6BBYN305 Literature Based Project in Neurosciences

The Role of Dopamine and Dopamine Receptor Signalling in Basal Ganglia-Mediated Action Selection

Arturo de la Cruz Libardi

1601652

Faculty of Life Sciences & Medicine

School of Bioscience Education

King's College London

Guy's Campus

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Abstract

The basal ganglia command action selection amongst other motor and cognitive functions. The Direct Indirect model of Basal ganglia function emerges from neuroanatomical considerations of the neuronal pathways within the Basal ganglia and the cellular composition of its nuclei, specifically the striatum. This model posits the existence of a direct pathway which facilitates the execution of movement, and an indirect pathway whose role is to inhibit movement. The model is characterised as a rate-coding model because it relies on explaining its activity in terms of the firing rate of its neuronal ensembles. The latest evidence in support of this model stems from optogenetic studies. These studies focused on striatal medium spiny neurons and the downstream effects of their activity. Due to the heterogeneous and segregated expression of type 1 and type 2 dopamine receptors on medium spiny neurons, dopamine is thought to be a vital regulatory element in the basal ganglia system.

Recent evidence of concurrent pathway activity as well data from Deep Brain Stimulation studies has cast doubts on two assumptions holding the Direct Indirect model. First, simultaneous activity of direct and indirect pathway runs against the precept that the pathways have a purely opposing function. Indeed, it would be challenging to explain how an action is being facilitated and inhibited at the same time. Second, data from Deep Brain Stimulation Studies as well as other treatments cannot be clearly explained through rate-coding. Instead, a more fruitful approach seems to stem from the investigation of oscillatory patterns. Given these two lines of evidence and additional observations regarding the influence of dopamine in goal-directed action selection, I examine the classical model and propose features of an updated model. The novel model builds on the remaining backbone of the Direct Indirect model, emphasizing a pattern-based approach, the search for integratory mechanisms and the enveloping influence of dopamine.

Introduction

The Basal ganglia (BG) are a group of subcortical nuclei that have been identified as the neural substrate for a variety of motor and cognitive programs. The main nuclei of the BG are the Striatum, the Globus Pallidus externus and internus (GPi, GPe), the Subthalamic Nucleus (STN) and the Substantia Nigra pars compacta and pars reticulata (SNpc, SNpr). These nuclei are embedded in a system which includes the thalamus and the cerebral cortex. The largest among these nuclei are the Striatum and the Globus pallidus.

The Direct/Indirect model of BG function, here referred to as classical model or D/I model. Simply put, this model states that two segregated information processing pathways, termed direct and indirect, coexist in the BG where each drive the facilitation or inhibition of movement in an opposing manner. Both pathways originate from one of two distinct types of Medium Spiny Neurons (MSNs), identifiable

through their target structure and proteome. MSNs that innervate the output nuclei and express type 1 Dopamine receptors (D1R) belong to the direct pathway and are referred to as D1-MSNs. MSNs that innervate the GPe and express type 2 Dopamine receptors (D2R) belong to the indirect pathway and are referred to as D2-MSNs.

Dopamine (DA) is synthesised from its precursor L-DOPA and acts as a hormone and neurotransmitter. Several neuronal pathways are dedicated to the transmission of dopaminergic signals, which have widespread role in motivation and reward associated behaviour, as well as movement. Dopamine is especially relevant in BG function due to the high density of DA receptors in the Striatum and the dopaminergic nucleus found in the SNpc.

Action selection in biological systems refers to the choice of performing one action over another. Evolutionary pressures have developed organisms with mechanisms that solve the action selection problem by receiving environmental and internal input, and selecting the optimal action for the survival of the organism.

Neuroanatomy of Basal Ganglia Pathways and Direct/Indirect Model

Input, Output and Pathways of the Basal Ganglia

The striatum acts as the primary input receiver of the BG and houses mainly GABAergic projection cells that target the GPe and the output nuclei of the BG, GPi and SNpr. Striatal projection neurons to SNpr and GPi exhibit numerous collaterals, as many as half target the GPe (10, 11). Conversely, striatum to GPe projections are more consistently direct (12). The Globus pallidus is located medial to the Striatum, and its distinct parts, GPe and GPi, respectively target the STN and the Thalamus with GABAergic projections. The STN sits beneath the Thalamus and consists mainly of excitatory glutamatergic neurons which target the GPi and the SNpr. The SNpc receives most of its input from the Striatum and targets the same structure with numerous dopaminergic projections. Figure 1 shows a schematic of BG neuroanatomy. Before proceeding it is important to note the characteristics of striatal input and BG output.

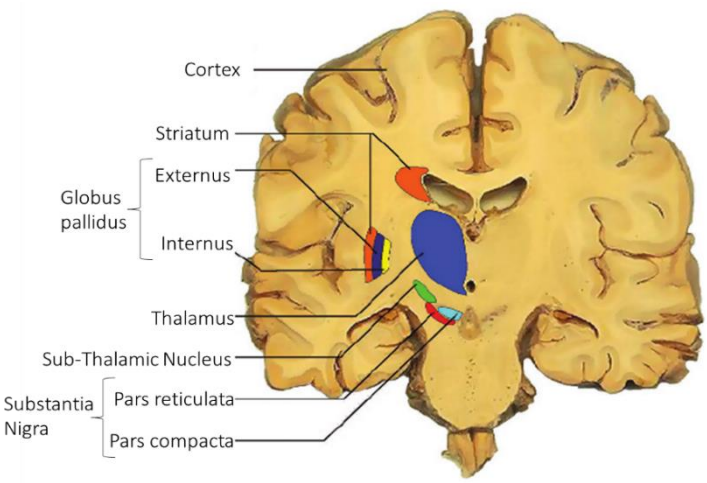

Figure 1 (Adapted from Pereira et al, 2006)(1): Coronal section of the brain. Coloured BG nuclei and thalamus.

The Striatum receives both cortical and thalamic input in the form of somatotopically organised divergent and convergent glutamatergic projections (13-15). Cortical projections exhibit divergence as a projection from a single cortical area can target several striatal zones. Additionally, convergence onto the same striatal zone was observed from several areas of the cortex carrying motor and sensory input from the same body part (16). This organization suggests that the basal ganglia act as an integrator of both sensory stimuli, which are processed in the Thalamus, and voluntary movement triggers, which originate in the motor cortex. The output nuclei (GPi/SNpr) operate through inhibitory GABAergic projection neurons and maintain tonic inhibition on their targets. These targets are the Thalamus, the Cortex and brainstem motor nuclei. The purpose of the output nuclei is to control downstream activity by momentarily withdrawing their inhibitory action, thus allowing movement to occur.

An influential early model of BG function proposed the existence of segregated groups of functionally distinct circuits, each circuit representing a motor program (17). This concept inspired the long-lived Direct/Indirect model of BG function.

Direct/Indirect Model of Basal Ganglia Function

Even though they have different outputs and protein expression profile, D1 and D2-MSNs do not receive a significantly different input. Using BAC transgenic mice and a combination of in vivo labelling and 3D reconstruction, Huerta-Ocampo (18) found that individual D1/D2-MSNs receive convergent input from cortex and thalamus. Shuen et al (3), used Drd1a-tdTomato BAC transgenic mice to simultaneously visualise both types of MSNs. Figure 2 shows the heterogeneous distribution of D1/D2-MSNs in the Striatum. Apart from receiving glutamatergic cortical and thalamic input, MSNs synapse with numerous dopaminergic terminals originating from the Substantia Nigra pars compacta. Axons from the SNpc exhibit vast arborization within the Striatum and very little or none outside of it (19). Dopaminergic neurons in the SNpc contain an endogenous calcium-dependent oscillatory mechanism which allows them to fire in a highly regular pacemaker-like manner in the absence of input (Fig 3a). In the presence of afferent activity, the SNpc exhibits different firing patterns which can be random, or stimulus related as shown by Figure 3 b and c(2). The SNpc is a key element of the D/I model as its dopaminergic output directly influences D1/D2-MSNs triggering activity in either pathway.

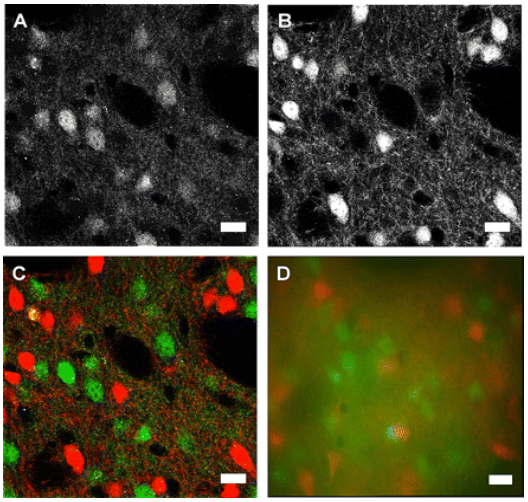

Figure 2 (Adapted from Shuen et al 2008,)(3): Confocal microscope image of *Drd1a*-tdTomato^{tg}/*Drd2*-EGFP^{tg} mice striatum. **A-C** 50µm brain slices showing (A) EGFP (B)

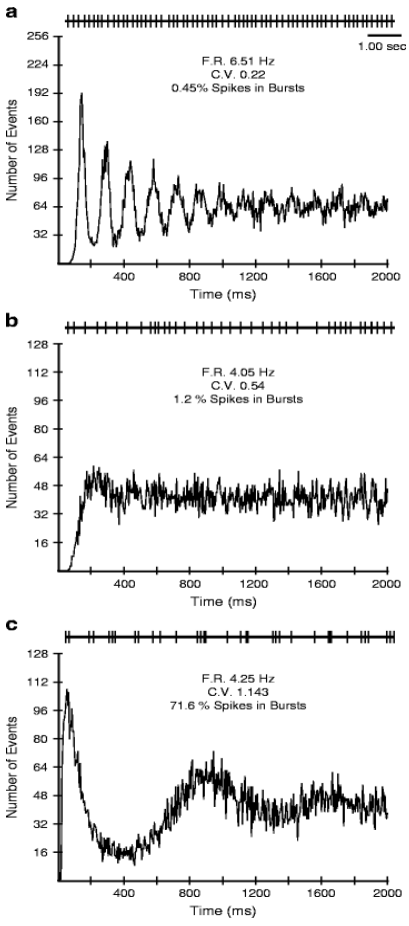

Figure 3 (Adapted from Lee and tepper 2009)(2): Correlograms of SNpc neurons exhibiting 3 distinct firing modes **(a)**Tonic, **(b)**Random, and **(c)** Bursty. The spike-trains above each chart were used to generate the correlogram.

The direct pathway is activated at stimulation of D1-MSNs, which target the BG output nuclei with GABAergic projections. Ensuing inhibition of GPi/SNpr releases thalamic inhibition, consequently increasing thalamocortical activity, which facilitates movement execution.

The indirect pathway is triggered by stimulation of D2-MSNs which target the GPe with inhibitory GABAergic projections. The GPe then releases its inhibition on the STN which sends

excitatory glutamatergic projections to the output nuclei. Increased inhibitory activity of the output nuclei decreases activity in both thalamus and brainstem motor areas, thus suppressing movement. Figure 4 shows a schematic representation of direct and indirect pathways.

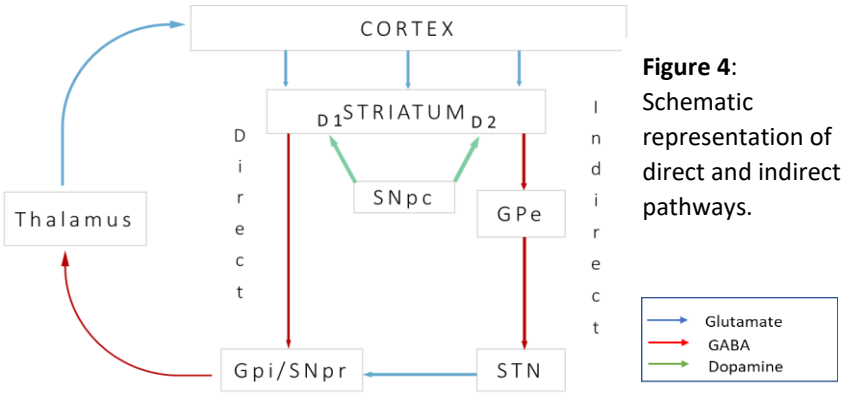

Figure 4: Schematic representation of direct and indirect pathways.

Along with the Direct and Indirect pathways, many studies include the hyperdirect pathway (HD) in their considerations of BG function. The HD pathway runs from the motor cortex to the STN, bypassing the Striatum with excitatory glutamatergic projections. This pathway has been proposed as the main circuit through which motor programs are suppressed, due to its targeting of the STN and its higher conduction velocity. The STN targets the output nuclei with excitatory glutamatergic projections thus increasing their inhibitory activity. Hyperdirect pathway activity is potentially derivative of direct pathway activity as D1-MSNs stimulation cause increased cortical activity.

The differential expression of Dopamine receptors on MSNs is central to the model as it allows for highly flexible modulatory input from the SNpc. D1 and D2 receptors differ amongst other things, in the G-protein to which they are coupled. Gs-alpha, a subunit of the D1R, activates adenylyl cyclase and increases cAMP concentration and PKA activity. Gi-alpha is a subunit of the D2R, this subunit inhibits adenylyl cyclase promoting a decrease in cAMP production and PKA activity. Both cAMP and PKA are signalling molecules which modulate neuronal excitability (20). Some co-expression of Dopamine receptors has been observed, but the experimental results are dependent on the sensitivity of the method used. Methods with relatively high detection threshold show a high degree of receptor segregation which concurs with the difference in projection targets. More sensitive and often non-linear detection methods allow researchers to observe co-expression of D1 and D2 receptors although unaccompanied by functional significance (21).

Evidence for Direct/Indirect Model

Evidence for the classical direct indirect pathway model has slowly accumulated, thereby increasing the solidity of the model. Optogenetics has allowed researchers to obtain the most conclusive and up to date evidence yet by making it possible to accurately target and stimulate genetically specified neuronal ensembles (22). Kravitz et al, (6) reported a contrasting effect upon the bilateral excitation of D1/D2-MSNs. Stimulation of D1-MSNs increased ambulatory behaviour and fine movement velocity while stimulation of D2-MSNs increased freezing behaviour and decreased

initiation of movement. Figure 5 charts the locomotor behaviour of a mouse in either condition and provides additional data.

In 2013, Freeze et al, (23) carried out a similar experiment with the addition of single unit recordings of the SNpr. The researchers confirmed the behavioural effect of differential D1/D2-MSN stimulation (6). Additionally, the study showed that direct pathway activation, through stimulation of D1-MSNs, inhibits a subset of SNpr neurons, whereas indirect pathway activation resulted in excitation of a different subset of SNpr neurons. These results match the hypothesised role of the SNpr as the brake for downstream pathways, allowing movement when inhibited by direct pathway activation and suppressing it when excited by indirect pathway activation.

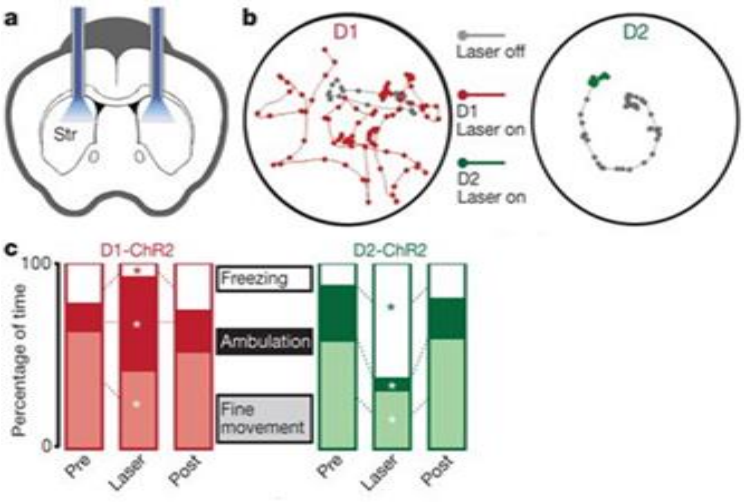

Figure 5 (Adapted from Kravitz et al, 2010)(6): **(a)**schematic of optrode placement for bilateral stimulation, **(b)** Mouse locomotor behaviour during striatal stimulation through D1-Chr2 (left) and D2-ChR2 (right). Dots represent mouse position every 300ms for 20s before (grey) and during (coloured) stimulation. **(c)**Mice motor activity before during and after striatal stimulation through D1-ChR2 (left) and D2-ChR2 (right).

In a third study of similar nature, Lee et al, (7) looked at the brain wide effects of direct and indirect pathway stimulation by combining the previously mentioned methods with fMRI. Targeted stimulations of D1/D2-MSNs in the Striatum resulted in the generation of BOLD signals in several nuclei of the BG as well as Thalamus and Cortex. The polarities of most of these signals were in agreement with the predicted values derived from the classical model. Activation of D1-MSNs resulted in extensive fMRI BOLD signal increase across the brain whereas activation of D2-MSNs caused a decrease in activity. Single unit recordings in Striatum and Thalamus confirmed the accuracy of the fMRI signals and the behavioural effect observed matched that of previous experiments (6, 23). Figure 6 shows the effects of D1 and D2 stimulation as an fMRI time series. In the figure we can see the generalised increase in activity from D1 and decrease from D2 stimulation. Interestingly, the STN, which is in principle uninvolved in the direct pathway, displays a positive signal after D1 stimulation and a negative signal after D2 stimulation. Additionally,

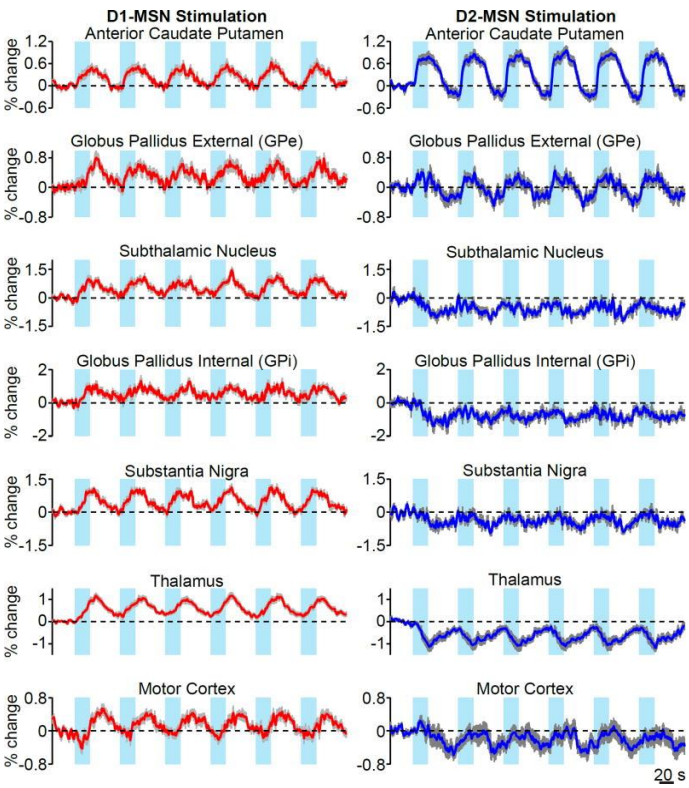

Figure 6 (Adapted from Lee et al, 2016)(7): Average BOLD signal of active voxels in the ipsilateral basal ganglia-thalamocortical loop of 11 D1 and 12 D2-Cre animals. Values expressed as the percentage change in signal compared to 30s before stimulation. Error bars shown by grey shading.

the expected decrease and increase in GABAergic output from the GPi was not observed and in its place was a positive response to D1-MSN stimulation and negative response to D2-MSN stimulation. These data were unexpected and ran contrary to the D/I model. Lee et al, (7) suggested that these results could be explained through activity of the HD pathway.

This review has examined the strongest evidence accounting for the solidity of the Direct/Indirect model. Although not perfect, this model serves as a good guide for understanding BG circuitry and function at a basic level. The Striatum, which houses the cells from which the direct and indirect pathway originate is a key structure in the model. Also essential is the role of the structure innervating MSNs with numerous dopaminergic projections, the SNpc. Common between these two elements is the need for dopamine to function correctly.

Contrasting Evidence

The classical model has recently been subject to criticism and a general consensus has been reached regarding its adequacy and accuracy. While the model is adequate to superficially investigate the origin of some motor disorders it is certainly not the most accurate model from which to build a complete understanding of normal BG function. The evidence delineated below emerged from different lines of study to downgrade the status of the Direct indirect model.

Concurrent Activity

In a study by Cui et al, (5), a genetically encoded calcium indicator (GCaMP3) was used to detect activity in D1/D2-MSNs as trained mice performed behavioural tasks. The behaviour of the performing mice was labelled as “active” when the mice engaged in lever pressing or checked the food dispenser. The label “inactive” was applied when the mice were not exhibiting any engaging behaviour. The research team found that activity of both D1/D2-MSNs increased during “active” states

and decreased during “inactive” states. Further examination of the behaviour in relation to the observed calcium transients was carried out by singling out individual actions. Depending on the speed, acceleration, direction or motivational state behind the movement, different degrees of MSN activity can be observed (24). Actions were grouped for analysis in base of direction of movement. Recording of left striatal neurons revealed activation of both D1/D2-MSNs as the mouse executed a rightward movement. The researchers propose that self-paced contra-lateral movement initiation is associated with concurrent activation of both direct and indirect pathways. Figure 7 visualises the findings.

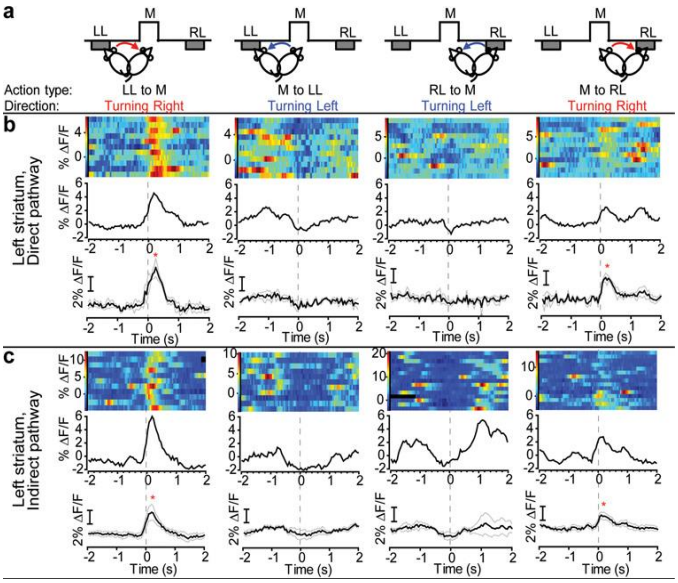

Figure 7 (Adapted from Cui et al, 2013)(5): (**a**) different movements included in analysis in **b** and **c**. Left lever (LL) to magazine (M) conveys a right turn. The heatmaps in (**b**-**c**) show GCAMP3 fluorescence in direct (**b**) and indirect (**c**) MSNs recorded in left striatum and aligned to initiation of actions in **a.**

If, as per the classical model, direct and indirect pathways have opposite effects on movement, “active” states should be accompanied by a direct pathway increase and “inactive” states by an indirect pathway increase. The results of this experiment are at odds with the classical model and clearly indicate a much more complex relationship between pathways than the model hypothesises. Additional evidence of concurrent activation comes from the previously mentioned Freeze et al study (23). This study found supporting evidence for the classical model. However, it also found that both D1 and D2-MSN activation have a dual excitatory and inhibitory effect on different groups of neurons in the SNpr. In other words, activation of the direct pathway had downstream effects on the SNpr that mimicked concurrent direct and indirect pathway stimulation.

Firing Rate Perspective

In 1926, Adrian and Zotterman (25) recorded the number of action potentials (Aps) triggered in sensory nerves as an increasingly heavier weight was attached to them. As the weight increased so did the number of recorded APs. This led the researchers to believe that it was the frequency of events and not their magnitude that encoded information about the stimulus. Measuring firing-rates as in the aforementioned experiment became the accepted method of abstracting information coding properties from neuronal activity.

The classical model of basal ganglia functions as a firing rate model by focusing primarily on the average firing of neurons involved in the different pathways and output nuclei (26). For example, explaining the akinetic symptoms of Parkinsons Disease (PD) could be done as follows. Loss of DA input to Striatum from SNpc leads to an increase in firing rate (hyperactivity) of the GABAergic output nuclei. Their inhibitory effect causes decreased activity in thalamus, motor cortex and downstream targets, which behaviourally translates into hypokinetic symptoms. This model was initially used to explain the beneficial effects of Deep Brain Stimulation (DBS). DBS was hypothesised to work by inhibiting activity the STN and therefore restoring normal firing rates to the BG, much like the effect of a GABA agonist (27) or a targeted lesion (28). However, further research indicated that DBS was not decreasing but increasing STN activity immediately after stimulation. This paradoxical finding still puzzles researchers and a variety of explanations have emerged. These can be classified into local and systemic, with local explanations involving proposed neuroprotective properties of the stimulation (29) and systemic ones involving the suppression of patterned oscillations (4, 30). The evidence obtained through DBS has had such profound changes on our outlook of the BG system that a recent review suggests a name change from DBS to Deep Brain Neuromodulation (31).

The rate-model disregards the information contained in the exact timing of the APs or spikes, therefore although clearly fruitful, it is too simplistic. Indeed, in additional non-DBS studies researchers have been unable to observe the expected GPi hyperactivity in Parkinsonian mice (32).

Basal Ganglia and the Function of Neural Oscillations

The influence of BG dysfunction in movement disorders has been in long-standing agreement (33), though the contrasting mechanisms of information processing in health and disease have been object of much more recent debate. In 1998, Bergman et al, (9) set out to ascertain whether a difference in correlated activity could be observed in the output nuclei of the BG of healthy versus parkinsonian monkeys. The study found that firing of neurons in the output nuclei of healthy monkeys was random and highly uncorrelated (Figure 8A), this was not the case with parkinsonian monkeys. After MPTP treatment and Dopamine depletion, the firing of pallidal neurons became highly correlated (Figure 8B). The authors suggest that DA acts to decorrelate the network

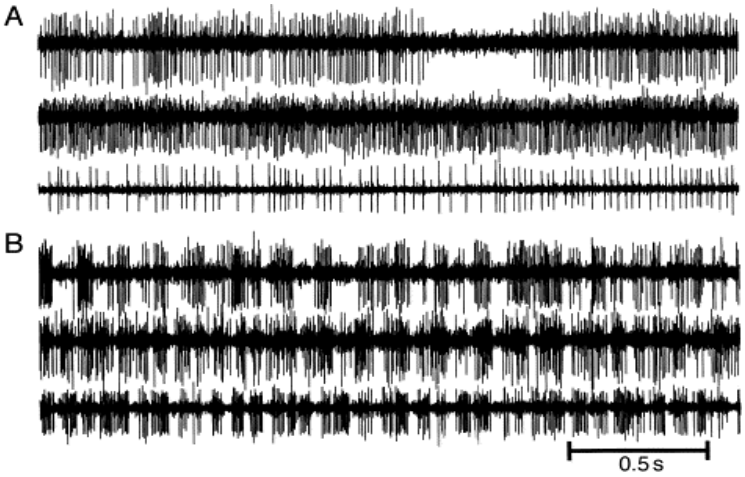

Figure 8 (Adapted from Bergman, 1998)(9): Multi-electrode Globus pallidus recording from **(A)** normal and **(B)** parkinsonian monkey.

by maintaining the segregation of functional circuits in the BG. Furthermore, the authors correctly predicted that such synchronous activity would be observable in human PD patients.

Supporting evidence has accumulated and it is certain now that the BG and cortex of PD patients exhibit an abnormal degree of synchronization at multiple levels of cortico-basal circuits, particularly in the beta frequency (34). This pathological exacerbation of beta frequency is reduced with dopaminergic treatments and Deep Brain Stimulation (DBS), which are uncoincidentally used to ameliorate parkinsonian symptoms such as bradykinesia and rigidity (35-37).

Efforts to further characterise the role of beta frequencies in functional and dysfunctional brains have yielded significant results. Beta oscillations have been detected in a variety of structures in awake and healthy animals including non-human primate sensorimotor cortex (38), and human, non-human primate and rat striatum (39-41). Put in motor context, cortical beta power increases both during freezing and at voluntary arrest of movement initiation (42, 43). A review of the literature lead Engel and Fries (44) to assert the "maintenance of the status quo" as the role of beta oscillations. Although this concept seems in agreement with the emergence of beta waves in PD, their role in the BG is yet to be well characterised. This is because most studies of beta oscillations within BG did not focus on examining natural correlates of beta power emergence and instead used irreversibly dopamine-deficient, anesthetised and disengaged subjects.

Leventhal et al, (4) attempted to characterise the correlates of beta oscillations in the BG by comparing recorded neural activity of rats performing four variations of a behavioural task (Table 1). Throughout the whole study the recording tetrodes captured localised, single and simultaneous surges of beta-activity demonstrating their ubiquitous nature in healthy freely-behaving rats. The study focused on the effect of auditory cues in the emergence of beta Event Related Synchronization (ERS). In order to illustrate this, I will use the results from the STOP-signal task. Like the other tasks, the STOP-signal starts by instructing the rat to place its nose in a porthole via an optical cue. Then, an auditory cue instructs the rat to move and a following one instructs it to stop. In this paradigm, the first cue is a 1 or 4kHz tone meaning left or right shift respectively and the second cue consisted of white noise. The distance between cues was adjusted so that rats succeeded in about half of the trials. Figure 9A shows a comparison between the events in both success and failure trials. Figure 9B shows the emergence of beta-ERS in success and failure trials in the STOP-signal task through a Gabor spectrogram. Interestingly, the second beta-ERS was only

Task	*Instruction*
Immediate-Go	Quickly make a specific movement
Deferred-Go	Delay movement execution until cue
GO/NOGO	Inhibit movement
STOP-Signal	Cancel planned movements

Table 1 (From Leventhal et al, 2012) (4)

observed if the trial was a successful one, in other words, if the cue led to behavioural output and was subsequently utilised. This result also confirmed that the mere exposition to a cue does not suffice to induce beta-ERS. Taking these results together the researchers concluded that beta-ERS could not be related to sensory or motor processing but rather that beta oscillations play a role in sensorimotor integration.

The above evidence clearly suggests an important role for neural oscillations both at the physiological BG level and at the Action Selection level. If oscillations, particularly those at the beta frequency, are indeed essential, the modulatory mechanism behind them must have an equally important role. This modulatory mechanism is bound to consist of a variety of signals, for the purpose of this review I will focus on the influence of the DA/DAR signalling system.

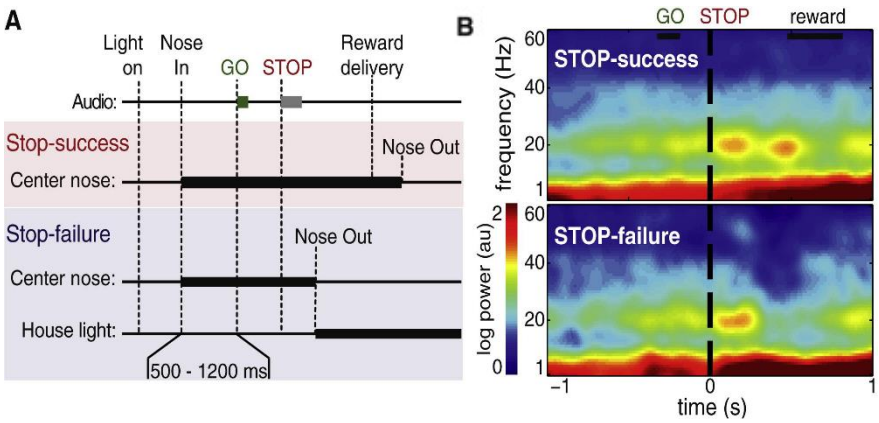

Figure 9 (Adapted from Leventhal et al, 2012)(4): **(A)** Event chart of successful and unsuccessful GO/STOP task trials. **(B)** Mean Gabor spectrograms from one GP tetrode in one rat throughout 12 sessions, compares successful (top) and unsuccessful (bottom) trials. Vertical line represents the white-noise stop signal and black bars the time ranges of Go-cue and reward delivery.

Dopamine and Neural Oscillations

In 2006, Costa et al, (45) set out to investigate whether sudden changes in DA levels caused changes in the oscillatory activity of neuronal populations in corticostriatal circuits. The researchers recorded single and ensemble activity from neurons in the dorsolateral striatum and the motor cortex during conditions of hyperdopaminergia and extreme DA depletion. Both conditions were achieved in the same animal through pharmacogenetic methods. These methods consisted of dopamine transporter gene Knock-Out (DAT-KO) and delivery of either AMPT or LevoDopa/CarbiDopa (LD/CD). In order to trigger hyperdopaminergia the rats were placed in a novel environment, to achieve dopamine depletion the rats were administered AMPT. Recovery from the DA depleted state was achieved through delivery of LD/CD. In agreement with the literature, hyperdopaminergia co-occurred with hyperkinesia whereas DA depletion was accompanied by akinetic behaviour. Cortex recordings during state-transition (hyperdopaminergia to DA depletion and recovery) revealed that overall cortical activity remained the same throughout. Conversely, striatal population firing rate decreased after delivery of AMPT. This first finding indicates that PD and other DA related disorders may not originate from alterations in overall cortical activity. Simultaneous recording of neuronal populations in cortex

and striatum allowed the researchers to investigate the synchronous and oscillatory activity of corticostriatal circuits. Transition between DA states was found to cause a rapid alteration in the oscillatory profile of these circuits. Local Field Potentials (LFPs) of each population were obtained showing an increase in theta and gamma frequencies during hyperdopaminergia and an increase in delta and beta frequencies during DA depletion. Additionally, hyperdopaminergia seemed to facilitate asynchronous activity while dopamine depletion promoted synchronicity between cortical and striatal ensembles.

The researchers finally suggest that pathological states are promoted by sudden alterations in the synchronicity of corticostriatal networks. These sudden alterations leading to excessive or insufficient synchronicity are parallel with rapid alteration of DA states. Dopamine is therefore suggested as a modulator of current activity in corticostriatal circuits.

Dopamine and Action Selection

Howard et al, (46) investigated the effects on DA levels in mice striatum as they performed an operant behaviour task. The various paradigms required the animal subjects to switch from a selected action to another based on internal cues. The experiment was designed such that the internal cue that promoted the switch was the animal's internal monitoring of the passage of time. Trials were initiated by the retraction of two levers placed side by side in an operant chamber, after an interval of either 2 or 8 seconds the levers extended. A reward was provided after selection of left or right lever in 2 or 8 second trials respectively. After training, the mice were tested using intermediate time intervals. Animals were prone to choose the short duration lever when the interval fell under 4s and the long duration lever when the interval duration was over 4s. Striatal DA levels in the 2 or 8s paradigm increased at the start of the trial followed by a gradual decline. While DA concentration remained elevated, the mouse favoured the early left lever, this preference gradually fell off as DA concentration decreased. This suggests that shifts in DA concentration are linked with action selection. Indeed, the researchers were able to predict with above chance accuracy, the outcome of individual trials by examining the DA profile in the Striatum.

After recording DA levels in un-modified conditions, the researchers used a combination of genetic and optogenetic methods consisting in the expression of photo-sensitive ChannelRhodopsin2 (ChR2) in nigrostriatal dopaminergic neurons and their subsequent optogenetic stimulation (47). This stimulation consistently raised DA levels in striatum and, as in the un-modified condition, the profile of these changes was recorded during task-performance. Three different paradigms were used to assess the effect of modified striatal dopamine concentration. First, extension of levers 1 s after stimulation which occurred at 1, 3 or 7s after trial onset. Second, extension of levers 8s after trial onset with stimulation occurring at different time points in the interval (0 – 7 s). Third, archaerhodopsin was

inserted instead of ChR2 to inhibit dopamine activity promptly after trial onset. The first and second experiment showed that stimulation biased choice towards the early lever choice. In the first experiment, lever extension at 4 s, taken to represent maximum uncertainty, resulted in the strongest early lever choice bias. This finding supports the concept that better learned actions, analogous with conditions of higher certainty, are less dependent on dopaminergic input (48). The third experiment showed an increase in late-lever choice after a decrease in striatal DA activity. These results taken together suggest that bidirectional modification of behavioural output and influence on the action-selection process of the animal subject can be achieved through modulation of nigrostriatal dopaminergic activity. Furthermore, the authors posit that the artificial modulation present in their experiment can be accounted for by the tuning of basal ganglia output via the action of D1/D2-MSNs.

In 2017, Ueda et al, (8) sought to characterise the potential role of direct and indirect pathways in flexible and stable action selection strategies. To do this, the researchers injected either D1 or D2 antagonists into the putamen of macaque monkeys and observed changes in their adaptive behaviour. The behaviour consisted of a "free choice task for probabilistic reward". Turning a handle left or right provided the monkeys with an increased or decreased chance to obtain a large reward, the reward-associated side changed over the course of 30-150 trials requiring the monkeys to learn the higher value choice through outcome-history. Occasionally, the same direction that would yield a high reward returned a smaller reward. In the control condition, the monkeys consistently learned to choose the higher value side and kept choosing the same side despite occasionally receiving a smaller reward. However, after receiving two or three small rewards from the high value side, the monkeys changed their selection strategy and switched side.

The injection of D1 and D2 antagonists served the purpose of disrupting the adaptive effects contributed by the direct and indirect pathways respectively.

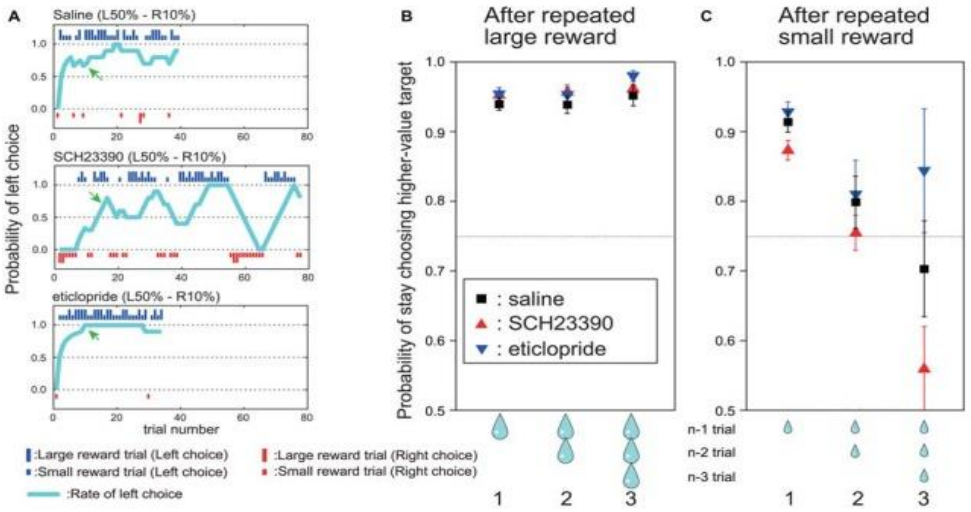

Figure 10 (Adapted from Ueda et al, 2017)(8): **(A)** probability of left or right choice after saline (top), SCH23390 (middle), and eticlopride (bottom) injection. (**B)** Mean probability of continuing to choose the higher-value target after successive trials with large reward. (**C)** Mean probability of continuing to choose higher-value target after successive small reward trials. SEM given by vertical bars.

Figure 10 maps the effects of the injections in the monkeys' selection strategy. As we can see in 10B, the probability of continuing to make the high value choice after repeatedly obtaining the large reward remains relatively unchanged regardless of condition (with or without antagonist). In 10C however, we can observe that the probability of continuing to make the high value choice is significantly affected by antagonist injection. The black square representing the control condition marks how the tendency to switch side naturally increases after two and then further after three consecutive small rewards. Injection of the D1 antagonist results in a higher than control probability to switch side in any trial number, reaching almost 50% after the third consecutive small reward. Contrarily, injection of D2 antagonist biases the monkey to continue making the higher value choice and to forego a change in action selection strategy, even after successive smaller rewards. The results obtained indicate a differential and complementary function of D1 and D2 receptor signalling in action-selection strategies. The direct-D1R related pathway seemingly encourages a stable action-selection strategy targeting highly rewarded choices while the indirect-D2R related pathway advances strategy switching when faced with smaller rewards.

Discussion

The aim of this section will be to integrate the knowledge examined beforehand into a coherent guideline for the creation of a more accurate and comprehensive model of BG function. An emphasis will be placed on the role of Dopamine as the proposed key regulatory component of the system.

Pattern Model

The firing rate approach to decoding the information behind action potentials has been used in adherence with the D/I model. The model benefitted from this approach since its inception as it was partially built on the assumption of rate-coding. Together, rate-coding and the D/I model have emboldened researchers to dig deeper into the causes of motor disorders focussed around the BG, with considerable success. Several hypotheses with highly beneficial consequences were ideated and even led to the creation of effective pharmacological and surgical symptomatic remedies to notoriously complex and harmful diseases. These new treatments prompted the surfacing of evidence that put in doubt some of the assumptions from which the research had been initiated. Specifically, evidence from DBS and pallidotomies, which still worked as treatments, indicated that perhaps rate-coding was not the tell-all measure for BG function. As with other medical procedures like general anaesthesia, these treatments are still used and safe, but it is not entirely clear how they work. Due to the demonstrated inaccuracy of a rate-coding approach, I believe a novel model of BG function should be pattern-based.

Opposed to a firing rate model, a pattern model focuses on the exact timing and sequence of APs and acknowledges the potential information encoded in their temporal distribution. Within a pattern model, neural activity can be described using mathematical concepts like sinusoidal waves. With terms such as frequency and amplitude, the behaviour of a single neuron as well as a population of neurons can be reliably mapped through a Fourier transform. The view of neuronal activity as this aggregation of oscillating entities leads to the recognition of the brain as a Non-linear dynamical system. A system of these characteristics is able to generate fast and adaptive responses to theoretically infinitely variable input. It is perhaps easier to see now why the accuracy of the BG model would increase by describing it in such a way. I have examined research that takes this perspective on BG function in the section on neural oscillations. This approach is primarily focused on the patterned oscillations emerging from neuronal activity of individuals with motor disorders such as PD. The interrelatedness of several motor disorders and DA is undeniable, for this reason I believe future research should focus on the role of DA in the oscillatory behaviour of neuronal populations in the BG.

Admittedly, a firing-pattern-type model would not appear as an immediate and total problem solver. For example, this model runs into at least one major issue if it is to fully explain parkinsonian symptoms through neural oscillations. This issue is the apparent non-causal relationship between the rise of rhythmic oscillations and parkinsonian symptoms. Oscillatory activity appears only after DA depletion and induction of parkinsonian symptoms by MPTP. The fact that oscillatory activity does not precede the symptoms suggests that the effect of increased beta frequency is not that of DA depletion (49).

Recognising the observed phenomena that cannot yet be explained is the first step to orient effective research. A pattern-based model will initially appear more complex, but an investment in complexity will return increased accuracy and stronger explanatory power.

Pathway Integration

The D/I model was in its initial stages a competitive model featuring two pathways with opposing roles. This accelerator/brake metaphor persisted and has guided research until quite recently. Investigating the direct and indirect pathways as separate entities is still valid and useful, as the pathways are in fact segregated to a significant degree (Figure 2). However, this rigid dichotomy has limited the scope of research and has given priority to a competitive perspective over a collaborative one. Reports of concurrent activity have sparked the debate and have opened the floor to new interpretations of the pathways as one collaborative unit.

The D/I model is relatively simple in the description of inter-nuclei connections in the BG. There is no attempt at identifying the points at which crosstalk between pathways occurs, and this is surprising given that it is agreed that some level of communication must occur. If the pathways were completely segregated the system would be simpler and easier to characterise as the input into one pathway

would consistently result in same pathway output. In the current model, the pathways are being represented as being in the open but truly they are inside a metaphorical black box, operating in a way we cannot discern.

The investigation of the mechanisms through which D1/D2-MSNs pathway integration occurs should be two-pronged. Focusing on the potential points where crosstalk is possible and on the minor connections that had been left out of the classical model.

Calabresi et al, (50) review several points of potential crosstalk, these include heteromers of DA receptors, the endocannabinoid system and striatal interneurons. The minor connections include axonal collateralisation exhibited by BG structures (10, 51), the heterogeneity of input into MSNs (52) and the influence of other established pathways such as the HD pathway.

Learning of Action Units and Selection Strategy.

The number of actions we can perform is limited by our physical attributes, and while some athletic feats defy the imagination, no one can turn right and left simultaneously. Encoding all the potential actions one-to-one is impossible and would require infinite space and processing power, not to mention the difficulty of implementing them. It is likely then, that the range of possible actions are compartmentalised in a hierarchical manner. This organisation is not infused into the BG and must be learned. In other words, there must be plastic changes that allow actions to group together from distinct to joint activation patterns. Graybiel describes the grouping of activity patterns as chunking and states that it is a gradual process that occurs parallel to the learning of new action sequences (53). This notion has implications in both motor and cognitive control as patterns coding for either can be subject to this re-grouping.

The D/I model of BG function is a guide to the mechanism that facilitates or inhibits movement, this guide does not deal with the specific activation patterns resulting in specific actions. While at face-value it appears a challenging task, I believe that it would be possible to utilise this proposed hierarchical organisation of action units to determine with more accuracy the role of distinct neuronal populations. An approach of this kind was taken by Hikosaka et al, to show direct BG influence on saccadic movement (54).

As mentioned above, the D/I model is primarily focussed on movement, yet the aforementioned research would not have been possible unless the BG also influenced action selection through the implementation of strategies. Previously, this review has examined evidence showing the distinct influence of DA activity in the behaviour of primates and mice. This role in the determination of behaviour is closely linked to action selection and decision-making and I believe should be integrated into any new model. However, this raises the issue of maintaining the antagonistic role of distinct DAR

activation and the necessity of simultaneous activation for the implementation of action selection strategy.

Conclusion

In the D/I model, the direct and indirect pathways are the mechanisms through which facilitation and inhibition of movement respectively occur. The discovery of simultaneous activity challenges the notion that the role of the pathways is merely that of facilitation or inhibition of action. An action cannot be facilitated and inhibited at the same time as it would result in no-action implemented. To reconcile the existence of two separate and functionally distinct pathways with concurrent activity, we must accept that direct and indirect pathway activity operate in a collaborative manner. During any action sequence, some programs must be facilitated while others must remain inhibited, to achieve this, both pathways must communicate and update their activation profile. As we have seen in relation to chunking, it is highly unlikely that each single action we perform is processed by the BG. Grouping of action-units serves to reduce the processing power expenditure and gradually create semi-rigid hierarchies of re-usable and useful action-sequences. The coding of these sequences is another contentious item. While the classical model operated through a firing-rate approach, a pattern-based model is likely to provide stronger explanatory power, and might improve translatability to additional neuronal systems outside the BG.

Concurrent activity and its associated integratory mechanisms, the specific role of neural oscillations as well as the role of DA in the generation of oscillatory patterns, and the behavioural influence of BG activity all should be explored methodically as has been done until now. Departing from the assumptions of firing-rate and purely competitive pathways will enable the community to build a model with the potential to keep improving treatment of widespread disorders.

Finally, it would be interesting to attempt to place the new model under the wing of a whole-brain theory such as the Free-Energy principle (55).

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Due to action of the formatting software, the references inserted into textboxes were given overall priority resulting in their placement as the first nine in the reference list.

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