

## Review



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# Inhibitory dysfunction contributes to some of the motor and non-motor symptoms of movement disorders and psychiatric disorders

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Recently, it has been proposed that similar to goal-directed and habitual action mediated by the fronto-striatal circuits, the fronto-striato-subthalamic-pallidal-thalamo-cortical network may also mediate goal-directed and habitual (automatic) inhibition in both the motor and non-motor domains. Within this framework, some of the clinical manifestations of Parkinson's disease, dystonia, Tourette syndrome and obsessive–compulsive disorder can be considered to represent an imbalance between goal-directed and habitual action and inhibition. It is possible that surgical interventions targeting the basal ganglia nuclei, such as deep brain stimulation of the subthalamic nucleus or the internal segment of the globus pallidus, improve these disorders by restoring a functional balance between facilitation and inhibition in the fronto-striatal networks. These proposals require investigation in future studies.

This article is part of the themed issue 'Movement suppression: brain mechanisms for stopping and stillness'.

## 1. Introduction

Inhibiting behaviour that is inappropriate in a particular context or socially unacceptable is a necessary feature of adaptive behaviour. Our daily lives are dotted with such inhibitory control: when dieting exerting, self-control and not eating donuts made available at tea breaks; censoring and not expressing one's true opinion to a senior colleague; not jumping the red light on the drive home. While the contribution of such inhibitory control to adaptive behaviour is perhaps underestimated because non-occurrence of behaviour is difficult to observe and quantify, nevertheless, it is likely that inhibitory processes operate across all domains: motor, cognitive and emotional. Inhibition of motor responses that is suppression of a movement or motor response that has been prepared or close to initiation and execution is perhaps the easiest to measure and for this reason the most widely investigated to date with the go no-go and the stop-signal reaction time tasks. Behavioural inhibition of inappropriate impulses or urges, cognitive inhibition (e.g. mental suppression of irrelevant information from memory) and emotional inhibition (e.g. inhibition of anxiety-provoking mental images) are more difficult to measure and study, but are also relevant to understanding inhibitory control for adaptive behaviour.

Several types of behavioural inhibition have been distinguished [1–4]. In contrast with automatic inhibition, volitional inhibition is intentional, controlled and effortful [3,4]. However, the automatic–volitional inhibition distinction is not fixed, as volitional inhibition has been shown to be triggered by masked 'no-go' stimuli of which the person is not overtly aware [5] and through learning, volitional inhibition can become automatic [6]. Another common distinction is between reactive inhibition triggered by external stimuli (e.g. stopping car at red traffic light) and proactive inhibition, which is prospective and necessary

for achieving goals and self-control over drinking, eating, smoking, etc. [1–3]. Somewhat overlapping with and encompassing the above two sets of distinctions are the concepts of goal-directed versus habitual/automatic inhibition [4]. Goal-directed inhibition (e.g. not smoking when trying to quit) is mainly volitional, intentional and proactive in the service of a specific goal achievement, whereas habitual inhibition (for instance, not swearing in public) is developed through practice and education, largely stimulus-driven and automatic [4]. Global (e.g. freezing when faced with a grizzly bear in a wood) versus selective (e.g. stopping singing while continuing to play the piano) inhibition has been a further distinction [1]. The indirect and hyperdirect cortico-basal ganglia pathways considered to, respectively, mediate proactive and reactive inhibition are shown in figure 1.

One of the executive functions of the frontal cortex is inhibitory control, with the inferior frontal cortex [7], the dorsolateral prefrontal cortex [8], the orbitofrontal cortex [9,10] and the supplementary motor area (SMA) [11,12] playing a role in inhibition. A wealth of information is now available supporting the role of the basal ganglia—particularly the subthalamic nucleus (STN) and the striatum—in inhibition, including evidence from lesion [13,14] and electrophysiological [15–17] studies in animals, functional imaging studies in humans [11,12,18–21], behavioural and imaging investigations in Parkinson's disease (PD) [22–25], assessment of the effects of surgical treatment of PD with subthalamotomy [26,27] or deep brain stimulation (DBS) of the STN [28–34] and recordings of local field potentials from the implanted electrodes after surgery [35–37]. From a review of this evidence, Jahanshahi *et al.* [4] proposed that the fronto-striato-subthalamic-pallidal network is involved in goal-directed and habitual inhibition. This parallels the role of these circuits in goal-directed and habitual action, respectively, mediated by the associative and motor fronto-striatal circuits [38,39]. With repetition and practice, both initiation and inhibition of action can shift from goal-directed to habitual/automatic, which frees up attentional resources and allows for concurrent engagement in other tasks. Goal-directed but not habitual actions are sensitive to outcome devaluation and it needs to be established if outcome sensitivity is also a criterion that distinguishes goal-directed inhibition from habitual inhibition and to identify other relevant criteria.

Lack of behavioural inhibition can manifest itself as disinhibition, impulsivity and perseveration, all of which are characteristic of patients with frontal lesions. Impulsivity can manifest itself as delay aversion or an inability to take time to reflect or defer decisions, actions or gratification [40]. Impulsivity is among the diagnostic criteria for attention-deficit hyperactivity disorder, substance abuse and trichotillomania and can also feature in mania. In this paper, we consider the relevance of inhibition to some of the clinical manifestations of a number of primarily basal ganglia disorders, namely, PD, dystonia, Tourette syndrome (TS) and obsessive-compulsive disorder (OCD). For each disorder, we will consider the specific clinical manifestations that reflect failure of inhibitory processes and then the empirical evidence for deficits in inhibition on experimental tasks or from imaging studies.

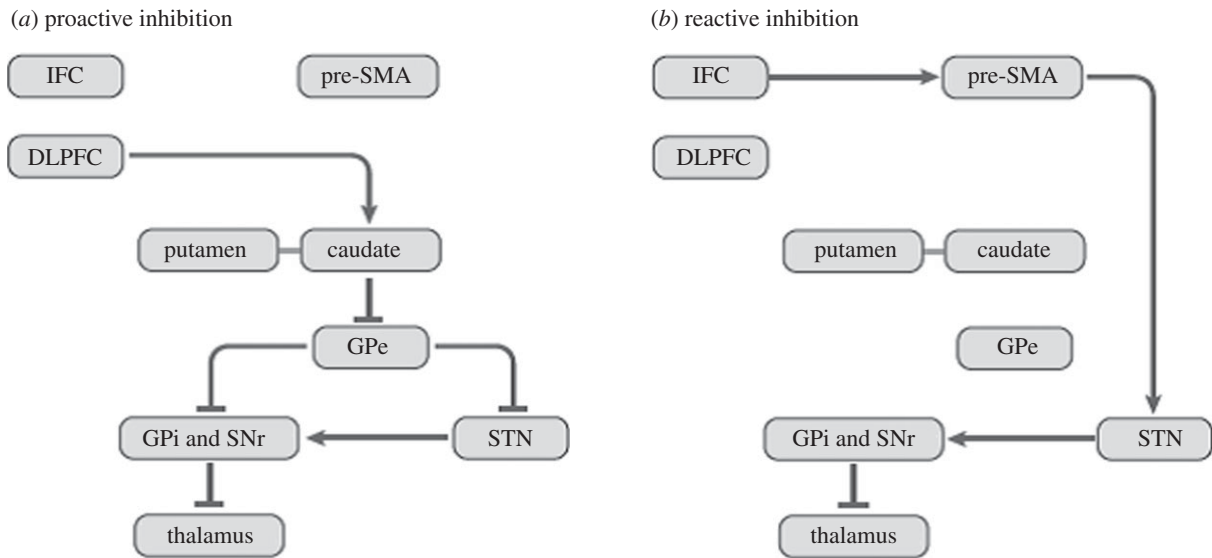
## 2. Parkinson's disease

PD is a movement disorder, characterized by the primary motor symptoms of akinesia, bradykinesia, tremor, rigidity,

postural instability and gait problems, and a host of non-motor symptoms including cognitive deficits, psychiatric problems such as depression, apathy, anxiety, hallucinations and delusions. According to the classical models, dopamine depletion in PD is associated with underactivity of the direct and overactivity of the indirect pathway, which results in excessive inhibitory output from the basal ganglia to motor, premotor and prefrontal cortical areas and to the brainstem [41,42]. This excessive inhibitory output from the basal ganglia is considered responsible for akinesia, characterized by the reduction or absence of a range of normally automatic movements such as blinking, facial expression, gesturing, turning in bed, arm swinging and handwriting in PD, which represents over-inhibition of habitual movements. Lesioning or DBS of the STN or the internal segment of the globus pallidus (GPi) reduces this excessive inhibitory output and improves akinesia [43,44]. There is some evidence in support of this. In an fMRI study [45], the delay in simple reaction times of PD patients relative to healthy controls was associated with the pre-go signal activation increases in the caudate, precuneus and thalamus: nodes of the proactive inhibitory network. This was interpreted as reflecting that PD patients were locked in a proactive inhibitory mode even in situations that did not call for such action restraint. A subsequent study by the same group showed that STN-DBS re-established the voluntary release of proactive inhibitory control in a cued reaction time task in PD patients [46].

Patients with PD have deficits in inhibitory control on a host of cognitive tasks requiring inhibition of prepotent or habitual responses such as the Stroop, random number generation and the Hayling sentence completion test [23]. Deficits in inhibitory control are also present in PD relative to age-matched controls on go no-go, stop-signal reaction time tasks, anti-saccade and Eriksen flanker tasks [22,23,47–49]. On the stop-signal task requiring motor inhibition, medicated or *de novo* never-medicated patients with PD have prolonged stop-signal reaction times indicative of delayed inhibition and this is associated with reduced task-related activation of the inhibition network, including the inferior frontal gyrus [24,25].

With progression of the illness, freezing of gait, episodes marked by a temporary motor block during walking, can be experienced by people with PD, triggered by turning, fatigue, confined spaces and stressful situations [50]. During freezing episodes patients are unable to initiate a step despite the intention to do so, and they report that their feet feel as if they are glued to the floor. Such freezing represents excessive motor inhibition [4,51]. It is possible that inhibitory output from the substantia nigra pars reticulata (SNr) and SMA to the mesencephalic locomotor region could be involved, as these areas can suppress locomotion in animal models [52]. From a review of the imaging studies of freezing of gait in PD [53], disruptions in the 'executive attention' network and tissue loss in the premotor cortex, inferior frontal gyrus, precentral gyrus, parietal and occipital areas of the right hemisphere were noted, areas that are involved not only in visuospatial function but also in inhibitory control. In addition, involvement of the caudate nucleus and the locomotor centres in the brainstem in freezing of gait was also identified. These findings, particularly grey matter atrophy in the inferior frontal gyrus [54], hypoactivation of the SMA and posterior parietal regions and overactivation of the



**Figure 1.** (a,b) The cortico-basal ganglia pathways involved in proactive and reactive inhibition, with proactive and reactive inhibition mediated, respectively, via the indirect fronto-striato-pallido-thalamo-cortical pathway and the hyperdirect cortico-subthalamic-pallidal-thalamocortical pathways. IFC, inferior frontal cortex; pre-SMA, pre-supplementary motor area; DLPFC, dorsolateral prefrontal cortex; GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. Some connections are not shown. Connections ending in arrows: excitatory; connections ending in line/dash: inhibitory. (With permission from [4]).

mesencephalic locomotor regions during motor imagery of walking [55] in patients with freezing of gait, are consistent with excessive inhibition of locomotion triggered by conflictual visual information. The hypothesis that the episodic motor blocks during walking characteristic of freezing of gait reflect excessive inhibition due to dysfunction of the cortical (SMA, inferior prefrontal cortex) and subcortical (caudate, SNr) areas engaged in inhibitory control, particularly triggered in situations when concurrent executive control of attention and gait are necessary, requires direct investigation in future studies. There is some preliminary support for this proposal from studies showing deficits in inhibitory control in patients with PD and freezing of gait on the stop-signal task [56,57], which becomes more pronounced with the addition of a cognitive load [57].

Apathy is a common psychiatric problem in PD [58,59]. It is a multidimensional syndrome with cognitive, emotional and behavioural components, whereby patients lack motivation, interest, concern, emotional reactivity and show no initiative or spontaneous activity and often report being devoid of thoughts and emotions. The biological basis of apathy remains unclear, with both dopaminergic and serotonergic systems implicated [60,61]. It is possible that excessive inhibition in the motor and non-motor domains mediated through the fronto-basal ganglia circuits contributes to the development of apathy in PD [4,62]. In support of this proposal, there is imaging evidence of decreased grey matter volume in the right SMA, the right inferior frontal gyrus, the left orbitofrontal cortex, left inferior and superior parietal areas and the nucleus accumbens bilaterally in non-depressed PD patients with apathy relative to those without apathy [63]. Other imaging evidence also implicates the right caudate or ventral striatum and the inferior frontal gyrus in apathy in PD. Compared with PD patients without apathy, *de novo* untreated non-depressed PD patients with apathy had lower dopamine transporter levels in the striatum, particularly the right caudate [64], and reduced metabolism in the right ventral striatum prior to surgery predicted

development of apathy following STN-DBS surgery [65]. Furthermore, imaging has identified an association between apathy in PD and right hemispheric metabolism in the inferior frontal gyrus, middle frontal gyrus and the anterior insula [66], and in another study reduced grey matter volume in the inferior frontal gyrus bilaterally was among the areas that correlated with high apathy scores in PD [67]. Some of these areas overlap with the brain inhibitory network, and their volume reduction may contribute to the reduction of spontaneous and self-generated activity and motivational deficits in PD patients with apathy. Also of interest is the finding from a longitudinal study that in *de novo* PD patients, reduced performance on the Stroop interference task, which requires inhibitory control and engages medial prefrontal areas, predicted subsequent development of apathy [61].

At the other extreme, some medication-related complications of PD can be considered as reflecting disinhibition of the networks involved in motor and non-motor inhibition. Dopaminergic medication used in the treatment of PD can give rise to levodopa-induced dyskinesias (LIDs) and impulse control disorders (ICDs). Both LIDs and ICDs may represent failures of habitual or automatic inhibition [4,62]. With LIDs, failure of automatic inhibition may result in fragments of movement and stereotyped behaviours being released. Recent imaging evidence has implicated the inferior frontal gyrus and the SMA, two key nodes in the motor inhibitory network, in dyskinesias [68–70], leading to the proposal that dysfunction of the neural network mediating motor inhibition may also induce LIDs. For example, in the on-medication state, for patients with LIDs the right inferior frontal cortex showed decreased functional connectivity with the motor cortex and increased connectivity with the putamen compared with patients with no LIDs [70]. This was interpreted as reflecting reduced inhibitory control from the right inferior frontal gyrus over the motor cortex in the on state, giving rise to LIDs. Furthermore, it has been shown that in PD patients with LIDs, intake of levodopa

medication tended to make inhibitory control and monitoring of failures of inhibition during a stop-signal motor inhibition task worse, which fMRI showed to be associated with decreased activity of the right inferior frontal cortex during motor inhibition, whereas patients without LIDs showed the reverse [71].

A range of ICDs, including hypersexuality, pathological gambling and shopping, overeating and punting, develop in approximately 25% of people with PD treated with dopamine agonists or levodopa [72]. As a result of deficient habitual/automatic inhibition, patients with ICDs respond excessively to rewarding stimuli associated with sex, food, money or shopping [4]. PD patients with ICDs show impulsive choice on delay discounting tasks, preferring small immediate rewards to larger delayed rewards [73]. Imaging has revealed that dopaminergic medication results in differential patterns of activation in brain areas implicated in response inhibition and impulse control, particularly the lateral orbitofrontal cortex, rostral cingulate, amygdala and external segment of the globus pallidus (GPe) in PD patients with (decreased dopamine-induced activation) or without (increased dopamine-induced activation) ICDs such as pathological gambling [74]. Enhanced sexual desire and increased activation in the ventral striatum, anterior cingulate cortex and orbitofrontal cortex were reported in response to sexual cues for PD patients with hypersexuality relative to patients without such ICDs [75]. Thus it is possible that ICDs in PD reflect impulsive choice and behaviour due to failure of habitual inhibition [4]. Cognitive behaviour therapy has some success in helping PD patients with ICDs to proactively impose goal-directed inhibition over their impulsive behaviour, but response to this can be variable [76].

### 3. Dystonia

Dystonia is a hyperkinetic movement disorder. The latest expert classification has defined it as 'a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.' [77, p. 863] The abnormal contractions can affect muscles of the eyes (blepharospasm), face and jaw (oromandibular dystonia), larynx (spasmodic dysphonia), neck (cervical dystonia) and the hand during writing (writer's cramp). Dystonia can be focal, affecting only one part of the body, segmental (two adjacent body parts affected), multifocal, hemi-dystonia (one side of body) or generalized (involving the trunk and two other body parts).

The exact cause of dystonia is not known. Dystonia is considered a movement disorder associated with dysfunction of the basal ganglia [78,79], and more recently, cerebellar involvement in dystonia has also been documented [80–82]. Many genes causing various forms of dystonia in association with environmental triggers have been identified [83].

According to the classical DeLong [42] and Albin *et al.* [41] models, hyperkinetic movement disorders such as dystonia are associated with reduced inhibitory output from the GPi, which gives rise to increased thalamic and cortical activation. There is some support for this model from

hyperkinetic transgenic mice model of *DYT1* dystonia [84] and neuronal recordings from the GPi of patients with dystonia undergoing DBS surgery [85], but the improvement of dystonia with GPi DBS [86], which reduces the activity of the GPi, is not consistent with the classical 'rate' models.

Imaging studies have shown movement-related overactivity of the dorsolateral prefrontal cortex, the anterior cingulate cortex, the SMA and the lenticular nuclei, and underactivation of the primary motor cortex in dystonia [87,88]. Using different transcranial magnetic stimulation (TMS) protocols, reduced cortico-cortical inhibition [89,90] and increased plasticity [91] have been demonstrated in dystonia. This loss of inhibition, particularly loss of 'surround inhibition', is considered responsible for loss of selectivity and overflow of activation to other muscles. The essence of 'surround inhibition' is that muscles that are not actively involved in producing a movement are inhibited during the movement. Surround inhibition can be demonstrated with TMS and in focal hand dystonia, it has been shown that surround inhibition is deficient [92–94]. This loss of selectivity in muscle activation has been demonstrated even when patients imagined making specific movements [95]. The loss of inhibition in dystonia is also associated with a delay in the ability to inhibit preplanned responses and patients required longer warning times than healthy controls to be able to do so [96]. It has been suggested that some of the sensory deficits such as increased spatial [97] and temporal [98] discrimination thresholds may reflect deficient inhibition. In fact, recent neurophysiological evidence has shown that increased somatosensory temporal discrimination thresholds in dystonia are related to reduced activity of inhibitory circuits within the primary somatosensory cortex [99,100]. These deficits and impairment of sensorimotor integration [101,102] in dystonia, as well as the increased plasticity, may all result from the loss of inhibition that could itself be due to a reduced number of inhibitory interneurons [103]. The latter hypotheses require verification in future investigations.

### 4. Tourette syndrome

TS is characterized by motor and/or vocal tics, the latter often consisting of obscene words. TS is frequently accompanied by comorbidities such as attention-deficit hyperactivity disorder, depression, obsessive compulsive behaviours and self-injurious behaviours. Tics are involuntary movements or vocalizations, but are often preceded by a premonitory sensation and urge, and patients describe a sense of relief after performing the tic. Patients with TS can suppress the tics temporarily and thus can impose goal-directed intentional inhibition to suppress their involuntary tics for brief periods.

TS has been considered a basal ganglia disorder of inhibition [104]. Mink [104] proposed that repeated inappropriate activation of striatal neurons leads to inhibition of the GPi and the SNr, the output pathways of the basal ganglia, which would normally be tonically active to prevent unwanted movements, and that this GPi/SNr inhibition leads to a disinhibition of thalamo-cortical targets and generates tics. Evidence from imaging and neuropathological studies implicates the cortico-basal ganglia circuits and abnormal distribution of inhibitory interneurons in the basal ganglia in TS [105–107]. On behavioural tasks that assess inhibitory control, the evidence in TS is inconsistent,

with some suggesting failure of inhibition [108,109] but others not finding such deficits [110] and even reporting enhanced cognitive and inhibitory control in TS [111] due to development of compensatory mechanisms to counteract the lack of inhibition. The neural correlates of intentional suppression of tics in TS have been investigated in several imaging studies. Success in intentional inhibition of tics by TS patients was found to be associated with a significant increase in a measure of local connectivity in the inferior frontal gyrus [112]. In another study, comparison of tic suppression with a 'free-ticcing' state was associated with significant activation of the prefrontal cortex, anterior cingulate cortex, caudate and putamen [113]. Compared with age-matched healthy controls, people with TS showed greater activation of the frontal cortex and caudate during suppression of the urge to blink [114]. These results indicate the central role of the basal ganglia and the frontal cortex in volitional and intentional tic suppression in TS. By exerting voluntary effort, goal-directed inhibition mediated by the frontal cortex, anterior cingulate cortex and the caudate can be mobilized by patients with TS to suppress tics. DBS of the GPi or the nucleus accumbens [115–117] may control tics by restoring the balance between facilitation and inhibition in the cortico-basal ganglia circuits. It was proposed that spontaneous tics emerge either by overactivity in the generation of habitual actions or reduced activation of the mechanisms of habitual/automatic inhibition [4].

## 5. Obsessive compulsive disorder

People with OCD experience intrusive unwanted thoughts and images (obsessions) and repetitive behaviours (compulsions), which are driven by doubt, exaggerated perceptions of danger and anxiety. Different types of repetitive behaviour may be engaged in, including washing, checking or hoarding. Imaging studies have established hyperactivity of the orbitofrontal cortex–caudate circuit in people with OCD, which is increased by symptom provocation and conversely reduced by successful treatment [118–120]. The orbitofrontal cortex not only plays a role in detecting motivational value and salience of stimuli [121], but also mediates inhibition as its lesioning in animals results in perseveration [9,10].

Other imaging evidence also supports inhibitory failure in OCD. During performance of a 'go no-go' task that requires action restraint/inhibition on no-go trials, a negative association between severity of OCD symptoms and inhibition-related activation of the orbitofrontal cortex was found [122]. A meta-analysis of imaging studies in OCD revealed that these patients show reduced activation in the caudate and putamen during performance of inhibition and interference tasks and reduced activation of the inferior frontal gyrus, anterior cingulate cortex, medial frontal cortex, dorsolateral prefrontal cortex and caudate during switching tasks [120]. A recent imaging study [123] demonstrated that during exposure to symptom-provoking stimuli, OCD patients had deactivation of the caudate–prefrontal circuits together with hyperactivation of the STN and putamen, which were interpreted as reflecting a dissociation between areas involved in goal-directed and habitual behaviours, respectively. This study also showed hyperactivity of the putamen during symptom provocation and subsequent

putaminal deactivation during avoidance of the provoking stimuli and relief, indicating that the putamen may play a significant role in habit formation in OCD [123]. OCD patients were more prone to 'slips of action' indicative of over-reliance on habits and were deficient in goal-directed control on an instrumental learning task [124]. OCD patients also develop excessive avoidance habits on a shock avoidance task [125]. On the basis of these results, OCD has been formulated as a shift from goal-directed to habitual responding [123–125]. However, in the light of the fact that patients with OCD can temporarily exert goal-directed inhibition to control their compulsive behaviours, it is likely that failure of habitual/automatic inhibition of unwanted and intrusive thoughts and images and emotions may play a role in the genesis of obsessions and compulsions [4]. OCD is characterized by an imbalance between goal-directed and habitual action and inhibition [4]. Successful treatment of OCD with DBS of several targets including the ventral internal capsule and ventral striatum [126], the nucleus accumbens [127] or the STN [128] has been documented. In OCD patients with bilateral STN-DBS, stimulation prolonged stop-signal reaction times resulting in delayed inhibition, and dynamic causal modelling of EEG suggested that STN stimulation significantly decreased the connection from the basal ganglia to the right inferior frontal gyrus [129]. In an imaging study of operated OCD patients, acute DBS in the ventral caudate and ventral striatum was associated with activation of the prefrontal cortex, anterior cingulate cortex, putamen and globus pallidus [130]. Thus, DBS may improve OCD symptoms by modulating the dysfunctional network in the disorder that overlaps with the inhibitory network, which may in turn restore the balance between goal-directed and habitual action and inhibition [4].

## 6. Conclusion

The basal ganglia are phylogenetically ancient structures whose basic organizational principle has remained unchanged for many millions of years [131]. In the lamprey, the basal ganglia have inhibitory projections to brainstem nuclei that appear to form the basis for action selection through release of inhibition, and it has been suggested that such an organizational arrangement has been co-opted in higher primates to control multiple cognitive, emotional and motor functions in a broad range of behaviours [131]. Although the work above suggests that this basic tenet is correct, the range of control has expanded considerably, to distinguish, e.g. proactive and reactive control or habitual and goal-directed inhibitory control of behaviour. The complexities that these additional functions require may explain the wide variety of pathologies of control that can be observed. It remains to be clarified how the recently elucidated 'pause then cancel' model of stopping, with subthalamic-SNr 'pause' and arypallidal-striatal 'cancel' components [132] contribute to some of the clinical manifestations of basal ganglia disorders outlined above.

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