. Thus, the negative effects on neural dynamics and plasticity have already accumulated over years in a hypodopaminergic state. Moreover, it remains uncertain to what degree levodopa induced dopamine signaling is contaminated by unspecific increases of dopamine in synaptic clefts that is unrelated to targeted dopamine release. Taken together, the continuous degradation of neural dynamics and the potential unspecific increase of dopamine availability after levodopa intake, could lead to hyperactivity of the direct pathway and consequently to strengthening of unspecific, seemingly random neural population dynamics. Levodopa induced dyskinesia, the involuntary movements commonly seen as a side-effect of dopamine replacement therapy (Kwon *et al.*, 2022), may provide a vivid image of a potential behavioral consequence of such an unspecific reinforcement.

Neural reinforcement as a target for adaptive deep brain stimulation

An alternative or complementary treatment option for PD is subthalamic deep brain stimulation (STN-DBS), a neurosurgical treatment that uses implanted electrodes and electrical stimulation to treat patients with PD and other basal ganglia disorders (Schuepbach *et al.*, 2013). While the mechanisms of STN-DBS are not completely understood (Neumann, Steiner, *et al.*, 2023), it is assumed that high frequency stimulation (130 Hz) inhibits neural firing in the STN and consequently suppresses indirect pathway output (Milosevic *et al.*, 2018). If indeed, indirect pathway activity is associated with weakening of ongoing cortico-basal ganglia circuit dynamics, suppression of indirect pathway activity through STN-DBS could therefore result in a net strengthening effect by shifting the balance between the pathways that converge in the internal pallidum. While no scientific study has addressed this hypothesis specifically, some findings can corroborate this idea. On the neural level, for instance, it has been shown that STN-DBS can induce LTP-like plasticity (Milosevic *et al.*, 2018) and on the behavioral level it was found that it can restore motor learning that is lost in the absence of stimulation (De Almeida Marcelino *et al.*, 2019) and it can counteract the sequence effect or decrement in amplitude and velocity (Kehnemouyi *et al.*, 2023).

If STN-DBS may be understood as modulator of basal ganglia reinforcement, how can this property be exploited to maximize therapeutic success? A key advantage of neurostimulation over drug treatment is the fact that it can be adapted within milliseconds. This constitutes an unprecedented spatiotemporal precision for the treatment of brain disorders (Neumann, Gilron, *et al.*, 2023). This potential, however, is currently not utilized for the treatment of PD, as stimulation is switched on chronically, similar to a chronic levodopa effect.

In the last decade, important advances have been made that pave the way for the application of adaptive STN-DBS. Activity in the beta band has been identified as a biomarker of symptom severity (Lofredi *et al.*, 2023), which can be disrupted by DBS (Neumann, Horn, *et al.*, 2023) and enables the adaptation of STN-DBS to the concurrent symptom severity (Neumann, Gilron, *et al.*, 2023). How this biomarker relates to dopamine release in PD, though, is unknown. In non-human primate studies, if any, negative correlations were reported between beta amplitude and dopamine release (Schwerdt *et al.*, 2020). While slow adaptive control algorithms over minutes or hours may account for differences in medication states and tonic dopamine levels in PD patients, fast millisecond precise control algorithms could always

switch on during a transient dip in dopamine release. In theory this could counteract the intrinsic dopamine signaling that is remaining in PD patients.

What if we could use the high-precision of closed-loop neurostimulation to mirror the transient dynamics of dopamine release to restore neural reinforcement of purposeful neural dynamics and their behavioral consequences? Instead of disrupting a noisy circuit, we could aim to restore the function of dopamine and basal ganglia communication, by tying DBS to intrinsic dopamine signaling. If indeed, transient dopamine release induces phasic decreases in beta activity, STN-DBS could be triggered to support the strengthening effects of intrinsic dopamine signaling. This would be diametrically opposed to the current beta-adaptive approach that triggers stimulation when beta activity is high. To provide an example, we can recapitulate the fact that spontaneous movement is associated with dopamine release as introduced above (Barter *et al.*, 2015; Dodson *et al.*, 2016; Coddington & Dudman, 2019; Cheung *et al.*, 2023; Markowitz *et al.*, 2023). Importantly, it is also accompanied by a consistent reduction of beta activity The beta based approach would likely turn off during movement, while a valid starting point for closed-loop STN-DBS targeting reinforcement could be the application prior or during movement initiation. This could support the intrinsic reinforcement effects required for motor performance, and may counteract akinesia, the difficulty to initiate movement (Hallett, 1990), in PD.

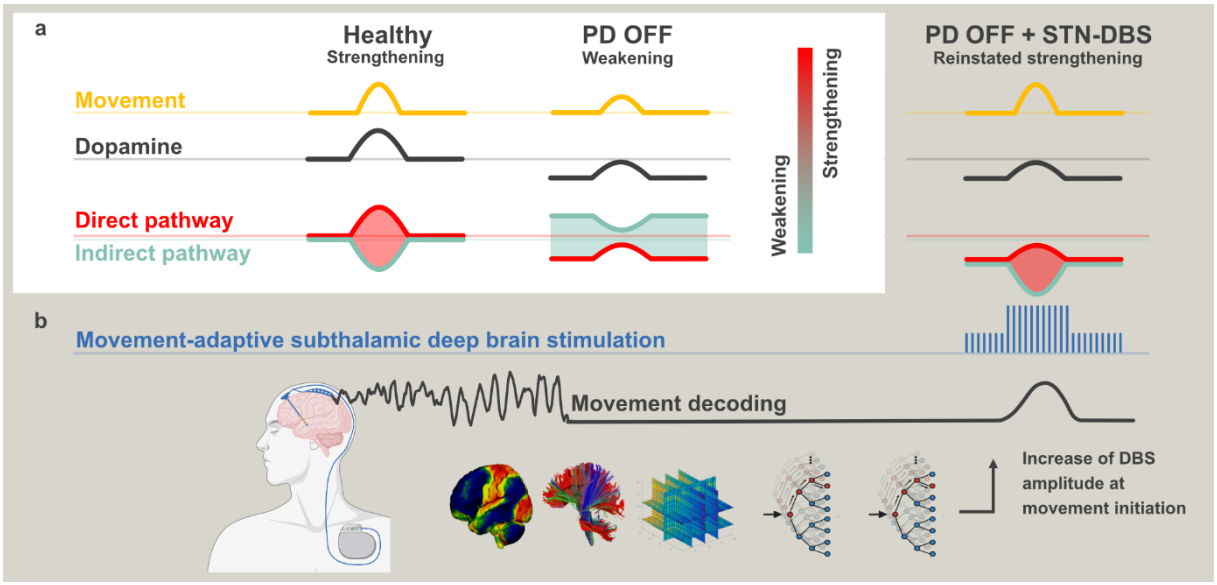

FIGURE 4 Next generation closed-loop DBS intervention. a In the healthy state, increases in dopamine could be associated with a strengthening of movement related population dynamics. In the dopaminergic OFF state in Parkinson's disease (PD OFF), though, the decrease in dopamine release shifts the equilibrium between the pathways and impedes dopamine induced strengthening. Rather, movement related activity patterns may be weakened. **b** Subthalamic deep brain stimulation (STN-DBS) may be able reinstate the intrinsic reinforcement orchestrated by dopaminergic activity. By suppressing indirect pathway activity, and thereby shifting the balance towards the direct pathway, STN-DBS may strengthen neural activity patterns present at the time of stimulation. STN-DBS could be applied chronically at a mild level to restore the reinforcement homeostasis and increased in amplitude to mimic phasic increases in dopamine release and induce strengthening. As increased dopaminergic activity has been tied to the initiation and execution of movements, machine learning methods based on intracranial recordings could be used to predict those events and trigger increases in stimulation amplitude.

In experimental settings, as a proof of concept study, adaptive stimulation could first be triggered by kinematic recordings, e.g. through motion sensors or specific hardware that can track movement. In the future, a fully embedded system that decodes behavioral intent from invasive brain signals could close the loop and act as a dopamine and basal ganglia neuroprosthetic. Here, machine learning methods, such as contrastive learning (Schneider *et al.*, 2023) could be used to decode movement intention or presence from cortical activity and trigger stimulation (Merk *et al.*, 2022). Thus, closed-loop STN-DBS could be used to adaptively strengthen favorable activity patterns in the cortico-basal ganglia circuit, which could

persist even beyond the stimulation time. Moreover, selective stimulation of a behavioral subset could potentially enable a more efficient and longer lasting symptom alleviation when stimulation consistently strengthens intrinsic circuit dynamics in a targeted and individualized manner. Taken together, the perspective that dopamine orchestrates neural reinforcement, which becomes aberrant in PD, has the potential to inspire entirely new treatment strategies that might improve quality of life for millions of patients.

Open questions and future outlook

Even though a small number of findings exist, the majority of the abovementioned concepts must be seen as speculative. More research is needed to provide definite evidence supporting the general role of dopamine in neural reinforcement, its aberration in Parkinson's disease and the ability of STN-DBS to restore dynamic reinforcement. Firstly, open questions remain regarding the bidirectionality of movement-related dopamine release. While it has been demonstrated that dopaminergic firing undergoes transient increases and decreases in response to the presence and absence of reward, dopaminergic activity in relation to movement has only been reported to be modulated positively (Dodson *et al.*, 2016; Coddington & Dudman, 2019; Greenstreet *et al.*, 2022; Markowitz *et al.*, 2023). It is therefore crucial to understand whether movement related dopamine fluctuates bidirectionally, thus can strengthen and weaken motor output, which is fundamental to the outlined view of dopamine and its' pathophysiological role in PD. Secondly, the majority of the data supporting a view of PD as chronic weakening of present circuit dynamics stems from PD models in rodents. As rodent PD models are limited in capturing the full extent of PD pathophysiology (Potashkin *et al.*, 2011), it is necessary to translate these studies to humans. For instance, it has to be examined whether in PD patients decline in motor performance and medication-induced rescue are experience and task-dependent in accordance with results in mice (Cheung *et al.*, 2023). Lastly, a series of studies employing closed-loop STN-DBS should assess which parameters, such as stimulation timing, novel patterns and medication state might enable the reinforcement of neural and behavioral states. While it has been reported that dopamine modulation is highest during the initial phase of the movement (Markowitz *et al.*, 2023), motivating the use of movement-triggered STN-DBS, it remains unclear whether more effective temporal targets for STN-DBS exist. Here, the detailed temporal characterization of phasic dopamine in relation to diverse behavioral states and specific DBS patterns is crucial to inform the timing of closed-loop DBS. Moreover, it has to be identified which medication state optimally supports DBS-driven reinforcement. Under strong dopaminergic medication, which is already associated with a disbalance in favor of the direct pathway, further shifting the balance through STN-DBS might result in a negligible effect. If, on the other hand, dopamine release is severely reduced, STN-DBS might firstly not be strong enough to shift the balance towards the direct pathway and secondly, reduced dopamine-dependent plasticity at cortico-striatal and cortico-cortical synapses might impede a strengthening of neural activity patterns. Ultimately, the further development of cell-type specific electrical stimulation, as recently achieved in GPe, could revolutionize DBS based reinforcement (Spix *et al.*, 2021). Thus, further research is required to corroborate the concepts before clinical utility can be expected for PD patients. Nevertheless, the general concept of a brain circuit neuroprosthetic may have further implications beyond closed-loop STN-DBS for PD. In the future, it could inspire the development of neurochemical therapies for closed-loop sensing and delivery of dopamine to normalize reinforcement. It may provide computational neuroscientists and machine learning engineers with inspiration for novel reinforcement algorithms for bionic control and artificial intelligence. Augmenting neural learning could significantly accelerate the adaptation of human brain circuits to sensory and motor prosthetics, e.g. by reinforcing learned input-output relationships for a) brain spine interfaces after spinal cord injury (Capogrosso *et al.*, 2016) b) auditory brainstem implants (Glennon *et al.*, 2020) or c) artificial retinas (Mills *et al.*, 2017). Ultimately, it could pave the way for a precision medicine approach to restore the intrinsic reinforcement capacity of cortex – basal ganglia pathways: Towards closed-loop brain circuit therapeutics that can restore healthy brain function.

Funding statement

Funded by European Union (ERC, ReinforceBG, 101077060). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council. Neither the European Union nor the granting authority can be held responsible for them.).

Conflict of Interest statement

AC has nothing to disclose. WJN received honoraria for consulting from InBrain – Neuroelectronics that is a neurotechnology company and honoraria for talks from Medtronic that is a manufacturer of deep brain stimulation devices unrelated to this manuscript.

References

Albin, R.L., Young, A.B., & Penney, J.B. (1995) The functional anatomy of disorders of the basal ganglia. *Trends Neurosci.*, **18**, 63–64.

Alexander, G.E., DeLong, M.R., & Strick, P.L. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.*, **9**, 357–381.

Amaya, K.A. & Smith, K.S. (2018) Neurobiology of habit formation. *Curr. Opin. Behav. Sci.*, Habits and Skills, **20**, 145–152.

Athalye, V.R., Carmena, J.M., & Costa, R.M. (2020) Neural reinforcement: re-entering and refining neural dynamics leading to desirable outcomes. *Curr. Opin. Neurobiol.*, **60**, 145–154.

Barter, J.W., Li, S., Lu, D., Bartholomew, R.A., Rossi, M.A., Shoemaker, C.T., Salas-Meza, D., Gaidis, E., & Yin, H.H. (2015) Beyond reward prediction errors: the role of dopamine in movement kinematics. *Front. Integr. Neurosci.*, **9**.

Baunez, C., Nieoullon, A., & Amalric, M. (1995) Dopamine and complex sensorimotor integration: Further studies in a conditioned motor task in the rat. *Neuroscience*, **65**, 375–384.

Beninger, R.J. (1983) The role of dopamine in locomotor activity and learning. *Brain Res. Rev.*, **6**, 173–196.

Berridge, K.C. (2007) The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl.)*, **191**, 391–431.

Bromberg-Martin, E.S., Matsumoto, M., & Hikosaka, O. (2010) Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*, **68**, 815–834.

Capogrosso, M., Milekovic, T., Borton, D., Wagner, F., Moraud, E.M., Mignardot, J.-B., Buse, N., Gandar, J., Barraud, Q., Xing, D., Rey, E., Duis, S., Jianzhong, Y., Ko, W.K.D., Li, Q., Detemple, P., Denison, T., Micera, S., Bezard, E., Bloch, J., & Courtine, G. (2016) A brain-spine interface alleviating gait deficits after spinal cord injury in primates. *Nature*, **539**, 284–288.

Cheung, T.H.C., Ding, Y., Zhuang, X., & Kang, U.J. (2023) Learning critically drives parkinsonian motor deficits through imbalanced striatal pathway recruitment. *Proc. Natl. Acad. Sci.*, **120**, e2213093120.

Coddington, L.T. & Dudman, J.T. (2019) Learning from Action: Reconsidering Movement Signaling in Midbrain Dopamine Neuron Activity. *Neuron*, **104**, 63–77.

Coddington, L.T., Lindo, S.E., & Dudman, J.T. (2023) Mesolimbic dopamine adapts the rate of learning from action. *Nat. 2023 6147947*, **614**, 294–302.

Cui, G., Jun, S.B., Jin, X., Pham, M.D., Vogel, S.S., Lovinger, D.M., & Costa, R.M. (2013) Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature*, **494**, 238–242.

Daniel, R. & Pollmann, S. (2014) A universal role of the ventral striatum in reward-based learning: Evidence from human studies. *Neurobiol. Learn. Mem.*, **0**, 90–100.

De Almeida Marcelino, A.L., Horn, A., Krause, P., Kühn, A.A., & Neumann, W.J. (2019) Subthalamic neuromodulation improves short-term motor learning in Parkinson's disease. *Brain*, **142**, 2198–2206.

Dodson, P.D., Dreyer, J.K., Jennings, K.A., Syed, E.C.J., Wade-Martins, R., Cragg, S.J., Bolam, J.P., & Magill, P.J. (2016) Representation of spontaneous movement by dopaminergic neurons is

cell-type selective and disrupted in parkinsonism. *Proc. Natl. Acad. Sci. U. S. A.*, **113**, E2180-2188.
Dorsey, E.R., Sherer, T., Okun, M.S., & Bloem, B.R. (2018) The Emerging Evidence of the Parkinson Pandemic. *J. Park. Dis.*, **8**, 3–8.
Fishman, R.H.B., Feigenbaum, J.J., Yanai, J., & Klawans, H.L. (1983) The relative importance of dopamine and norepinephrine in mediating locomotor activity. *Prog. Neurobiol.*, **20**, 55–88.
Foffani, G. & Obeso, J.A. (2018) A Cortical Pathogenic Theory of Parkinson's Disease. *Neuron*, **99**, 1116–1128.
Glennon, E., Svirsky, M.A., & Froemke, R.C. (2020) Auditory cortical plasticity in cochlear implant users. *Curr. Opin. Neurobiol.*, **60**, 108–114.
Grace, A.A., Floresco, S.B., Goto, Y., & Lodge, D.J. (2007) Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends Neurosci.*, **30**, 220–227.
Greenstreet, F., Vergara, H.M., Pati, S., Schwarz, L., Wisdom, M., Marbach, F., Johansson, Y., Rollik, L., Moskovitz, T., Clopath, C., & Stephenson-Jones, M. (2022) Action prediction error: a value-free dopaminergic teaching signal that drives stable learning. *bioRxiv*, 2022.09.12.507572.
Hallett, M. (1990) Clinical neurophysiology of akinesia. *Rev. Neurol. (Paris)*, **146**, 585–590.
Kehnemouyi, Y.M., Petrucci, M.N., Wilkins, K.B., Melbourne, J.A., & Bronte-Stewart, H.M. (2023) The Sequence Effect Worsens Over Time in Parkinson's Disease and Responds to Open and Closed-Loop Subthalamic Nucleus Deep Brain Stimulation. *J. Park. Dis.*, **13**, 537–548.
Kravitz, A.V., Tye, L.D., & Kreitzer, A.C. (2012) Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat. Neurosci.*, **15**, 816–818.
Kwon, D.K., Kwatra, M., Wang, J., & Ko, H.S. (2022) Levodopa-Induced Dyskinesia in Parkinson's Disease: Pathogenesis and Emerging Treatment Strategies. *Cells*, **11**, 3736.
Ling, H., Massey, L.A., Lees, A.J., Brown, P., & Day, B.L. (2012) Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. *Brain*, **135**, 1141–1153.
Lofredi, R., Okudzhava, L., Irmen, F., Brücke, C., Huebl, J., Krauss, J.K., Schneider, G.-H., Faust, K., Neumann, W.-J., & Kühn, A.A. (2023) Subthalamic beta bursts correlate with dopamine-dependent motor symptoms in 106 Parkinson's patients. *Npj Park. Dis.*, **9**, 1–9.
Markowitz, J.E., Gillis, W.F., Jay, M., Wood, J., Harris, R.W., Cieszkowski, R., Scott, R., Brann, D., Koveal, D., Kula, T., Weinreb, C., Osman, M.A.M., Pinto, S.R., Uchida, N., Linderman, S.W., Sabatini, B.L., & Datta, S.R. (2023) Spontaneous behaviour is structured by reinforcement without explicit reward. *Nat. 2023*, 1–10.
Marsden, C.D. & Obeso, J.A. (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain J. Neurol.*, **117 (Pt 4)**, 877–897.
Marshall, J.F., Levitan, D., & Stricker, E.M. (1976) Activation-induced restoration of sensorimotor functions in rats with dopamine-depleting brain lesions. *J. Comp. Physiol. Psychol.*, **90**, 536–546.
Merk, T., Peterson, V., Lipski, W.J., Blankertz, B., Turner, R.S., Li, N., Horn, A., Richardson, R.M., & Neumann, W.-J. (2022) Electrocorticography is superior to subthalamic local field potentials for movement decoding in Parkinson's disease. *eLife*, **11**, e75126.
Mills, J.O., Jalil, A., & Stanga, P.E. (2017) Electronic retinal implants and artificial vision: journey and present. *Eye*, **31**, 1383–1398.
Milosevic, L., Kalia, S.K., Hodaie, M., Lozano, A.M., Fasano, A., Popovic, M.R., & Hutchison, W.D. (2018) Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. *Brain J. Neurol.*, **141**, 177–190.
Neumann, W.-J., Gilron, R., Little, S., & Tinkhauser, G. (2023) Adaptive Deep Brain Stimulation: From Experimental Evidence Toward Practical Implementation. *Mov. Disord.*, **38**, 937–948.
Neumann, W.-J., Horn, A., & Kühn, A.A. (2023) Insights and opportunities for deep brain stimulation as a brain circuit intervention. *Trends Neurosci.*, **0**.
Neumann, W.-J., Steiner, L.A., & Milosevic, L. (2023) Neurophysiological mechanisms of deep brain stimulation across spatiotemporal resolutions. *Brain*, awad239.
Nieoullon, A. (2002) Dopamine and the regulation of cognition and attention. *Prog. Neurobiol.*, **67**, 53–83.

Oishi, Y. & Lazarus, M. (2017) The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci. Res.*, Cutting-edge Approaches to Unwrapping the Mysteries of Sleep, **118**, 66–73.
Phillips, A.G., Vacca, G., & Ahn, S. (2008) A top-down perspective on dopamine, motivation and memory. *Pharmacol. Biochem. Behav.*, Microdialysis: recent developments, **90**, 236–249.
Poewe, W., Seppi, K., Tanner, C.M., Halliday, G.M., Brundin, P., Volkmann, J., Schrag, A.-E., & Lang, A.E. (2017) Parkinson disease. *Nat. Rev. Dis. Primer*, **3**, 1–21.
Potashkin, J.A., Blume, S.R., & Runkle, N.K. (2011) Limitations of Animal Models of Parkinson's Disease. *Park. Dis.*, **2011**.
Sabandal, J.M., Berry, J.A., & Davis, R.L. (2021) Dopamine-based mechanism for transient forgetting. *Nature*, **591**, 426–430.
Salgado-Pineda, P., Delaveau, P., Blin, O., & Nieoullon, A. (2005) Dopaminergic Contribution to the Regulation of Emotional Perception. *Clin. Neuropharmacol.*, **28**, 228.
Schneider, S., Lee, J.H., & Mathis, M.W. (2023) Learnable latent embeddings for joint behavioural and neural analysis. *Nature*, **617**, 360–368.
Schuepbach, W.M.M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., Hälbig, T.D., Hesekamp, H., Navarro, S.M., Meier, N., Falk, D., Mehdorn, M., Paschen, S., Maarouf, M., Barbe, M.T., Fink, G.R., Kupsch, A., Gruber, D., Schneider, G.-H., Seigneuret, E., Kistner, A., Chaynes, P., Ory-Magne, F., Brefel Courbon, C., Vesper, J., Schnitzler, A., Wojtecki, L., Houeto, J.-L., Bataille, B., Maltête, D., Damier, P., Raoul, S., Sixel-Doering, F., Hellwig, D., Gharabaghi, A., Krüger, R., Pinsker, M.O., Amtage, F., Régis, J.-M., Witjas, T., Thobois, S., Mertens, P., Kloss, M., Hartmann, A., Oertel, W.H., Post, B., Speelman, H., Agid, Y., Schade-Brittinger, C., & Deuschl, G. (2013) Neurostimulation for Parkinson's Disease with Early Motor Complications. *https://doi.org/10.1056/NEJMoa1205158*, **368**, 610–622.
Schultz, W. (1994) Behavior-related activity of primate dopamine neurons. *Rev. Neurol. (Paris)*, **150**, 634–639.
Schultz, W., Dayan, P., & Montague, P.R. (1997) A Neural Substrate of Prediction and Reward. *Science*, **275**, 1593–1599.
Schwerdt, H.N., Amemori, K., Gibson, D.J., Stanwicks, L.L., Yoshida, T., Bichot, N.P., Amemori, S., Desimone, R., Langer, R., Cima, M.J., & Graybiel, A.M. (2020) Dopamine and beta-band oscillations differentially link to striatal value and motor control. *Sci. Adv.*, **6**, eabb9226.
Shen, W., Flajolet, M., Greengard, P., & Surmeier, D.J. (2008) Dichotomous Dopaminergic Control of Striatal Synaptic Plasticity. *Science*, **321**, 848.
Shohamy, D. & Adcock, R.A. (2010) Dopamine and adaptive memory. *Trends Cogn. Sci.*, **14**, 464–472.
Simonyan, K., Cho, H., Hamzehei Sichani, A., Rubien-Thomas, E., & Hallett, M. (2017) The direct basal ganglia pathway is hyperfunctional in focal dystonia. *Brain*, **140**, 3179–3190.
Smith, Y. & Kieval, J.Z. (2000) Anatomy of the dopamine system in the basal ganglia. *Trends Neurosci.*, **23**, S28–S33.
Spix, T.A., Nanivadekar, S., Toong, N., Kaplow, I.M., Isett, B.R., Goksen, Y., Pfenning, A.R., & Gittis, A.H. (2021) Population-specific neuromodulation prolongs therapeutic benefits of deep brain stimulation. *Science*, **374**, 201–206.
Stephenson-Jones, M., Samuelsson, E., Ericsson, J., Robertson, B., & Grillner, S. (2011) Evolutionary Conservation of the Basal Ganglia as a Common Vertebrate Mechanism for Action Selection. *Curr. Biol.*, **21**, 1081–1091.
Tambasco, N., Romoli, M., & Calabresi, P. (2018) Levodopa in Parkinson's Disease: Current Status and Future Developments. *Curr. Neuropharmacol.*, **16**, 1239–1252.
Tecuapetla, F., Jin, X., Lima, S.Q., & Costa, R.M. (2016) Complementary Contributions of Striatal Projection Pathways to Action Initiation and Execution. *Cell*, **166**, 703–715.
Turner, R.S. & Desmurget, M. (2010) Basal ganglia contributions to motor control: a vigorous tutor. *Curr. Opin. Neurobiol.*, **20**, 704–716.
van der Hoorn, A., Burger, H., Leenders, K.L., & de Jong, B.M. (2012) Handedness correlates with the dominant Parkinson side: A systematic review and meta-analysis. *Mov. Disord.*, **27**, 206–210.
Wang, D.V. & Tsien, J.Z. (2011) Conjunctive Processing of Locomotor Signals by the Ventral Tegmental Area Neuronal Population. *PLOS ONE*, **6**, e16528.

Wood, A.N. (2021) New roles for dopamine in motor skill acquisition: lessons from primates, rodents, and songbirds. *J. Neurophysiol.*, **125**, 2361–2374.
Yttri, E.A. & Dudman, J.T. (2016) Opponent and bidirectional control of movement velocity in the basal ganglia. *Nature*, **533**, 402.