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Basal Ganglia Paths Support Acute vs. Learned Execution, Not Movement vs. Stopping

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The basal ganglia (BG) are a central component of the brain, crucial to the initiation, execution and learning of adaptive actions. The BG are the major site of the action of dopamine. An important aspect of the BG architecture is the existence of two paths, direct and indirect, having different projection targets and dopamine receptor expression. To understand the BG, dopamine, and related disorders, it is imperative to understand the two paths. The standard account used in neuroscience research for decades posits that the direct path supports movements, while the indirect path suppresses unselected or completed movements. This account is contradicted by converging evidence. Here, we explain why the arguments supporting the standard account are flawed, and present a new account, in which the role of the indirect path is completely opposite: to support learned execution. During acute events, ongoing execution is stopped, and the direct path allows coarse responses. These are refined by competition, and the resulting focused response is executed and learned by the indirect path, assisted by cholinergic interneurons. The new account allows a novel understanding of the symptoms of Parkinson's disease, and of its treatment by deep brain stimulation of the subthalamic nucleus.

Keywords: basal ganglia, dopamine, subthalamic nucleus, Parkinson's disease, brain learning, cholinergic interneurons, deep brain stimulation.

The basal ganglia (BG) are a set of large bilateral subcortical nuclei at the centro-frontal part of the brain. The BG are involved in all types of execution except low-level innate responses (e.g., reflexes), and are a major site of dopamine (DA) action in the brain. Impairment of BG DA is the central feature of Parkinson's disease (PD). Understanding BG function is essential for understanding the brain and movement disorders.

The major aspect of the BG architecture is the existence of two flow paths from the input nuclei, the striatum (STR) and the subthalamic nucleus (STN), to the output nuclei, the internal

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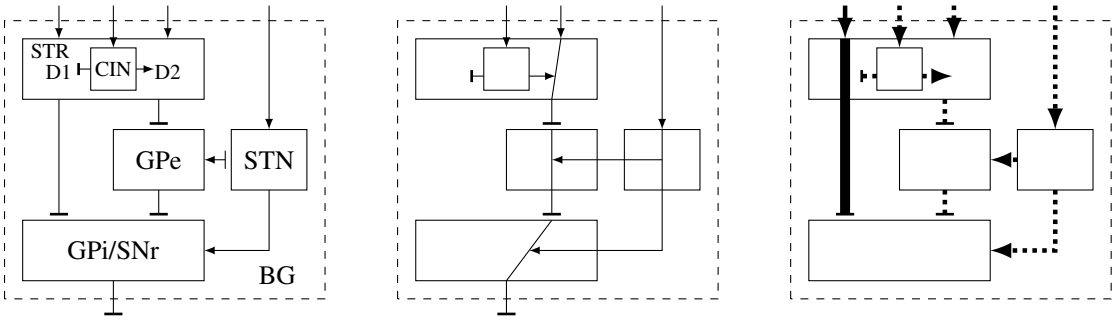

Figure 1: The basal ganglia in learned and acute responses. The role of the indirect (D2) path, which cooperates with the STN and cholinergic interneurons (CINs), is to support focused learned execution. Left: BG connectivity. Arrows and T junctions indicate excitatory and GABAergic flow, respectively. Only the main connections are shown. Middle: Learned actions use a focused synchronized channel via the indirect path, which is synchronized with the BG targets. Right: Acute events induce BG input bursts that suppress execution in the indirect path by interfering with its synchrony (dotted lines, right), and a DA surge that suppresses the indirect path via D2Rs. These are followed by D1-mediated activation of the direct path that suppresses BG output and disinhibits its motor targets to allow rapid coarse responses (thick line, left). After competition resolution, the coarse D1 path is focused, the indirect path joins execution, and the direct path eventually closes. With repeated training, execution gradually shifts from the scenario on the right to that in the middle.

globus pallidus (GPi) and substantia nigra reticulata (SNr) [Graybiel and Mink, 2009] (Figure 1, left). The so-called **direct** path projects from the STR to the output nuclei, while the **indirect** path utilizes the external globus pallidus (GPe) and STN as well. Projection neurons in the direct path express dopamine D1 receptors, dynorphin and substance P, while those in the indirect path express D2Rs and enkephalin. There is some overlap between the paths [Kupchik et al., 2015], but there is no dispute that two prototypical paths (direct/D1 and indirect/D2) exist.

The BG output nuclei tonically inhibit the thalamus and other motor centers, whose support is essential for the execution of responses. The standard account of the two paths is that the direct path supports movements by disinhibiting the thalamus, while the indirect path enhances thalamic inhibition to suppress movements. This uniformly accepted account, cited by almost every paper reporting results related to the BG, is contradicted by substantial amounts of evidence. Here we present a new account (see Figure 1, middle and right), and show why the arguments used to support the classical account are flawed. The new account accords with the evidence and has implications for the understanding and treatment of PD.

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The standard account

In the standard account, the direct path supports movement while the indirect path suppresses movement. There are two variants, one in which suppression is done in order to terminate completed movements, the other in which it is done to suppress actions that have competed for execution but were not selected [Graybiel and Mink, 2009, Wichmann, 2018]. Both variants are based on anatomical, molecular and experimental arguments.

The anatomical argument is based on counting the number of GABAergic links in a path. The projection neurons of the STR (medium spiny neurons, MSNs), GPe and SNr/GPi are GABAergic, while those of the STN, as well as of all BG inputs (from cortex, thalamus, amygdala, and hippocampus) are glutamatergic. Since GABA is an inhibitory neurotransmitter, activation of the direct MSNs suppresses the output nuclei to allow movement, while activation of indirect MSNs suppresses the GPe and removes its suppression of the output nuclei, inhibiting movement. That is, activating a path with two or three GABAergic links is disinhibitory or inhibitory, respectively.

The molecular argument is based on DA. Valence-carrying surprises such as reward cues [Schultz, 2016] or aversive events [Bromberg-Martin et al., 2010] yield phasic excitation of DA neurons, inducing a DA surge in the STR. D1Rs are G-protein-coupled receptors (GPCRs) that bind to Gs to yield rapid excitation via cAMP and GIRK currents [Podda et al., 2010], and D2Rs are GPCRs that usually bind to Gi/o, yielding cell suppression. The DA surge induces the activation of the direct path, whose MSNs express D1R. Since DA is essential to movement vigor [Panigrahi et al., 2015], and rapid phasic STR DA is capable of triggering accelerated locomotion [Howe and Dombeck, 2016], the DA data seem to support the standard account.

The DA surge also suppresses indirect path MSNs, which express D2R. This is presumably necessary for movement because before the DA surge, indirect path MSNs actively suppress movement. This seems to be supported by the fact that passive posture is associated with beta oscillations in the BG [Engel and Fries, 2010], showing that there is continuous BG activity during non-movement. The oscillations desynchronize when movement starts, further supporting the story.

On the experimental side, several paradigms have shown that movement initiation and stopping involve the direct and indirect (including the STN) paths, respectively. For example, when direct/indirect MSNs were optogenetically stimulated, movement initiation/suppression correlated with inhibited/excited SNr neurons [Freeze et al., 2013]. In ablation experiments, phasic SNr excitation through the indirect path had a key role in stopping movements [Sano et al., 2013]. In behavioral experiments, both EEG and fMRI imaging show that rapid global stopping is induced via cortical (rIFC, preSMA) projections to the STN [Wessel and Aron, 2017].

The standard account is also supported by the freezing and slow movements exhibited by PD patients, in whom the indirect path is excessively active (see PD section below).

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Problems with the standard account

The standard account is cited by almost every paper dealing with the BG. However, accumulating evidence of different types contradicts it, there are theoretical arguments against it, and some arguments supporting it are conceptually flawed.

Evidence of path cooperation during execution. If the indirect path terminates movements, it should be active only at the end of a movement. Conversely, if it suppresses competitors, it should be active only at the beginning of movement. However, several labs have shown that both paths are active throughout movement [Cui et al., 2013, Barbera et al., 2016, Parker et al., 2018]. Moreover, the latter paper reported that direct and indirect clusters seem to encode specific movement types, directly contradicting the standard account. It also reported that the clusters are of similar size, while the competitor suppression variant predicts a larger participation of indirect MSNs [Wichmann, 2018].

In addition to the above, the two paths were shown to specifically cooperate during reward-related execution [Isomura et al., 2013], which involves phasic DA that activates D1Rs and thus the direct path.

A possible answer here is that the movements terminated and/or selected by the indirect path are low-level ones that are replaced at a high pace. However, this explanation does not conform to the experimental and DA arguments cited in support of the standard account. In addition, there is large flow convergence along the cortex-STR-SNr/GPi axis [Bar-Gad et al., 2003], reducing the likelihood that low-level actions are supported by different BG neurons.

Evidence of indirect path association with learned execution. There is clear evidence that the indirect path is associated with learned motor execution. In a behavioral task that used D1 and D2 antagonists, the direct path was essential for the initiation of attended actions, but execution of learned sequences mostly used the indirect path [Agnoli et al., 2013]. In a motor training paradigm, autoradiography showed strong dorsomedial STR D1 reduction after the first execution, while dorsolateral STR D2 showed progressive reduction after extended training [Sommer et al., 2014]. The acquisition of habits yielded plasticity in the indirect path [Shan et al., 2015]. Cortical sensory and internal need areas, which are more involved in action initiation, preferably target the direct path, while motor execution areas target the indirect path [Wall et al., 2013, Reiner et al., 2010].

BG outputs can recruit the thalamus. Focused GPi excitation in low DA states (i.e., the states in which the direct path is inactive and the indirect path can be active) can induce excitatory thalamic motor signals [Kim et al., 2017]. This result undermines the logic behind the anatomical and DA arguments for the standard account.

The STN. The view of the standard account of the role of the STN is not clear. The STN is supposed to induce stopping by exciting the indirect path. Indeed, it excites the GPi, which should enhance its firing and suppress movement. However, the STN also excites the GPe, which inhibits the GPi and should allow movement. A possible answer is that GPe suppresses the STN, but it does not explain why the STN excites the GPe. A more elaborate account

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posits that the STN (the hyperdirect path) participates in the first of three stages of response suppression, and is suppressed by the indirect path in the third stage [Nambu et al., 2002]. However, if the role of both STN and GPe is to induce stopping, it is still not clear why they should oppose each other.

Molecular expression. The standard account does not address salient molecular expression data showing that it is the indirect, more than the direct, path that the brain expects to be active during prolonged execution.

Enkephalin (ENK) is an opioid released by excessively active neurons, retrogradedly suppressing presynaptic activity via delta-opioid receptors to protect neurons from oxidative stress [Xia, 2015]. ENK is strongly associated with locomotion, and is selectively expressed in indirect MSNs. This implies that prolonged locomotion involves the indirect path.

Adenosine (ADN) is an astrocytic and neuronal by-product of metabolism, and affects the inputs to the BG via A1 and A2A receptors located presynaptically on the inputs to the direct and indirect paths, respectively. A1 is inhibitory and is of much higher affinity to ADN than A2A, which is excitatory. A2A reverses the effect of D2 in MSNs [Azdad et al., 2009]. Thus, intense activity releases large amounts of ADN, which acts on A2ARs to enhance the activity of the indirect path and oppose its suppression by DA. This shows that it is the indirect, not the direct, path which is normally expected to be intensely active in a prolonged manner.

The direct path is activated during strong survival-related events and is also in danger of oxidative stress. Indeed, like the indirect path, it is protected by an opioid, dynorphin (DYN). DYN is present in alert areas such as the central nucleus of the amygdala, and interacts with stress agents such as corticotropin-releasing hormone [Van't Veer and Carlezon, 2013]. It is selectively expressed by direct path MSNs and retrogradedly suppresses them to halt acute responses. In general, the role of DYN is to promote innate disengage (freeze, withdraw) responses, so it opposes D1Rs, which promote engage actions [Rappoport, 2018].

Endocannabinoids (ECBs) released by MSNs also retrogradedly suppress their inputs, affecting both paths [Shen et al., 2008]. ECBs cooperate with glucocorticoids to suppress adaptive execution during prolonged stress.

The anatomical argument. To understand why the standard anatomical argument is flawed, it is necessary to discuss the effect of GABAergic neurons (GNs). When a GN fires just before its target fires, it inhibits its firing, via GABAA receptors whose activation allows charged ions to enter and leave the cell. However, when a GN fires after its target fires, its effect is only to enhance the target's already polarized state. When a GN has several targets, it suppresses targets of the former type, and synchronizes the firing of targets of the latter type (because it resets their states at the same time). That is, GNs implement a winner-takes-all **competition** mechanism that synchronizes the firing of neurons whose firing has a certain phase relationship with the GNs (winners), and suppresses the others (losers). Indeed, it is well-known that GABAergic inhibitory interneurons (IINs) expressing parvalbumin (PV) and powerfully acting on cell somas induce synchronized gamma oscillations [Bartos et al., 2007].

Local IINs (GABAergic and/or glycinergic) are located in all brain areas, including the BG

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nuclei. IINs are innervated by the excitatory neurons adjacent to them[1], such that they are recruited whenever flow reaches their location. In the majority of cases, the brain activates more than a single response candidate to incoming flow. The selection of the winning response is done via competition mediated by local IINs [Karnani et al., 2016, Letzkus et al., 2015]. After competition resolution, some of the IINs (mostly PV- and CCK-expressing basket cells) support sustained execution via synchrony.

This analysis implies that the number of inhibitory links in a path is irrelevant for the state of its output during post-competition execution. It is relevant only during strong uncorrelated activity, before competition resolution. All indirect path neurons receive excitatory input (from BG inputs and the STN), and can form a synchronized chain if not suppressed by D2Rs. This chain can include neurons in the BG's motor targets, most notably the thalamus, and can thus support execution. Thus, the anatomical argument in favor of the standard account only holds for the very initial stage of acute responses.

The DA argument. In the second variant of the standard account, indirect MSNs suppress competing action plans. Since the DA surge inhibits indirect MSNs, this suppression of competing plans needs to occur before the DA surge. However, the DA surge is extremely rapid, and it is not reasonable to expect that competition is always resolved before it occurs. In fact, there are two DA surges, a short latency one due to surprise [Redgrave and Gurney, 2006] and a longer latency one due to valence (reward) [Joshua et al., 2009]. This means that DA affects the BG for a relatively long time, starting almost immediately after the event starts, not allowing time for resolving competitions.

A new account

This paper presents a new account for the roles of the BG paths. We propose that *the role of the indirect path is to support learned execution, and the role of the direct path is to support the formation and initiation of acute (novel) responses* (Figure 1, middle and right respectively). With respect to the indirect path, our account is exactly opposite to the standard account. With respect to the direct path, we partially agree with the standard account, but disagree with it on the core issue of supporting movement. The direct path does not support all movements, only those made as part of acute responses, commonly rapid coarse movements.

The new account is supported by the evidence cited above for cooperation of the two paths during execution and for the association of the indirect path with learned execution. It relies on the notion of learned vs. acute responses, and on GABAergic interneurons as mediating competition and synchronized execution. It also provides an integrative view of the roles of D2Rs, the STN, STR cholinergic interneurons. These points are discussed below.

Learning (automaticity). Acute responses are associated with surprises, because sensory input is by definition not surprising if there is a learned responses ready for it. Surprises first induce innate orienting of attention responses, and then innate or adaptive responses that depend on the

[1] In addition to innervation by other IINs.

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specific input. Surprises induce high frequency bursts of action potentials [Cheong and Shin, 2013] in relatively large neuronal populations. Conversely, learned responses involve smaller populations.

The overarching principle of brain plasticity is Hebbian learning, which states that learning enhances the neuronal connections that participate in responses. Meaningful responses are virtually always comprised of sequences rather than of single actions. One result of Hebb's principle is that when a learned response executes, the neurons implementing the possible next responses in the sequence are excited. Such **predictions** prevent surprises and minimize competition. In other words, neuronal activity in learned tasks mostly reflects focused post-competition responses. Automated responses utilize synchronized, focused (narrow) execution paths, while non-automated responses utilize coarser (wider), less synchronized paths.

Indeed, D2 MSNs are more excitable than D1 MSNs [Day et al., 2008], as expected from neurons that have undergone greater automaticity. Direct path MSNs are active upon action initiation even for automated tasks, because the trigger for starting a task or movement (e.g., the appearance of a learned cue) is usually surprising even if task execution has been automated. During normal everyday behavior, there are many sensory inputs that are not expected and thus attract attention. This is why both paths are active during movement.

Note that our learned vs. acute distinction is mechanistically concrete and is not equivalent to the the commonplace view that the BG are involved in learning. The latter trivially holds for all brain parts involved in adaptive responses, being an corrollary of Hebbian learning.

Dopamine. DA is released in the STR by neurons located in two nuclei, SNc and VTA. These nuclei receive wide topographic inputs from all over the brain. The large populations activated during surprise induce the phasic DA responses and the DA surges in the STR. In other words, DA suppresses the indirect path and allows the direct path if and only if a surprise occurs.

The cortical neurons that project to the DA nuclei are thick-tufted pyramidal neurons in layer 5 (mostly L5b), the same neurons that induce motor responses (they are the only cortical neurons that project out of cortex) [Harris and Shepherd, 2015]. When responses are already learned (automated), surprises do not occur, and the direct path is not enabled by DA. Thalamic neurons synchronize with the indirect path and innervate the apical dendrites of the L5b neurons, providing these large neurons with sufficient energy to fire responses. After firing, L5b neurons induce DA release via their projections to the DA nuclei, and this small amount of DA terminates the activity of indirect neurons.

In other words, *the role of D2 receptors is to terminate automated responses*. This accords with their high DA affinity, since automated responses involve the release of small DA amounts, done after the response is made.

It may seem as if this account is similar to the standard account in that the indirect path is used to terminate responses, but in fact it is completely opposite to it. The execution of automated responses normally involves response *sequences*. In out account, D2Rs suppress an executed automated response to allow the next response in the sequence. The activation of indirect path MSNs is part of the execution of a learned response, and the activation of D2Rs

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on these MSNs is part of the execution of the next response in the learned sequence.

The paths passing through the BG are topographic, giving rise to the well-known cortico-BG-thalamic-cortical loops [Graybiel and Mink, 2009]. Because surprises yield bursts, they can rapidly activate many response neurons without thalamic support, yielding a coarse (less specific, less accurate, highly vigorous) response, both in cortex and through the direct path.

The experimental paradigms involving 'reward' usually involve learning (conditioning) to associate a cue with food, which excites DA release via beta-endorphin, directly and indirectly [Fields and Margolis, 2015]. The surprising appearance of the cue induces phasic DA release, explaining why direct (indirect) MSNs increase (decrease) activity with reward value [Shin et al., 2018].

The focus here is on DA action in the BG. A complete account of DA in the brain, which includes the brain process stage that it promotes, its association with specific cortical networks, its goal setting role, and its relationship with acetylcholine, serotonin, and opioids, is given in [Rappoport, 2018], which presents a comprehensive theory of brain function.

Cholinergic interneurons (CINs). The STR contains a population of cholinergic interneurons [Gonzales and Smith, 2015]. These are small in number (about 3-5% of STR neurons) but are extensively arbored, receiving inputs from the thalamic centromedian-parafascicular (cmpf) complex, whose source of innervation is incoming sensory flow. The CINs release acetylcholine (ACh), which suppresses direct MSNs and excites indirect MSNs via presynaptic M2/4 and M1 muscarinic AChRs, respectively [Ding et al., 2010].

Following surprise, cmpf bursts strongly activate the CINs, yielding a large excitation of the indirect path, and of IINs throughout the BG via nicotinic AChRs, followed by a pause induced by D2Rs [Chuhma et al., 2014] and afterhyperpolarization. The burst interferes with any synchronized ongoing action executing through the BG, and the pause releases direct MSNs from the CIN's suppression to let them support coarse acute responses. After competition resolution, the CINs return to their tonic (learned) activity. This explains the well-known CIN firing pattern.

STN. In our account, *the role of the STN is to sustain the focused execution path used by indirect path neurons during execution.* The cortical projections to the STN are mostly from collaterals of L5b neurons [Kita and Kita, 2012], the same type of neurons that implement responses and innervate DA nuclei. Thus, the STN is recruited exactly when responses are made, supporting its role as providing energy to the chain implementing the next response in a sequence. Naturally, stopping actions are also responses, so the STN is expected to participate in stopping actions too, as is indeed the case (see above). Notably, it stops actions in learned tasks [Bevan, 2017], supporting a role in learned responses.

STN neurons have a strong autonomous spiking capacity, continuously exciting the BG output neurons. Unlike most other neurons, the main effect of their inputs is not to generate action potentials but to modify their timing [Bevan, 2017], further supporting our view of the STN as supporting a narrow synchronized channel (center) while suppressing interference (surround).

Suppression of the STN by lesions or pharmacological intervention can lead to dyskinesia

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and involuntary ballistic movements [Hamani et al., 2004]. This is caused by the removal of the continuous unsynchronized excitation by the STN of non-executing output neurons, which guarantees the suppression of BG targets (see also the PD section below). Without this restraint, thalamic and other motor neurons can be accidentally recruited by noisy activation of motor cortical neurons, amplifying noisy activity and making it capable of driving motoneurons.

PV. As noted above, parvalbumin (PV) is expressed in fast-spiking IINs that support synchronized execution. In the middle nucleus of the indirect path, the GPe, most STN-projecting neurons express PV. This implies that the role of the GPe-STN projection is to support synchrony of STN neurons, not to suppress them as assumed by the standard account.

Substance P (SP). SP is released in situations requiring sustained need-driven action, such as pain inputs and sexual approach [Rappoport, 2018]. It is expressed by direct path MSNs, but excites the indirect path via the neurokinin 1 (NK1) receptor. SP excites the so-called prototypical GPe neurons that project to the STN [Mizutani et al., 2017], and enhances STR CINs [Govindaiah et al., 2010]. Thus, SP seems to be one mechanism through which the direct path bootstraps the activity of the indirect path to yield prolonged execution.

In summary, learned actions use a focused synchronized channel in the indirect path. Acute events first suppress execution via D2Rs and BG bursts that impair synchrony, and then open the direct path via D1Rs. This disinhibits the BG motor targets to allow a rapid coarse response. The strong flow induces competition, mediated by IINs. Competition results in a focusing of the coarse D1 path, slower input rates, and DA reuptake, which allow the indirect path to join execution. When the effect of D1R activation subsides, the indirect path alone supports execution, and this role strengthens with each repetition of the task.

Parkinson's disease

PD is characterized by motor symptoms such as difficulty and slowness in initiating and executing movement, freezing, ridigity, rest tremor, and postural instability, and also involves cognitive and emotional symptoms [Obeso et al., 2017]. The main pathological feature is the degeneration of SNc DA neurons. Serotonin and ACh neurons also degenerate. There have been recent advances in understanding the etiology of PD [Surmeier et al., 2017]. Here we only highlight aspects related to the two paths.

Motor symptoms appear after most of the DA axons innervating the dorsal STR have degenerated. That is, relatively small amounts of DA, affecting only the indirect path, are sufficient to support movement, supporting its role in execution. Without DA, the direct path is less excitable, and the indirect path is more excitable. Moreover, the cortical neurons innervating the STR and STN, many of which express D2Rs, are also more excitable. Since the indirect path tends to synchronize its neurons, we expect synchronized oscillatory activity to be increased in PD, and the synchronized channels to be wider than normal. Indeed, a well-known feature of PD is increased beta oscillations in the indirect, but not in the direct, path. In DA-depleted rats, half of the recorded indirect MSNs were phase-locked to the beta trough [Sharott et al., 2017].

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DA-depleted animals showed a decline over time in the spatial clustering of active indirect MSN [Parker et al., 2018], also supporting a wider channel. Since the STN is the excitatory engine of the indirect path, it is not surprising that abnormal beta in PD mostly resonates via the STN [Deffains et al., 2016].

Further supporting a central role of the indirect path in PD pathology, DA depletion is rapidly followed by a decrease in MSN dendritic spine density and a loss of corticoSTR synapses, and these changes are specific to D2R (indirect) MSNs [Cenci, 2017].

Reduced function of the direct path explains the PD difficulties in movement initiation, slow voluntary movement, and reduced vigor. Over-excitability of the indirect path explains freezing, because execution of learned actions is stopped when the focused channel implementing them is widened. The exaggerated synchronization tendency of the indirect path explains rigidity, as follows. A wider indirect channel is associated with a wider motor cortex (M1) channel. In a reduced D2 situation, the cortical M1 neurons controlling motoneurons are over-excited. These M1 neurons control motoneurons that innervate both agonist and antagonist muscles. Normally, competition would suppress one of them. However, in a reduced D2 state, both channels can easily join the synchronized oscillations. This is how isometric force is exerted in normal movements, but in PD it manifests as rigidity.

PD rest tremor can be explained in a similar manner. Here, instead of being activated at the same time, agonist and antagonist muscles are alternately activated. Since agonist and antagonist motoneurons suppress each other via low-level spinal IINs, relatively low-frequency synchronized activity easily translates to tremor. Contraction of an agonist muscle activates muscle spindles, which excite proprioceptive sensory neurons. These directly excite the antagonistic motoneuron to induce contraction in the opposite direction (the stretch reflex). The proprioceptive inputs also convey their excitation to somatosensory cortex neurons, which excite M1 neurons. This amplifies tremor in two ways, by directly exciting alpha motoneurons of the agonist muscle, and possibly by exciting gamma motoneurons and thereby enhancing ascending proprioceptive inputs.

Indeed, PD tremor involves mainly output from contralateral M1, and exhibits coherence between many areas, including premotor cortex, SMA, S2, and the cerebellum [Timmermann et al., 2003]. Motor beta activity has been argued to involve corticospinal loops [Aumann and Prut, 2015], and M1 is hyperactive in PD, with specific increase in corticospinal activity and excessive cortico-STR beta [Lindenbach and Bishop, 2013]. The key role of cortex is indicated by the fact that PD rest tremor is most common in the organs directly controlled by cortex, such as the hands and jaw.

Quick learned movements are made by the cerebellum, which is disynaptically innervated by the STN [Bostan et al., 2013] and projects to motor cortices. The cerebellum has been shown to be involved in the tremor generation loop, mediating tremor amplitude, while the BG mediate tremor initiation [Helmich, 2018].

The involvement of the indirect path in PD is also supported by the fact that patients have difficulty in executing learned actions automatically [Wu et al., 2015]. In a mouse model, optogenetic stimulation of the indirect path, which emulates an acute burst, induced a PD state

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[Kravitz et al., 2010].

The standard treatment of PD uses L-DOPA, from which the brain can generate DA. This reduces indirect path and cortical over-excitability and allows usage of the direct path. The positive effect of L-DOPA is reduced after prolonged use, probably because G-protein-coupled receptors such as D1R and D2R desensitize over time with excessive use [Ferguson, 2001]. When this occurs, PD is commonly treated by deep brain stimulation (DBS) of the STN or the GPi. DBS is effective in ameliorating symptoms when it uses high frequency (gamma and above) stimulation, and can exacerbate symptoms when used in beta frequency. The latter is as expected, because beta stimulation only enhances the over-synchronized state of the indirect path.

Currently, it is not fully clear why high frequency STN DBS ameliorates symptoms [Ashkan et al., 2017]. The initial assumption was that it reduces hyperactive STN/GPi neurons, but this contradicts evidence for their increased activity following DBS. The analysis in the present paper implies that a major effect of DBS is the disruption of the wide PD synchronized channel that includes the indirect path and cortical and spinal neurons. This accords with the view that DBS works by modifying BG output pattern by a more tolerable one [Wichmann and DeLong, 2016]. Our account explains this view in mechanistic terms.

Another possible mechanism of STN DBS is the rapid waves of cortical excitation that it induces [Kuriakose et al., 2010]. DBS is applied in conjunction with L-DOPA, and its excitatory power may enhance cortical capacity to recruit neurons and (at least temporarily) overcome the desensitization of DA receptors.

Prolonged L-DOPA treatment commonly leads to a set of symptoms called L-DOPA induced dyskinesia (LID), presenting as large involuntary tics [Bastide et al., 2015]. LID is a complex phenomenon (e.g., it may involve DA synthesis by serotonin neurons), and it is not well understood. In general, evidence shows that changes in DA receptor expression (including D3Rs) and/or signaling play a major role in LID.

An in-depth examination of PD treatment and LID is out of the scope of this paper. Nonetheless, a preliminary conclusion from the presented account is that treatment of PD patients can be improved in the following ways. First, continuous provision of L-DOPA in smaller doses that is stopped when not needed (e.g., during sleep) should delay DA receptor desensitization. Second, our account supports the view that performing DBS before L-DOPA treatment could yield overall better results. DBS may not rescue the direct path, but PD symptoms appear only after an almost complete DA degeneration, showing that they mainly result from indirect path dysfunction. Of course, the procedure for installing DBS is much more complicated than using medication, and DBS has its own side effects.

Discussion

We argued that the standard account of the BG paths is based on flawed arguments and contradicts the evidence, and proposed a new account. The central notions in the new account are learned vs. acute execution, and GABA as a mediator of competition.

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There is a line of research emphasizing the role of the BG in habit learning [O'Hare et al., 2018] and action chunking [Graybiel and Grafton, 2015], which are related to our learned vs. acute distinction. Generally, this line does not address the difference between the two paths, focusing on the differences between STR regions. The dorsolateral STR (dlSTR) is viewed as supporting habits, while the dorsomedial STR (dmSTR) suppresses them. It has been noted that the main locus of DA axon degeneration is the dlSTR, and that PD mainly involves impaired automatic control of habits [Redgrave et al., 2010].

In our view, the relationship between a STR region and habits is determined by the nature of the inputs arriving to the region. In general, the dorsal STR supports movements and thoughts, while the ventral and medial STR support motivation (need-driven responses). Low-level motor actions are repeated more often than other actions and are hence more automated. Consequently, if an area receives inputs from cortical areas supporting motor actions (e.g., the dlSTR), experimental paradigms would identify it as being involved in the execution of habits. Similarly, suppression of STR areas receiving inputs related to acute valence events, such as the dmSTR, whose inputs are from orbitofrontal cortex and the amygdala, suppresses such responses and strengthens habitual actions [Gremel et al., 2016].

This issue highlights the importance of distinguishing between movements and responses. We have phrased our new account in terms of 'responses' rather than 'movements', because the nature of the response varies depending on STR region. An acute response in dmSTR may stop an innate or conditioned movement. For example, optogenetic stimulation of the direct path induces dyskinesia in healthy mice [Ryan et al., 2018] when targeting the dlSTR, but rescues from dyskinesia when targeting the dmSTR [Kravitz et al., 2010]. That is, as expected, strong abrupt stimulation in motor areas induces large involuntary movements (the former case), but improves movement control in an area specializing in adaptive responses to acute events (the latter case).

Another line of thinking related to the learned vs. acute distinction states that the BG control response urgency/vigor, not selection between actions [Thura and Cisek, 2017, Turner and Desmurget, 2010]. However, this line emphasizes the link between response urgency and activity patterns of the output nuclei, without addressing the two paths.

Some of the experiments supporting the standard account of the paths are optogenetic experiments. Optogenetics can certainly be useful, but conclusions from experiments should be drawn with utmost care. In particular, optogenetic activation of neuronal circuits is generally not suitable when synchronized activity is important. Synchrony occurs between neuronal populations that are much smaller than those targeted by optogenetic methods, and depends on specific firing frequencies. Thus, current optogenetic methods are useful for studying acute responses, but can be misleading with respect to learned responses.

The direct and indirect paths are the most important architectural feature of the BG, but there are other features that are significant to BG function. The distinction between striosomes (patches) and matrix, the role of serotonin, the participation of the BG in imagery, and BG plasticity are independent of the paths and should be included in a complete theory of BG function (see [Rappoport, 2018]). Histamine is an important agent that acts in the STR, generally

serving to signal urgency of response execution. It excites both STR paths via postsynaptic H1 and H2Rs [Zhuang et al., 2018], and was reported to suppresses them or excite the direct path via presynaptic H3Rs [Rapanelli, 2017]. This may indicate that H3R supports automated responses, but the precise effect of histamine needs to be further studied.

In this paper we only discussed major PD symptoms that have a direct relationship with the two paths. Other symptoms and disorders (e.g., essential tremor) are also relevant and will be discussed elsewhere.

In summary, we proposed a new account of BG paths. The existing standard account is based on experiments showing what happens when the indirect path is disturbed, not ones exposing its normal function, and on a flawed analysis of GABA and BG anatomy. This account is contradicted by converging evidence. Our proposed account is simple and accords with all types of available evidence. In particular, it can explain the symptoms and treatment results of Parkinson's disease better than the standard account.

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