
1 Clinical Motor and Cognitive Neurobehavioral 2 Relationships in the Basal Ganglia

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4 Additional information is available at the end of the chapter

5 <http://dx.doi.org/10.5772/55227>

6 **1. Introduction**

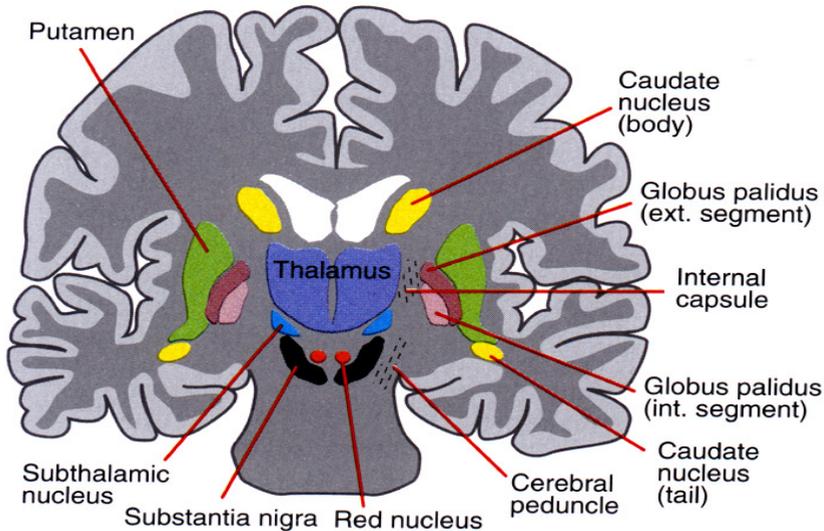
7 The traditional view that the basal ganglia and cerebellum are simply involved in the
8 control of movement has been challenged in recent years. One of the pivotal reasons for this
9 reappraisal has been new information about basal ganglia and cerebellar connections with
10 the cerebral cortex. In essence, recent anatomical studies have revealed that these
11 connections are organized into discrete circuits or 'loops'. Rather than serving as a means for
12 widespread cortical areas to gain access to the motor system, these loops reciprocally
13 interconnect a large and diverse set of cerebral cortical areas with the basal ganglia and
14 cerebellum. The properties of neurons within the basal ganglia or cerebellar components of
15 these circuits resemble the properties of neurons within the cortical areas subserved by these
16 loops. For example, neuronal activity within basal ganglia and cerebellar loops with motor
17 areas of the cerebral cortex is highly correlated with parameters of movement, while
18 neuronal activity within basal ganglia and cerebellar loops with areas of the prefrontal
19 cortex is more related to aspects of cognitive function. Thus, individual loops appear to be
20 involved in distinct behavioral functions. Studies of basal ganglia and cerebellar pathology
21 support this conclusion. Damage to the basal ganglia or cerebellar components of circuits
22 with motor areas of cortex leads to motor symptoms, whereas damage of the subcortical
23 components of circuits with non-motor areas of cortex causes higher-order deficits. In this
24 report, we review some of the new anatomical, physiological and behavioral findings that
25 have contributed to a reappraisal of function concerning the basal ganglia and cerebellar
26 loops with the cerebral cortex.

27 **2. The basal ganglia in the context of behavior**

28 The basal ganglia is part of a neuronal system that includes the thalamus, the cerebellum
29 and the frontal lobes [1]. Like the cerebellum, the basal ganglion was previously thought to

2 Basal Ganglia

1 be primarily involved in motor control. However, recently there has been much written
2 about and the role of the basal ganglia in motor and cognitive functions has now been well
3 established [2-6].



4
5 **Figure 1.** The basal ganglia that clinical include clinically includes subthalamic nucleus & substantia
6 nigra whose component structures are highly interconnected. The striatum is associated with input
7 signal and output associated with the globus pallidus & substantia nigra.

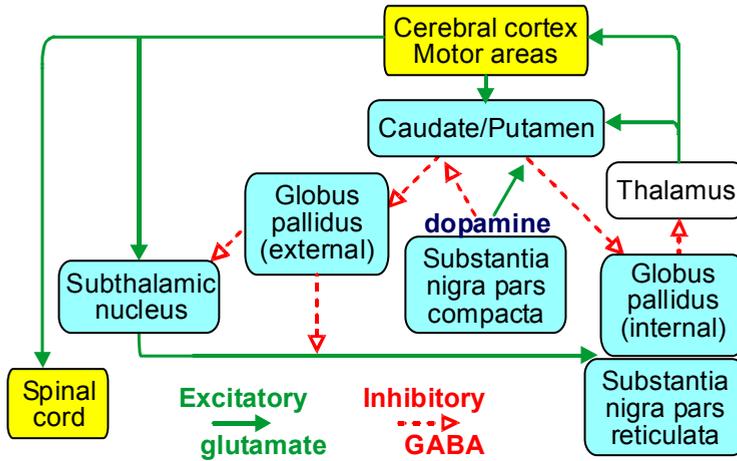
8 The basal ganglia is located in the diencephalon and is made up of five subcortical nuclei
9 (represented in Fig.1): globus pallidus, caudate, putamen, substantia nigra and the
10 subthalamic nucleus of Luys. The basal ganglia is thought to have expanded during the
11 course of evolution as well and is therefore divided into the neo and paleostriatum. The
12 paleostriatum consists primarily of the globus pallidus, which is derived embryologically
13 from the diencephalon. During the course of its development it further divides into two
14 distinct areas, the external and internal segments of the globus pallidus. The neostriatum
15 is made up of two nuclei, the caudate and putamen. These two nuclei are fused anteriorly and
16 are collectively known as the striatum. They are the input nuclei of the basal ganglia
17 and they are derived embryologically from the telencephalon. The subthalamic nucleus of Luys
18 lies inferiorly to the thalamus at the junction of the diencephalon and the mesencephalon or
19 midbrain. The substantia nigra lays inferiorly to the thalamus and has two zones similar to
20 the globus pallidus. A ventral pole zone called pars reticulata exists as well as a dorsal
21 darkly pigmented zone called the pars compacta. The pars compacta contains dopaminergic
22 neurons that contain the internum. The globus pallidus internum and the pars reticulata of
23 the putamen are the major output nuclei of the basal ganglia. The globus pallidus internum
24 and the pars reticulata of the putamen are similar in cytology, connectivity, and function.
25 These two nuclei can be considered to be a single structure divided by the internal capsule.
26 Their relationship is similar to that of the caudate and putamen. The basal ganglia is part of

1 the extrapyramidal motor system as opposed to the pyramidal motor system that originates
2 from the sensory-motor cerebral cortex. The pyramidal motor system is responsible for all
3 voluntary motor activity except for eye movement. The extrapyramidal system modifies
4 motor control and is thought to be involved with higher-order cognitive aspects of motor
5 control as well as in the planning and execution of complex motor strategies, as well as the
6 voluntary control of eye movements. There are two major pathways in the basal ganglia, the
7 direct pathways, which promote movement, and the indirect pathways, which inhibit
8 movement.

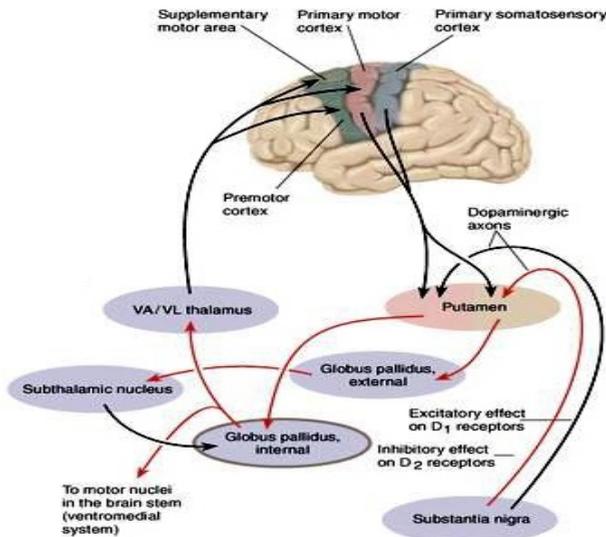
9 The basal ganglia receive afferent input from the entire cerebral cortex but especially from
10 the frontal lobes. Almost all afferent connections to the basal ganglia terminate in the
11 neostriatum (caudate and putamen). The neostriatum receives afferent input from two
12 major sources outside of the basal ganglia, the cerebral cortex (cortico-striatal projections),
13 and the intralaminar nucleus of the thalamus. The cortico-striatal projections contain
14 topographically organized fibers originating from the entire cerebral cortex. An important
15 component of that input comes from the centro-median nucleus from the thalamus and
16 terminates in the putamen. Because the motor cortex of the frontal lobes projects to the
17 centro-median nucleus, this may be an additional pathway by which the motor cortex can
18 influence the basal ganglia. The putamen appears to be primarily concerned with motor
19 control whereas the caudate appears to be involved in the control of eye movements and
20 certain cognitive functions. The ventral striatum is related to limbic function, and therefore
21 may affect autonomic and emotional functions.

22 The major output of the basal ganglia arises from the internal segment of the globus pallidus
23 and the pars reticulata of the substantia nigra. The nuclei project in turn to three nuclei in
24 the thalamus, the ventral lateral nuclei, the ventral anterior nuclei, and the mesio-dorsal
25 nuclei, as well as the anterior thalamic nuclei. Internal segments of the globus pallidus
26 project to the centro-median nucleus of the thalamus. Striatal neurons may be involved with
27 gating incoming sensory input to higher motor areas such as the intralaminar thalamic
28 nuclei and *premotor* cortex that arise from several modalities to coordinate behavioral
29 responses. These different modalities may contribute to the perception of sensory input [7]
30 leading to motor response. The basal ganglia are directed, in a way similar to the
31 cerebellum, to premotor and motor cortices as well as the prefrontal cortex of the frontal
32 lobes.

33 Experiments where Herpes simplex virus 1 (HSV-1) was administered into the dorsal lateral
34 prefrontal cortex of monkeys to determine its axonal spread or connection, labeled the
35 ipsilateral neurons in the internal segments of the globus pallidus and the contralateral
36 dentate nucleus of the cerebellum [8]. It is therefore thought that this may show a role of
37 both the cerebellum and basal ganglia in higher cognitive functions associates with the
38 prefrontal cortex. This would also substantiate a cortico-striato-cerebello-thalamo-cortical
39 loop, which would have a cognitive rather than motor function, exemplified in Fig. 2 below.
40 The putamen is also thought to connect to the superior colliculus through non-
41 dopaminergic axons that forms an essential link in voluntary eye movement.



1
 2 **Figure 2.** Circuitry of the basal ganglia. The cerebral cortex (and thalamus) projects to the striatum
 3 (excitatory pathways). The striatum also receives dopaminergic projections from the substantia nigra's
 4 pars compacta (SNc). The striatum inhibits the globus pallidus (GP) as well as the substantia nigra's
 5 pars reticulata (SN pr). The STN sends excitatory projections to the GPi, GPe & SNpr. GPi or SN pr
 6 inhibits (GABAergic) the thalamus. The thalamus projects to the cortex (also excitatory). The direct path
 7 leads to less inhibition of the thalamus, (i.e. the striatum inhibits GPi which in turn inhibits its normal
 8 (inhibitory) action on the thalamus, thus leading to greater excitation from the thalamus to the cortex.
 9 This allows for sustain actions or initiation of action. The indirect path excites the GPi thereby
 10 increasing its inhibition of the thalamus and thus suppresses unwanted movements.



11
 12 **Figure 3.** Cortical-basal ganglia pathways. All regions of cerebral cortex project to the basal ganglia, but
 13 output of basal ganglia is directed towards the frontal lobe, particularly pre-motor and supplementary
 14 motor cortex.

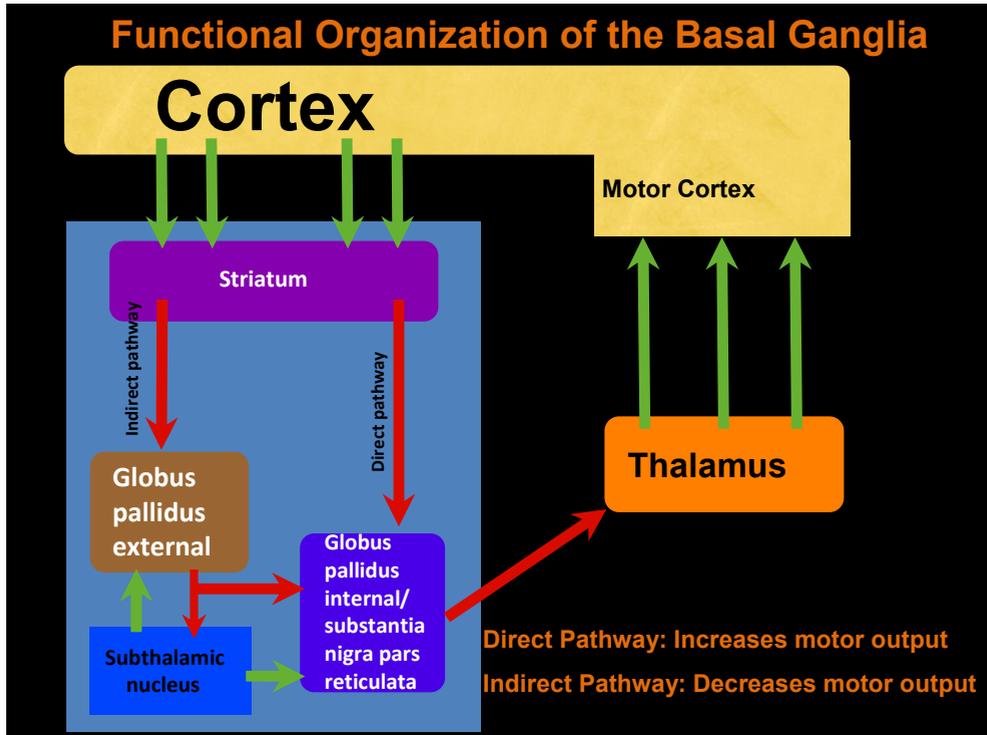
1 It is thought that normal basal ganglia function results from a balance of the direct and
2 indirect striatal output pathway and different involvement of these pathways account for
3 hyperkinesia or hypokinesia observed in disorders of the basal ganglia [9]. Hypokinesia is a
4 disinhibition or increase in spontaneous movement (tics, tremors). It is thought that
5 hypokinesia and hyperkinesia may relate to hypoactive behavior and hyperactive behavior
6 associated with subcortical hypo-stimulation or hyper-stimulation of medial and orbito-
7 frontal cortical circuits [10]. It is important to review these connections further to
8 understand the role of basal ganglia in control of cognitive function.

9 Five fronto-subcortical circuits unite regions of the frontal lobe (the supplementary motor
10 area; frontal eye fields; dorsolateral, prefrontal, orbito-frontal and anterior cingulate
11 cortices) with the striatum, globus pallidus and thalamus in functional systems that mediate
12 volitional motor activity, saccadic eye movements, executive functions, social behavior and
13 motivation [10,11].

14 **3. Direct and indirect pathways**

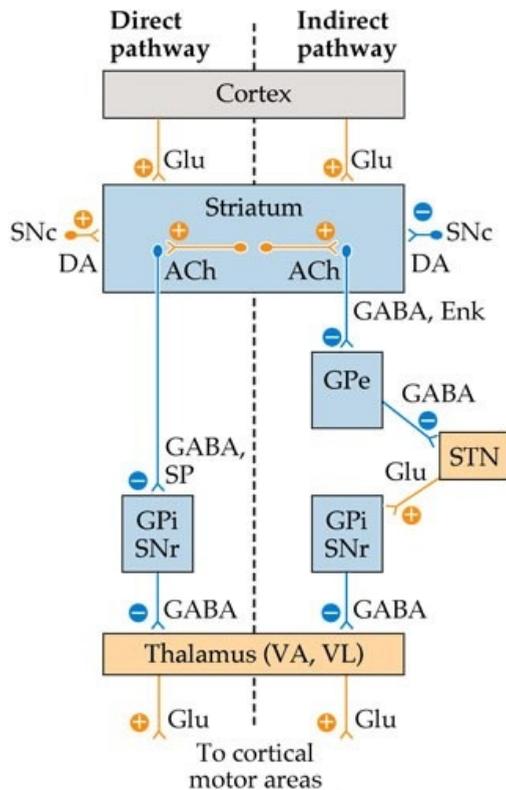
15 Five major cortical to subcortical loops exist that make up cortico-striatal pathways. All
16 cortical pathways initiate the direct and indirect pathways with the basal ganglia through
17 excitatory glutamatergic cortico-striatal fibers (the general circuitry is described in Fig. 3 and
18 direct and indirect pathways exemplified in Fig. 4). The direct pathway from the striatum
19 sends GABA fibers (associated with dopamine receptors) from the striatum to the *globus*
20 *pallidus* and putamen. The indirect pathway sends inhibitory GABA/enkephalin fibers
21 (associated with D2 dopamine receptors) from the striatum to the globus pallidus. Indirect
22 pathways then continue with inhibitory GABA fibers from the globus pallidus to the
23 subthalamic nucleus of Luys. Indirect excitatory glutamatergic fibers then connect from the
24 subthalamic nucleus to the globus pallidus and putamen. The basal ganglia then sends
25 inhibitory outflow by GABA fibers from the globus pallidus and putamen to specific
26 thalamic nuclei. The thalamus has excitatory fibers that return to the cortex [10].
27 Abnormalities of direct and indirect pathways result in different pathological functions.

28 The nature of the balance between components of these pathways is described in greater
29 detail in the section below and described in Figs. 3-5. Hyperkinetic disorders (increased
30 movement) are thought to be a selective loss of GABA/enkephalinergic intrinsic striatal
31 neurons projecting to the lateral globus pallidus and substantia nigra. This results in
32 decreased inhibitory stimulation to the thalamus leading to increased activity of the
33 excitatory glutamatergic thalamocortical pathways and in turn greater neuronal activity in
34 the premotor-motor and supplementary motor cortices [12]. The result is over-facilitation of
35 motor programs resulting in increased motor activity. Hypokinetic disorders (decreased
36 movement) are associated with decreased dopaminergic nigrostriatal stimulation from the
37 substantia nigra to the striatum. This results in both excess outflow of the indirect striatal
38 pathway and an inhibited direct striatal pathway. Both of these pathways increase thalamic
39 inhibition and therefore decrease thalamocortical stimulation of motor cortical areas
40 resulting in hypokinesia or decreased output of the frontal cortex [10,13,14]. It is possible



1
2 **Figure 4.** Direct and Indirect pathways. Direct pathway runs: Cortex→striatum→GPI→
3 thalamus→cortex. Two links are excitatory & two inhibitory, so the net effect of the whole
4 sequence is excitatory. The cortex excites itself via the direct pathway. The Indirect pathway runs:
5 cortex→striatum→GPe→ STN→Gpi→thalamus→cortex. Three links are inhibitory and two excitatory,
6 so the net effect of the sequence is inhibitory: The cortex inhibits itself via the indirect pathway. The
7 total effect of basal ganglia upon the cortex results from complex interplay between these two
8 pathways.

9 that the difference between hypokinetic and hyperkinetic syndromes may be different only
10 in the timing and or the severity of the dysfunction. In this model, decreased thalamic
11 excitation of the frontal cortex results in decreased excitation of the cortico-striatal fibers of
12 the neostriatum. The neostriatum therefore decreases its inhibitions of the globus pallidus.
13 There is then increased inhibition of the thalamocortical pathways leading to progressive
14 hypokinesia. Eventually the lack of striatal inhibition of the globus pallidus results in its
15 metabolic dysfunction and the rapid loss of GABA neurons. This can then result in
16 decreased inhibition of thalamocortical pathways causing a sudden onset of hyperkinesia
17 (increased movement) with the increased thalamic firing of the frontal cortex. There also
18 appear to exist cognitive symptoms that parallel the motor effects. Previous studies have
19 shown that patients with hyperkinetic, hypokinetic, Tourette's, and Obsessive-Compulsive
20 disorders may exhibit neuropsychiatric disturbances such as apathy, depression, agitation,
21 or excitability [15-20].



1
 2 **Figure 5.** Circuit diagram for direct & indirect pathways. *Neurotransmitters:* Ach, acetylcholine; DA, dopamine; Glu, glutamate; Enk, enkephalin; SP, substance P. *Nuclei:* SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; STN, subthalamic nucleus; VL, ventral lateral nucleus; VA, ventral anterior nucleus.

6 **4. Clinical behavioral implications of pathway activity balance**

7 Most disorders that involve the basal ganglia produce dysfunction by promoting an
 8 imbalance between the direct and indirect pathways. An increase in the relative activity in
 9 the direct pathways results in hyperkinetic movements and behaviors. This has been
 10 hypothesized to be a result of decreased activity of the indirect or increased activation of the
 11 direct pathway [11,13,14]. Increased relative activity in the indirect pathway is associated
 12 with hypokinetic movement and behaviors [21-23]. The majority of input to the basal
 13 ganglia comes from a top down direction through the five loops from the frontal lobe [24]
 14 referenced above. The premotor and supplementary motor areas, frontal and supplemental
 15 eye fields, the orbital frontal cortex, the dorsal lateral prefrontal cortex, and the anterior
 16 cingulate all connect into the basal ganglia governing voluntary motor activity, voluntary
 17 saccadic eye movement, social behavior, executive function, and motivation. These are then

1 connected to various areas within the thalamus and back to the cortex. The indirect pathway
2 increases the output of the globus pallidus internis [25,26] and increases the inhibition of the
3 thalamus and motor activity or behaviors. Increase in direct pathway function inhibits the
4 output of the globus pallidus thereby promoting increased movement and cognitive
5 behaviors.

6 One of the main clinical questions especially in the absence of any obvious damage or
7 pathology is what promotes a functional imbalance between these pathways (represented in
8 Fig. 5). Various disorders such as ADHD, Tourette's, OCD among other are known to
9 involve the basal ganglia. In these disorders there is hyperkinetic movement and or
10 behaviors that coincide with the particular loop that is affected, but in all cases the increase
11 seems to be in the direct loop not the indirect loop [9,11,17-21].

12 The principle question here is why these disorders would target an increase in this pathway
13 in particular. One of the differences may have to do with the receptors that are involved in
14 one pathway more than the other. The D1 receptor is known to be found in the direct
15 pathway while the D2 receptor is found in the indirect loop. The nigrostriatal pathway is
16 believed to help promote movement through its dopaminergic activity in the zona compacta
17 by connecting to the Putamen and increasing the activity of the D1 receptor and inhibiting
18 the D2 receptor [27]. Parkinson's Disease which is manifest as a hypokinetic disorder is, in
19 part, related to this loss of increased activity to the direct pathway following degeneration of
20 the dopaminergic neurons in the zona compacta. Using this as an example, other pathways
21 that connect and enhance one receptor over the other is a way to functionally bias
22 complementary pathways. We can understand the direct pathway as a behavioral activating
23 pathway and the indirect as the behavioral inhibiting pathway [28]. This description can
24 also be applied to the two cerebral hemispheres and their role in behavioral control. The
25 left hemisphere is thought to promote approach behaviors [29,30], motor activity [24],
26 intention [29] and positive emotions [30]. The right hemisphere is thought to promote
27 withdrawal behavior [29], sensory and attentional activity [29], and negative affect [29]. The
28 left hemisphere promotes motor and increases behavioral activity and motivation while the
29 right hemisphere is known to do the opposite [29]. Therefore it is reasonable to assume that
30 when utilizing top-down control, the two cerebral hemispheres may differentially enhance
31 or inhibit motor activity and cognitive behavior.

32 The premotor areas and frontal eye fields increase volitional as well as involitional motor
33 activity and saccadic eye movements [31], the left orbital frontal cortex increases social
34 motivation and awareness [29], the left dorsal lateral prefrontal cortex increases executive
35 and cognitive function [24,30], while the left anterior cingulate increases motivation [29].
36 The right hemisphere decreases or inhibits those same pathways [32]. This would give even
37 greater top-down control over these behaviors and it would make sense that this is done by
38 enhancing the direct or indirect pathway.

39 The left hemisphere would promote and increase movement and behavior by selectively
40 increasing the direct pathways perhaps by favoring the D1 receptors in the caudate and or
41 putamen. The right hemisphere could promote the indirect pathway function by selectively

1 enhancing or stimulating the D2 receptors in these same areas. Since many of the
2 hyperkinetic disorders like ADHD, Tourette's and OCD have all been associated with a
3 decreased function of the right hemisphere and an increased function of left hemisphere
4 activity [24,33,34] that would also seem to fit with the argument that a decrease in right
5 hemisphere function would be associated with an increase in left hemisphere function and
6 enhancement of the direct pathway and the D1 receptor promoting hyperkinetic movement
7 and behaviors.

8 The right hemisphere could also have stronger connections to the subthalamic nucleus of
9 Luys which would also enhance the indirect pathway whereas stronger left hemisphere
10 connections to the caudate and putamen may also enhance direct pathway activation over
11 indirect [14]. There are other receptors that could be selectively targeted by one hemisphere
12 more than the other. The hemispheres are well documented to have this type of differential
13 top-down control over other functions such as the immune system [35], autonomic system
14 [30] as well as top down control of sensory processing at the thalamic level with cortico-
15 thalamic fibers outnumbering thalamocortical fibers by a 10 – 1 ratio [36].

16 The recent discovery of a hyperdirect pathway [37] confirms that this hemispheric
17 relationship exists and in fact it seems to affect both pathways as we described. The right
18 hemisphere generally is known to be more involved with behavioral inhibition whereas the
19 left hemisphere generally is involved in behavioral excitation. This effect in part seems to be
20 due to the relationship between the cortex, and the prefrontal cortex and basal ganglia. The
21 five primary loops from the frontal lobe to the basal ganglia as we described include the
22 premotor cortex for movement, the orbital frontal cortex for social behavior, the dorsolateral
23 prefrontal cortex controls executive function, the anterior cingulate regulates motivation,
24 and the frontal eye fields control saccadic eye movements. Together these loops help to
25 regulate all human behaviors. The left hemisphere control appears to have an excitatory
26 influence whereas the right hemisphere seems to subservise primarily an inhibitory control of
27 these functions. This appears to mainly be accomplished by the hyperdirect pathway of the
28 right hemisphere. The hyperdirect pathway accomplishes this through its influence on the
29 D2 receptor which initiates the indirect pathway. This pathway increases the inhibitory
30 output of the GPi and its influence on the thalamic relay nuclei.

31 The second way that the right hemisphere exerts this inhibitory control is through the
32 hyperdirect connection from the inferior frontal gyrus directly through an excitatory
33 glutamatergic connection to the subthalamic nucleus of Luys. This increases the output of
34 excitatory connections to the Gpi and an inhibitory connection to the GPe, which is
35 inhibitory to the SNL. This also activates the indirect pathway increasing the inhibitory
36 output of the GPi to the thalamus. Without this activity, the left hemisphere will have a
37 relatively increased output to the D1 receptor activating the direct pathway, which
38 decreases the output of the GPi through its inhibitory GABAergic connections. This, in
39 turn, decreases the inhibition of the thalamic nuclei thereby increasing activity in these
40 prefrontal loops. The clinical implications of this are significant especially in functional
41 lesions of the brain where there are no anatomic lesions but rather a primary imbalance
42 between the direct and indirect pathways.

1 A functional imbalance and/or a functional disconnection between the two hemispheres,
2 that may be the result of an activation imbalance in the cortex between the two hemispheres,
3 can lead to an imbalance in these loops producing either hyperkinetic or hypokinetic
4 disorders. This would explain why symptoms of hyperkinetic disorders like ADHD also
5 seem to be associated with a decrease in many right hemisphere functions along with
6 relative increases in left hemisphere functions. This also would mean that therapeutically
7 increasing the activation through target stimulation to one hemisphere and possibly to one
8 or more dysfunctioning basal ganglionic loops may help to restore a balance and temporal
9 coherence between the hemispheres and between the direct and indirect loops.

10 For instance if someone is experiencing symptoms of OCD they have obsessions and
11 compulsions in the absence of a specific lesion in the basal ganglia and specifically in the
12 indirect pathway, this may be explained by decreased activation in the loops that involve
13 the premotor cortex which control motor activity (compulsions) and the dorsolateral
14 prefrontal cortex which controls executive functions, planning and behavior (obsessions) on
15 the right hemisphere. This may result in a relative increase in those same loops on the left
16 hemisphere leading to a relative increase of the direct pathway over the indirect pathway in
17 those specific loops leading to OCD symptoms.

18 If this is the case then providing specific targeted stimulation to the premotor areas and the
19 dorsolateral prefrontal cortex on the right hemisphere with the proper frequency, intensity
20 and duration may produce an equilibration between the loops in those hemispheres and in
21 the direct and indirect pathways. This may provide the best therapeutic option because it is
22 specific, noninvasive and can provide long term correction which would be the ultimate
23 goal.

24 **5. Dynamic inter-regional effects**

25 Disconnection syndromes were originally conceptualized as a disruption of communication
26 between different cerebral cortical areas [30,31]. Schmahmann and Pandya [38] in an elegant
27 review, indicate that the concept could be expanded. In overviewing their anatomical
28 studies of monkeys, they found that efferent fibers emanate from every cortical area, and are
29 directed with topographic precision via association fibers to ipsilateral cortical areas,
30 commissural fibers to contralateral cerebral regions, striatal fibers to basal ganglia, and
31 projection subcortical bundles to thalamus, brainstem and/or pontocerebellar system. They
32 concluded that cortical areas are definable by their patterns of subcortical and cortical
33 connections.

34 In applying their findings to humans, they note that motor, cognitive and neuropsychiatric
35 disorders in patients with basal ganglia lesions, as well as those of the thalamus, or
36 cerebellum, tend to mimic deficits resulting from cortical lesions, with qualitative
37 differences between the manifestations of lesions in functionally related areas of cortical and
38 subcortical nodes. These basal ganglia based behavioral conditions are viewed by
39 Schmahmann and Pandya as disconnection syndromes reflecting loss of the contribution of
40 subcortical nodes to the distributed neural circuits. They concluded that neural architecture

1 determines function, i.e., each architectonically distinct cortical and subcortical area
2 contributes a unique transform, or computation, to information processing as suggested by
3 Leisman and Melillo [30]. Anatomically precise and segregated connections between nodes
4 define behavior and association fiber tracts that link cerebral cortical areas with each other
5 enable the cross-modal integration required for evolved complex behaviors.

6 Co-contraction of muscle groups is realistically the co-activation of competing motor
7 programs that serves as a fundamental mechanism used to achieve postural
8 stabilization. Thus motor and cognitive signs associated with basal ganglionic lesions
9 should also have a postural component that aids clinicians in the identification of lesions as
10 well as providing a window for outcome observations when dealing with cognitive strategy
11 efficacy.

12 The effective function involving the basal ganglia is traditionally thought to be achieved via
13 a balance of excitation and inhibition of competing motor programs. In the context of this
14 review, cognitive and motor functions need to be linked with postural control
15 systems. These systems are known to be dynamic, rather than static. Hyperkinetic
16 dystonias, for example, reflect excessive function of dynamic postures, rather than abnormal
17 movements. Anne Blood [39] has suggested that the range of functional roles served by the
18 postural system is hypothesized to include direct control of movement, suggesting a
19 postural basis for task-specific dystonias. Further, by defining posture as a neural system
20 that maintains body stabilization, it can be shown that the range of mechanical means of
21 implementing stabilization, including co-contraction of antagonistic muscles, matches the
22 range of presentations of dystonia reflecting abnormal integration in the basal ganglia.
23 Inhibitory influences that stabilizing mechanisms exert on movement, suggest that the
24 broad functional role of posture may be the function served by the indirect pathway of the
25 basal ganglia. Specifically, the integrated pathway that centrally coordinates function of the
26 distributed network of brain regions controlling posture and, in conjunction with the direct
27 pathway, coordinates posture and movement. Postural systems are probably involved in
28 cognition as well as the motor volitional and reflexogenic parameters of basal ganglionic
29 influence. The involvement of posture in the basal ganglia and behavioral relationships is
30 further supported by Marsden and Rothwell [41] who noted that co-contraction is
31 realistically the co-activation of competing motor programs that serves as a fundamental
32 mechanism used to achieve postural stabilization.

33 Numerous other investigators have recently begun to notice the relationship of posture to
34 basal ganglia and cognitive function serving as a basis for the clinical discussions in the
35 subsequent section. Mitra and colleagues [40] noted that the performance of a cognitive task
36 while maintaining upright stance is associated with changes in body sway depending on
37 tasks and experimental conditions. As increased sway is taken to indicate loosened postural
38 control the precise impact of cognitive load on postural stability has remained unclear.
39 These investigators noted that body sway increased during cognitive tasks while quiet
40 standing but not while performing a visuo-postural alignment task suggesting that
41 constraints placed on posture control by supra-postural task goals may significantly alter
42 interactions between posture control and cognitive task.

1 Fujiwara and associates [42] investigated the effect of neck flexion on discriminative and
2 cognitive processing in postural control during bilateral arm movement while standing,
3 using event-related potential (ERP) and electromyogram. They noted significant positive
4 correlations with neck flexion and P3 latency and anterior deltoid reaction time, and
5 between N2 latency and the onset time of erector spinae, suggesting that with neck flexion,
6 attention allocation to discriminative and cognitive processing increases, and the processing
7 speed increases with shortening of reaction time in focal muscles.

8 Thus there is enough preliminary evidence to indicate that motor and cognitive signs
9 associated with basal ganglionic lesions should also have a postural component that would
10 aid clinicians in the identification of lesions as well as providing a window for outcome
11 observations when dealing with cognitive strategy efficacy.

12 **6. Clinical implications**

13 It has been hypothesized that neuropsychiatric symptoms exhibited by patients with basal
14 ganglia disorders are a consequence of an involvement of fronto-striatal connections. In
15 addition to expressing contrasting motor dysfunction patterns, these disorders would also
16 differ in the presenting psychiatric symptoms [10]. In this study patients with Huntington's
17 disease (hyperkinetic) and Parkinson's disorder (hypokinetic) were observed to determine if
18 they would present with hyperactive behavior (agitation, isolation, euphoria, or anxiety)
19 and hypokinetic behavior (apathy) respectively. The results of this study demonstrated that
20 patients with Huntington's (hyperkinetic) more frequently exhibited hyperactive behaviors
21 such as agitation, irritability, euphoria, and anxiety whereas patients with Parkinson's
22 (hypokinetic) frequently displayed hypoactive behavior (high levels of apathy). The
23 investigators thought that in Huntington's, these behaviors result from excitatory
24 subcortical output through the medial and orbito-frontal circuits to the pallidum, thalamus,
25 and cortex as well as premotor and motor cortex. In contrast, patients with Parkinson's
26 (hypoactive) in whom apathy is present were thought to demonstrate these behaviors as a
27 consequence of hypo-stimulation of frontal subcortical circuits resulting from damage to
28 several integrated nuclei (putamen, striatum and globus pallidus) [14,43,44].

29 It had been previously noted that patients with Huntington's and other hyperkinetic
30 disorders like Tourette's exhibit mania, OCD, and intermittent explosive disorder [45,46-48].
31 PET studies of Huntington's patients without hyperactive behavior have shown frontal
32 metabolism to be normal but with decreased caudate and putamen metabolism [49,50].
33 However is it thought that normal frontal metabolism in Huntington's may result from a
34 coexistent neurological degeneration and the resultant thalamo-frontal hyper-stimulation.
35 This may result in normal appearing frontal-cortical regional blood flow even when overt
36 prefrontal type cognitive defects are manifested. This suggests that in this case, a
37 dysfunctional prefrontal cortex may appear to be at baseline levels that appear normal when
38 in fact the prefrontal cortices may be over stimulated by the thalamus. [51,52]. In fact, it was
39 noted that with further atrophy of the caudate there was increased fronto-cortical
40 metabolism while the patient performed cognitive tasks (set-shifting) and a greater increase

1 in cerebral metabolism over baseline. The poorer the subject performed on cognitive tasks,
2 the greater the cortical activation. [51,52]. It has been speculated that in early Huntington's
3 when there are no frontal lobe lesions, a relative balance between frontal and increased
4 thalamic functions may explain behavioral symptoms [10].

5 PET scans of patients with Parkinson's have also provided support that frontal-subcortical
6 connections are disrupted by subcortical dysfunction showing decreased glucose
7 consumption in frontal cortex, and decrease nigrostriatal D2 receptor uptake ratios [53,54].
8 Researchers at Stanford University may have observed similar results in children with
9 *ADHD* also known as childhood hyperkinetic disorder [55]. The Stanford study used
10 functional MRI to image the brains of boys between the ages of 8 and 13 while playing a
11 mental game. Ten of the boys were diagnosed with *ADHD* and six were considered normal.
12 When the boys were tested there appeared to be a clear difference in the activity of the basal
13 ganglia with the boys with *ADHD* having less activity in that area than the control subjects.
14 After administering methylphenidate, the participants were scanned again and it was found
15 that boys with *ADHD* had increased activity in the basal ganglia whereas the normal boys
16 had decreased activity in the basal ganglia. Interestingly, the drug improved the
17 performance of both groups to the same extent.

18 This may be a similar finding as the PET scans on patients with hyperactivity disorder,
19 where normal appearing frontal metabolism existed with decreased caudate and putamen
20 metabolism [56]. Methylphenidate, a dopamine reuptake inhibitor, may increase function in
21 a previously dysfunctional basal ganglia whereas raising dopamine levels in normal
22 individuals would most likely result in decreased activity of the basal ganglia to prevent
23 overproduction of dopamine. The previously dysfunctional basal ganglia would have most
24 likely resulted in decreased frontal metabolism with increased thalamo-cortical firing; this
25 would result in decreased cognitive function with increased hyperkinetic (hyperactive)
26 behavior. Increasing dopamine levels may increase frontal metabolism due to increased
27 activity of the striatum with decreased firing of the globus pallidus thereby inhibiting
28 thalamo-cortical firing decreases which in turn decreases hyperkinetic behavior. This would
29 make sense based on the findings of fMRI before and after, and the fact that both groups
30 showed equal improvement in performance.

31 **7. Basal ganglia in obsessive compulsive disorder**

32 Cognitive and brain maturational changes continue throughout late childhood and
33 adolescence. During this time, increasing cognitive control over behavior enhances the
34 voluntary suppression of reflexive/impulsive response tendencies [29,30]. We presently
35 have the capacity to characterize changes in brain activity during cognitive development.
36 Optimized top-down modulation of the ability to voluntarily suppress context-
37 inappropriate behavior of reflexive acts is not fully developed until adulthood and this
38 process provides a context to examine the nature of obsessive-compulsive disorder in a
39 maturational context and within the framework of the basal ganglia and its networks.

1 The basal ganglia-thalamo-cortical circuits appear to play a modulating role in a wide range
2 of behaviors. At the cortical level, given convergence upon specified regions within the
3 frontal lobes, the behaviors in question would be those dependent upon the sensory-motor,
4 premotor, frontal eye fields, and dorsolateral and orbito-frontal outflow targets. Processes
5 such as the generation, maintenance, switching, and blending of motor, mental, or
6 emotional sets would be involved. In disorders that primarily affect basal ganglia function,
7 the planning and the execution of both motor and cognitive function within these behavioral
8 domains could be affected. As we have seen, there is a high degree of diversity and
9 complexity of activity within the basal ganglia. Despite the nature of the reverberating
10 circuits, consequences of disruption will depend upon the site of the lesion and the
11 associated interplay of neurochemical factors. For example, in the motor system, damage to
12 various striatal circuitry levels can result in either hypo- or hyperkinetic disorders of
13 movement. Following this analogy, it can be said that diverse lesions, depending on site, can
14 result in problems with the development and maintenance of behavioral sets
15 ("hypophrenic") versus problems in relinquishing preferential sets ("hyperphrenic"). In
16 OCD, a "hyperphrenic" pattern would apply to those behaviors which are part of
17 obsessional rituals.

18 There is evidence of basal ganglia dysfunction from imaging studies of OCD, with both
19 reduced and increased volumes of caudate nuclei reported [57-59]. Increased caudate
20 metabolism has been found to be reduced after effective treatment of the OCD [60,61 and in
21 provoked or activated conditions, patients with OCD have shown increased caudate blood
22 flow [62. Such imaging studies point to the importance of orbito-frontal-basal ganglia-
23 thalamocortical circuits in the pathogenesis of OCD. In autism stereotyped, ritualistic and
24 repetitive behaviors including compulsive rituals and difficulties in tolerating changes in
25 routine or environment, are characteristic. It has been suggested [24,63,64] that these
26 behaviors may share related pathophysiological mechanisms. Sears and colleagues [63]
27 analyzed with high resolution MRI the volume of the bilateral caudate, putamen, and
28 globus pallidus regions in a group with autism and a control group. No differences were
29 detected in volumes of the globus pallidus or the putamen. Significant enlargement of 8
30 percent of the total caudate volume was found in the subjects with autism. This greater
31 caudate volume was proportional to the increased total brain volume and enlargement of
32 other brain structures earlier reported in the patients with autism. [65].

33 Based on the aforementioned studies and the basis of this chapter, the cortico-basal ganglia
34 circuits linking the orbito-frontal and anterior cingulate cortex to the caudate nucleus might
35 account for the cardinal features of OCD. All of these structures have been implicated in the
36 evaluation of the significance of stimulating as positive or negative (rewarding or
37 punishing) and all, as we have seen, have been linked to aspects of executive function.
38 Cortical-basal ganglia circuits have been suggested to form a neuronal system critical for
39 habit learning and for the routine performance of habits, and structures of the OCD circuit
40 have specifically been implicated in the acquisition of stereotyped behaviors [66,67].

41 The basal ganglia are thought to exert control over action release through antagonistic
42 "push-pull" output pathways, which serve to select intended actions [68]. As explained

1 earlier in the chapter, these functions are disrupted in hypokinetic disorders such as
2 Parkinson's disease, in which action is diminished, and in the hyperkinetic disorders such as
3 in Huntington's disease, in which action is excessive. Analogously, it has been suggested
4 that the function of these cortico-basal ganglia pathways may also occur in some
5 neuropsychiatric disorders including OCD and Tourette's syndrome.

6 Different sets of cortical-basal ganglia loops are thought to have specialized functions
7 depending on the cortical areas participating in the loops. This organization may account for
8 the symptom specificity of OCD as compared to other disorders of the basal ganglia and its
9 pathways. For example, in Tourette's syndrome, in which the characteristics of actions are
10 the predominant symptoms, the "motor loop" through the putamen is more effective than it
11 is in OCD according to neuroimaging data [69-71]. In OCD, which typically involves
12 obsessions as well as compulsive actions, the neuronal circuits interconnecting the orbito-
13 frontal and anterior cingulate cortex with the basal ganglia are involved.

14 The caudate nucleus has been implicated in repetitive actions in monkeys. The orbital-
15 frontal and the anterior cingulate cortex both project to the ventral part of the caudate
16 nucleus and to the ventral striatum. In the monkey, these regions have been found to send
17 outputs not only to the pallidum, but also to a large part of the dopamine-containing
18 substantia nigra pars compacta, from which the nigro-striatal tract originates. The caudal
19 orbito-frontal and anterior cingulate/caudal medial cortex are also a major source of input to
20 the striosomal system in the head of the caudate nucleus. Striosomes in this region have
21 been linked to reward effects and may appear to be differentially active under conditions in
22 which the animals perform repetitive, stereotyped behaviors in response to dopamine
23 receptor agonists [72].

24 These features of the orbito-frontal and anterior cingulate cortical-basal ganglia circuits are
25 important not only for understanding OCD symptomatology, but also for understanding
26 the developmental aspects of these disorders. The basal ganglia may influence of motor
27 pattern generators in the brainstem as well as "cognitive pattern generators" in the cerebral
28 cortex. The loops running from the neocortex to the basal ganglia and then to the thalamus
29 and back to the neocortex may help to establish cognitive habits, just as they may influence
30 the development of motor habits. If so, the cortical-basal ganglia loop dysfunction in OCD
31 could reflect both sides of basal ganglia function, motor and cognitive, to bring about
32 repetitive actions (compulsions) and repetitive thoughts (obsessions).

33 Alternatively, the basal ganglia may have as its task a process that takes input from cortical
34 and other sources and releases the output as "chunks" in order to sequence behavior,
35 important in forming coordinated, sequential motor actions and in developing streams of
36 thoughts and motivation, and perhaps playing the violin [63]. The architecture of cortical-
37 basal ganglia circuitry could support the smooth progression from a cognitive framework
38 establishing priorities for potential behaviors to behavioral selection, thereby facilitating
39 fluid and adaptive behavioral output. Dysfunction of this cortical-basal ganglia system
40 could contribute to the symptoms of OCD. Individuals become stuck in a conceptual
41 framework, unable to shift from one priority set to the next, and thus remain locked into a
42 specific behavioral output program.

1 A large part of the frontal cortex receives inputs from the basal ganglia conveyed via the
2 thalamus. These same cortical regions not only project to the basal ganglia (mainly to the
3 striatum) but also to other regions including the thalamus. Cortical-thalamic loops are
4 critical for integrative and optimized cortical functioning. The adequacy of basal ganglia
5 function is necessary to facilitate associations among cortical inputs on the basis of context
6 and evaluative signals, and thereby promote behavioral automation, normally necessary to
7 reduce the information load on the system. The basal ganglia can relieve the frontal cortex of
8 the substantial computational load in carrying out executive functions. With both cortical-
9 thalamic and cortical-basal ganglia systems functioning under normal conditions, parallel
10 processing can occur with the cortical-thalamic circuits supporting conscious (explicit)
11 information processing and cortical-basal ganglia supporting automatic (implicit)
12 processing functions. If cortical-basal ganglia pathways functional abnormally, as in OCD
13 such parallel processing capabilities would be compromised. Information normally
14 processed automatically could intrude into the conscious domain of sessions, and
15 behavioral selection could become narrowed to compulsive acts. Such dysfunction could
16 contribute to the compelling nature of obsessions in OCD and to the stereotypic behaviors
17 carried out as compulsions.

18 The cortical-basal ganglia circuits appear dysfunctional in OCD, but the mechanisms are not
19 adequately understood at present. While we have seen that striatal lesions can induce
20 intense compulsive behaviors and stereotypies, we have not as yet found the existence of
21 subtle lesions of the striatum in OCD, perhaps as a result of the inadequacies of our current
22 measuring instruments. Magnetic resonance spectroscopy studies have suggested that there
23 exists reduced N-acetylaspartate levels within the striatum of persons with OCD, so that
24 neuronal density there may actually be reduced [17,74]. Abnormal brain chemistry in OCD
25 could affect neurotransmission in cortical-basal ganglia circuits leading to the abnormal
26 metabolic activity seen in imaging studies indicated earlier. While little is known about
27 neurochemistry of OCD, the most successful pharmacologic therapy for OCD is treatment
28 with inhibitors of serotonin reuptake (SRIs) sites. Effective therapy with SRIs can reverse the
29 abnormal metabolic activity seen in OCD circuits, suggesting that the modulatory effects of
30 serotonin can act on the cortical-basal ganglia circuit defined in scanning studies [75].

31 Despite the clinical results, strong evidence of a primary serotonergic or other
32 neurotransmitter abnormality in OCD is still lacking. One suggestion is that SRIs have their
33 beneficial effects via downregulation of 5HT-1D autoreceptors within the orbito-frontal
34 cortex [75]. Even though neuroimaging studies have pointed to cortico-basal ganglia circuits
35 as being dysfunctional in OCD, it is still not clear what the functional abnormality is in the
36 circuits in OCD and how they contribute to the expression of OCD symptoms. Nor is it clear
37 how these circuits were normally, or help multiple loops of the system interconnecting
38 cortex, thalamus, and basal ganglia actually operate. Improvements in the temporal and
39 spatial resolution of imaging also now make it possible to follow the cascade of neuronal
40 activity changes that occur during the evolution of OCD symptoms. It should be possible in
41 the relatively near future to identify brain sites participating in the buildup of an obsession,
42 the attendant anxiety, the escalation of an urge, the performance of a compulsion, and the
43 resolution of the obsession and accompanying anxiety.

1 **8. Basal ganglia in tourette's syndrome**

2 Tourette's syndrome (TS) is a neurobehavioral disorder characterized by involuntary motor
3 and vocal tics beginning in childhood [76]. Approximately 50 percent of individuals with TS
4 also exhibit obsessive-compulsive disorder (OCD) in addition; tics and OCD individuals
5 demonstrate similar features and both are thought to arise from frontal-cortical-basal
6 ganglia-thalamo-cortical circuit dysfunction. Recent advances in understanding the
7 neurobiology of TS come from neuroimaging, post-mortem, and from physiological and
8 behavioral studies in human and non-human primates and rodents. These advances allow
9 us to understand the nature of the complex dynamics of the basal ganglia pathways and
10 how this disorder connects with other forms of cognitive dysfunction.

11 Tourette's syndrome is defined by motor and vocal tics that start during childhood, persist
12 for more than one year, and fluctuate in type, frequency and anatomical distribution over
13 time. A specific tic can be present for weeks, months or years and then suddenly cease.
14 Other tics emerge and disappear with no predictable time course. The motor patterns of tics
15 can involve individual muscles or small groups of muscles (simple tics), or more muscles
16 acting in a coordinated pattern to produce movements that can resemble purposeful
17 voluntary movements (complex tics). Many individuals with TS exhibit both simple and
18 complex tics. Simple tics include eye blinking, nose twitching, head jerking, eye deviation,
19 mouth opening, sniffing and throat clearing. Complex tics include head shaking, scratching,
20 touching, throwing, hitting, gestures or uttering phrases. There is a tendency for tics to
21 occur in 'bouts' that wax and wane over hours, days, weeks or months [77].

22 OCD is strongly associated with TS both within individuals with TS and within families
23 [78]. As indicated above, OCD is characterized by repetitive thoughts that are involuntary,
24 senseless and often associated with anxiety, coupled with repetitive ritualistic behaviors that
25 are often performed in response to the premonitory thought or idea. There are striking
26 similarities between tics and OCD, and it is sometimes difficult to distinguish complex tics
27 from compulsions. Both tics and OCD include premonitory experiences such as sensations
28 (tics) or thoughts (OCD) that precede involuntary repetitive movements (tics) or behaviors
29 (OCD). Performance of the tic or compulsion typically terminates the premonitory
30 symptoms, at least temporarily.

31 Another feature common to both phenomena but important for placing OCD and Tourette's
32 within the cortico-basal ganglia loop process, is the impaired ability each disorder to inhibit
33 unwanted actions [79,80]. The spectrum of simple tics, complex tics, and compulsions
34 suggests that similar or shared pathophysiological mechanisms, but separate neural circuits,
35 might underlie these phenomena. These overlaps can be seen in cases of poisoning
36 especially with carbon monoxide in which the basal ganglia is selectively affected and
37 symptoms have been reported not dissimilar from those of Tourette's syndrome [79].

38 It is useful for us to examine cursorily issues related the neuropharmacology of TS to better
39 understand the nature of the loops and the connection of TS to OCD. Tics are suppressed
40 reliably by dopamine antagonists and OCD is improved by selective serotonin-reuptake

1 inhibitors (SSRIs) [81]. These facts implicate the dopaminergic and serotonergic pathways
2 and suggest the candidate loci for TS abnormalities. The implicated regions include the
3 striatum, the substantia nigra, and the prefrontal cortices. The dopaminergic complex of the
4 substantia nigra and ventral tegmental area and the serotonergic dorsal raphé nuclei both
5 send major projections to the striatum. The striatum, prefrontal cortices and substantia
6 nigra are further interlinked by a web of pathways that form the cortical–basal ganglia–
7 thalamo–cortical circuits [82-85].

8 We can infer from the literature cited previously that TS is a disorder of the basal ganglia
9 and its respective pathways in general, and a disorder of striatal organization and/or
10 function in particular. Some correlative data from other disorders supports the idea that
11 striatal dysfunction is involved in TS. Tics are seen also in disorders with known striatal
12 pathology, such as Huntington’s disease [21,76]. Abundant data implicates ventral striatal
13 dopaminergic neurotransmission in drug abuse and drug craving, attributes of which
14 overlap with obsessive–compulsive disorder (OCD) [86].

15 The clinical presentation of TS should reflect involvement of striatal function. Tics, in
16 general, are abnormal repetitive and stereotyped movements, but repetitive stereotyped
17 behaviors also occur normally. These behavioral effects are consistent with the effects of D1
18 receptor agonists on the response of medium spiny striatal neurons to stimulation [87]. D1
19 agonists tend to potentiate the current state of striatal neurons and reinforce ongoing
20 behaviors. The complex and perseverative behaviors caused by D1 agonists differ from the
21 effects of D2 receptor agonists, which tend to cause simple repetitive stereotyped
22 movements. Kelly and Berridge [86] suggest that super-stereotypy is analogous to complex
23 tics or OCD. Other stereotyped behavioral sequences are modulated by the basal ganglia
24 include complex defensive behaviors and facial movements.

25 Charles Darwin [88] had indicated that many facial movements are stereotyped among
26 mammals and important in non-verbal communication. Because tics commonly involve
27 involuntary head, neck and face movements, the importance of facial and related
28 movements in social communication might explain the disruptive nature of tics. There are
29 suggestions that regulation of socially relevant forms of communication is a
30 phylogenetically ancient function of the basal ganglia.

31 Additionally, the basal ganglia participate in brain circuits responsible for habit formation
32 and fixed action patterns [29]. Habits are physiological analogs of stereotyped,
33 unconsciously executed behavioral sequences such as tics, obsessions and compulsions. The
34 basal ganglia participate in circuits responsible for learning incremental stimulus–response
35 associations epitomized by classical Pavlovian and instrumental conditioning [89]. Graybiel
36 has emphasized that the basal ganglia might combine or ‘chunk’ individual stimulus–
37 response associations into more complex behavioral sequences executed as stereotyped
38 ‘units’ as we had seen earlier [68]. In addition, fMRI study of higher-order aversive
39 conditioning, in which key computational strategy that humans use to learn predictions
40 about pain was investigated. The investigators showed that neural activity in the ventral
41 striatum and the anterior insula display marked correspondence to the signals for sequential

1 learning predicted by temporal difference models. They identified the ventral striatum as a
2 key locus of such sequential learning [90]. Tics could represent a form of inappropriate habit
3 formation in which inappropriate stimulus–response associations are formed. This
4 interpretation might correlate with the fluctuating nature and ‘sensory’ component of tics.

5 In the study of non-human primates, electrophysiological studies of the intralaminar
6 thalamic nuclei have revealed that these nuclei influence striatal attentional mechanisms
7 and the processing of reward information [91]. These studies also suggest that intralaminar
8 thalamic nuclei encode information complementary to the reward prediction error
9 information provided by the dopaminergic nigrostriatal projection.

10 Basal ganglia circuitry models that we had described earlier in the paper view the normal,
11 tonically active inhibitory output of the basal ganglia as a ‘brake’ on motor pattern
12 generators (MPGs) in the cerebral cortex and brainstem [92]. For a desired movement
13 controlled by a particular MPG, a specific set of striatal neurons is activated; these neurons
14 inhibit basal ganglia output neurons in the GPi and substantia nigra pars reticulata (SNr)
15 that project back, via the thalamus, to the cortical MPGs. The removal of tonic inhibition
16 from the GPi and SNr (the ‘brake’) enables the desired motor pattern to proceed. In parallel,
17 neurons in the subthalamic nucleus (STN) excite the surrounding majority of GPi and SNr
18 output neurons. These surround neurons project via the thalamus to competing MPGs,
19 increasing their inhibitory output and applying the “brake” to competing MPGs. The net
20 result is facilitation of intended movement with inhibition of competing movements. In the
21 generation of tics, it is hypothesized that an aberrant focus of striatal neurons becomes
22 inappropriately active, causing unwanted inhibition of a group of basal ganglia output
23 neurons, which in turn disinhibit an MPG leading to an involuntary movement. Repetitive
24 over-activity of a given specific set of striatal neurons would result in repeated, stereotyped,
25 unwanted movements [92]. Multiple tics would result from abnormal excessive activity of
26 multiple discrete sets of striatal neurons According to this hypothesis, each tic corresponds
27 to the activity of a discrete set of striatal neurons [79].

28 **9. Basal ganglia in ADHD**

29 Attention-deficit/hyperactivity disorder is a highly heritable and prevalent neuropsychiatric
30 disorder estimated to affect six percent of school-age children [24]. It is manifested by
31 inattention, hyperactivity and impulsivity, which often respond substantially to treatment
32 with methylphenidate or dextroamphetamine. Etiological theories suggest a deficit in
33 cortico-striatal circuits, particularly those components modulated by dopamine and
34 therefore discussed in comparison with the other basal ganglia related disorders in the
35 paper. Teicher and colleagues [94] developed a functional magnetic resonance imaging
36 procedure (T2 relaxometry) to indirectly assess blood volume in the striatum (caudate and
37 putamen) of boys 6–12 years of age in steady-state conditions. Boys with attention-
38 deficit/hyperactivity disorder had higher T2 relaxation time measures in the putamen
39 bilaterally than healthy control subjects. Daily treatment with methylphenidate significantly
40 changed the T2 relaxation times in the putamen of children with attention deficit/

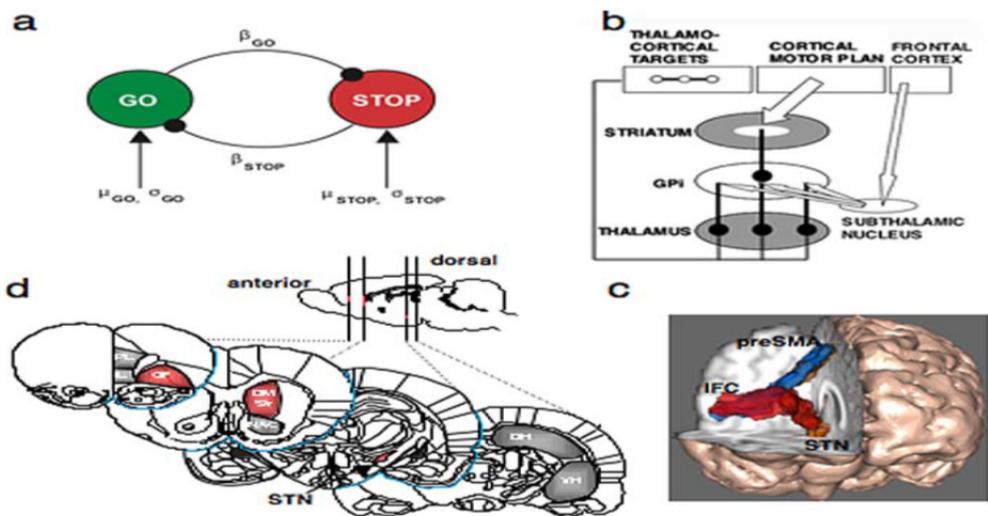
1 hyperactivity disorder. There was a similar but non-significant trend in the right caudate.
2 Teicher and colleagues concluded that attention-deficit/hyperactivity disorder symptoms
3 may be closely tied to functional abnormalities in the putamen, which is mainly involved in
4 the regulation of motor behavior.

5 Converging evidence implies the involvement of dopaminergic fronto-striatal circuitry in
6 ADHD. Anatomical imaging studies using MRI have demonstrated subtle reductions in
7 volume in regions of the basal ganglia and prefrontal cortex [e.g., 95]. Cognitive functioning
8 is mildly impaired in this disorder [for review, see 90]. In particular, cognitive control, the
9 ability to inhibit inappropriate thoughts and actions, is also affected and therefore we are
10 again dealing with a disorder of inhibition. Several studies have shown that this impairment
11 is related to the reduction in volume in fronto-striatal regions [96], and functional studies
12 have suggested that older children and adults with ADHD may activate these regions less
13 than controls during tasks that require cognitive control [e.g. 98, 99]. Durston et al. [100]
14 showed that the development of this ability is related to the maturation of ventral fronto-
15 striatal circuitry.

16 Volumetric abnormalities have also been associated with the basal ganglia and in turn with
17 attention deficit hyperactivity disorder (ADHD). Qiu and colleagues [101], to specify
18 localization of these abnormalities, employed large deformation diffeomorphic metric
19 mapping (LDDMM) to examine the effects of ADHD, sex, and their interaction on basal
20 ganglia shapes. The basal ganglia (caudate, putamen, globus pallidus) were manually
21 delineated on magnetic resonance imaging from typically developing children and children
22 with ADHD. LDDMM mappings from 35 typically developing children were used to
23 generate basal ganglia templates. These investigators found that boys with ADHD showed
24 significantly smaller basal ganglia volumes compared with typically developing boys, and
25 LDDMM revealed the groups remarkably differed in basal ganglia shapes. Volume
26 compression was seen bilaterally in the caudate head and body and anterior putamen as
27 well as in the left anterior globus pallidus and right ventral putamen. Volume expansion
28 was most pronounced in the posterior putamen. They concluded that the shape
29 compression pattern of basal ganglia in ADHD suggests an atypical brain development
30 involving multiple frontal-subcortical control loops, including circuits with premotor,
31 oculomotor, and prefrontal cortices.

32 Aron and colleagues [102] brilliantly outlined the nature of inhibition in fronto-basal-
33 ganglia networks relative to cognition. Their paper was not about the problems of ADHD
34 individuals per se but a thorough analysis of the neurophysiology of stopping. They had
35 indicated that sensory information about a stop signal is relayed to the prefrontal cortex,
36 where the stopping command must be generated. They collected the evidence together
37 indicating that the right inferior frontal cortex (IFC) is a critical region for stop signal
38 response inhibition [103,104] with the most critical portion likely being the pars opercularis
39 (Brodmann area 44) in humans. The right IFC can send a stop command to intercept the Go
40 process via the basal ganglia (represented in Fig. 6b from Aron et al., [102]. The Go process
41 is likely generated by premotor areas that project via the direct pathway of the basal ganglia
42 (through striatum, pallidum, and thalamus), eventually exciting primary motor cortex and

1 generating cortico-spinal volleys to the relevant effector each interacting with the globus
 2 pallidus [105]. The Stop process could activate the globus pallidus via a projection from the
 3 subthalamic nucleus (STN). High resolution fMRI has shown activation of a midbrain
 4 region, consistent with the STN, when subjects successfully stop their responses [105], and
 5 diffusion tractography shows that this STN region is directly connected to the right IFC via a
 6 white matter tract [102] (Fig. 6c). Thus, once the Stop command is generated in frontal
 7 cortex, it could be rapidly conveyed to the basal ganglia via the so-called “hyperdirect
 8 pathway” to intercept the Go process in the final stages of the race. Two recent studies
 9 identified a third critical node for the stopping process in the dorso-medial frontal cortex,
 10 including the pre-supplementary motor area) [106,107].



11
 12 **Figure 6.** A, The interactive race model between Go and Stop processes [108]. The parameters were
 13 estimated by fitting the model to thousands of behavioral trials from a monkey neurophysiology
 14 study. B, Schematic of fronto-basal-ganglia circuitry for Going and Stopping. The Go process is
 15 generated by premotor cortex, which excites striatum and inhibits globus pallidus, removing inhibition
 16 from thalamus and exciting motor cortex (see text for details). The stopping process could be generated
 17 by inferior frontal cortex leading to activation of the subthalamic nucleus, increasing broad excitation of
 18 pallidum and inhibiting thalamocortical output, reducing activation in motor cortex. C, Diffusion-
 19 weighted imaging reveals putative white matter tracts in the right hemisphere between the dorsomedial
 20 preSMA, the ventrolateral PFC or IFC, and the putative region of the STN. Reproduced with permission
 21 from Aron et al. [102]. D, Regions of the rat brain implicated in behavioral stopping. Stopping is
 22 significantly impaired following excitotoxic lesions within the regions highlighted in red, whereas
 23 lesions within the gray-colored regions have no effect on stopping. OF, Orbitofrontal cortex; IL,
 24 infralimbic cortex; PL, prelimbic cortex; DM Str, dorsomedial striatum; NAC, nucleus accumbens (core);
 25 DH, dorsal hippocampus; VH, ventral hippocampus; GPi, globus pallidus pars interna. (From Aron et
 26 al. [102]),

1 **10. Conclusions**

2 Neural circuits linking activity in anatomically segregated populations of neurons in
3 subcortical structures and the neocortex throughout the human brain regulate complex
4 behaviors such as walking, talking, language comprehension and other cognitive functions
5 including those associated with frontal lobes. Many neocortical and subcortical regions
6 support the cortical-striatal-cortical circuits that confer various aspects of language ability,
7 for example. However, many of these structures also form part of the neural circuits
8 regulating other aspects of behavior. For example, the basal ganglia, which regulate motor
9 control, are also crucial elements in the circuits that confer human linguistic ability and
10 reasoning. The cerebellum, traditionally associated with motor control, is active in motor
11 learning. The basal ganglia are also key elements in reward-based learning. Data from
12 studies individuals with Tourette's syndrome, Obsessive-Compulsive Disorder as well as
13 with Broca's aphasia, Parkinson's disease, hypoxia, focal brain damage, and from
14 comparative studies of the brains and behavior of other species, demonstrate that the basal
15 ganglia sequence the discrete elements that constitute a complete motor act, syntactic
16 process, or thought process. Imaging studies of intact human subjects and
17 electrophysiologic and tracer studies of the brains and behavior of other species confirm
18 these findings. Dobzansky had stated, "Nothing in biology makes sense except in the light
19 of evolution" (cited in [108]). That applies with as much force to the human brain and the
20 neural bases of cognition as it does to the human foot or jaw. The converse follows: the mark
21 of evolution on the brains of human beings and other species provides insight into the
22 evolution of the brain bases of human language. The neural substrate that regulated motor
23 control in the common ancestor of apes and humans most likely was modified to enhance
24 cognitive and linguistic ability. Language and cognition played a central role in this process.
25 However, the process that ultimately resulted in the human brain may have started when
26 our earliest hominid ancestors began to walk.

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6 **Acknowledgement**

7 This work was supported by the Ministry of Science of the State of Israel, the F., R. Carrick
 8 Research Institute, Inc., and Help the Hope Foundation.

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