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CHAPTER 14

Neurocomputational models of motor and cognitive deficits in Parkinson's disease

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Abstract: We review the contributions of biologically constrained computational models to our understanding of motor and cognitive deficits in Parkinson's disease (PD). The loss of dopaminergic neurons innervating the striatum in PD, and the well-established role of dopamine (DA) in reinforcement learning (RL), enable neural network models of the basal ganglia (BG) to derive concrete and testable predictions. We focus in this review on one simple underlying principle – the notion that reduced DA increases activity and causes long-term potentiation in the indirect pathway of the BG. We show how this theory can provide a unified account of diverse and seemingly unrelated phenomena in PD including progressive motor degeneration as well as cognitive deficits in RL, decision making and working memory. DA replacement therapy and deep brain stimulation can alleviate some aspects of these impairments, but can actually introduce negative effects such as motor dyskinesias and cognitive impulsivity. We discuss these treatment effects in terms of modulation of specific mechanisms within the computational framework. In addition, we review neurocomputational interpretations of increased impulsivity in the face of response conflict in patients with deep-brain-stimulation.

Keywords: Parkinson's Disease; Dopamine; Basal Ganglia; Computational Model; Cognition

Introduction

Early onset of Parkinson's disease (PD) is characterized by loss of dopaminergic neurons innervating the striatum in the basal ganglia (BG) (Kish et al., 1988). The symptomatology is most prominent in the motor domain and progressively manifests itself as bradykinesia, akinesia and tremor. More recently, however, cognitive and learning deficits have received increased recognition and interest (e.g. Cools, 2005; Cunha et al., 2009; Frank, 2005; Grahn et al., 2009; Moustafa et al., 2008b). Although traditionally cognitive deficits are often interpreted as resulting from decline in prefrontal cortical function, these reviews have highlighted a more central role for the BG in cognitive function.

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From a computational and cognitive neuroscience point of view, PD is a highly intriguing disorder. Because PD results in depleted striatal dopamine (DA) levels, but increased striatal DA levels following DA medication (Pavese et al., 2006; Tedroff et al., 1996), researchers can directly test the influence of different BG DA configurations in human subjects. Further, in early disease stages, cognitive deficits in PD are linked to depleted striatal DA levels, with frontal DA levels spared (Nobukatsu et al., 2008). Similarly, cognitive deficits in healthy ageing are correlated with striatal DA depletion rather than frontal DA (Bckman et al., 2000, 2006; Kaasinen and Rinne, 2002). Better understanding of this system will ultimately lead to better treatment options for PD, but also to other diseases involving DA in the BG such as addiction, schizophrenia and Tourette's syndrome (TS).

The BG consists of multiple interconnected nuclei (Mink, 1996) that are part of several complex anatomical/functional loops (Gerfen and Wilson, 1996; Graybiel et al., 1994; Haber, 2004; Haber et al., 2000; Nakano et al., 2000). The inherent complexity of this dynamic system, the role of learning and the existence of feedback loops often let classic box-and-arrow diagrams fall short in their predictive capabilities. Moreover, data about the BG (and PD) are contributed from across different domains reaching from psychology to cellular neurobiology. Although not without caveats, biologically constrained computational models offer a disciplined approach to (1) integrate data from different domains and (2) derive novel and unintuitive predictions which can then be tested experimentally to possibly refine the model. These models are inherently dynamic and are governed by concrete activation and learning rules.

One example of where these models furthered our understanding was to reject the notion that under chronic DA depletion most synaptic plasticity in the striatum would be lost (Calabresi et al., 2007b; Kreitzer and Malenka, 2007). The computational model by Frank (2005) challenges this assumption by hypothesizing that only one class of striatal cells – those that are activated in response to positive reinforcement – would lose synaptic plasticity; another class of cells activated in response to negative outcomes would actually show *increased* synaptic plasticity. This computational prediction has subsequently been confirmed behaviourally (Frank et al., 2004) and neurobiologically (Shen et al., 2008).

This review is structured as follows. First, we introduce basics of neural network models of the BG, focussing on an intuitive understanding of principles rather than mathematical formulations (which can be found elsewhere). We then establish the simple notion of an activation and learning imbalance of the facilitatory and suppressive pathway in the BG and their implication in PD. By this account, the diverse symptomatology of unmedicated and medicated PD (caused by a lack and excess of DA in the striatum, respectively) represent two sides of the same coin. Increased activation and learning in the suppressive pathway (i.e. unmedicated PD) accounts for progressive decline of motor functions, increased avoidance learning and reduced updating of working memory (WM). Conversely, increased activation and learning in the facilitatory pathway (i.e. medicated PD) accounts for excess of motor functions (i.e. dyskinesias), increased anticipatory learning and excessive updating of WM. Thus, PD is not only a motor disorder, but rather a more general disorder of action selection, exacerbated by a learning process that induces a bias in the system to avoid selecting actions. This process can lead to a poverty of movement, but also of more cognitive actions.

Note that we focus this review mainly on the predictive power of this dopaminergic account. While this is sufficient for the data we describe, the neurotransmitters noradrenalin, serotonin and acetylcholine have also been implicated with cognitive deficits of PD (Calabresi et al., 2006, 2007a).

Neural network models of basal ganglia

Computational models in systems neuroscience (sometimes also called mechanistic or neural

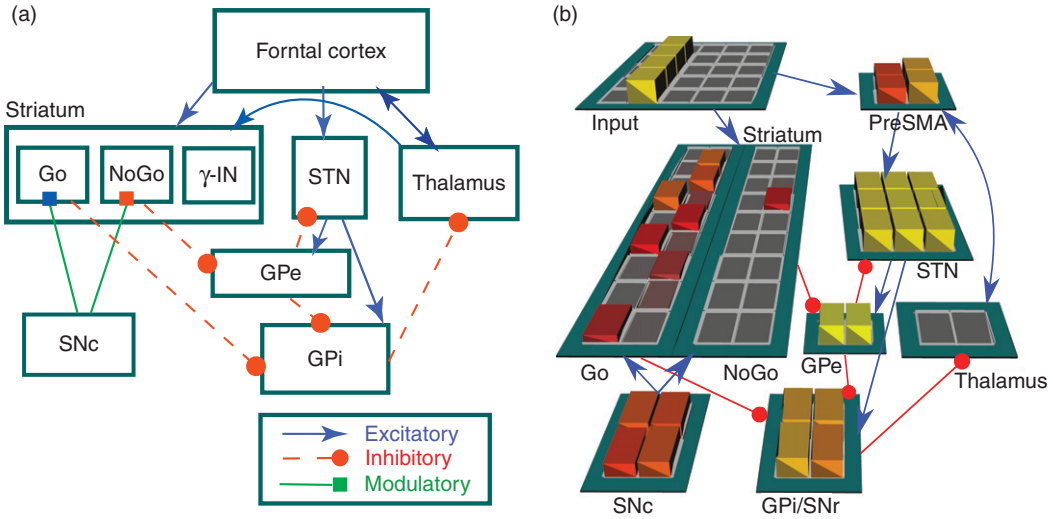

Fig. 1. (a) Box-and-arrow diagram of the basic anatomy of the BG. Frontal cortex projects to striatonigral neurons (Go) of the direct pathway and to striatopallidal neurons (NoGo) in the indirect pathway. Dopaminergic projections from the SNc innervate the striatum and excite and inhibit Go and NoGo neurons, respectively via simulated D1/D2 receptors. Fast-spiking GABAergic interneurons (γ-IN) regulate striatal activity via inhibitory projections. Activation of striatonigral neurons disinhibits the thalamus by inhibiting tonically active GABAergic neurons in the GPi. Activation of striatopallidal neurons removes inhibition of the GPi by inhibiting the GPe – thus ultimately inhibiting the thalamus. The STN is part of the hyperdirect pathway which dynamically activates BG output, and thereby suppresses behaviour, as a function of cortical response conflict. (b) Implementation of the box-and-arrow diagram in form of a neural network model by Frank (2006). Cylinders represent individual simulated neurons, their height and colour encodes their activity level. The computational model complies with current anatomical and physiological BG data.

network models) consist of layers of simulated neurons (i.e. units) that are interconnected according to the anatomy of the brain. The units used in different models – though varying in their degree of biological plausibility – generally try to focus on the computational properties of real neurons and not on all aspects of their anatomy (like biophysical models do). As such, they are often implemented as point-neurons with the dendritic tree and the soma shrunken to a tiny point. The influence of presynaptic inputs is controlled via *weights* which model synaptic efficacy (receptor affinities, densities, number of presynaptic vesicles released, etc). The Leabra framework, for example, computes the units' voltage according to excitatory, inhibitory and leak conductance channels (O'Reilly and Munakata, 2000). Individual excitatory and inhibitory channel conductances are computed by multiplying the presynaptic input activity with the respective synaptic weight. Once the unit exceeds a certain voltage threshold, it communicates output to other downstream units, in the form of either a rate-coded variable (normalized firing rate), or discrete spiking.

Architecture of basal ganglia models

The BG is generally conceptualized as an adaptive action selection device gating information flow from and to cortex via the thalamus (Graybiel, 1996). Its basic anatomy can be appreciated in Fig. 1. Two opposing pathways – the direct and indirect pathway – dynamically and selectively facilitate and suppress action representations in the frontal cortex, respectively (Alexander and

Crutcher, 1990; Brown et al., 2004; Frank, 2005; Frank et al., 2001; Mink, 1996). In the context of motor control, the BG were suggested to selectively facilitate a single motor command via the direct pathway while suppressing all others via the indirect pathway (Chevalier and Deniau, 1990; Mink, 1996). The computational models described below retain the basic functionality of the direct and indirect pathway proposed in the classic model, while also extending the static model to incorporate dynamics, plasticity and updated aspects of anatomical and physiological data (Cohen and Frank, 2009). As one example, while the original model suggested that the subthalamic nucleus (STN) was a key part of the indirect pathway, the updated model places the STN as another input nucleus from cortex, forming a third 'hyper-direct' pathway (Miller, 2008; Nambu et al., 2000) that is functionally distinct. Below we discuss the relevance of this distinction for PD.

At the heart of BG models is the striatum, a large structure that consists collectively of the caudate, putamen and nucleus accumbens. Almost all mechanistic BG models include at least the direct pathway originating in the striatum, projecting through BG output nuclei to the thalamus. The main effect of striatal activity in these models is to facilitate excitatory thalamic responses, which in turn amplifies cortical activity associated with the corresponding action plan. The striatum receives input from multiple cortical areas and consists mainly of medium spiny neurons (MSNs) (Gerfen and Wilson, 1996). Direct pathway MSNs (i.e. striatonigral neurons) express excitatory dopaminergic D1 receptors and send inhibitory projections to the substantia nigra pars reticulata (SNr) and to the internal segment of the globus pallidus (GPi). In the absence of striatal firing, neurons in SNr and GPi are tonically active and inhibit the thalamus, preventing a frontal action plan from being executed. Activation of the direct pathway leads to disinhibition of the thalamus. Disinhibition implies that thalamic units are not directly excited by direct pathway activity, but are instead enabled to get excited if they also receive excitatory glutamatergic input (i.e. from descending cortical signals) (Chevalier and Deniau, 1990; Frank et al., 2001). Striatal MSNs of the direct pathway are sometimes labelled as 'Go'-neurons (e.g. Frank, 2005; O'Reilly and Frank, 2006), because they act to gate or facilitate frontal action plans, the details of which are specified by cortical representations.

The role of the indirect pathway is more contentious, and is sometimes omitted altogether in computational models (e.g. Arthur et al., 2006; Bogacz and Gurney, 2007). Although debated for several years, methodological advances have now confirmed the original suggestion that D1 and D2 receptors are largely segregated in MSNs, with D1 receptors predominating in the direct pathway and D2 receptors in the indirect pathway (Gerfen et al., 1990; Gong et al., 2003; Matamales et al., 2009; Surmeier et al., 2007; Valjent et al., 2009). Striatopallidal neurons expressing D2 receptors send inhibitory projections to the external segment of the globus pallidus (GPe). The GPe sends focussed inhibitory projections to GPi/SNr (Bolam et al., 2000; Kincaid et al., 1991; Smith and Bolam, 1989, 1990). Due to this additional inhibitory projection, activity in the indirect pathway ultimately results in inhibition of the thalamus and thus suppression of frontal action plans. Because of this motor suppression property (Albin et al., 1989), striatal MSNs of the indirect pathway are sometimes labelled as 'NoGo'-neurons (Frank, 2005). Electrophysiological studies from different domains support the existence of both, facilitatory and suppressive pathways (Apicella et al., 1992; Jiang et al., 2003; Kimchi and Laubach, 2009a, 2009b; Samejima et al., 2005; Watanabe and Munoz, 2009). Further, selective ablation of striatopallidal (indirect pathway) cells leads to increased locomotion (Pierre et al., 2009). Moreover, actions coded specifically in the striatal region in which the striatopallidal ablation was administered are selectively increased (Sano et al., 2003). These results support the notion that the indirect pathway acts to suppress

behaviours, such that when ablated, these behaviours are expressed more readily (Miller, 2008).

How are only certain actions facilitated or suppressed depending on the context? First, neurons in these pathways are highly structured according to the actions they encode (Deniau et al., 1996; Fger and Crossman, 1984; Mink, 1996). Striatal neurons that receive from a particular cortical region (e.g. encoding hand movements) reciprocally, via the loop through BG output and thalamus, project back to influence activity in that same cortical region (Kelly and Strick, 2004; Middleton and Strick, 2000). Evidence for this 'closed-loop' has also been reported in humans (Draganski et al., 2008). Second, striatal neurons receive diffuse projections from posterior cortical areas (Frank, 2005). These corticostriatal projections represent the input to most models and are implemented in the form of units which code for abstract properties of the environment (e.g. stimulus colour or context) (Frank, 2005; Guthrie et al., 2009; Wiecki et al., 2009). This many-to-many connection pattern enables the model to represent all possible stimulus–response pairs and to learn facilitation or suppression for each action in response to stimulus properties. In addition, action selection may be further contextualized by the cognitive state encoded in prefrontal cortex (PFC). Indeed, there appears to be some hierarchical structure to BG–PFC circuits: in addition to closed loops among BG and particular frontal regions, it is also the case that PFC areas in a particular loop can innervate striatal areas in more posterior loops (Haber, 2004; Haber and Calzavara, 2009). In this way, cognitive action plans in PFC can provide additional contextual input to lower level actions, for example, to influence motor control.

As mentioned above, multiple cortico-striatal loops innervate the striatum. The ventral pathway, innervating the ventral striatum (nucleus accumbens), represents the motivational loop. It plays a major part in the development of addiction (Dagher and Robbins, 2009). The dorsal pathway, innervating the dorsal striatum (i.e. caudate and putamen), represents the motor loop. It plays a major role in habit formation (Everitt and Robbins, 2005; Henry et al., 2004; Tricomi et al., 2009). In PD, nigrostriatal dopaminergic projections innervating the dorsal striatum are strongly affected, while mesolimbic dopaminergic projections innervating the ventral striatum are relatively spared (Kish et al., 1988).

Dopamine as a reinforcement learning signal

Recordings of midbrain dopaminergic neurons in awake behaving monkeys reveal phasic firing patterns in response to unexpected rewards and punishments (Bayer et al., 2007; Ljungberg et al., 1992; Montague et al., 1997; Pan et al., 2005; Roesch et al., 2007; Schultz, 1998; Waelti et al., 2001). Specifically, a DA burst is observed whenever an outcome of an action is better than expected, and, conversely, a drop below tonic DA firing (i.e. DA dip) whenever the outcome is worse than expected. Importantly, the same patterns were observed in human PD patients who receive abstract (financial) rewards and punishments (Zaghloul et al., 2009). Computational models show that this DA-mediated reward prediction error signal can be used to efficiently learn reward contingencies and to maximize reward intake in simple reinforcement learning (RL) environments (Barto, 1995; Friston et al., 1994; Montague et al., 1997; Schultz et al., 1997; Sutton and Barto, 1990).

Based on this insight, mechanistic models explore how such action selection and contingency learning to maximize rewards is implemented in the anatomy of the BG. As mentioned above, synaptic strengths are implemented as weights that can change dynamically over time. Specifically, co-activation of two connected units results in an increase of their connection's weight [corresponding to long-term potentiation (LTP)], otherwise the weight remains stable or is decreased [corresponding to long-term depression (LTD)]. In the corticostriatal pathway, this plasticity is strongly modulated by DA, leading to a '3-factor' Hebbian learning rule (Berke and Hyman, 2000;

Calabresi et al., 1997, 2000; Kerr and Wickens, 2001; Reynolds and Wickens, 2002; Reynolds et al., 2001; Shen et al., 2008). Importantly, DA effects on postsynaptic activity and plasticity depend on the receptor class. Active Go neurons expressing D1 receptors are depolarized by DA (Hernandez-Lopez et al., 1997), whereas NoGo neurons expressing D2 receptors are inhibited by DA (Hernandez-Lopez et al., 2000). Thus a DA burst in response to reinforcement further activates Go neurons (particularly those that are concurrently excited by corticostriatal glutamatergic input), but inhibits NoGo neurons. Conversely, a DA dip in response to punishment or lack of reward activates NoGo neurons by removing tonic inhibition of DA onto postsynaptic D2 receptors (Frank, 2005). [See Cohen and Frank (2009) for a detailed discussion of the plausibility of this mechanism.]

In the model, the above plasticity dynamics are adaptive. Simulated DA activity depends on whether the network selected the correct response according to the task at hand. If the network chose correctly, a DA burst will further activate those Go neurons encoding that action in the current environmental state (stimulus). This increased activity is associated with synaptic potentiation, such that the corticostriatal weights from active inputs are increased. The next time the same stimulus is presented, and the corresponding motor action represented in cortex, striatal Go activity encoding that action will be stronger, increasing the probability that the rewarded action will be gated. Conversely, if the network is chosen incorrectly, a DA dip will increase weights between active cortical units and corresponding NoGo units, ultimately decreasing the probability that the punished action will be repeated. Across multiple trials of experience, this system is able to learn to gate actions that are most likely to produce positive outcomes and to suppress those that are most likely to yield negative outcomes – a corner stone of adaptive behaviour. A recent study provides direct support for this model by showing that direct and indirect pathway cells are required for reward/approach and punishment/avoidance learning, respectively (Hikida et al., 2010).

Cognitive learning deficits

Parkinson's disease: too much 'NoGo' learning?

PD patients are impaired in cognitive tasks that require learning from trial-and-error feedback (i.e. RL) (Ashby et al., 1998; Knowlton et al., 1996; Shohamy et al., 2004). Computational explorations with the above-described mechanistic BG model (Frank, 2005) provide an explicit account for these deficits. Reduced dynamic range of DA signals in PD lead to a reduced ability to learn to distinguish between different probabilities of rewards associated with multiple actions and stimuli. Moreover, the model predicted that reduced DA levels should particularly impair learning from positive outcomes (DA bursts) but would spare learning from negative outcomes (DA dips). This prediction was supported by a subsequent experiment: unmedicated PD patients showed intact or even enhanced learning from negative outcomes, but impaired learning from positive outcomes of their decisions (Frank et al., 2004). This RL bias was established by testing models and human subjects with a novel behavioural experiment. In this task, multiple pairs of stimuli are presented to participants, who have to select one stimulus in each pair. Participants receive positive or negative feedback (i.e. winning or losing) depending on their choice, but this feedback is probabilistic. Choices of some stimuli are most often associated with positive feedback, whereas others are most often associated with negative feedback. Unmedicated patients showed better performance when avoiding choices that had been associated with a high probability of negative outcomes, but were less reliable in making choices associated with positive outcomes. Crucially, medication reversed this bias, increasing learning from positive outcomes but actually impairing learning from negative outcomes (Frank et al., 2004) (see Fig. 2). This basic pattern

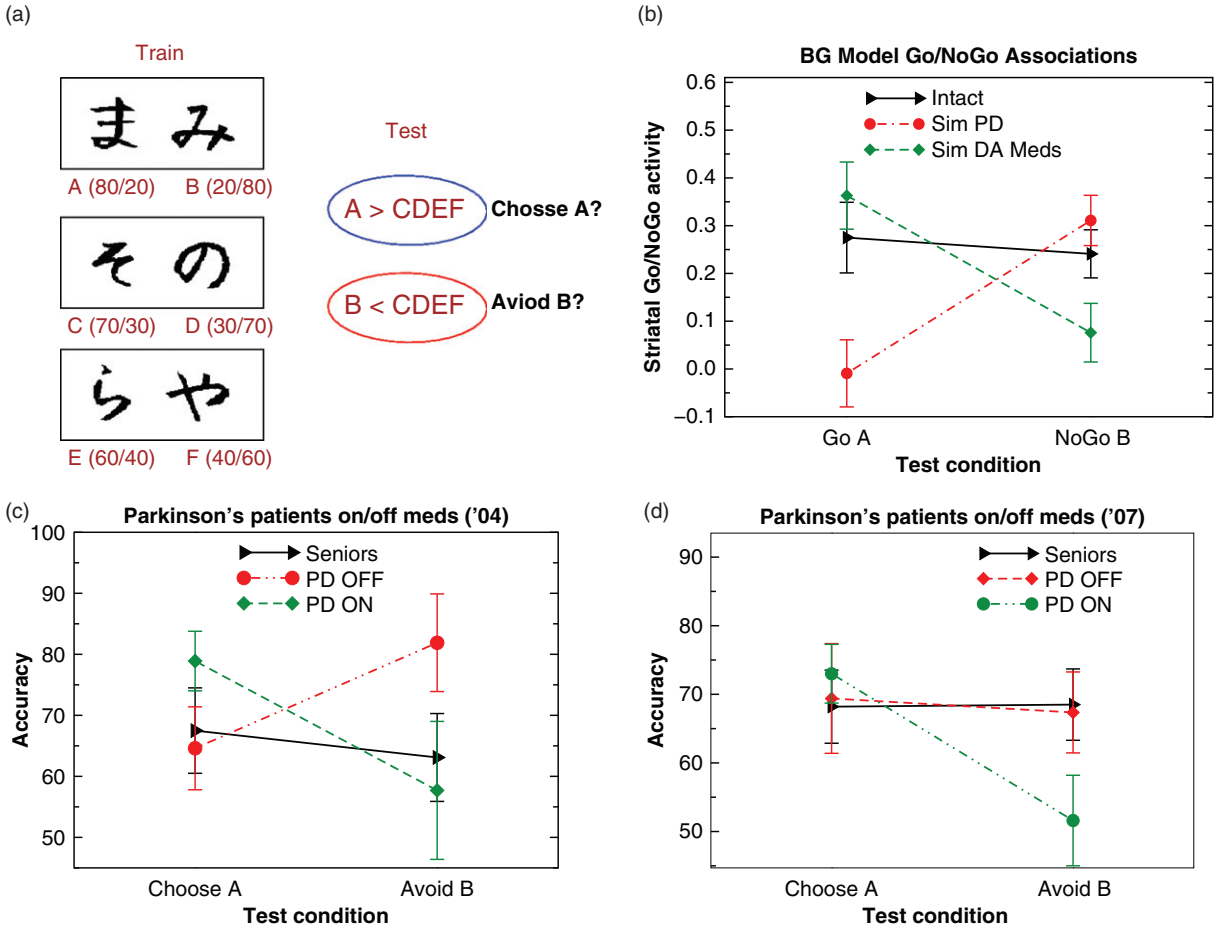

Fig. 2. (a) Probabilistic selection RL task. During training, participants select among each stimulus pair. Probabilities of receiving positive/negative feedback for each stimulus are indicated in parentheses. In the test phase, all combinations of stimuli are presented without feedback. Go learning is indexed by reliable choice of the most positive stimulus A in these novel pairs, whereas NoGo learning is indexed by reliable avoidance of the most negative stimulus B. (b) Striatal Go and NoGo activation states when presented with input stimuli A and B, respectively. Simulated Parkinsons (Sim PD) was implemented by reducing striatal DA levels, whereas medication (Sim DA Meds) was simulated by increasing DA levels and partially shunting the effects of DA dips during negative feedback. (c) Behavioural findings in PD patients on/off medication supporting model predictions (Frank et al., 2004). (d) Replication in another group of patients, where here the most prominent effects were observed in the NoGo learning condition (Frank et al., 2007b).

has since been replicated across multiple experiments, tasks and labs (Bodi et al., 2009; Cools et al., 2006; Frank et al., 2007b; Moustafa et al., 2008a; Palminteri et al., 2009; Voon et al., 2010).

Here, the mechanistic model provides insight into the neurobiological underpinnings that give rise to the pattern observed behaviourally. Depleted DA levels (both tonic and phasic) results in increased activity of NoGo units expressing inhibitory D2 receptors, while Go units expressing excitatory D1 receptors receive less excitation. As a result of Hebbian learning, fronto-striatal

projection weights to NoGo units are increased while inactive Go units do not adapt their weights. Consequently, the system has a relative bias towards NoGo learning to avoid negative outcomes (Frank, 2005). To summarize, the model predicts that decreased DA leads to (1) over-activation of NoGo neurons and subsequent and (2) LTP in these neurons. Empirical evidence for this system level prediction comes from multiple sources. First, neurons in the indirect pathway show abnormal burst firing in parkinsonism (Albin et al., 1989; Bergman et al., 1999; Mallet et al., 2006). It is now clear that this over-excitability of striatal MSNs in the DA-depleted state is specific to the striatopallidal cells, and concomitant decreased GPe, and increased GPi, activity (Boraud et al., 2002; Day et al., 2008; Mallet et al., 2006; Miller, 2008; Miller and Delong, 1987). Moreover, as predicted by activity-dependent plasticity mechanisms in the model, DA depletion causes increased LTP in striatopallidal cells (Shen et al., 2008). The implications of this enhanced plasticity (NoGo learning) for both cognitive and motor symptoms of PD are discussed extensively below.

Levodopa and positive reinforcement learning

DA replacement therapy [i.e. levodopa (L-Dopa)] is still the gold-standard treatment of PD. However, while reducing cognitive and motor deficits, L-Dopa introduces a new set of cognitive deficits that have been attributed to an 'overdose' of DA in regions that are relatively spared in PD (Cools et al., 2001; Gotham et al., 1988). Furthermore, chronic L-Dopa treatment has been shown to increase DA bursts (Harden and Grace, 1995; Keller et al., 1988; Wightman et al., 1988), and the expression of zif-268, an immediate early gene that has been linked with synaptic plasticity (Knapska and Kaczmarek, 2004) in striatonigral (Go), but not striatopallidal (NoGo) neurons (Carta et al., 2005).

As predicted by computational simulations, PD patients medicated with L-Dopa showed an increased preference to seek rewarding stimuli and *reduced* preference to avoid non-rewarding or punishing stimuli (Bodi et al., 2009; Cools et al., 2006; Frank et al., 2004, 2007b; Moustafa et al., 2008a; Palminteri et al., 2009) (see Fig. 2). In the model, L-Dopa is simulated by an increase in both tonic and phasic DA levels (Frank, 2005). Consequently, active Go units receive overall more D1-mediated excitation and are thus subject to more learning, while NoGo units are chronically inhibited. Thus even when a DA dip occurs, the NoGo units remain largely suppressed as exogenous medication continues to bind to D2 receptors. In other words, the system is biased to learn stronger from rewards due to over-activation of the direct pathway and less from punishments because of over-suppression of the indirect pathway. Thus this pattern is the mirror inverse of that observed in unmedicated PD patients, as described above – on a behavioural *and* a neuroscience level.

Intriguingly, this susceptibility towards rewards and relative immunity against negative outcomes could help explain cases of pathological gambling and addiction in some PD patients medicated with L-Dopa [recently reviewed by Dagher and Robbins (2009)]. Although the probability of financial gains at a casino may be roughly 48%, the medicated PD patient's brain may distort this learned probability to be closer to, for example, 60%, thereby reinforcing gambling behaviours.

Recent data support this assumption. PD patients were tested off medication, after L-Dopa treatment, and after a D2 agonist on a gambling task (van Eimeren et al., 2009). This study found that D2 agonists and L-Dopa diminished the influence of negative reward prediction errors in the ventral striatum. Similar results were reported by Voon et al. (2010). These authors specifically showed that PD patients with compulsive disorders show distorted (abnormally increased) learning from financial gains in response to DA medications. 'Control' PD patients without such disorders showed reduced learning from losses, and blunted striatal responses to negative prediction errors. The authors' conclusion from both of these studies is in agreement with the model's prediction – D2

agonists and L-Dopa block the effects of DA dips and thus of negative RL. Another recent fMRI study found differences in dorsal striatum activation in medicated PD patients under RL conditions (Schonberg et al., 2010).

Individual differences

Why are only a minority of PD patients susceptible to pathological gambling in response to medication? It may be that this, too, is explained in accordance with the theory proposed above. PD patients with pathological gambling disorder have lower baseline striatal D2 receptor density (Steeves et al., 2009). This result might be inherently linked to RL learning differences of healthy humans carrying different polymorphisms of DA signalling genes (Frank and Hutchison, 2009; Frank et al., 2007a, 2009; Klein et al., 2007). Among the tested genes, the polymorphism of the DRD2 gene, associated with D2 receptor function, has been reliably linked to the degree of learning from negative outcomes (i.e. NoGo learning). Those genotypes associated with reduced striatal D2 receptor density (Hirvonen et al., 2005) are accordingly associated with reduced NoGo learning (Frank and Hutchison, 2009; Frank et al., 2007a, 2009; Klein et al., 2007). Thus it is possible that the PD patients who are most susceptible to pathological gambling from DA medications are those who are genetically predisposed to exhibit reduced learning from negative outcomes. This hypothesis has yet to be directly tested, but the observed reduced D2 density in pathological gambling patients is supportive, whether or not due to genetic factors. Moreover, if this predisposition is coupled with increased Go learning resulting from dopaminergic medications (Voon et al., 2010), compulsive disorders may be especially evident.

This same logic may suggest that a distorted bias to learn more from positive than negative outcomes in RL may help explain other addictive personality types in otherwise healthy individuals. Polymorphism of the DARPP-32 gene relates to synaptic plasticity in response to D1 stimulation. Carriers of the polymorphism have increased synaptic plasticity and show relatively stronger positive RL (Frank et al., 2007a, 2009). Similarly, individual differences of baseline striatal DA synthesis are predictive of the extent to which participants learn from positive versus negative reward prediction errors (Cools et al., 2009). These biological factors may predispose individuals to have a greater risk for pathological gambling and other addictions. Indeed, these same factors may also play a role in the development of addiction to L-Dopa observed in some PD patients (Borek and Friedman, 2005; Dagher and Robbins, 2009). For example, a recent review highlights similarities between methamphetamine addiction and L-Dopa sensitization (Fornai et al., 2009).

Intriguingly, Palminteri et al. (2009) found similar patterns of RL deficits in patients with TS. Crucially, these patients show the opposite RL pattern – unmedicated TS patients learned better from gains than losses. While this pattern can best be explained by DA hyperactivity in TS patients, this evidence for this account of TS remains controversial (Albin and Mink, 2006; Leckman, 2002; Singer, 1995; Wong et al., 2008). Nevertheless, TS patients are treated with D2 antagonists, such that the DA system is manipulated in opposite direction to PD. Critically, TS patients treated with D2 antagonists exhibited relatively better learning from negative than positive outcomes, very similarly to unmedicated PD patients (Palminteri et al., 2009).

These data are also consistent with model predictions: D2 antagonism selectively increases excitability and plasticity of striatopallidal cells (Centonze et al., 2004; Day et al., 2008; Mallet et al., 2006), thereby enhancing NoGo learning.

Motor impairments

Progressive development of motor symptoms: sensitization?

As described above, unmedicated PD patients exhibit increased negative RL, inducing avoidance

behaviour (Frank et al., 2004). A stream of rodent experiments performed by Schmidt and colleagues suggest that this behaviour is not limited to environments in which behaviours are explicitly reinforced, but may underlie a fundamental aspect of the cardinal symptoms of PD – akinesia and rigidity (i.e. catalepsy). In these experiments, DA depletion was induced in rats via 6-hydroxy-dopamine lesions or administration of the D2 antagonist haloperidol. Catalepsy was assessed *repeatedly* on consecutive days. Initially, catalepsy expression was very low (due to partial DA depletion or subthreshold doses of the D2 antagonist). Notably, catalepsy *progressively increased* with each consecutive test. This progressive manifestation of symptoms is also referred to as *sensitization*. This sensitization is not simply due to receptor upregulation, as it did not occur in control conditions in which the drug was administered on each day only after the catalepsy test had finished. Moreover, catalepsy expression was context-dependent – it was expressed only in the environmental context in which the animal was sensitized, and not in other novel contexts (Klein and Schmidt, 2003; Wiecki et al., 2009).

These data imply that in the presence of DA depletion/D2 blockade, the animal learns an avoidance response in a particular environmental state. Consistent with this depiction, after haloperidol sensitization rats continued to exhibit catalepsy in this context in a subsequent test even when the drug was replaced with a placebo, despite no residual haloperidol being present (Amtage and Schmidt, 2003). After a few days of testing with the placebo, rats' catalepsy expression returned to baseline (i.e. it was not different from control rats that had never been administered haloperidol). Notably, however, a subsequent single administration of haloperidol yielded stronger catalepsy expression in the rats that had been sensitized than the haloperidol-naive rats. Thus, although catalepsy expression had been extinguished, these data indicate that catalepsy sensitization features a non-extinguishable component.

Does the same neurobiological process underlie enhanced NoGo learning in PD patients and catalepsy sensitization in rodents? As mentioned above, striatal DA depletion increases striatopallidal excitability and plasticity. Haloperidol also potently blocks D2 receptors, induces LTP and enhances phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) receptors in striatopallidal neurons (Centonze et al., 2004; Haakansson et al., 2006). Furthermore, catalepsy induced by D2 antagonism is abolished following injection of a GABA blocker into the GPe (Ossowska et al., 1984) – suggesting that catalepsy expression results from enhanced striatopallidal inhibition of GPe (and therefore increased GPi inhibition of motor programs). Thus it is plausible that the same mechanisms underlie the two effects. To evaluate this hypothesis, we tested the Frank (2006) BG model under the influence of simulated haloperidol (Wiecki et al., 2009). To simulate the D2 antagonistic properties of haloperidol, we partially reduced the inhibitory effects of DA onto D2 receptors in striatal NoGo units. As can be seen in Fig. 3, the models produced behaviour qualitatively similar to that of rats – with each consecutive test, the time at which the network facilitated a response was progressively slowed. Again, by closely analysing the model dynamics, we can derive a prediction of the underlying neural mechanisms causing this behaviour. In this case, simulated DA depletion or D2 blockade resulted in an over-activation of NoGo units [as observed empirically (Boraud et al., 2002; Day et al., 2008; Mallet et al., 2006; Miller, 2008; Miller and Delong, 1987)]. This excitability resulted in activity-dependent plasticity such that the synaptic corticostriatal weights in the NoGo pathway increased each time the same context was presented. Thus with each consecutive test, the probability to gate a response was reduced, resulting in longer and longer response latencies (Fig. 3). Thus our results are much in line with those of Frank et al. (2004) and subsequent studies in PD, but in a completely different domain and species. Interestingly, sensitization, context dependency and resistance to extinction are all properties observed also

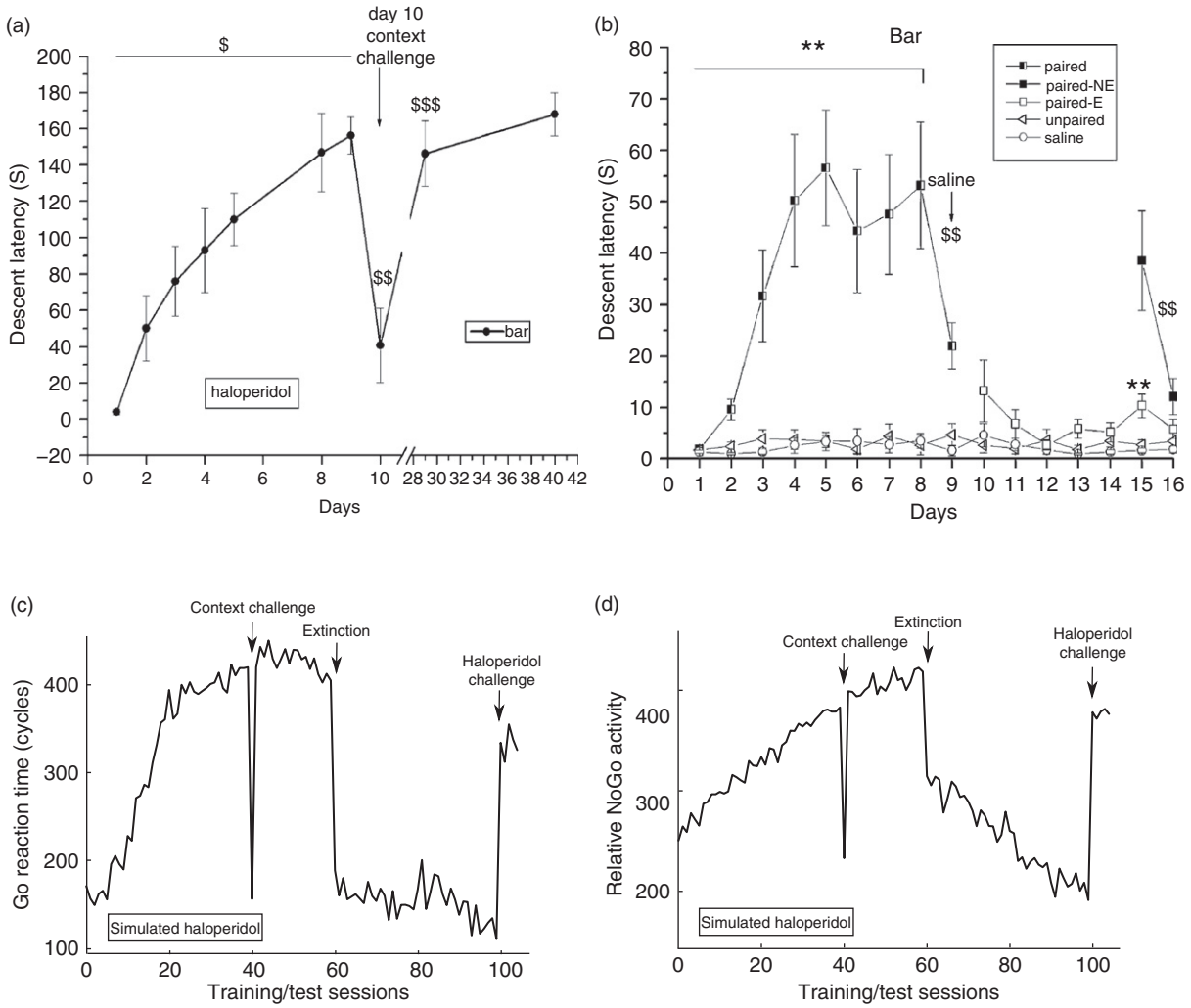

Fig. 3. Striatal DA depletion or D2 blockade produces context-dependent catalepsy sensitization. (a) Repeated administration of haloperidol results in a progressive increase of catalepsy across days, the expression of which is *context-dependent* (see context change on day 10) (Klein and Schmidt, 2003). (b) After this sensitization, catalepsy is observed even in absence of haloperidol (extinction, days 9–14), but progressively decreases to baseline levels. However, when challenged with haloperidol on day 15, sensitized rats showed significantly elevated cataleptic response relative to haloperidol-naive rats, thereby revealing a *non-extinguishable component* (Amtage and Schmidt, 2003). (c) and (d) Modelling results of the basal ganglia model, adapted from Wiecki et al. (2009). Haloperidol is simulated by reducing D2 receptor inhibitory effects on the striatopallidal pathway, leading to increased excitability (see text). (c) With repeated testing, simulated haloperidol led to progressively slowed response times relative to intact networks [intact data not shown; see Wiecki et al. (2009)]. (d) This slowing is due to increases in NoGo (relative to Go) activity which is further enhanced due to corticostriatal Hebbian learning. As observed behaviourally, this learning is context-dependent, and is not seen when switched to a new context (different cortical input pattern of activation, training session 40). Networks are switched to the intact mode (normal D2 function) in training session 60 (i.e. extinction), resulting in speeded responding and declining relative NoGo activity. A non-extinguishable component is also revealed in session 100 when networks are again switched back to haloperidol mode.

in the appetitive domain of addiction (Schmidt and Beninger, 2006). It is possible that the same principles apply in that case, but with sensitization occurring in the Go pathway.

Moreover, this logic has recently been applied to a novel RL experiment in human PD patients (Moustafa et al., 2008a). In this study, rather than choosing among multiple stimuli to maximize rewards, participants had to press just a single button, but had to learn to speed or slow responses in order to maximize positive outcomes and minimize negative outcomes. As predicted by the Go/NoGo model, unmedicated patients were more adept at learning to slow down (relative to their baseline speed) to avoid negative outcomes – that is, they showed a bias towards NoGo learning from negative prediction errors leading to slowed responding. In contrast, medicated patients showed the opposite pattern, learning better to speed responses to increase positive outcomes. This same pattern naturally emerged in the computational model when PD and medications were simulated as previously (Moustafa et al., 2008a).

A recent study found learning impairments in a rotarod movement task of mice with selectively denervated dorso-striatal DA (due to PITx3 genetic knockout) which could be rescued by L-Dopa administration (Beeler et al., in print). Crucially, cessation of L-Dopa treatment in trained mice did not result in an immediate performance drop, but rather a *progressive* decline. Relatedly, healthy mice treated with a D2 antagonist showed the same progressive decline. However, treatment with a D1 antagonist resulted in an immediate performance deficit. In light of our computational framework, this pattern can be explained in terms of learning. D1 antagonists would reduce the signal-to-noise ration in Go neurons such that those cells encoding learned motor associations in the rotarod task are relatively suppressed. This same effect would also diminish synaptic plasticity in these cells (indeed, unpublished simulations of a D1 antagonist in the same model as described above also show an immediate impairment of motor function). D2 antagonists, on the other hand, would increase NoGo activity while still leaving Go expression of learned associations intact. Initially, learned Go activity may be sufficient to overcome the drug-induced NoGo activity. After repeated exposure, however, NoGo neurons would become progressively active due to LTP and lead to the progressive decline in performance observed experimentally. In sum, these data further support the hypothesis that synaptic plasticity in the indirect pathway is the root of sensitization under low levels of DA (Wiecki et al., 2009).

The progressive worsening of symptoms in PD is generally attributed to the progressive cell death of dopaminergic neurons. However, the data reviewed above, along with modelling results, let this symptom progression appear in a different light. Even though it might sound counter intuitive, it seems that motor (and cognitive?) symptoms in PD are, at least partially, learned. To better treat PD patients, we have to explore if and how much of the motor and cognitive symptoms of PD are actually learned due to a dysfunctional learning signal. Ultimately, this could open the door to a whole new set of treatment options if we manage to find a way to *unlearn* these symptoms.

Dyskinesia and Go learning

While L-Dopa is quite effective in the beginning of treatment, following progressive treatment, L-Dopa-induced dyskinesia (LID) begin to appear in certain patients. LID are characterized by excessive and uncontrollable movements. Chronic L-Dopa treatment has been shown to increase DA bursts (Harden and Grace, 1995; Keller et al., 1988; Wightman et al., 1988), and the expression of zif-268, an immediate early gene that has been linked with synaptic plasticity (Knapska and Kaczmarek, 2004) in striatonigral (Go), but not striatopallidal (NoGo) neurons (Carta et al., 2005). In this regard, LID can be seen as the opposite of some PD symptoms (e.g. catalepsy). Like the progressive manifestation of catalepsy in parkinsonian rats, LID are also not present at first but get

more severe with time. Is the same process underlying catalepsy sensitization at work here, just in the opposite direction (i.e. hyperactivity and LTP of the direct pathway)?

Evidence supports this hypothesis. Increased DA levels promote LTP in Go neurons (Carta et al., 2005; Knapska and Kaczmarek, 2004; Shen et al., 2008), and to a higher propensity to learn from positive decision outcomes in medicated PD patients (Frank et al., 2004). Furthermore, LID development is dependent on functional D1 receptors (Lindgren et al., 2009b) and is accompanied by excessive expression and sensitization of D1 receptors in striatonigral neurons in rodent and primate models (Aubert et al., 2005; Berthet et al., 2009; Corvol et al., 2004; Gerfen, 2003). Moreover, dyskinesia development in these models is accompanied by long-term changes in intra-cellular signalling cascades involved in plasticity (Berthet et al., 2009; Crittenden et al., 2009; Gerfen, 2003; Westin et al., 2007) and, perhaps relatedly, loss of bidirectional corticostriatal synaptic plasticity (Berthet et al., 2009; Picconi et al., 2003). Crucially, these cellular changes were selectively found in those animals who had developed dyskinesias, and not others receiving chronic L-Dopa treatment.

Computationally, this effect can be explained along the same lines as outlined above. Chronic high levels of DA due to L-Dopa first alleviate the symptoms by inhibiting the over-active indirect pathway and exciting (or increasing the signal-to-noise ratio in) the under-active direct pathway. With time, however, LTP in now-active direct pathway neurons causes inappropriate actions to be gated seemingly at random (Bezard et al., 2001; Cenci, 2007; Cenci and Lindgren, 2007; Vitek and Giroux, 2000). This could feasibly arise via artificially elevated DA levels and fluctuations in phasic signals, leading to inappropriate reinforcement of striatonigral neurons, ultimately producing erratic behaviour.

Why might there be fluctuations in phasic DA signals unrelated to environmental reinforcement? According to the false-transmitter hypothesis, in the DA denervated striatum, L-Dopa is decarboxylated to DA and promptly released by serotonergic terminals belonging to presynaptic neurons of the dorsal raphe nucleus. Thus phasic DA signals would be released even if DA neurons themselves are not burst-firing. A similar hypothesis has been invoked to explain impairments in behavioural learning as a function of L-Dopa treatment in PD (Shohamy et al., 2006). In accordance with this theory, the serotonin system is critically involved in the development and the expression of LID (Cenci and Lindgren, 2007; Carta et al., 2007; Eskow et al., 2009). Serotonergic neurons lack DA autoreceptors and DA transporters causing unregulated DA efflux and defective DA clearance [reviewed in Cenci and Lundblad (2006)] which results in increases of extracellular DA levels following L-Dopa administration (Kannari et al., 2001; Lindgren et al., 2009a; Tanaka et al., 1999). Moreover, recent evidence shows that peak extracellular DA levels are about twice as large in dyskinetic animals compared to non-dyskinetic animals. However, high DA release alone was not sufficient to explain dyskinesias, indicating that both, high DA release in response to L-Dopa *and* increased responsiveness to DA must coexist for dyskinesia expression (Lindgren et al., 2009a). Future research will explore the role of these serotonin dynamics in the BG model and its role in the development of dyskinesias and other behavioural phenomena.

Response vigour

Additional support for PD as a disease of action selection rather than motor function per se is provided by Niv et al. (2007). By extending an abstract model of RL to include the average expected reward rate (hypothesized to be encoded by tonic DA activity), the authors explain reduced response vigour observed in PD patients. According to their model, response latency in a free operant task is chosen according to the average reward rate: higher frequency of rewards is associated with increased vigour. Decreased tonic DA in PD lowers this effective rate and thus the

vigour. Experiments support this hypothesis. In a grasping task, PD patients were able to achieve the same maximal movement speeds as healthy individuals, their average speed was just lower overall (Mazzoni et al., 2007). In a review highlighting the close connection between these findings, the authors conclude that 'it is not that PD patients cannot move, it is that their DA circuitry does not "want" to'. (Niv and Rivlin-Etzion, 2007).

Working memory impairments

Among movement and learning defects, PD is also characterized by WM impairments (Cools, 2005; Frank, 2005; Owen et al., 1992, 1998). Neuroimaging studies reveal that WM impairments in PD patients are associated with decreased BG activity (Lewis et al., 2003; Owen et al., 1998; Postle et al., 1997). Can the same hypothesis that explains cognitive and motor deficits (as outlined above) also explain specific WM impairments of PD? The conceptualization of the BG as a gating device of motor commands (Mink, 1996) is hypothesized to also gate information flow into WM (Frank and O'Reilly, 2006; Frank et al., 2001; Moustafa et al., 2008b; O'Reilly and Frank, 2006). The mechanism is very similar to that described above for gating action plans, only here we simulate BG circuits interacting with PFC rather than premotor cortex, and the 'action' is whether or not to maintain the current stimulus in PFC. In this context, Go activity indicates that a representation is task-relevant and should be stored in memory, whereas NoGo activity indicates that the stimulus should be ignored or filtered out of WM. Recent neuroimaging data provide support for this notion (Cools et al., 2007; McNab and Klingberg, 2007).

According to this framework, DA depletion as in PD would lead to an increased threshold for updating WM (because of too much NoGo activity), such that most information is treated as irrelevant. In contrast, chronic DA elevations by replacement therapy would result in too much WM updating and the gating of distracting information into WM. This specific pattern was found in a conjoint behavioural WM task (Moustafa et al., 2008b). Medicated patients were also impaired at ignoring stimulus information that had previously been relevant but is subsequently distracting, consistent with the hypothesis that Go activity for initially relevant information, combined with medication-induced suppression of NoGo activity, results in difficulty filtering out stimuli from WM. Recent evidence further supports this hypothesis. In a task where subjects had to keep certain stimuli in WM while ignoring distracting stimuli, unmedicated PD patients showed abnormally enhanced resistance to distractors (Cools et al., 2010). PD patients were impaired, however, in a task which required repeated updating of WM contents. Did DA depletion block gating of relevant and distracting information into WM? Indeed, susceptibility to distractors was reintroduced by DA replacement medication. Furthermore, a recent study showed that PD patients specifically showed reduced transient (phasic) activation of the BG during WM updating, consistent with impaired gating functionality (Petter et al., 2009).

The subthalamic nucleus, deep brain stimulation and behavioural inhibition

A critical aspect of controlled cognition and behaviour is not only knowing which action to select, but also knowing when to cancel a planned response, or to slow down to take more time to make a more considered decision. The original 2005 BG model was extended to include the STN (Frank, 2006). In the model, this nucleus is conceptualized as a dynamic brake on the output structures of the BG. Rather than being part of the classical indirect pathway, the STN receives input directly from cortex and sends diffuse excitatory projections to GPi – the so-called hyperdirect pathway (Nambu et al., 2000). The computational model simulates the dynamics of

STN activation in response to cortical activity, and how this may be adaptive. Specifically, the STN receives excitatory input from presupplementary motor area (preSMA), which in turn is most active under conditions of response conflict. In the model, preSMA represents the candidate motor actions available in a given context and conveys this information to the striatum, which then gates one of the responses and suppresses others. Response conflict occurs when multiple motor actions are represented concurrently in preSMA in response to a particular environmental stimulus. The resultant increased STN activation provides a temporary brake on action selection by exciting BG output (which then inhibits action selection in the thalamus), allowing more time to resolve conflict such that the optimal decision can be made (Frank, 2006).

In PD patients, the STN is pathologically hyperactive (DeLong, 1990; Miller and Delong, 1987), leading to global inhibition of motor programmes (in addition to the NoGo pathway) deep brain stimulation (DBS) of the STN has been successfully applied in PD patients where other therapy options have failed. In this surgical procedure, a stimulating electrode is placed into the pathologically hyperactive STN, which is thought to act similarly to an STN lesion (e.g. Bergman et al., 1990). However, as predicted by the simulations and subsequently confirmed behaviourally (Frank et al., 2007b), the chronic STN stimulation comes at the cost of increased impulsivity because it prevents adaptive slowing in the face of response conflict. This was tested in a version of the probabilistic selection task as described above (Frank et al., 2004). The model and subjects were again trained to select stimuli with different probabilistic reward contingencies. In a successive test it was found that healthy individuals, PD patients on and off medication and PD patients off DBS exhibited relatively slowed responding when selecting among stimuli associated with conflict (i.e. both stimuli had been associated with similar reinforcement contingencies). In contrast, patients on DBS did not exhibit such slowing and even showed speeded responding under conflict (Frank et al., 2007b). This same pattern was predicted when the STN was disabled in the models to simulate the DBS. Without the dynamic braking signal, models had no way to slow down in high conflict scenarios until the conflict was resolved.

For the first time, a link between DBS and impulsive personality changes, so far only reported to neurologists on an individual basis, had been made. Recently, it was reported that DBS induces impulsivity to patients in their every day lives (Hlbig et al., 2009). More recent our lab has recorded EEG from both mediofrontal scalp electrodes and local field potentials in STN depth electrodes in PD patients undergoing DBS surgery. In both scalp EEG and STN local field potentials, power in the theta band (4–8 Hz) is enhanced under conditions of response conflict (Cavanagh et al., in progress). Furthermore, patients off DBS exhibit slower response times when cortical theta power is high, suggesting that cortical conflict produces controlled behaviour. When DBS stimulators were turned on, patients no longer slowed responses with increased cortical theta and the relationship between theta power and conflict was also reduced. These data support the hypothesis that mediofrontal cortical signals recruit the STN to slow behavioural responding under conditions of conflict, and that DBS disrupts this mechanism by preventing the STN from responding naturally to its cortical inputs.

In the future, computational models might aid the development of a new generation of DBS systems, which, instead of disabling the STN, will stimulate the STN dynamically, depending on the task at hand. One could imagine, for example, a closed-loop system in which STN stimulation is set according to recorded electrophysiological activity correlating with response conflict.

The STN does not solely respond to response conflict. A recent rat study identified neural subpopulations in the STN that respond to different reward types available to the animal (Lardeux et al., 2009). Theoretically, if multiple rewards would be made available, multiple subpopulations

should get activated simultaneously and thus result in higher overall STN activation. In light of the putative response inhibition role of STN, this would mean that the STN not only halts action selection in the BG during motor response conflict, but also when multiple rewards are present. This conceptualization is still hypothetical and needs further exploration, but may also be adaptive to enable controlled selection of action plans that would produce the most desirable reward.

Conclusion and outlook

Neural network models allow us to bridge the gap between the behavioural and neuronal level. By integrating data from different domains into one conglomerate model, we might start to see the 'bigger picture'. For this approach to be successful, it must stay close to empirical data and provide concrete predictions which have to be tested experimentally to possibly refine the model. These models pose an advantage to the classic box-and-arrow diagrams: neural network models provide a more disciplined approach that is grounded by mathematics and allows exploration of more complex dynamics than are considered by static anatomical diagrams. As the research described above has hopefully shown, this approach has already proven to be very valuable in understanding the BG and associated disorders. Nevertheless, we look forward to revising the models to incorporate other existing and future biological data.

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Abbreviations

BG	basal ganglia
DA	dopamine
DBS	deep brain stimulation
GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
L-Dopa	levodopa
LID	L-Dopa-induced dyskinesia
LTD	long-term depression
LTP	long-term potentiation
MSN	medium spiny neuron
PD	Parkinson's disease
PFC	prefrontal cortex
preSMA	presupplementary motor area
RL	reinforcement learning
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
TS	Tourette's syndrome
WM	working memory

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