New Models of Frontal-Subcortical Skeletomotor Circuit Pathology in Tardive Dyskinesia

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Tardive dyskinesia (TD) is a hyperkinetic movement disorder that can occur as a side effect of treatment with antipsychotic medications. Because antipsychotics block the D2 family of dopamine receptors in the striatum, it has long been suspected this blockade contributes to the development of TD. Specifically, increased sensitivity of the dopamine receptors following chronic blockade has been thought to result in abnormal functioning of the frontal-subcortical (FSC) skeletomotor circuit and the symptoms of TD. However, this hypothesis remains unproven. In recent years, substantial research has focused on the basal ganglia and FSC circuits. This research has resulted in the development of the focused selection model of skeletomotor circuit function. This hypothesis provides a compelling model of neurocircuit abnormalities in TD. A greater understanding of the neuropathology of TD may lead to the development of better treatment and prevention strategies for this disorder. Furthermore, this information may contribute to a more complete understanding of normal skeletomotor circuit function and the role of circuit pathology in numerous neuropsychiatric conditions. NEUROSCIENTIST 12(3):186–198, 2006. DOI: 10.1177/1073858406288727

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Tardive dyskinesia (TD) is an iatrogenic hyperkinetic movement disorder caused by chronic dopamine-receptor blockade secondary to treatment with antipsychotics. The underlying neuropathology of this condition remains unknown. However, because antipsychotics block the D2 family of dopamine receptors in the striatum (Creese and others 1976; Seeman and others 1976), it has long been suspected this blockade contributes to the development of TD. The striatum serves as the input nucleus for the skeletomotor circuit, which is one of the parallel information-processing loops known as the frontal-subcortical (FSC) circuits. Therefore, it has been hypothesized that TD may be associated with abnormal functioning of the skeletomotor FSC circuit (Tamminga and Woerner 2002).

The FSC circuits are involved with motor, emotional, and cognitive processing (Alexander and others 1986; Alexander and others 1990; Cummings 1993; Mink 1996; Lichter and Cummings 2001; Heimer 2003). Evidence is accumulating that these circuits play a major role in the affective, motor, and cognitive symptoms of a number of neuropsychiatric disorders (Swerdlow and Koob 1987; Cummings 1993; Soares and Mann 1997; Blumberg and others 2000; Drevets 2000; Strakowski and others 2000; Strakowski and Sax 2000; Baxter and others 2001; Lichter and Cummings 2001; Mink 2001; Caligiuri and others 2003; Heimer 2003).

Recently, a significant effort in neuroscience research has focused on the basal ganglia and skeletomotor circuit. As a result, new models of circuit function have been developed. These models may lead to an increased understanding of the neuropathology of numerous movement disorders including TD. This article reviews current models of skeletomotor circuit anatomy and function and discusses potential implications for the understanding of neurocircuit pathology in TD.

Anatomy of the Skeletomotor Circuit

The basal ganglia along with the thalamus are the subcortical structures that make up the skeletomotor circuit (Fig. 1). The basal ganglia include the caudate nucleus, putamen, nucleus accumbens, substantia nigra (pars compacta and pars reticulata), globus pallidus (pars interna and externa), and subthalamic nucleus and consist of large numbers of cell bodies organized into nuclei (Kingsley 2000, p 285–310).

The caudate, putamen, and nucleus accumbens, derived from the telencephalon, make up the striatum. The ventromedial caudate, the ventral putamen, the olfactory tubercle, and the nucleus accumbens are often referred to as the ventral striatum (Heimer 2003; Jankovic and DeLeon 2003). The ventral striatum is primarily involved with the emotional FSC circuit functions (Heimer 2003), whereas the putamen mediates skeletomotor circuit function (Cummings 1993).

The globus pallidus and subthalamic nuclei are derived for the diencephalon. The globus pallidus lies between the internal capsule and the putamen. It consists

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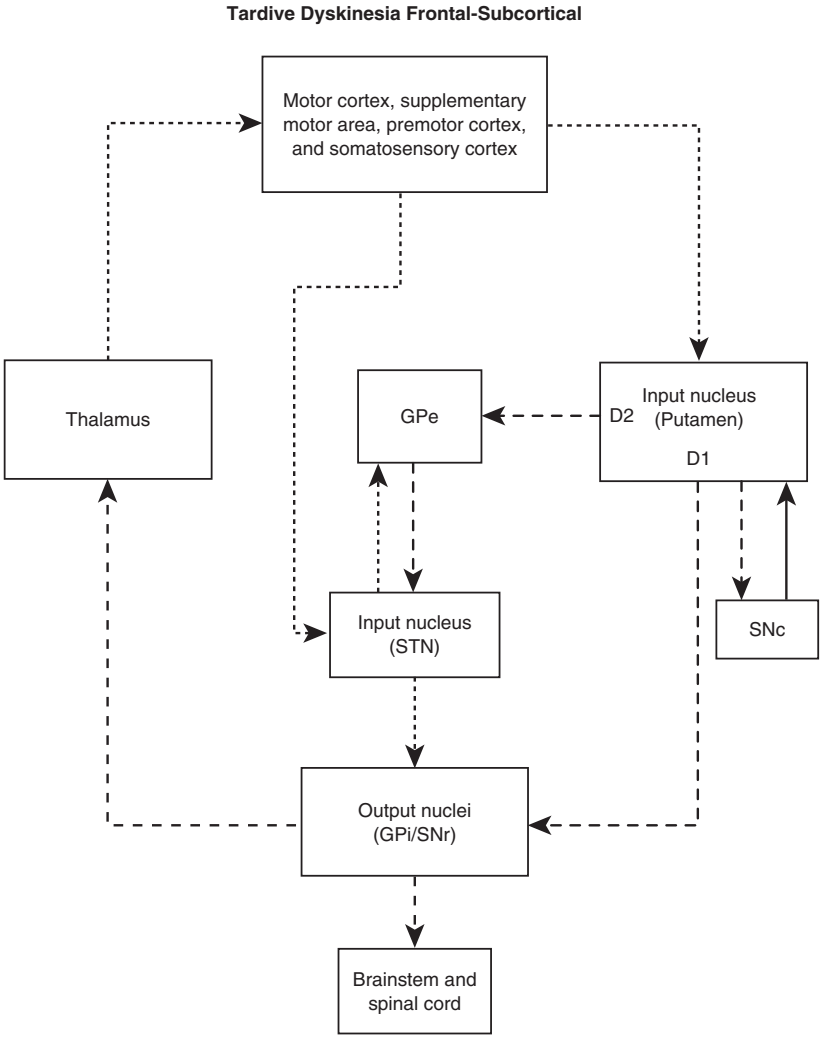

Fig. 1. Skeletomotor circuit. This figure illustrates the skeletomotor frontal-subcortical circuit. Neurotransmitters are indicated by dashed lines (GABA), solid lines (dopamine), and dotted lines (glutamate). GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus; SNc = Substantia nigra, pars compacta; SNr = substantia nigra, pars reticulata.

of two nuclei, the pars interna (GPi) and externa (GPe). Each nucleus has separate connections. The GPi and the reticular division of the substantia nigra (SNr) are nearly identical (Carpenter 1981) and thus will be designated GPi/SNr when appropriate in this review. The subthalamic nucleus (STN) is located medial to the internal capsule and ventral lateral to the thalamus. The substantia nigra is a nucleus derived from the mesencephalon. Two subnuclei, the SNr and pars compacta (SNc), make up this structure. The thalamus is a complex paired structure located medial to the posterior limb of the internal capsule. Each half is an egg-shaped structure with many nuclei.

Functional Organization of the FSC Circuits

FSC circuit information flow is topographically organized from the frontal cortex through basal ganglia structures to the thalamus and back to the frontal cortex (Fig. 1). Historically, five parallel segregated FSC circuits have been recognized (Cummings 1993; Lichter and Cummings 2001). These are skeletomotor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate.

Basal ganglia structures can be categorized as input, output, or intrinsic nuclei of the FSC circuits (Mink 1996). The striatum and the STN are the input nuclei (Fig. 1). The input nuclei connect by way of inhibitory GABA fibers to the output nucleus, which is the GPi/SNr. The GPi/SNr receives fast, divergent, excitatory input from the STN and a slower, focused, convergent inhibitory input from the striatum (Mink 1996). The GPi/SNr sends inhibitory GABA efferents to various brainstem and thalamic nuclei.

The intrinsic nuclei are the GPe and the SNc (Mink 1996). The GPe receives excitatory input from the

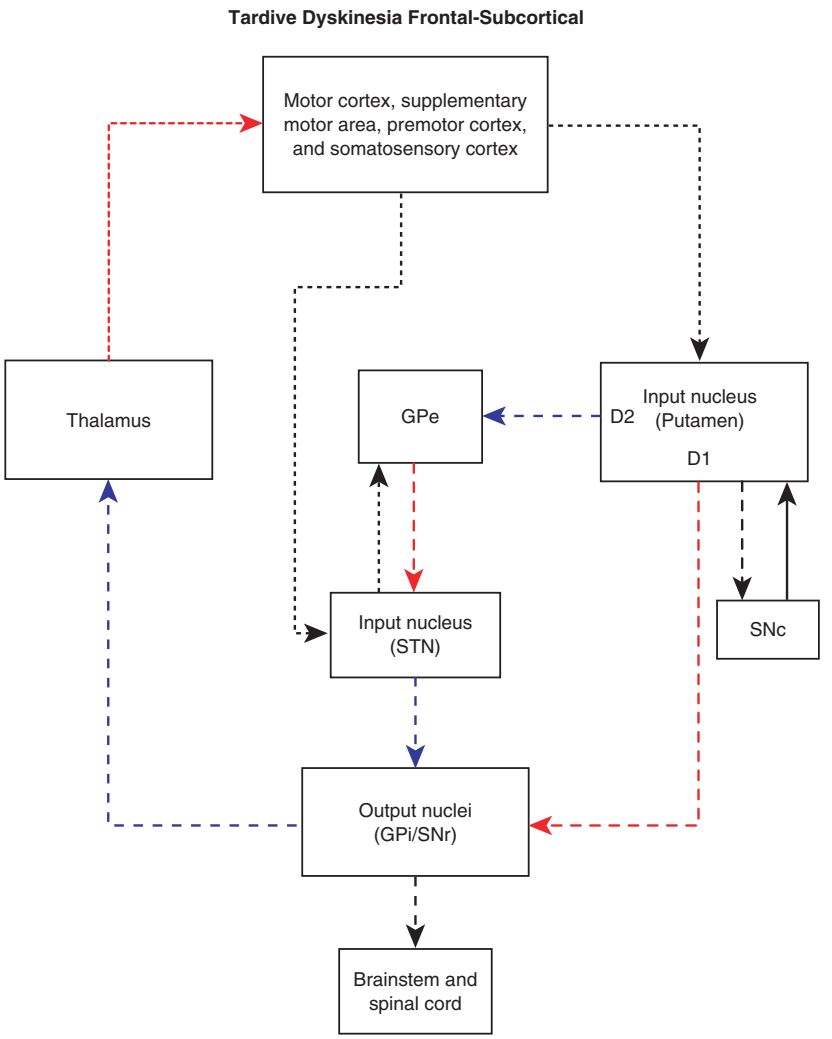

Fig. 2. Dopamine modulation of the skeletomotor circuit. This figure illustrates the mechanism of dopamine modulation of the skeletomotor circuit. The connections of the circuit are shown by dashed lines (GABA), solid lines (dopamine), and dotted lines (glutamate). Increased activity is shown in red and decreased activity in blue. Increased firing of dopaminergic nigrostriatal neurons results in an increase in GABA-mediated inhibition of the GPi/SNr via D1 receptors (direct pathway). This results in decreased inhibitory output to the thalamus and therefore increased glutamate-mediated output to the cortex. Stimulation of the striatal D2 receptors (indirect pathway) results in decreased GABA-mediated inhibition to the GPe, then subsequent increased inhibition by way of the GPe to the STN pathway, and finally decreased glutamate excitation by way of the STN to GPi/SNr projections. This has the net result of decreased indirect pathway inhibitory activity, which complements the increased direct pathway activity. GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus; SNc = substantia nigra, pars compacta; SNr = substantia nigra, pars reticulata.

STN and inhibitory input from the striatum, but it sends inhibitory output to the STN. The SNc is the locus of dopamine-containing neurons. It receives most of its input from the striatum and sends much of its output back to the striatum (Fig. 2).

Historically, the FSC circuits have been thought to consist of two separate subcircuits (Alexander and others 1986; Mink 1996; Baxter and others 2001), the direct and indirect pathways (Fig. 3). The direct pathway is the cortex–putamen–GPi/SNr–thalamus–cortex loop. The indirect pathway also originates in the striatum (Bronstein and Cummings 2001) and connects by way of GABA projections to the GPe. The GPe then connects, utilizing GABA fibers, to the STN, which projects to the GPi/SNr by way of glutamate neurons (Fig. 3). For both pathways, inhibitory GABA fibers from the GPi/SNr project to the thalamus and the circuits are completed by thalamocortical excitatory glutamate fibers, which provide the final link back to the cortex (Fig. 3).

The predominate hypothesis of FSC function has been that the direct pathway (striatum directly to the GPi) tends to have a net disinhibitory effect on the thalamus and increases excitatory outflow to the cortex, whereas the indirect pathway tends to inhibit that thalamus and

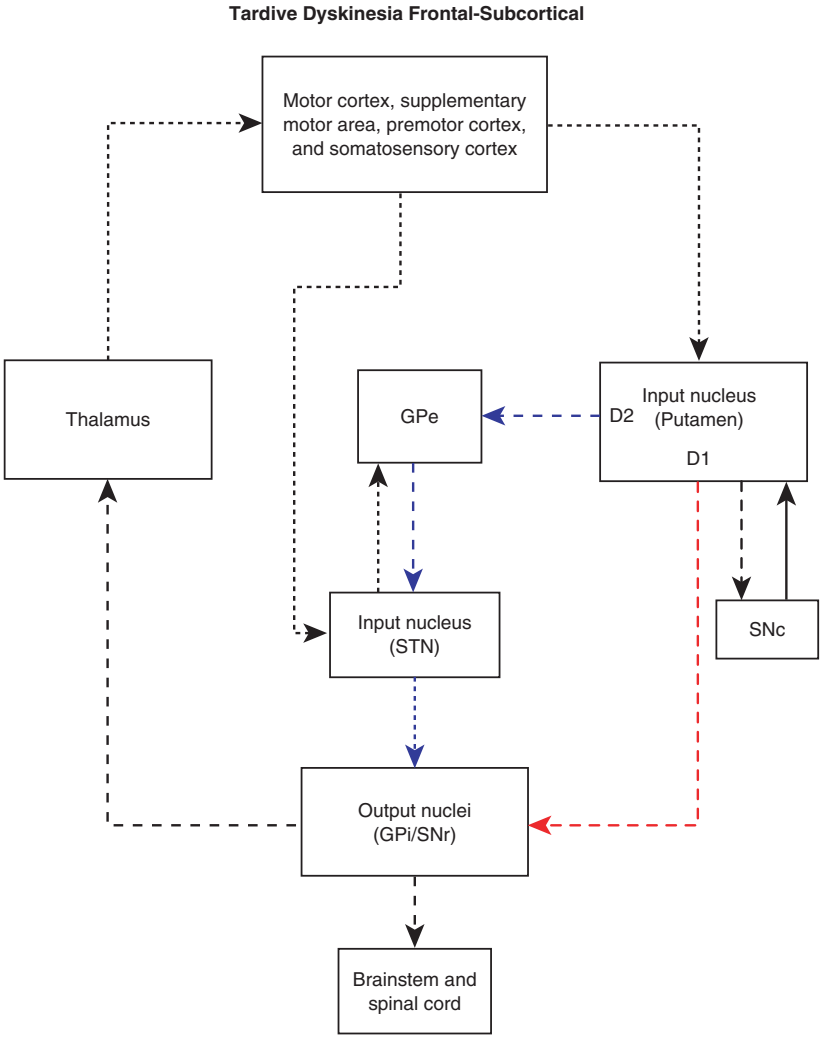

Fig. 3. Skeletomotor circuit direct and indirect pathways. This figure illustrates the skeletomotor direct (excitatory) and indirect (inhibitory) pathways. The direct pathway is in red and the indirect pathway in blue. Neurotransmitters are shown by dashed lines (GABA), solid lines (dopamine), and dotted lines (glutamate). GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus; SNc = substantia nigra, pars compacta; SNr = substantia nigra, pars reticulata.

decreases excitatory drive to the cortex. Thus, the direct and indirect pathways have been thought of as having reciprocal functions, with the direct pathway being responsible for sustaining and the indirect pathway for halting various behavioral routines.

The Skeletomotor Circuit

The skeletomotor circuit is involved with the control of voluntary motor movements. It consists of movement-related neurons, which maintain discrete somatotopic organization throughout the pathway. Neurons originate from the motor cortex, supplementary motor area, premotor cortex, and somatosensory cortex and project primarily to the putamen, which serves as the input nucleus for this circuit (Alexander and others 1986; Alexander and others 1990). The GPi/SNr serves as the output nucleus (Fig. 1) and connects to the ventrolateral, ventral anterior, and centromedianum nuclei of the thalamus. The circuit is completed by efferents from the thalamus to the supplementary motor area, premotor cortex, and motor cortex. Finally, thalamic nuclei also have reciprocal connections with the putamen and cortex.

Unlike most components of the motor system, the skeletomotor circuit does not connect directly with the spinal cord. This resulted in the circuit originally being designated as the "extrapyramidal" motor system, as it was thought to be independent of the corticospinal (or pyramidal) system. This was an oversimplification, as the two systems are not independent but are extensively interconnected and work together to control movement.

Input Nuclei

The striatal structures (primarily putamen) compose the input nuclei for the skeletomotor circuit. The striatum

has a patch-matrix composition (Mink 1996; Bronstein and Cummings 2001). The matrix is acetylcholinesterase and dopamine D2 receptor-rich and surrounds islands or patches with different neurochemical properties (Graybiel and Ragsdale 1978). The patches, also known as striosomes, have much less acetylcholinesterase. These areas receive prominent limbic and prefrontal cortical input, have high levels of dopamine D1 receptors, and project primarily to the SNc (Gerfen 1992).

Four types of neurons have been described in the striatum (for review, see Mink 2003). Medium spiny neurons make up 95% of the total number of striatal neurons and serve as the skeletomotor circuit output fibers (Kemp and Powell 1971; Gerfen 1988). These are GABA neurons, which originate in the matrix and project to both the GPi/SNr (direct pathway) and the GPe (indirect pathway) as described above (Fig. 3). These neurons have large dendritic trees and extensive local axon fibers, which may serve to inhibit neighboring striatal neurons. The other three neuron types are all interneurons. These include large spiny acetylcholine neurons, medium aspiny neurons, and small aspiny neurons. Other neurotransmitters found in the striatum include substance P and enkephalin.

Skeletomotor projections from the cortex terminate on the heads of the dendritic spines of the medium spiny neurons. The medium spiny neurons receive excitatory, glutamatergic input from the entire cortex except for primary visual and auditory areas (Kemp and Powell 1970; Kitai and others 1976; McGeer and others 1977; Cherubini and others 1988). The cortical projections have a general topographical organization, with projections from each cortical area terminating in longitudinal bands in the striatum (Selemon and Goldman-Rakic 1985), and interconnected cortical areas terminate in adjacent zones in the striatum (Yeterian and Van Hoesen 1978; Selemon and Goldman-Rakic 1985; Flaherty and Graybiel 1991; Parthasarthy and others 1992; Flaherty and Graybiel 1993; Yeterian and Pandya 1993; Flaherty and Graybiel 1994). Thus, the large dendritic fields of the medium spiny neurons receive input from multiple cortical areas and input from a single cortical area projects to multiple striatal zones.

It has been estimated that one striatal cell receives input from thousands of cortical neurons (Wilson 1995). Therefore, activation of a medium spiny neuron appears to require concurrent excitatory input from a large number of cortical afferents (Mink 1996). This organization provides a mechanism for the striatal integration of information from several cortical areas and suggests that one function of the striatum is to focus divergent input (Mink 1996). This concept will be discussed further below.

Medium spiny neurons also receive multiple other inputs. These include cholinergic input from large aspiny interneurons (Izzo and Bolam 1988); GABA, enkephalin, and substance P input from adjacent medium spiny neurons (Penny and others 1986); and excitatory glutamatergic inputs from the intralaminar and ventrolateral thalamus (Lapper and Bolam 1992; Sadikot and others 1992). Finally, these dendritic fields receive substantial dopaminergic projections from the SNc (discussed below).

Subthalamic Nucleus

The STN is the second structure in the indirect pathway and receives GABA inhibitory output from the GPe (Fig. 3). In addition, the STN also serves as an input nucleus for the skeletomotor circuit as a result of excitatory, glutamatergic input directly from the cortex. This includes short-latency input from motor areas of the ipsilateral primary motor cortex, premotor and supplementary motor cortex, and frontal eyefields (Hartmann-von Monakow and others 1978; Fujimoto and Kita 1993). STN output is by way of excitatory glutamatergic neurons projecting to the GPi/SNr (Smith and others 1990). Also, there is direct excitatory feedback to the GPe. Unlike the striatum, which has multiple mechanisms for information processing, the STN appears to have little intrinsic processing of transmitted cortical signals (Mink 1996).

Intrinsic Structures

Globus Pallidus Externa

The GPe is the first structure specific to the indirect pathway. Its inputs are GABA inhibitory fibers from the striatum and excitatory glutamate fibers from the STN. Striatal medium spiny neurons that project to the GPe preferentially express the D2 subtype dopamine receptors (Bronstein and Cummings 2001). The majority of GPe output consists of inhibitory GABA fibers to the STN (Rouzaire-Dubois and Scarnati 1987). However, there are also inhibitory GABA output fibers to the GPi, SNr, and striatum.

Substantia Nigra Pars Compacta

Fibers from the SNc provide the primary source of dopaminergic modulation of neurotransmission from the cortex to the striatum (Bronstein and Cummings 2001). Nigrostriatal dopamine fibers from the SNc terminate primarily on the shafts of the dendritic spines of medium spiny neurons in the striatum (Bouyer and others 1984). A single nigrostriatal axon may synapse at several locations on a single dendrite as well as on multiple dendrites of multiple striatal neurons (Groves and others 1994). Therefore, input from activity in a single SNc neuron may influence cortical inputs to many medium spiny neurons (Mink 1996).

The action of dopamine depends on the type of receptors located on the target neurons (Bronstein and Cummings 2001). Dopamine receptors from the D1 family (D1 and D5) stimulate adenylate cyclase activity and are thought to potentiate the effect of cortical excitation on the medium spiny neurons. D2 family receptors (D2, D3, and D4) inhibit adenylate cyclase activity and thus decrease the effect of cortical input. Thus, dopamine plays a major role in the modulation of skeletomotor circuit activity (Fig. 2). Furthermore, there is evidence that D1 receptors are preferentially expressed

on direct pathway medium spiny neurons projecting to the GPi/SNr whereas D2 receptors are preferentially expressed on indirect pathway neurons projecting to the GPe (Gerfen and others 1998). Thus, increased nigrostriatal dopaminergic activity results in an increase in direct pathway cortical excitation and decreased indirect pathway cortical inhibition (Fig. 2). Therefore, dopamine exerts complementary actions on the skeletomotor circuit via both the direct and indirect pathways resulting in a net enhancement of cortical activation (Bronstein and Cummings 2001). The activity of SNc neurons is unrelated to specific motor movements but rather occurs in response to reward or instructional clues presented in the context of a movement task (Mink 1996), and it is thought that SNc inputs play a critical role in motor learning (Groves and others 1995).

Output Nuclei

The GPi/SNr complex is the output nucleus for the skeletomotor circuit. The GPi and the SNr are from a cytoarchitectural standpoint one structure; however, the SNr is primarily associated with the oculomotor circuit, whereas the GPi is the output nucleus for limb movements. The GPi receives both direct and indirect FSC skeletomotor circuit input. Direct input is by way of projections of the medium spiny striatal neurons that preferentially express the D1 subtype of dopamine receptors. Output is by way of large inhibitory GABA neurons that project to the thalamus and brainstem (Penney and Young 1981; Francois and others 1984; DiFiglia and Rafols 1988). Projections to the brainstem go to an area termed the "midbrain extrapyramidal area" (Mink 2003), whereas those to the thalamus terminate on the ventrolateral and ventral anterior thalamic nuclei (DeVito and Anderson 1982).

An important aspect of the connection from the striatum to the GPi is that these neurons sparsely contact several GPi output neurons and then project to a single output neuron with a dense termination (Parent and Hazrati 1993). The termination pattern of striatal projections to the GPi suggests a focused influence of the striatum on this structure (Mink 1996). Thus, there is initial circuit divergence (from the cortex to the striatum) and reconvergence both within the striatum and from the striatum to the GPi (Mink 1996). The glutamatergic indirect pathway from the STN is more divergent, with each input neuron terminating on many GPi output neurons.

Thalamus

GABA inhibitory fibers from the GPi terminate on the ventrolateral and ventral anterior thalamic nuclei (DeVito and Anderson 1982). These thalamic nuclei then project by way of excitatory glutamate fibers to the motor, premotor, supplementary motor, and prefrontal cortex (Tokuno and others 1992; Hoover and Strick 1993; Middleton and Strick 1994; Inase and Tanji 1995). These cortical areas also receive input from other thalamic nuclei that receive projections from the cerebellum. However, there is little or no overlap of the basal ganglia and cerebellum inputs to the thalamus (Yamamoto and others 1983; Rouiller and others 1994).

Role of the Skeletomotor Circuit in Normal Motor Activity

To elucidate the possible role of skeletomotor circuit pathology in TD, it is first necessary to have a reasonable working model of normal circuit function. The recurring theme in the skeletomotor circuit literature is that this circuit is involved in the facilitation of desired motor activity and the inhibition of activity that is undesirable or in competition with the desired behavior (Mink 1996). Historically, it has been difficult to develop a model with sufficient detail so that it can be tested.

One early model suggested that circuit facilitation of desired motor activity was primarily involved in the initiation of the action. However, input nuclei neurons have low baseline discharge rates of 0.1 to 1 spike/second (Crutcher and DeLong 1984) and movement-related activity occurs after the onset of muscle activity responsible for creating the movement. Furthermore, movement-related neurons in the putamen fire later than those in the motor and premotor cortex (Crutcher and Alexander 1990). Output nuclei neurons have tonic activity in the 60 to 80 Hz range, and firing in relation to movement also occurs late compared to muscle activation. Furthermore, lesions of the basal ganglia do not delay the initiation of movement (Mink 2003). Thus, it has been suggested that basal ganglia output is not likely to be involved with movement initiation (Mink 1996, 2003).

Two-Pathway Hypothesis

For many years, the predominate model of skeletomotor circuit function has been that of two reciprocal pathways as discussed above (Fig. 3). This hypothesis suggests that a dynamic balance exists between the two skeletomotor circuit pathways (Lighter 2001). When direct pathway activity predominates, there is increased excitatory input from the thalamus to the cortex and the facilitation of movement. When indirect pathway activity predominates, there is a decrease of cortical excitation and inhibition of movement. This two-pathway model has been used to suggest pathological mechanisms for movement disorders. According to this model, movement disorders involve a disruption of the dynamic balance between the two pathways (Lighter 2001). The two-pathway model has provided a useful framework for conceptualizing the pathology of movement disorders; however, it does not adequately explain normal skeletomotor circuit function. For example, it does not explain the role of the direct pathway from the cortex to the STN. More important, it does not explain how the "facilitation" and "inhibition" functions actually contribute to motor control. These shortcomings have led to the development of more elaborate models of circuit function.

Focused Selection Hypothesis

Mink initially suggested that the skeletomotor circuit functions in a role of focused selection (1996). His

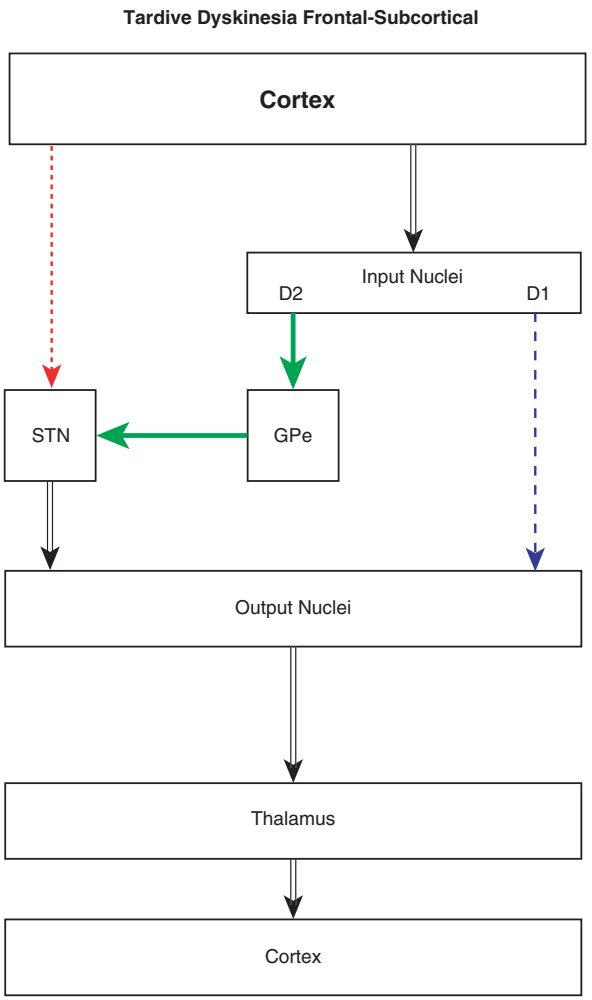

Fig. 4. Skeletomotor circuit focused-selection model. This figure illustrates the skeletomotor frontal-subcortical focused-selection model. This model postulates three pathways, two for selection and one for control. The direct pathway (dashed blue lines) preferentially expresses D1 receptors and serves as the "select on" circuit. The pathway direct from the cortex to the STN (dotted red lines) serves as the "select off" circuit. The indirect pathway (solid green lines) preferentially expresses D2 receptors and serves as the "control" circuit. GPe = globus pallidus pars externa; STN = subthalamic nucleus.

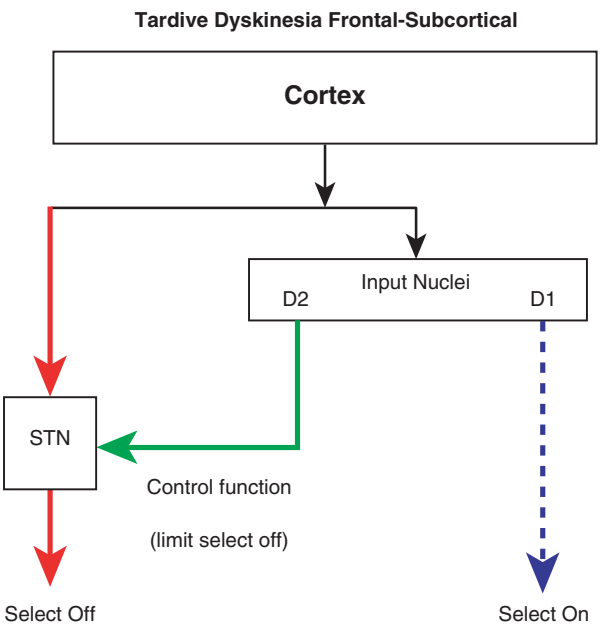

Fig. 5. Skeletomotor circuit focused-selection simplified model. This figure illustrates the skeletomotor frontal-subcortical focused-selection model omitting details for simplification. The direct pathway (dashed blue lines) preferentially expresses D1 receptors and serves as the "select on" circuit. The pathway direct from the cortex to the subthalamic nucleus (STN) (solid red lines) serves as the "select off" circuit. The indirect pathway (solid green lines) preferentially expresses D2 receptors and serves as the "control circuit." Hypothetically, the control circuit limits the "select off" function so that posture and basic limb movement is maintained but still allows for inhibition of motor activity that competes with the primary movement. Dopamine has the effect of turning on both the "select on" and "control" circuits in the normally functioning skeletomotor circuit.

hypothesis states that the tonically active inhibitory output of the circuit acts as a "brake" on motor pattern generators (MPGs) in the cortex and brainstem. He suggested that when a particular MPG initiates movement, circuit output neurons projecting to competing MPGs increase their firing rate, thereby increasing inhibition and applying a braking action on those generators. At the same time, other basal ganglia output neurons projecting to the generators involved in the desired movement decrease their discharge rate and decrease the tonic inhibition and braking action for the desired MPG. Thus, selected movements are facilitated and competing postures and movements are inhibited (Mink 1996).

Mink's model provides a more complete explanation of skeletomotor circuit function than the two-pathway model (Fig. 4). First, it supplies a reason for the circuit's existence, which is unclear in the two-pathway model. As Mink explains, numerous MPGs must gain access to the motor neuron pools to produce complex movements and maintain posture (1996). These various MPGs may act through common descending pathways and interneurons in the brainstem and spinal cord. Activation of a pathway by one MPG may produce an action that is in direct competition with the action of another. This would result in abnormal postures and movements. Furthermore, this model makes use of the direct cortical to STN pathway.

Mink's model suggests a different interpretation of the skeletomotor circuit connections than that of a simple direct versus indirect pathway (Fig. 4). In this model, the "select off" function inhibits MPGs competing with the primary movement. This select-off function starts with signals from the cortex exciting the STN by way of

glutamate projections (Fig. 5). Subsequently, glutamate projections from the STN to GPi/SNr excite this structure, resulting in increased GABA-mediated inhibitory output to the brainstem and cortex (by way of the thalamus) turning off unwanted MPGs. Simultaneously, signals come from the cortex to the striatum (direct pathway). These cortical inputs are transformed by the striatal integrative circuitry to a focused output that inhibits specific neurons in the GPi/SNr. The focally decreased activity in GPi/SNr then selectively disinhibits the desired thalamocortical and brainstem MPGs. Finally the indirect pathway activity results in further focusing of the output (Fig. 5). In summary, this model utilizes the cortical-STN pathway to inhibit competing MPGs, the direct pathway to enhance desired signals, and the indirect pathway for additional focusing or control (Mink 1996).

Subsequent to the publication of Mink's hypothesis, the utilization of computational modeling (Beiser and Houk 1998; Berns and Sejnowski 1998; Suri and Schultz 1998; Fukai 1999; Joel and others 2002; Bar-Gad and others 2003) of basal ganglia function (for reviews, see Gillies and Arbuthnott 2000; Gurney and others 2004) has increased dramatically. This has provided a means of accurately testing models of skeletomotor circuit function. Gurney and colleagues (Gurney and others 2001; Gurney and others 2004; Prescott and others 2006) developed a computational focused selection model similar to the qualitative model of Mink.

The first step in this model is that the striatum may act as a high-pass filter to exclude "weak" cortical requests, that is, those with minimal input from the cortex (Prescott and others 2006). As discussed above, each striatal cell receives input from thousands of cortical neurons and activation of a medium spiny neuron requires concurrent excitatory input from a large number of cortical afferents. Thus, the first step in the circuit would only be initiated when multiple cortical inputs send requests.

As with Mink's model, Prescott and colleagues suggest that the second step of the model is implemented by three pathways, the cortex-to-STN pathway and the direct and indirect pathways (Figs. 4 and 5). Two of the pathways are involved with selection and the third with control (Humphries and Gurney 2002; Prescott and others 2006). The select-off function occurs as a result of diffuse excitation of the output nuclei by fibers from the STN, which inhibits competing cortical inputs. The "select on" function is the result of focused direct pathway striatal inhibition of the output nuclei, which results in cortical excitation of the selected activity (Figs. 4 and 5). Finally, the indirect pathway serves as a "control function." In this model, the selection "on" function is controlled by the projection targets of the D1 striatal neurons and the control function by D2 subpopulations of striatal neurons (Fig. 5). Thus, in the normally functioning model, dopamine increases select-on activity and decreases "control" activity, which would have the effect of inhibiting the select-off function.

These authors reported analytical and simulation studies that demonstrated that this model has the capacity to support effective switching between multiple competitors (Gurney and others 2001). Furthermore, they were able to generate signal characteristics in the component circuits of their model that follow similar temporal patterns to single-unit recordings of neural firing in the GP. To determine whether their model is truly able to operate as an effective action selection mechanism in a real-time sensorimotor interaction with the physical world, Prescott and others reported results of embedding in a mobile robot. They found that an embedded skeletomotor circuit model succeeded in generating sequences of integrated behavior in a robot model, which was provided with a repertoire of alternative behaviors and varying levels of simulated motivations (Prescott and others 2006). They reported that the robot switched cleanly between successive behaviors, interrupting an ongoing behavior whenever there was a competitor with significantly higher salience. They argued that this outcome supports the hypothesis that the functional properties of basal ganglia circuitry allow for the task of resolving motor behavior selection conflicts. Finally, they suggested a role for the circuit in behavioral timing as well as maintenance and termination of action as part of the solution to the overall action selection problem (Prescott and others 2006).

In summary, there is now considerable evidence for the focused selection model of skeletomotor circuit function. Therefore, the question arises as to whether this model might be useful to clarify the neuropathology of TD.

Potential Mechanisms of Tardive Dyskinesia

Research diagnostic criteria for TD suggested by the *Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision* (*DSM-IV-TR*) include involuntary movements present for at least four weeks, which are choreiform (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continual), or rhythmic (stereotypies) in nature (American Psychiatric Association 2000). TD is characterized by these involuntary purposeless movements, which may involve the tongue, jaw, lips, face, trunk, upper extremities, or lower extremities. Involuntary movements of the tongue are particularly prominent, including incessant rolling movements and sucking or smacking movements of the lips. TD is generally a persistent illness; however, the course often waxes and wanes and periods of spontaneous remission are possible (Chouinard and others 1988; Gardos and others 1994). TD usually occurs after several years of antipsychotic treatment; however, it can also occur after short-term exposure for as few as two months (Chouinard and others 1980; Chouinard and others 1982). Acute effects of antipsychotic treatment are hypokinetic in nature and include parkinsonism and dystonias.

Inasmuch as antipsychotics block the D2 receptors in the striatum (Creese and others 1976; Seeman and others 1976), it has long been suspected this blockade contributes to the development of TD. Specifically, increased sensitivity of the dopamine receptors following chronic blockade has been thought to play a role (Gerlach 1977). It has been hypothesized that the neuron's attempt to overcome the blockade results in the D2 receptors either

up-regulating (increasing in number) and/or becoming more sensitive to dopamine. Thus, eventually the skeletomotor circuit would be abnormally reactive to dopaminergic modulation. However, this hypothesis has been questioned (Jeste and Wyatt 1982).

Most research into the of origin of TD has involved rodent and, to a lesser extent (Gerlach and others 1974), nonhuman primate models. When treated with first-generation antipsychotics, rats develop a syndrome of both acute and late onset involuntary purposeless chewing behaviors (Ellison and others 1987; See and others 1987; Ellison and See 1989; Egan and others 1996) known as vacuous chewing movements (VCMs). The late onset VCMs have many similarities with TD and are used as a rodent model for this condition (Egan and others 1996).

In addition to dopamine, abnormalities of GABA neurotransmission have also been postulated to play a role in TD. Early studies reported decreased activity of glutamic acid decarboxylase synthesis, the rate-limiting synthetic enzyme for GABA, in both the GP and an area equivalent to the human GPi/SNr in monkeys (Gunne and Barany 1976; Gunne and others 1984). These findings led Gunne and colleagues to propose that TD is related to decreased GABAergic transmission in the skeletomotor circuit. Tamminga and Woerner reported evidence of thalamic GABA receptor up-regulation, which supports this hypothesis (2002). Furthermore, this up-regulation is correlated with rat VCMs, which adds even greater support for the role of GABA in TD. Also in support of this hypothesis is the fact that GABA agonists have some benefit for TD symptoms (Thaker and others 1987; Cassady and others 1992). Finally, more recent rodent studies suggest that D2 receptor blockade in the striatum acutely results in disinhibition of the medium spiny neuron projections to the GPe (Tamminga and Woerner 2002). Based on these data, Tamminga and Woerner hypothesized that early onset antipsychotic-induced parkinsonism is a result of increased skeletomotor circuit indirect pathway activity and TD is a result of the loss of GABA-mediated thalamic inhibition. They also point out the direct skeletomotor pathway activity is altered by antipsychotic treatment. This may be the result of antipsychotic-induced increased availability of dopamine in the striatum and thus its action on the unblocked D1 receptor (Casey and others 1980).

Acetylcholine enhances dopamine release in the striatum likely by way of presynaptic muscarinic and nicotinic receptors located on dopamine neuron terminals (Di Chiara and Morelli 1993). Miller and Chouinard proposed that TD occurs secondary to degeneration of striatal cholinergic interneurons (1993). They suggested that acetylcholine neuron damage is caused by prolonged overactivation of these neurons, which occurs when they are released from dopaminergic inhibition as a result of antipsychotic treatment. Rodent studies have revealed evidence of cholinergic degeneration after treatment with haloperidol and fluphenazine (Mahadik and others 1988; Jeste and others 1992; Grimm and others 2001). An excess of choline in brain tissue signifies a loss of cholinergic neurons, which can be measured by proton magnetic resonance spectroscopy. Schizophrenic subjects have been found to have greater than normal choline levels using this method (Shioiri and others 1996), and these levels are even higher in those with TD (Ando and others 2002). Finally, evidence for the effectiveness of the anticholinesterase agent donepezil for the symptoms of TD (Caroff, Campbell, Havey, Sullivan, Katz, and others 2001; Caroff, Campbell, Havey, Sullivan, Mann, and others 2001) supports this hypothesis.

Although these studies provide compelling evidence of abnormalities of neurotransmission in TD, it is difficult to determine how these findings actually contribute to the development of this condition. The major problem is the complex interactions between various neurotransmitters and the fact that the same neurotransmitter may have opposite roles in different brain areas. For example, in the direct pathway, GABA-mediated neurotransmission results in activation of the cortex, whereas in the indirect pathway, it results in cortical inhibition. These problems have limited the ability of hypotheses based upon neurotransmitters and receptors to provide useful models of neuropsychiatric disorders in general. This suggests the alternative of using circuit-based models to explain the neuropathology of TD and various psychiatric disorders. Although these models will clearly have limitations, they may provide a more useful "big picture" of brain functional abnormalities. Furthermore, these models are potentially testable by computational modeling, as described above, and neuroimaging. Therefore, the focused selection model of skeletomotor circuit function may provide a useful model of TD.

Focused Selection as a Model of Tardive Dyskinesia

Although undoubtedly an oversimplification, the focused selection model provides a way to conceptualize the development of TD. Prior to treatment, activation from the cortex leads to increased activity of the select-on circuit for the specific motor behavior selected (Fig. 5). It also leads to activation of the select-off pathway for competing motor behaviors. Dopaminergic input to the striatum enhances the select-on circuit by way of D1 receptors. By way of the D2 receptors (which function to inhibit), the control circuit is turned on. This may function to limit the select-off pathway so that competing motor behaviors are decreased in intensity but not turned off completely.

After acute treatment with antipsychotics (Fig. 6), D2 blockade results in loss of control pathway function with a resulting excess of activity of the select-off circuit. The D1 select-on circuit function is unchanged. This could explain the acute side effects of antipsychotic treatment. These side effects are primarily hypokinetic, such as antipsychotic-induced parkinsonism, and are opposite of TD.

Chronic treatment with first-generation antipsychotics results in D2 up-regulation and sensitization. This leads to excessive activity of the control circuit (Fig. 7) and secondary decreased activity of the select-off circuit. At the same time, select-on pathway activity is increased as

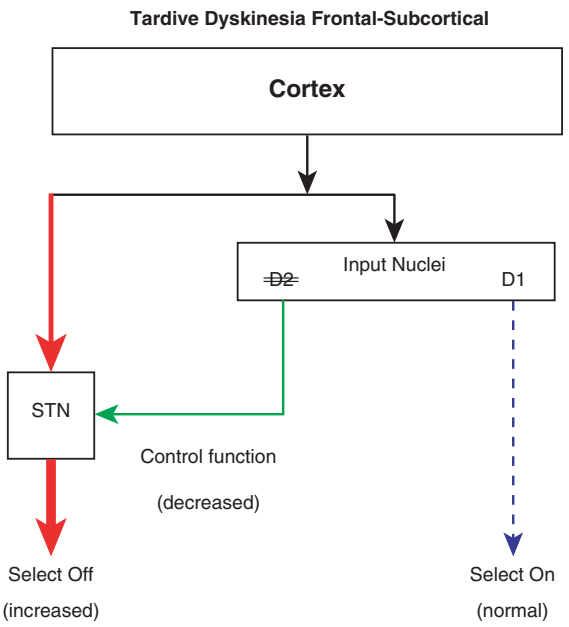

Fig. 6. Skeletomotor circuit focused-selection model with acute D2 blockade. This figure illustrates the skeletomotor frontal-subcortical focused-selection model with acute D2 blockade. The "select on" (dashed blue lines) function preferentially expresses D1 receptors and is unchanged with D2 blockade. The "control" circuit preferentially expresses D2 receptors and is therefore turned off. As a result, the "select off" pathway (solid red lines) activity is enhanced. Hypothetically, this could result in hypokinetic symptoms, such as antipsychotic-induced parkinsonism and dystonic reactions. STN = subthalamic nucleus.

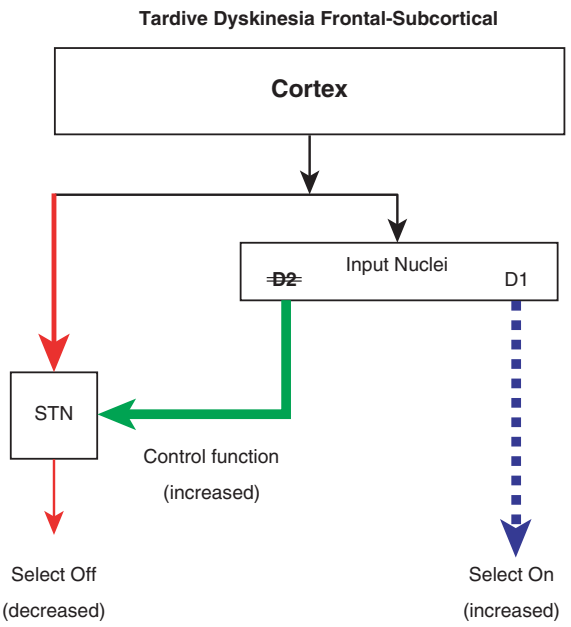

Fig. 7. Skeletomotor circuit focused-selection model with chronic D2 blockade. This figure illustrates the skeletomotor frontal-subcortical focused-selection model with chronic D2 blockade. The "select on" (dashed blue lines) pathway activity is increased as a result of antipsychotic-induced increased availability of dopamine in the striatum and thus its action on the unblocked D1 receptor. The "control" circuit preferentially expresses D2 receptors and exhibits increased activity as a result of up-regulation and increased sensitivity. As a result, the "select off" pathway (solid red lines) activity is decreased. Hypothetically, this could result in hyperkinetic symptoms, such as tardive dyskinesia. STN = subthalamic nucleus.

a result of antipsychotic-induced increased availability of dopamine in the striatum and thus its action on the unblocked D1 receptor. This combination of effects results in a change from hypokinetic parkinsonism and dystonia to hyperkinetic TD.

This model also fits relatively well with the existing literature on neurochemical abnormalities associated with TD. First, it supports the role of D2 up-regulation in the role of TD (Gerlach 1977) as well as antipsychotic-induced increased availability of dopamine in the striatum (Casey and others 1980) and thus its action on the unblocked D1 receptor. In regard to the role of GABA, this model agrees with rodent studies showing that D2 receptor blockade in the striatum acutely results in disinhibition of the medium spiny neuron projections to the GPe (Tamminga and Woerner 2002), which has a net effect of decreasing "control circuit" function (Fig. 6). Furthermore, it agrees with the evidence for decreased output nucleus inhibition of the thalamus (Tamminga and Woerner 2002) found in rodent models of TD (Fig. 7). Finally, this model fits data reported by Egan and colleagues who treated rats with haloperidol and assessed for mRNA levels of D1 and D2 dopamine receptors (1994). They reported that the overall pattern of mRNA changes suggests that alterations in both the D1-mediated striatonigral and the D2-mediated striatopallidal pathways play a role in the expression of the VCM syndrome and that there is likely increased activity in both pathways.

Discussion

There are a number of limitations of this model, and undoubtedly if it is proven to be accurate, then further refinements will be needed. One limitation is that this model ignores GPe inhibitory GABA output fibers to the GPi, SNr, and striatum. This may be reasonable given that the majority of GPe output consists of inhibitory GABA fibers to the STN (Rouzaire-Dubois and Scarnati 1987). However, further research will be needed to clarify this point. Also, the model does not address the possibility of altered cholinergic neurotransmission in TD. Furthermore, a three-pathway model of basal ganglia function has been suggested (Graybiel and others 2000), which considers the striosomal pathway as a third pathway, and a recent study of x-linked recessive dystonia-parkinsonism supports this hypothesis (Goto and others 2005). Refinement of the focused selection hypothesis will require further consideration of this pathway that originates in the striosomes and exerts critical motor

control by modulating the nigral dopaminergic outputs. Finally, the use of deep brain stimulation has been attempted as a treatment for TD (e.g., Eltahawy and others 2004), and results of these studies will need to be incorporated into this model.

Conclusion

Neuroscience research is progressing at a rapid rate. It will be increasingly necessary to combine information from human neuroimaging, neuropathological, animal model, and computational studies to develop more useful neurocircuit models. This article has been an attempt to use this method to evaluate the focused selection hypothesis of FSC skeletomotor function as a model for TD. Although further research is needed, it appears there is a good fit between the model and research findings from other kinds of studies.

Based on these results, it may be useful to further explore the validity of this model for TD. One approach would be an attempt to develop a computational model of TD. Such a model could potentially help overcome some of the limitations of rodent and nonhuman primate methodologies. These results also suggest the possibility of using the focused selection model to further our understanding of other movement disorders and psychomotor symptoms associated with multiple neuropsychiatric disorders.

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