NI Feature: The Quest

COMMENTARY

Basal ganglia: Their role in complex cognitive procedures in experimental models and in clinical practice

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Abstract:

Apart from the well known role of the basal ganglia (BG) in motor control, their important role in regulating the cognitive functions is emerging. This article traces the scientific work that explores this role of BG in reinforcement learning, perceptual decision making, and other nonmotor pathways (speech fluency, cognition, attention and behaviour). It also highlights the important role played by the BG networks in determining the development of a child's brain. It retraces the various pathways and connections of the BG with the cerebral cortex, cerebellum and other regions that may be utilized in the establishment of complex cognitive procedures. Various diseases that may be the direct result of disruption of these basal ganglionic networks and interconnections are also recounted.

Key Words:

Basal ganglion, behaviour, brain development, cognition, networks, speech

Key Message:

Basal ganglia have an important role in determining complex cognitive behavioural patterns and in influencing the development of a child's brain. Several primary developmental cognitive, learning, memory, language, behavioural and speech disorders related to extrapyramidal syndromes directly owe their genesis to disruption of specific basal ganglionic networks.

The role of the basal ganglia (BG) in motor control has been extensively studied and is now well known. In addition, the role of BG in reinforcement learning, perceptual decision making, and other nonmotor pathways (speech fluency, cognition, and behaviour) has become an arena of new interest for researchers.[1-6]

Converging evidence from single-cell recordings, lesion studies in humans and animals, and brain imaging studies in humans have made it clear that the BG has several important roles outside the motor sphere. Data from literature showed that the range of contributions of the BG spans many different cognitive faculties.[1-7] These include the procedural memory,[7] habit and skill learning,[8] attention,[9,10] perception,[1] and language.[11-13] BG circuitry may be a key component of a specialized memory subsystem that involves the acquisition of stimulus related response associations.[14,15] Experimental

evidence suggests that the BG contributes to even higher levels of cognitive functions, such as planning,[16,17] syllogistic reasoning,[18] and mathematical problem solving.[19]

Different studies in rats[20] and monkeys[21,22] have shown that the BG lesions may influence the acquisition of motor responses that occur as a conditional response to a discriminating stimuli. These mechanisms seem to be involved in the transmission of cortical signals that may subserve to influence several cognitive functions of the BG.

Main Cortical Basal Ganglia Functional Networks and Introduction

Historically, the projections from the cerebral cortex to the BG are recognized as highly organized topographic projection systems.[6,23-26] Anterior cortical areas project to anterior striatal regions; posterior cortical areas project to

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posterior striatal regions;ventromedial regions of cortex project to ventromedial striatal regions; and, dorsolateral areas of cortex project to dorsolateral striatal regions.[6] Almost all areas of the cerebral cortex send cortical inputs to the striatum.

Striatum, considered to be the entry point of the BG main circuits, receives glutamatergic inputs from the cerebral cortex and thalamus,[27,28] dopaminergic inputs from the substantia nigra (SNpr) [pars compacta], and serotonergic and noradrenergic inputs from the brain stem.

The sensory and motor cortical areas project to the putamen; the frontal–parietal–temporal association areas project to the putamen and caudate nucleus. Similarly, the caudate nucleus, nucleus accumbens, and anterior ventral part of the putamen also receive information from the limbic cortex.[27-29]

The SNr and internal globus pallidum (GPi) constitute the output nuclei of the BG. Their main targets are the ventral anterior, ventral lateral, and the medial dorsal nuclei of the thalamus.[30-32] In turn, thalamic nuclei mainly project to the frontal lobe,[33,34] and in a minor proportion of subjects, also to the temporal and parietal areas.[35-37]

Basal Ganglia Behavior and Learning

BG were thought to be having the ability to integrate sensory, limbic, and cognitive information with the commands for movement. Alexander *et al*.,[25,26] suggested that, rather than serving as a tunnel for information from widespread cortical areas, the BG actually participated in multiple parallel segregated circuits with different regions of the frontal lobe. These regions included cortical areas concerned with skeleton-motor and oculomotor control, as well as three regions of the prefrontal cortex involved in cognitive and limbic functions. More recently,[38,39] it has been suggested that the original 'five circuit' scheme, proposed by Alexander *et al*., should be broadened to include seven general categories of circuits, namely, the skeletomotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, medial orbitofrontal, cingulate, and inferotemporal-posterior parietal categories of circuits.

Within each of these categories, anatomical evidence supports the existence of multiple parallel cortical-basal ganglia circuits.

Imaging studies have shown that the activity of the putamen is associated with repetitive and well-learned movements. Involvement of the supplementary motor area, anterior striatal areas, and the caudate nucleus has been recorded during the learning of sequential movements.

The frontal eye field sends projections to the striatum and to the body of the caudate nucleus (areas that are referred as the supplementary eye fields), and is also involved in learning and acquisition of oculomotor behaviour, for example, the rostral and caudal motor regions are programmed to learn the behavioural sequences of hand movements.[40-43]

Inputs from posterior cortical areas are integrated in the BG circuits and influence regions of the frontal lobe. Results from positron emission tomography (PET) studies (3 series) of regional cerebral blood flow (CBF) show a double dissociation between selection of movements, which induces differential effects in the BG, but not the cerebellum; and, sensory information processing, which involves the cerebellum but not the BG [Figures 1 and 2].[44,45] Regarding motor learning of a sequence of finger movements, there was a shift of activation in the anterior–posterior direction of the BG, which paralleled changes in the motor areas of the frontal cortex. During new learning, the dorsolateral prefrontal cortex and striatum were activated; for selected movements, the premotor cortex and mid-putamen were activated; whereas for automatic movements, the sensorimotor cortex and posterior putamen were activated. When participants paid attention to overlearned actions, the activation shifted back to the dorsolateral prefrontal cortex and striatum. The cerebellum was not activated when participants made new decisions and attended to their actions or selected movements.[44]

Second, a visuomotor coordination task was examined. In the absence of visual control over arm movements, participants were required to use a computer mouse to either generate new lines or to retrace the lines on a computer screen.[44] The neocerebellum, not the BG, was more engaged when lines were retraced (compared with new line generation). Animal experiments have shown that error detection and correction occur during line retracing but not during line generation. These data suggest that the neocerebellum (not the BG) is involved in monitoring and optimizing movements using sensory (proprioceptive) feedback.[44]
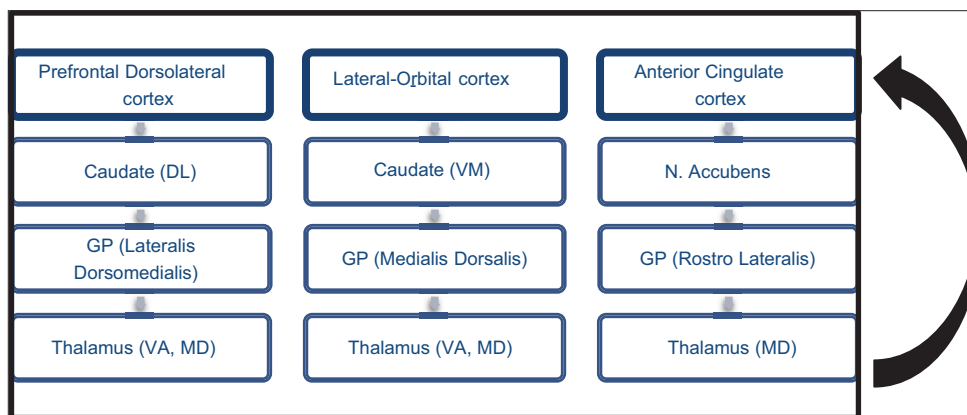
Figure 1: Direct frontal subcortical loops; schematic representation of the three direct frontal-subcortical loops. Caudate DL: Dorsolateral, Caudate VM: Ventro medialis, GP: Globus pallidus, Thalamus VA MD: Ventral anterior and medialis
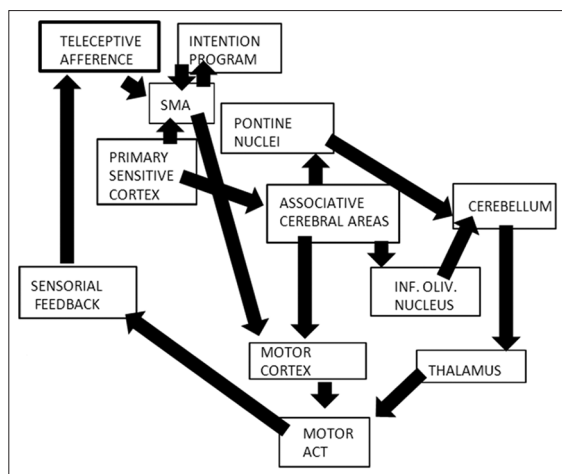
Figure 2: The complex system of motor memory and online control of motor act. SMA: Supplementary motor area

Third, the relative contributions of the sensory information processing of the signal during active/passive execution of a motor task (flexion and extension of the elbow) was examined; it was found that 80–90% of the neocerebellar signal could be attributed to sensory information processing. BG was not involved in sensory information processing; however, it was involved with movement/muscle selection (efferent motor component); the neocerebellum may be concerned with monitoring the outcome and optimizing the movements using sensory information.

Data suggest that the BG mediates the acquisition of nondeclarative knowledge, whereas the declarative subsystem is supported by the hippocampus.[46-50] Patients with BG disorders, such as Parkinson's disease (PD), have an impairment of mirror reading, whereas amnesic patients with hippocampal damage do not have this impairment.[51] Patients affected by Huntington's disease have an impaired ability at adapting to wearing prism goggles, whereas patients with Alzheimer's disease (with limbic-temporal region involvement) perform as well as controls.[52]

Similar to isolated nondeclarative learning, some groups of researchers employed the probabilistic classification tasks such as the weather prediction task;[53,54] participants have to predict "sun" or "rain" on the basis of drawings on four different cards, each configuration of cards has a different probability of being associated with either of the two outcomes. The underlying assumption is that complex arrangements of stimuli and nondeterministic association between stimuli and response make this type of task impossible to solve by relying on declarative memory.[55]

Cognition and executive function
Neuronal activity within the BG and cerebellar loops involves motor areas of the cerebral cortex, mainly correlated with execution of movement; it also involves areas of the prefrontal cortex that are more related to the aspects of cognitive function.

BG are closely related to cognition and behaviour, not in a focused manner, rather via their dense and widespread projections to different cortical and limbic areas.

Areas 9 and 46 project to adjacent regions of the dorsal and lateral caudate nucleus, which in turn innervate adjacent regions of the rostral and dorsal GPi and SNpr. These last regions are known to project back upon areas 9 and 46 via neurons in VA/VL(ventralis anterior / ventralis lateralis) and MD (mediodorsal nuclei),[38,39] completing the parallel circuit with these cortical areas. Area 12, in contrast, projects more ventrally in the caudate nucleus and appears to receive its input largely from the SNpr, but not GPi.[6,38,39]

The physiological properties of the dorsal and lateral prefrontal cortex suggested that areas 9, 46, and 12, each appear to be involved in at least four different types of cognitive functions. First, many neurons in these areas display changes in activity related to the performance of delayed-response tasks. These tasks require sensory cues to be stored for a brief period of time and then used to generate a specific response.[56-61] Selective changes in neuronal activity could be reported during the presentation of cues (cue-related activity), the delay period following cue presentation (delay-related activity), and the response preparation and execution periods (response-related activity). There are additional task parameters that determine the relative proportion of neurons involved in the performance of these delayed response tasks.[6,56,61]

In studies on Parkinson's disease (PD), functions of motor behaviour,[62] learning,[63] temporal coupling,[64] temporal ordering,[65] or temporal discrimination that is dopamine (DA)-dependent[66] were conducted. BG involvement in the grouping and processing together of action sequences, learning of these sequences, and sequential information processing[67-72] has been described.

Wei *et al*., described the contribution of the globus pallidus externa (GPe) in the perceptual decision-making process. GPe has been already suggested to be essential in action selection;[73-75] subthalamic nucleus activity balances the direct inhibition, mediated by the caudate nucleus, with the SNpr; it delays reaction time until sufficient evidence has been accumulated and suppresses the selection of alternative options.[73,76]

Leisman *et al*., studied the contribution of BG and cerebellar loops in neuropsychological disorders.[4,5] Tourette's syndrome (TS) is a neurobehavioral disorder, which is characterized by involuntary motor and vocal tics; concomitant obsessive–compulsive disorder is also observed. Both tics and obsessive disorder arise due to fronto-cortical–basal ganglia–thalamo–cortical circuit dysfunction. An alteration in brain perfusion in patients with TS has been reported (cerebral blood flow [CBF] was significantly reduced in the central region, as well as the frontal, and parietal lobes, while it was increased in the cerebellum). Similarly, it has been shown that the pathologically reduced frontal cortex perfusion observed in these patients can be reversed by GPi and thalamus deep brain stimulation (DBS).[77]

In attention-deficit/hyperactivity disorder (ADHD), the cognitive control and the ability to inhibit inappropriate thoughts and actions is affected. Anatomical imaging studies using magnetic resonance imaging (MRI) have demonstrated reductions in volume in regions of the BG and prefrontal cortex in affected patients.[78] A reduction in volume in fronto-striatal

regions has been observed in ADHD patients compared to controls; moreover, these regions are less activated during tasks that require cognitive control.[79]

Behaviour

Houk proposed that the BG is involved in the selection and/ or initiation of cortical patterns of activation for both planned behaviour and thoughts.[80] Within areas 9 and 46, many neurons have cue- and delay-related activity that is tuned to the spatial position of stimuli (spatially-tuned activity) or the order in which the stimuli are present (sequentially-tuned activity). Area 12 appears to be much less involved in spatial and sequential information and more involved in remembering the identity of particular objects (object-tuned activity).

Throughout areas 9, 46, and 12, many neurons appear to be more involved in the learning and remembering of specific rules or associations used in the performance of conditional response (forced choice) tasks (rule-related activity).[6] A relatively small but consistent proportion of neurons in areas 9, 46, and 12 also display changes in activity that coincide with the expectation or anticipation of primary reinforcement or food rewards (reward-related activity).[81] Bilateral damage to area 9 in monkeys produces severe and long-lasting impairments in order monitoring and in the identification of different objects (but not spatial position), in particular, when the sequence of cues to be remembered is self-ordered.[6,82] Similarly, as evident from animal studies, BG lesions impair the acquisition of motor responses that are a conditional response to the discriminating stimuli.[21,22,83] Similar damage is seen in humans with dorsal prefrontal lesions,[84] leading to deficits in tasks that require the categorization and sorting of different stimuli,[85] or the planning and monitoring of script events or sequential actions.[86] These types of tasks are considered to impose significant demands on planning and short-term (or working) memory for objects or sequential actions. Experimental lesions of area 46 result in an inability of animals to perform spatial delayed-response tasks, spatial delayed-alternation tasks, and go/no-go tasks.[6,87]

Lesions of area 12 in monkeys produce an inability of animals to make switches in behavioural set. This leads to perseverative responses on delayed-response tasks, in which the identity of different objects or colors must be remembered (object matching, object reversal, or object alternation tasks), or to inappropriate responses in auditory-cued go/no-go tasks.[88] Large lesions of area 12 produce deficits in the learning and performance of visual discrimination tasks that do not involve delayed-responses.[6,89]

Widespread connectivity differences between healthy controls, precocious schizophrenic patients and patients with major depression has been seen. Decreased connectivity was found between the medial prefrontal area and a ventral mood processing region in major depressed patients compared to controls.[90]

A decreased connection network starting from the medial prefrontal area and ending in the orbital frontal cortex in schizophrenic patients has been shown. The dorsal anterior cingulate cortex is overactive early in schizophrenia, which might lead to decreased activity in the ventral anterior cingulate cortex, leading to affective symptoms and poor motivation.[91,92]

The role of BG in neuropsychiatric symptoms exhibited in Huntington's disease (that usually shows hyperactive disorders with agitation, euphoria, or anxiety) and PD (hypokinetic disorder with apathy) is well known. In the first case, the behavioural disorder may be caused by excitatory subcortical output through the medial and orbitofrontal circuits to the pallidum, thalamus, and cortex as well as premotor and motor cortex; whereas in PD, apathy results from hypostimulation of frontal subcortical circuits resulting from damage to putamen, striatum, and globus pallidus.

Memory and attention

Tasks that require sequential planning, monitoring of bilateral fine sequences, or learning of new movement sequences[6,93,94] produce sites of peak activations in lateral portions of area 9, such as for verbal working memory (including word generation tasks).[6,95] Further, area 46 is particularly active during spatial working memory tasks, difficult planning tasks, go/no-go tasks, some nonspatial object and verbal working memory tasks, and verb generation tasks,[96] during the generation and monitoring of multiple movement sequences involving the hand or fingers.[97,98] Prefrontal activations in areas 9 and 46 are related to the elaboration or learning of novel sequences compared to when the task is well learned.[6] The human equivalent of area 12 (area 47) has been shown to be active during tasks that employ verbal working memory, including word generation tasks,[6,99] but not during spatial working memory tasks. Brown and Marsden studied BG involvement on attention focus. The study was conducted among patients with PD who were incapable of carrying out dual tasks or self-monitoring,[100] as well as in carrying out simultaneous actions.[101] Patients with PD also have problems with covert[102] and overt attentional priming,[103] with set-shifting.[104,105] Hayes reports that the treatment of motor-symptoms with L-dopa medication results not only in the improvement of motor behavior, but also in attentional set-shifting, suggesting a regulatory role of dopamine in motor and attentional control. Loss of striatal dopamine also impairs predictive control (ability to use current information to adapt future behaviour).[106] Saint-Cyr speculates that the deficit in attentional control may result from two disrupted pathways, namely, the thalamo-cortical pathway and the thalamic nuclei under the control of the pallido-nigral projections. In addition, direct projections from the GPe to thalamic reticular shell nuclei may be essential because this mechanism modulates the signal-to-noise ratio of information processing.[107-110]

DBS has been showed to decrease "off" motor symptoms and motor fluctuations in PD; however, it may also induce amelioration of cognitive performances.[111-113]

Language

Abdullaev *et al.*, examined the role of caudate nucleus during reading, naming, recognition memory tasks, categorization, and lexical decision making tasks. They found that caudate nucleus cells exhibited excitatory responses related to both semantic and phonological-articulatory encoding and that the delay-related firing of cells was increased whenever semantic processing was required.[6,114] Comparing the properties of striatal cells with those seen in the prefrontal (Broca's) area as well as the temporal and parietal lobe areas, the authors found that the caudate nucleus cells had properties that were "strikingly similar" to those in Broca's area.

In monkeys, striatal cells are involved during sequential working memory test. Many of these cells had visual-related responses that varied according to the order of a given target; many of the caudate nucleus cells seemed to anticipate the fixation of specific targets. Shuvaev and Shefer[115] found that the task-related striatal cells could be separated into two distinct groups, with one group of cells clearly tuned to response execution and another group more involved in the instructional decision-making process.[6]

Ford *et al*., studied the connectivity between Broca's area and the BG, suggesting the involvement of BG in primary language functions.[116-121] BG are involved in language processing, mostly enhancing cortical signals for selected items and suppressing cortical signals for competing items.

Direct connectivity between the Broca's area and the putamen has been demonstrated, suggesting an involvement of both these structures in the articulatory process and initiation of phonological responses; a direct electrode stimulation of the anterior putamen area leading to a temporary speech deficit was found.[122-125]

The dorsal and ventral lateral prefrontal cortex of macaques projecting to the anterior putamen, are implicated in different language processing domains, such as phonological processing,[126,127] reading,[128] semantic processing, and semantic priming.[129] In monkeys, part of the caudate nucleus responds specifically to the sight of food or food rewards.[130-131]

Large portions of the GPi and SNpr contain neurons whose activity is not modulated by simple skeletomotor or oculomotor tasks. Many of these regions fall within the regions that innervate areas of the prefrontal cortex involved in cognitive processing. Hikosaka *et al*., recorded the activity of neurons in the SNpr of monkeys trained to perform an oculomotor spatial-delayed response task.[132,133]

More recently Ford *et al*., studied the Broca's area and striatal thalamic connections through a tractography study. The results suggested a correlation between the BG and the Broca's area, particularly, an input from two adjacent cortical areas subserving different but closely related language functions converging on the same region of the anterior putamen.[134]

Newer Aspects of the Role of Basal Ganglia: Their Possible Involvement in the Development of a Child's Brain

It has been known for a while that individuals who are markedly late in achieving developmental milestones are at a high risk of developing subsequent cognitive impairment.[135,136] The mechanisms underlying infantile motor and adult cognitive associations remain poorly characterized.[137] One possibility is that the neural systems that subserve motor development in infancy also contribute to the development and operation of specific cognitive processes later in life. These are not well defined but can include different higher cognitive functions, such as language or motor development or executive procedural networks.[138]

Murray *et al*.,[139] examined these questions in a large British general population birth cohort study, in which measurements were available for development in language and motor domains in infancy, general intellectual functions in childhood and adolescence, and specific neuropsychological functions (e.g., verbal fluency, a test of executive/frontal lobe function, etc.) in adulthood. These authors noted that[138] faster attainment of motor developmental milestones is related to better adult cognitive performance in some domains, such as executive function.[137]

The complete realization of complex acts and movements[140-143] is played out in a group of collectively functioning components, i.e., the sensory, motor, and anterior cingulate areas of the cortex, the intralaminar thalamic nucleus (in conjunction with the reticular nucleus), the amygdala, and the striatum. In mammals, the latter has a heterogeneous structure,[144] in which the continuous matrix is inter-digitated with the isolated striosomes. The input to the striatum appears to be more intimately connected to the components just identified. Given that striatal output reaches the primary motor cortex (M1) via the GPi, whereas the matrix output does not, it seems that the striatum may be more essentially related to consciousness and is much like the individual motor elements of the infant.[137-142] Likewise, the pars intermedia appears to be have more intimate associations with consciousness-related part of the cerebellum because it has analogous projections. Moreover, the threshold for overt movements may be exceeded only when both the feeding components are dispatching signals concurrently.[137] The matrix, conversely, appears to serve already-established motor patterns because its output ultimately reaches the PMA/SMA (premotor area/supplementary motor area) and the prefrontal area. Its cerebellar partner is clearly the hemispherical region.[145]

The focus of competition for attention appears to be the PMA/SMA because it receives inputs from all the thalamic nuclei handling basal ganglia/cerebellum, in which remote regions might influence attention.[137] The inferior olive seems to play a complementary role to the cerebellum, sending signals through the climbing fibers when something unexpected occurs.[146]

The periodic shifting of attention, as when we simultaneously converse (or merely think) and drive in a busy thoroughfare, must be making considerable demands on the putative differential clutch mechanism, and this could be the dual responsibility of the substantia nigra pc and the subthalamic nucleus, which appear to serve as gain control for the striosome-related and matrix-related routes, respectively. This situation is exemplified by our ability to think of one thing while overtly performing another act.[136]

For a given set of synaptic coupling between the premotor and supplementary motor areas, and the primary motor area, a specific pattern of output signals from the former will produce a specific sequence of muscular movements. Efferent copies of these output signals, dispatched through axon collaterals, will carry the full information sent to the muscles, via the motor area; however, they will not directly produce movement because their target neurons are not immediately concerned with motor output.[137,139,144] The duality of routes, and the fact that these overlap in the premotor and supplementary motor region, could well underlie the interplay between the

explicit and implicit in brain function. The parallel loops from the frontal cortex traverse via the striatum to basal ganglia and thalamus, and again towards the frontal cortex.[147] The complex regulating system through the striatal neurons serves to disinhibit the thalamic neurons.[148]

This disinhibition produces a gating function enabling other functions to occur, but does not directly causing them to occur, so that the activation of striatal neurons enables, but does not directly cause, subsequent motor movements.[137]

It has been suggested that whatever information is encoded by striatal neurons, it must be vastly compressed or eliminated on its way up to the frontal cortex. This constraint coincides with the gating hypothesis, i.e., the basal ganglia do not need to convey detailed information to the frontal cortex; instead, they simply need to inform different regions of the frontal cortex to update themselves when the need arises.[137]

Another constraint to consider concerns the number of different subregions of the frontal cortex, for which the basal ganglia can plausibly provide separate gating control. Leisman *et al*.,[137] suggested that the fine-grained gating is important for mitigating conflicts where two representations require separate gating control and yet fall within one gating region. The number of neurons in the GPi/SNr provides an upper limit estimate, which is roughly 320,000 in the human. This suggests that the gating signal operates on a region of frontal neurons, instead of individually controlling specific neurons.

An interesting possible candidate that may be responsible for determining the regions of the frontal cortex that is independently controlled by the BG is a distinctive anatomical structure called stripe, consisting of interconnected groups of neurons.[149] It is plausible that each stripe or cluster of stripes constitutes a separately controlled group of neurons; each stripe can be separately updated by the BG system,[136] which might extend the functional circuits described by Alexander *et al*.,[147] to a much finer grained level.[150] Thus, it is possible to maintain some information in one set of stripes, while selectively updating other stripes.[137]

As Leisman *et al*.,[137] emphatically pointed out, intelligence, in general, should be considered as the ability to consolidate already-learned motor patterns into more complex composites. This type of consolidation is sometimes merely a covert operation, rather than an overt one. This definition was discussed in the context of autism.[151,152] A normal child, lying on its back and wanting to roll over onto its front, soon learns that this can be readily accomplished if at first, the head, then the shoulders, and finally the hips are swiveled in the same direction. If the timing of this sequence is correct, the supine-prone transition requires minimum effort. Autistic infants appear to experience considerable difficulty in learning this simple motor sequence. Indeed, the sequence does not even occur in their failed attempts. Instead, they awkwardly arch their backs and ultimately fall into the desired position.[137]

The most spectacular feature to evolve thus far has been seen in mammals. This permitted acquisition, during a subject's own lifetime, of novel context-specific reflexes, especially those relying on the sequences of muscular movements. This mechanism makes heavy demands on the neural circuitry because it requires an attentional mechanism. As attention is an active process, there has to be feedback from the muscles, carrying information about their current state, including their current rate of change of state, which is where the action of the BG is required. Without such information, anticipation would be impossible, and there could be no meaningful decision on the most appropriate way of continuing an ongoing movement. Without such a mechanism, novel context-specific reflexes could not be acquired, when the the brake from BG to the frontal cortex is released.[137,153]

Abnormal motor development can accurately be used as a marker to predict autism and other developmental disorders.[154] Many authors have noted a relationship between incoordination and clumsiness, especially of posture and gait, and autism, as well as with other neurodevelopmental disorders. The type of gait and motor disturbances have been compared mostly in subjects where these appear to be either basal ganglionic or, more commonly, cerebellar in origin.[155] The most common of all comorbidities in practically all neurobehavioral disorders of childhood is the developmental coordination disorder (DCD) or more simply put "clumsiness" or motor incoordination. In fact, practically all children in this spectrum have some degree of motor incoordination. The type of incoordination is also usually of the same type, primarily involving the muscles that control gait and posture or gross motor activity (many times, cerebellar alterations have been implicated as the causative factor)[144] sometimes, to a lesser degree, fine motor coordination has also been affected.[136]

Parkinson's disease is an excellent model that is influenced by the BG control, and also strongly on the intimate relationship between the basal ganglia and the frontal cortex.[156-159]

Children with developmental disabilities including autism spectrum disorders and attention deficit/hyperactivity disorder (ADHD) demonstrate locomotor difficulties. ADHD and autistic spectrum individuals have reported significant motor difficulties, both fine and gross.[152,160]

Although it has been fairly well known that attention deficit disorders also have coincidental motor and balance disorders, what is lesser known and is more significant is the association between ADD/ADHD and motor controlled dysfunction (developmental coordination disorder [DCD]; clumsiness). Motor control issues were first noted in what were then called 'minimal brain dysfunction syndromes' (MBD). MBD was the term used to describe children of normal intelligence, with attention deficit and/or motor dysfunction (that is, suffering form "soft" neurological signs). Several studies by Denckla and others[161,162] have shown that association exists between ADHD, dyscoordination, and/or motor perceptual dysfunction.

In Asperger's syndrome, it has been noted that individuals have significant degrees of motor incoordination, and sometimes, executive problems affect writing and drawing skills,[163,164] as well as posture, gait, and gesture incoordination.[165,166]

What emerges from neuroimaging studies is astonishing; although the literature on fiber tracts is limited in ADHD,[167] Makris *et al*., noted that gray matter abnormalities suggest

that white matter connections may be altered selectively in neural systems. This finding is in confirmation with the findings of a prior study,[168] that using diffusion tensor magnetic resonance imaging (DT-MRI), showed alterations within the frontal and cerebellar white matter in children and adolescents with ADHD. To this end, the cingulum bundle (CB) and superior longitudinal fascicle II (SLF II) were investigated *in vivo* in 12 adults with childhood ADHD using DT-MRI. Relative to controls, the fractional anisotropy (FA) values were significantly smaller in both regions of interest in the right hemisphere, in contrast to a control region (the fornix). This indicated the presence of an alteration of anatomical connections within the attention and EF (Executive Function) cerebral systems in adults with childhood ADHD. The demonstration of FA abnormalities in the CB and SLF II in adults with childhood ADHD provides further support for persistent structural abnormalities that persist into adulthood.[137]

Other works have observed that, in children with ADHD,[164] frontal-subcortical connections are disrupted by subcortical dysfunction showing decreased glucose consumption in the frontal cortex, along with a decrease in the nigrostriatal D2 receptor uptake ratios. When boys suffering from ADHD were tested, there appeared to be a clear difference in the activity of the BG. These children have less activity in that area than the control children. After administering methylphenidate, boys with ADHD had increased activity in the BG whereas normal boys had decreased activity in the BG.[137]

A similar finding was noted when PET scans were perfomed in patients with hyperactivity disorder, where a normal appearing frontal metabolism existed with decreased caudate and putamen metabolism.[165,169] Methylphenidate, a dopamine reuptake inhibitor, may increase the functioning in a previously dysfunctional BG, whereas raising dopamine levels in normal individuals would most likely result in decreased activity of the basal ganglia in order to prevent overproduction of dopamine. Increasing dopamine levels may increase frontal metabolism due to an increased activity of the striatum. This would lead to a decreased firing of the globus pallidus, thereby inhibiting the thalamo-cortical firing, which in turn decreased the hyperkinetic behavior.[136]

Anatomical imaging studies using MRI have demonstrated subtle reductions in volume in regions of the BG and prefrontal cortex.[170-173]

Quiu *et al*.[174] employed large deformation diffeomorphic metric mapping (LDDMM) to examine the effects of ADHD, gender, and their interaction on the BG shapes. The BG (caudate nucleus, putamen, globus pallidus) were manually delineated on MRI from normally developing children and children with ADHD. It has been found that boys with ADHD showed significantly smaller BG volumes compared with normally developing boys. The LDDMM also revealed that the groups remarkably differed in the basal ganglia shapes. Volume compression was seen bilaterally in the caudate head and body and anterior putamen as well as in the left anterior globus pallidus and right ventral putamen in patients with ADHD. Volume expansion was most pronounced in the posterior putamen. They concluded that the shape compression pattern

of BG in ADHD suggests an atypical brain development involving multiple frontal-subcortical control loops, including circuits with premotor, oculomotor, and prefrontal cortices.[175]

Moreover, also considering the necessity of voluntary control of motor action, it is important not only to detect the motor areas, which start action and release it, but also the area where motor act can be stopped; the 'go' process is likely to be generated by the premotor areas that project via the direct pathways of the BG (through striatum, pallidum, and thalamus), eventually exciting the primary motor cortex and generating corticospinal volleys to the relevant effectors, each interacting with the globus pallidus.[175] Aaron *et al*.,[176] brilliantly outlined the nature of inhibition in the fronto-basal-ganglia networks related to cognition. They collected evidence indicating that the right inferior frontal cortex (IFC) is the critical region for 'stop' signal response inhibition,[177] with the most critical portion likely being the pars opercularis (Brodmann area 44) in humans. The right IFC can send a 'stop' command to intercept the 'go' process via the activation of the globus pallidus through a projection from the STN.[175] Thus, once the 'stop' command is generated in the frontal cortex, it could be rapidly conveyed to the BG via the so-called "hyperdirect pathway" to intercept the 'go' process in the final stages of the race.[137]

In summary, BG, through their control on motor act and its refinement, can modulate the intelligence process to permit an interface of the human beings with the environment; this way 'go/no go' strategies determine our reaction times and their destruction or their impairment may be responsible for various cognitive manifestations of autism, ADHD, mental retardation, and Asperger syndrome.

Consideration and Conclusions

The physiological properties of many neurons in the striatum and pallidum of humans, as well as primates appear to be similar in many aspects such as those reported in studies of the physiology of the prefrontal cortex.

In addition to BG circuits, another system appears to be operating across circuit boundaries that integrates information about the rewarding value of a behavioral act. Shultz proposed that the neural substrate for this reward system is the phasic activity of dopamine synthesizing cells in the SNpc, which convey information regarding primary reinforcement and behavioural state to cells in the striatum. As such influences exist throughout the striatum, it is quite likely that many, if not all, BG circuits utilize the reward-related information to modify the properties of cells within them to carry out meaningful behavioral acts.[9,178,179] Owen *et al*., compared the activity of normal individuals and PD patients during the performance of a difficult planning task, a spatial working memory task, and a simple visually guided movement task.[180,181] PD patients had very little GPi activation during the cognitive tasks, compared to normal individuals; the greatest differences occurred in tasks with most cognitive demands; and, no differences were found in GPi activation in the simple motor task.[182-185]

The connection of BG with the prefrontal cortex suggests that it has different roles in cognition, memory, and emotion; this connection appears to be disrupted in psychiatric and

neurodegenerative diseases, in which disconnection with major feedback pathways to the neuraxis is also seen.

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