

Review

Open Interconnected Model of Basal Ganglia-Thalamocortical Circuitry and Its Relevance to the Clinical Syndrome of Huntington's Disease

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Abstract: The early stages of Huntington's disease (HD) present with motor, cognitive, and emotional symptoms. Correspondingly, current models implicate dysfunction of the motor, associative, and limbic basal ganglia-thalamocortical circuits. Available data, however, indicate that in the early stages of the disease, striatal damage is mainly restricted to the associative striatum. Based on an open interconnected model of basal ganglia-thalamocortical organization, we provide a detailed account of the mechanisms by which associative striatal pathology may lead to the complex pattern of motor, cognitive, and emotional symptoms of early HD. According to this account, the degeneration of a direct and several indirect pathways arising from the associative striatum leads to impaired functioning of: (1) the motor circuit, resulting in chorea and bradykinesia,

(2) the associative circuit, resulting in abnormal eye movements, "frontal-like" cognitive deficits and "cognitive disinhibition," and (3) the limbic circuit, resulting in affective and psychiatric symptoms. When relevant, this analysis is aided by comparing the symptomatology of HD patients to that of patients with mild to moderate Parkinson's disease, since in the latter there is similar dysfunction of direct pathways but opposite dysfunction of indirect pathways. Finally, we suggest a potential novel treatment of HD and provide supportive evidence from a rat model of the disease. © 2001 Movement Disorder Society.

Key words: Huntington's disease; Parkinson's disease; basal ganglia; motor symptoms; cognitive symptoms; psychiatric symptoms; affective disorder

Although the basal ganglia have long been viewed as playing a central role in motor control and movement disorders, it is now widely accepted that they contribute to a wide variety of behavioral functions, including cognitive and emotional. This functional diversity is also reflected in the complexity of the pathological conditions which are associated with basal ganglia dysfunction, such as Parkinson's disease, Huntington's disease, and schizophrenia.^{1–17} This is not surprising, given the fact that the basal ganglia receive inputs from virtually all cortical areas, and in turn affect the frontal cortex via their thalamic projections.

Current views of the organization of basal ganglia-thalamocortical connections is that of circuits connecting anatomically and/or functionally distinct frontocortical, basal ganglia, and thalamic areas.^{4,10,12,15,16,18,19} Each circuit receives input from several separate but functionally related cortical areas, traverses specific regions of the striatum, the internal segment of the globus pallidus (GPi), the substantia nigra pars reticulata (SNR), the ventral pallidum (VP), and the thalamus, and projects back upon a frontocortical area. Within each circuit, striatal output reaches the basal ganglia output nuclei (GPi, SNR, and VP) via a "direct" pathway and via an "indirect pathway," which traverses the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN).^{1–3,16,20,21} In the last 15 years, the most dominant view of these circuits, pioneered by Alexander et al.,^{2,3,18} is that they are organized in a parallel manner and remain structurally and functionally segregated from one another.

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Models of basal ganglia-thalamocortical organization have major implications for the construction of models of neuro- and psychopathology. The pioneer circuit models of basal ganglia-related disorders of Penney and Young^{15,16} and Swerdlow and Koob¹⁷ have had a major impact in this respect by promoting the view that complex behavioral pathology must reflect a malfunction of a circuit rather than of a lesion in an isolated brain structure. A major advantage of the parallel organization principle is that it enables delimiting the scope of symptoms of the different basal ganglia-related disorders that can be attributed to dysfunction of individual circuits, and moreover, to specific alterations in components within each circuit. For example, Penney and Young^{15,16} described how alterations at different levels of the motor circuit can lead to a wide range of motor symptoms ranging from hypokinesia to hyperkinesia.

However, the emphasis on the closed segregated nature of the circuits has a serious drawback, in view of the fact that most of the basal ganglia-related pathologies comprise motor, cognitive, and emotional symptoms, and are not limited to one class of symptoms. Since, according to the closed segregated scheme, dysfunction of a circuit can result only from a pathology of a station within this circuit, the only way that such a model can explain symptom coexistence is by postulating a disruption in each of the relevant circuits. For example, DeLong and Wichmann⁵ recently suggested that the segregated circuit model predicts that the behavioral deficits of Parkinson's disease reflect abnormal processes in the motor, oculomotor, and associative circuits, and possibly also in the limbic circuit.

Recently, we presented a new scheme of basal ganglia-thalamocortical organization, the split circuit scheme, which emphasizes the open interconnected nature of the circuits^{19,21,22} (see Fig. 1). A split circuit contains one frontocortico-striatal pathway and two striato-frontocortical pathways passing via the basal ganglia output nuclei and thalamus. One of the striato-frontocortical pathways reenters the frontocortical area of origin, thus forming a "closed circuit," and the other leads to a frontocortical area which is a source of a different circuit, thus forming an "open pathway."

Using a tripartite subdivision of the striatum and pallidum,¹⁴ we described a motor, an associative, and a limbic split circuit. The associative split circuit contains a closed associative circuit that reenters the associative prefrontal cortex and an open associative pathway that terminates in the premotor cortex, which projects to the motor striatum. The motor split circuit contains a closed motor circuit that reenters motor and premotor cortical areas and an open motor pathway that terminates in the

associative prefrontal cortex. Since only the striatonigral portion of this pathway belongs exclusively to the motor circuit, whereas the nigro-thalamo-cortical portion is also part of the associative split circuit, we termed the striatonigral portion an "open motor route." The limbic split circuit contains a closed limbic circuit that reenters the limbic prefrontal cortex, an open limbic pathway that terminates in the associative prefrontal cortex, that is, an "open limbic route," and possibly an additional open limbic pathway which terminates in motor/premotor cortices. Thus, the three split circuits are interconnected via their open pathways or routes.¹⁹

The open interconnected principle governs also the organization of indirect pathways. Thus, similarly to striato-frontocortical pathways, there are two types of indirect pathways. An indirect pathway which terminates in the same GPi/SNR subregion as the direct pathway forms a "closed indirect pathway," whereas an indirect pathway which terminates in a different GPi/SNR subregion than the direct pathway forms an "open indirect pathway." There is a closed indirect pathway within the motor, associative, and limbic closed circuits as well as within the open associative pathway. In addition, there is an open indirect pathway which connects the associative striatum to the motor GPi and possibly an open indirect pathway connecting the associative striatum to the limbic (ventral) pallidum.²¹

The open interconnected principle also fits well the organization of the connections of the striatum with the dopaminergic system. Thus, the basic design of these connections is that of a "loop" comprising the projections from a striatal subregion to a subregion of the dopaminergic system and from this subregion to a striatal subregion. A loop which terminates in the striatal subregion from which it originates forms a "closed loop," whereas a loop which terminates in a different striatal subregion than the one from which it originates forms an "open loop."^{22; for related views see 23-34}

Figure 1 presents a summary diagram of the structural organization of the motor, associative, and limbic split circuits. As can be seen, this structural organization enables four modes of between-circuit interaction: via open pathway, via open route, via open indirect pathway, and via open loop. It is noteworthy that the three split circuits differ in their modes of connectivity. Thus, the motor split circuit is connected to the associative split circuit at the level of SNR (via the open motor route). The associative split circuit is connected to the motor split circuit at the level of the cortex and pallidum (via the open associative pathway and the open indirect pathway, respectively). The associative split circuit may be connected to the limbic split circuit at the level of the pallidum.

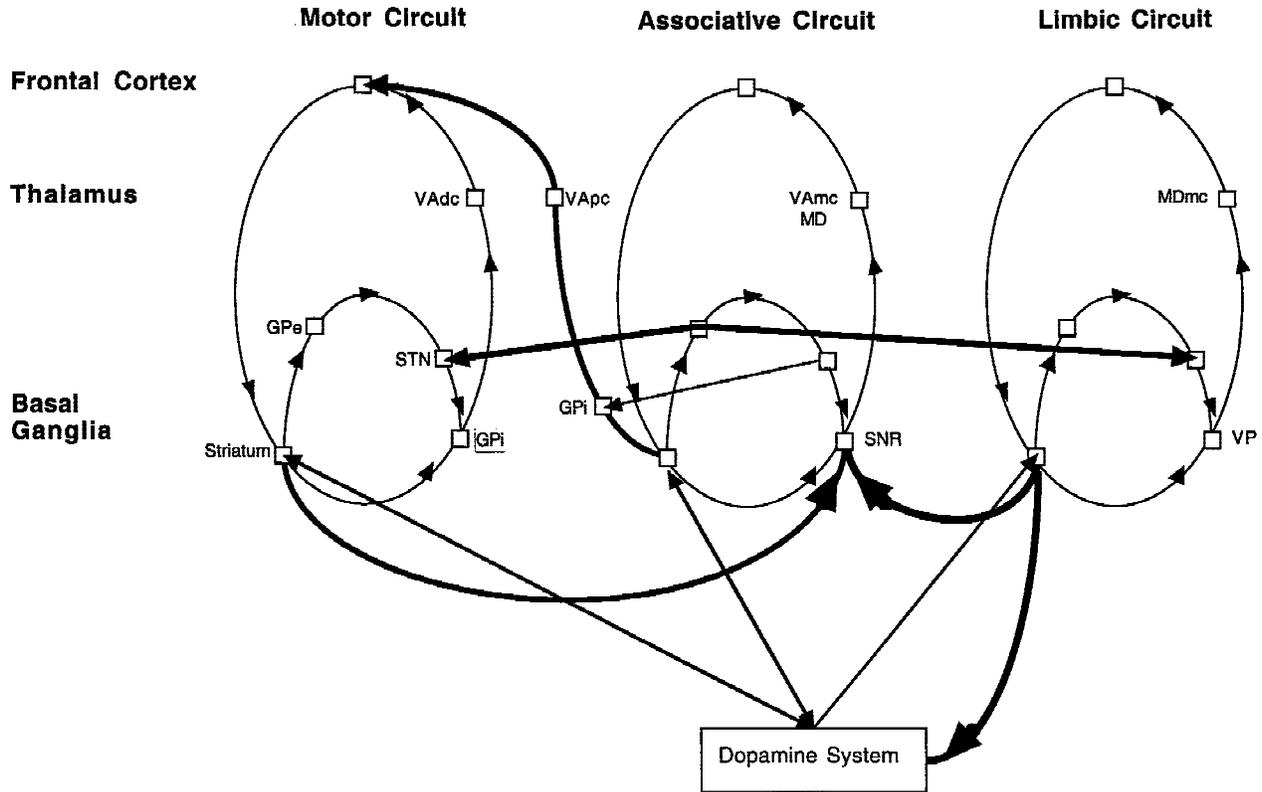


FIG. 1. A summary diagram of the structural organization of the motor, associative, and limbic split circuits. Each split circuit contains a closed circuit and an open route or an open pathway. The associative split circuit: the closed associative circuit comprises the associative striatum, substantia nigra pars reticulata (SNR), VAmc and MD thalamic nuclei, and the associative prefrontal cortex (including the frontal eye field and dorsolateral prefrontal cortex). The open associative pathway arises from the associative striatum, traverses the associative region of the internal segment of the globus pallidus (GPi), and VApc, and terminates in the premotor cortex, which projects to the motor striatum. The motor split circuit: the closed motor circuit comprises the motor striatum, motor GPi, VAdc, and the primary motor cortex and supplementary motor area. The open motor route consists of motor striatal projections to SNR. The limbic split circuit: the closed limbic circuit comprises the limbic striatum, ventral (limbic) pallidum, MDmc, and the limbic prefrontal cortex (including the orbitofrontal cortex and anterior cingulate area). The open limbic route consists of limbic striatal projections to SNR. Included within each of the closed circuits as well as within the open associative pathway is a direct and a closed indirect pathway. In addition, the associative split circuit contains an open indirect pathway which connects it with the motor split circuit, and possibly an open indirect pathway which connects it with the limbic split circuit. Each split circuit has a closed loop with the dopaminergic (DA) system, and in addition there are two open loops connecting the limbic split circuit with the motor and the associative split circuits. Pathways connecting between circuits are demarcated in thick lines. MD, mediodorsal thalamic nucleus; MDmc, mediodorsal thalamic nucleus, magnocellular subdivision; VAdc, ventral anterior thalamic nucleus, denticular subdivision; VAmc, ventral anterior thalamic nucleus, magnocellular subdivision; VApc, ventral anterior thalamic nucleus, parvocellular subdivision; GPe, globus pallidus, external segment; STN, subthalamic nucleus; VP, ventral pallidum.

idum (via an open indirect pathway). The limbic split circuit is connected to the associative split circuit at the level of SNR and the striatum (via the open limbic route and an open loop, respectively), and to the motor split circuit at the level of the striatum (via an open loop) and maybe also at the level of the cortex (via an open limbic pathway).

It should be noted that the split circuit scheme as presented here is based on a meta-analysis of anatomical data available at the time (for a detailed description and discussion of the data on which the model is based, see references 19, 21, and 22). In recent years, new data have been published³⁵⁻⁴² supporting the general notion of the open interconnected organization, namely, that pathways

of the same type (e.g., striato-frontocortical, indirect) may connect either functionally corresponding regions (e.g., closed circuits, closed indirect pathways), thus serving segregated processing, or functionally noncorresponding regions (e.g., open pathways, open indirect pathways), thus serving integrated processing. It should also be noted that the model does not include all the known connections of the basal ganglia,^{40,43-47} some of which may be of relevance in the context of Huntington's disease, e.g., the direct projections from GPe to the basal ganglia output nuclei.^{39,40,44-48}

The major strength of the open interconnected model for explaining neuropathological mechanisms is its ability to accommodate coexistence of different classes of

symptoms as a result of damage to only one station in one of the circuits. Thus, whereas the closed segregated organization provides a framework whereby damage to different stations of an individual circuit results in selective disturbances of motor, cognitive, *or* emotional behaviors, the open interconnected organization provides in addition a framework whereby such damage may lead to different combinations of motor, cognitive, *and* emotional symptoms. The spectrum of symptoms in a given disorder is suggested to reflect the specific disturbances at one or more of the different levels of a given circuit (frontal cortex, basal ganglia, thalamus) as well as the subsequent disruption of the normal interaction and flow of information between the different circuits.

The strength of the open interconnected model is best exemplified in disorders in which there is coexistence of motor, cognitive, and emotional symptoms with a restricted damage to only one of the basal ganglia circuits. One such case is Huntington's disease in its early stages.

Huntington's Disease

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder of midlife onset, characterized clinically by prominent motor dysfunction, cognitive deterioration, affective and psychiatric symptoms.^{1,15,49-51} Despite the recent discovery of the genetic mutation associated with HD, the biochemical basis of HD pathogenesis and of the differential vulnerability of different tissues to this pathological process is not understood.^{52,53}

Postmortem and *in vivo* neuroimaging techniques have revealed that in the early stages of the disease the striatum is most severely affected although other brain regions, including the cortex, may show some pathological changes.^{16,53-61} Postmortem studies further reveal that striatal degeneration progresses along mediolateral and dorsoventral gradients, at first affecting the dorso-medial caudate and dorsal putamen while sparing the more lateral and ventral aspects of the striatum, including the nucleus accumbens.^{53,57,59,62-65} The results of imaging studies are less conclusive. There are many reports of caudate atrophy,^{58,66-70} but relatively few studies which measured the putamen. Of these, some report that the caudate is affected earlier^{71,72} and to a greater extent than the putamen,^{73,74} whereas other report that the putamen is more affected.^{72,75,76} Although some functional imaging studies report similar changes in glucose metabolism in the caudate and putamen in the early stages of HD,^{73,77,78} most studies point to an earlier and greater caudate dysfunction.^{56,58,61,67,68,76,79,80} Imaging studies assessing dopaminergic markers report changes in D1-

and D2 receptor binding in the caudate and putamen of HD patients.^{73,74,81-84}

Taken together, the bulk of data points to a greater involvement of the associative striatum (which is comprised mainly of the caudate) than of the motor striatum (which is comprised mainly of the putamen), and no involvement of the limbic (ventral) striatum in the early stages of HD.

Striatal degeneration is progressive not only with respect to topography but also with respect to the targets of striatal projection neurons, so that the early stages of the disease are marked by a selective loss of the striatal innervation of GPe and SNR, while the striatal innervation of GPi is lost only in later stages.^{54,85-91} Thus, there is loss of striatal neurons of direct (to SNR) and indirect pathways. This can account for the findings of reductions in enkephalin and substance P^{62,65,92} and in D1- and D2 receptor binding^{74,81,83,84} in the striatum of HD patients, since neurons of the direct pathway contain gamma aminobutyric acid (GABA) and substance P and preferentially express D1 receptors, while neurons of the indirect pathway contain GABA and enkephalin and preferentially express D2 receptors.^{1,93,94}

There is some evidence that the striosomal compartment of the striatum is affected early in the disease.^{62,64} Hedreen and Folstein⁶⁴ suggested that the early loss of striosomal neurons leads to disinhibition of nigrostriatal dopaminergic neurons and thus to increased dopaminergic input to the striatum which leads to decreased activity of the indirect pathway. While this suggestion is consistent with other models of HD in postulating decreased activity of the indirect pathway (see below), there is no evidence in primates (as opposed to rats) that striosomes provide the main striatal input to the dopaminergic neurons of the substantia nigra pars compacta (SNc),²² and striatal projections to the dopaminergic neurons of SNc were found not to be affected at the early stages of HD.⁸⁸ Therefore, while it is possible that the striosomal compartment is the first to be affected, the functional implications of this selective degeneration are not clear. Finally, dopaminergic neurons are not affected in the early stages of HD.^{57,60,85,86,92}

Circuit Models of HD

It is widely accepted that most of the motor, cognitive, and emotional symptoms observed in the early stages of HD reflect frontostriatal dysfunction.^{49,51,95-97} However, the leading and most detailed model of HD, launched by Penney and Young,^{1,16} accounts only for the motor symptoms, most notably chorea. According to the model, these symptoms reflect a dysfunction of the motor circuit resulting from abnormal functioning of its indirect path-

way. More specifically, loss of striatal projections to GPe results in overactivity of GPe which leads to underactivity of STN, which in turn leads to underactivity of GPI and thus overactivity of the thalamus, resulting in chorea.^{1,16, see also 98-100}

Other writers had implicated dysfunction of the associative and limbic circuits in order to account for the nonmotor symptoms of HD. Thus, Alexander et al.³ suggested that in addition to the degeneration of neurons in the putamen, which results in the disruption of the motor circuit, there should be a degeneration of neurons in the caudate nucleus, i.e., a disruption of the "complex" circuits ("dorsolateral prefrontal" and "lateral orbitofrontal"), which underlies the cognitive symptoms of HD. Similarly, Cummings⁹⁶ suggested that dysfunction of the "complex" and limbic circuits ("dorsolateral prefrontal," "lateral orbitofrontal," and "anterior cingulate," according to the terminology of Alexander et al.³) underlies the cognitive and emotional symptoms of HD. These two accounts did not specify the specific circuit dysfunction underlying the cognitive and emotional symptoms. Recently, Litvan et al.¹⁰¹ suggested that the neuropsychiatric symptoms of HD (e.g., agitation, irritation, and euphoria) are secondary to underactivity of the indirect pathway of

the "lateral orbitofrontal" and of the "anterior cingulate" circuits. Since all three models adhere to the closed segregated scheme of basal ganglia circuitry, they postulate for each class of symptoms (motor, cognitive, and emotional) a disruption in the corresponding basal ganglia-thalamocortical circuit. Given that the three classes of symptoms coexist in the early stages of HD, dysfunction of the entire striatum is predicted. This contrasts, however, with the findings that the limbic striatum is not involved in the early stages of HD, and the associative striatum is much more affected than the motor striatum.

The Split Circuit Scheme and HD

According to the split circuit scheme, the complex motor, cognitive, and emotional symptomatology of the early stages of HD results primarily from loss of associative striatal projections to SNR and to the associative GPe, which leads to disruption of the following pathways (see Fig 2): (1) the direct pathway of the closed associative circuit (to SNR), (2) the closed indirect pathway of the closed associative circuit (via the associative GPe and associative STN to SNR), (3) the closed indirect pathway of the open associative pathway (via the associative GPe and associative STN to the associative GPI),

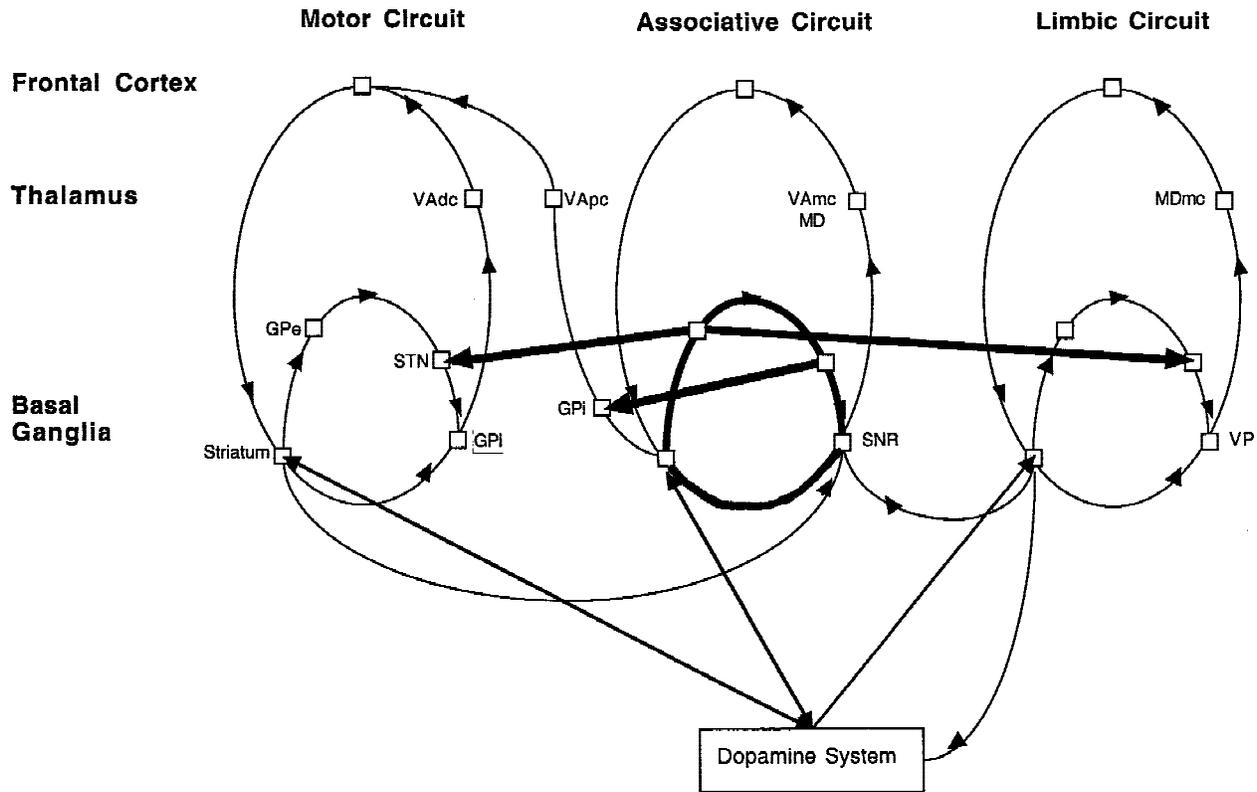


FIG. 2. A summary diagram of the direct and indirect pathways affected following selective loss of the associative striatal projections to GPe and SNR in the early stages of Huntington's disease (HD). Affected pathways are depicted in thick lines.

(4) the open indirect pathway (via the associative GPe and motor STN to the motor GPi), and if such a pathway exists (5) an additional open indirect pathway (via the associative GPe and limbic STN to the limbic pallidum). Disruption of these pathways leads to impaired functioning of all three (motor, associative, and limbic) circuits and subsequently to the corresponding symptoms. We would like to note, however, that some of the symptoms in each class may result directly from pathological processes in the cortex, which although not as pronounced as striatal pathology, are also present in the early stages of the disease (see below).

Prior to describing how different symptoms of HD result from disruption of each of the above pathways, a brief description of their role in the production of behavior is warranted. Of the wealth of functions ascribed to the striatum, the one which figures out most prominently is the selection and initiation of the elements of a motor program (which includes motor and cognitive components), as well as their serial ordering into a coordinated sequential pattern.^{11,13,20,102–115} The different functional regions of the basal ganglia are thought to subserve different aspects of this function. Performance of single movements depends on the function of the motor striatum and motor pallidum (that is, the closed motor circuit); performance of chains of movements depends on the associative striatum and associative pallidum (that is, the open associative pathway),^{20,102–104,106,108–111,115} and the sequencing of the elements of a motor program was suggested to depend on the closed associative circuit.^{7,19,116–119}

Direct and indirect pathways are considered to subserve different functions, with the former promoting the execution of motor programs by facilitating cortically driven elements of the program, and the latter suppressing unwanted elements.^{2,13,16} A major role in the suppression mechanism has been attributed to the STN, which provides excitatory input to the inhibitory output nuclei of the basal ganglia. The STN has been suggested to: (1) assist in the suppression of unwanted muscle activity during performance of single movements;^{118,120–122} (2) contribute to the ending of an action during performance of a single movement and to the beginning/ending of movements during execution of a sequence of movements;^{103,104,121,23} and (3) suppress the soon-to-be-executed motor acts while current components of the motor program are being executed.^{118,124}

We propose that each of these three functions is subserved by a different indirect pathway, namely, the closed indirect pathway of the closed motor circuit, the open indirect pathway which links the associative and motor split circuits, and the closed indirect pathway of

the open associative pathway, respectively. In addition, the latter pathway subserves the suppression of motor elements of competing motor programs, and the closed indirect pathway of the closed associative circuit subserves the suppression of the soon-to-be-executed cognitive elements of the motor program while current elements are being executed as well as the cognitive elements of competing motor programs.

Motor symptoms

Chorea is considered the hallmark of the motor abnormality of HD.^{1,15,125–127} Data from human and nonhuman primate research implicate the motor parts of the STN, GPi, and thalamus in the production of chorea,^{1,98–100,121,128–132} in line with the view that chorea reflects dysfunction of the motor circuit resulting from underactivity of its indirect pathway.^{1,6,98,100,127,130,133} However, as detailed above, anatomical and physiological studies in HD patients reveal that in the early stages of HD, when chorea is most prominent, striatal dysfunction is most evident in the associative striatum. Although some neuroimaging studies in HD patients failed to find significant correlations between chorea and measures of atrophy or glucose metabolism in the caudate,^{56,69} the involvement of the associative striatum in the production of chorea is strengthened by the findings that: (1) in patients with benign hereditary chorea there is caudate hypometabolism,¹³⁴ and (2) although chorea is a rare outcome after striatal lesions in humans, it is much more common after caudate than after putamen lesion.⁹⁸ Clearly, the involvement of the associative striatum in Huntington's chorea awaits confirmation by functional brain imaging of HD patients during choreiform movements; unfortunately, currently such data are extremely difficult to obtain since movements interfere with functional imaging.

It follows that Huntington's chorea reflects abnormal functioning of the motor circuit which results from pathology of the associative striatum. While this poses a serious difficulty for the parallel segregated scheme, because in this scheme abnormal functioning of the motor circuit cannot stem from pathology in a different circuit, it is readily accommodated by the split circuit scheme, according to which associative striatal pathology leads to disruption of the connections between the associative and motor split circuits and subsequently to dysfunction of the motor split circuit. More specifically, degeneration of associative striatal projections to the associative GPe leads to disruption of the open indirect pathway and of the closed indirect pathway of the open associative pathway. Since these indirect pathways subserve the transition between the motor elements of a motor program as

well as suppression of the soon-to-be-executed motor elements of the current motor program and of the motor elements of other motor programs, their disruption is expected to be manifested clinically as Huntington's chorea, which is described as representing the intrusion of fragments of undesirable motor programs into the normal flow of motor acts.¹

Bradykinesia is another fundamental, albeit less recognized, feature of the motor deficit in HD, seen already in the early stages of the disease.^{127,135-144} It was suggested^{91,144} that bradykinesia in the early stages results from underactivity of the direct pathway of the motor circuit, similar to the mechanism underlying bradykinesia in Parkinson's disease (PD).^{1,5,16} However, in HD the direct pathway of the motor circuit degenerates only in later stages. Therefore, although such degeneration is likely to contribute to the bradykinesia observed in the late stages of HD,^{85,88,91} it cannot account for the bradykinesia of the early stages.

It follows that although both HD and PD patients show bradykinesia, the underlying mechanisms and therefore some of the clinical manifestations are expected to differ. Indeed, several studies point to such differences. The electromyogram (EMG) patterns recorded during voluntary movement in early stage HD patients were characterized by prolongation and high within-subject variability of the first burst of activity in the agonist,^{140,144} in contrast to its reduced amplitude and normal duration in PD.^{133,144}

Moreover, ballistic movements, which are normally presented by a triphasic pattern of muscle activity (agonist, antagonist, agonist), are characterized in PD patients by a number of cycles of agonist-antagonist activity, whereas in HD patients a variety of patterns is observed, including tonic activation, cocontraction, and a triphasic pattern.^{133,143-148} A careful analysis of movement kinematics of HD and PD patients' handwriting revealed that although both groups exhibited bradykinesia, HD patients showed less efficient and more variable movements compared with PD patients.^{139,142,149} The authors suggested that PD patients may have problems in generating appropriate movement forces, whereas HD patients may have problems in force efficiency.^{139,142,149; see also 143} Taken together, these differences are consistent with the idea that different mechanisms underlie bradykinesia in the two diseases. We further suggest that whereas bradykinesia in PD results from underactivity of the direct pathway of the motor circuit and subsequently from difficulties in activation of relevant muscles,^{1,5,16,130,144} bradykinesia in the early stages of HD results from underactivity of indirect pathway(s), and subsequently from inappropriate termination of muscle activity.

Bradykinesia in HD and PD is even more pronounced during the performance of simultaneous and sequential movements. Under these conditions, movement times of PD and to a lesser extent of HD patients are prolonged to a greater extent than when performed alone.^{133,135,137,140,150} In addition, both patient groups exhibit longer pauses between movements in a sequence compared with control subjects,^{135,144} and HD patients show also a greater within-subject variability.¹³⁵ The difficulties in the performance of sequential and simultaneous movements in PD patients were suggested to result primarily from difficulties in the initiation and execution of movements, which reflect underactivity of the direct pathway.¹³⁰ We suggest that in HD patients these difficulties result primarily from difficulties in switching between movements, which reflect underactivity of indirect pathways.

Particularly revealing in the present context is a set of experiments by Bradshaw and colleagues^{136,151-153} comparing the performance of HD and PD patients on two versions of a sequential button-pressing task. In both tasks, information about the next button to be pressed was provided by illuminating it. In the first task,^{136,153} the next button to be pressed was illuminated after the release of the present button (no advance information), after depression of the present button (low advance information), or after release of the previous button (high advance information). In the second task,^{138,151} the entire sequence was illuminated in advance, but the illumination of the next button to be pressed was extinguished after the release of the present button (no information reduction), after depression of the present button (low information reduction), or after release of the previous button (high information reduction). Two measures were taken, time from the depression of a button to its release (down time), and time between the release of one button and the depression of the next (movement time).

Both PD and HD patients had longer down time than controls in the first task.^{136,153} However, whereas PD patients improved when advance information was provided, no such improvement was seen in HD patients. HD patients, and to a much lesser degree PD patients, had longer movement time. In addition, whereas controls and PD patients improved as the amount of advance information increased, HD patients' movement time improved when information about the next button to be pressed was provided before the release of the present button, but there was no further improvement (seen in controls and PD patients) when this information was provided after the release of the previous button. Importantly, several of the subjects at risk for developing HD had longer movement time than controls under this high

advance information condition.¹³⁶ A similar pattern was seen in the second task, namely, HD patients' down time and movement time were particularly prolonged at the high information reduction condition, in which information regarding the next button press was provided after the release of the previous button.¹³⁸ Finally, in the second task, HD patients had prolongation of down time and movement time comparable to those in the first task,¹³⁸ whereas PD patients showed an opposite pattern, i.e., a dramatic prolongation of movement time with relatively mild prolongation of down time.¹⁵¹

Bradshaw and colleagues^{138,151,153} concluded that both patient groups are deficient in sequencing motor programs effectively under conditions in which external cues are not available, as reflected in prolongation of movement preparation time (down time) and movement execution time (movement time) under these conditions.

This conclusion is consistent with the view that PD patients have difficulties in the initiation and execution of movements, particularly when no external guidance is available.^{143,154} However, the deficits exhibited by the HD group do not seem to follow the same pattern. Thus, PD patients had a very mild prolongation of movement time in the first task, in which an external cue to which the movement should be directed was always available once the movement was initiated, but they had a very large prolongation in the second task, in which such an external cue was absent. In contrast, HD patients exhibited similar down time and movement time prolongation in both tasks. Similarly, whereas PD patients had a particularly prolonged down time when there was no information on the target at the time of movement initiation (no advance information condition in the first task), HD patients exhibited similar down time under the no-advance information and the low-advance information conditions of the first task.

These results suggest that the slowed performance of HD patients does not stem from deficits in initiating or executing movements when external information is not available. Rather, we suggest that the prolonged down time of the HD group reflects difficulties in termination and initiation of sequential movements (e.g., pressing and then releasing a button), that is, difficulties in switching between two movements in a sequence. These difficulties reflect underactivity of the open indirect pathway connecting the associative striatum to the motor circuit, which contributes to the beginning/ending of movements during execution of a sequence of movements.

The prolonged movement time of the HD group in these button press tasks is suggested to reflect partly slowness in performing movements in a sequence and

partly slowness in performing single movements. The latter is subserved by the same mechanisms that underlie bradykinesia of single movements, i.e., underactivity of indirect pathway(s) (see above). The former results from interference in the performance of the current movement arising from the preparation of other movements in the sequence. Such interference may reflect underactivity of the closed indirect pathway of the open associative pathway, which suppresses the soon-to-be-executed motor acts while current components of the motor program are being executed. In this respect, it is of interest to note that the HD group showed a particularly prolonged movement time (compared with controls) under conditions in which two movements had to be prepared in advance, i.e., information regarding the next button press was provided after the release of the previous button (high advance information condition in the first task, and high information reduction condition in the second task). Since these conditions necessitate the preparation of the second movement, the interference of the execution of the first movement was most pronounced.

Our emphasis on difficulties in switching between movements and in suppressing movements is in line with Bradshaw and colleagues' interpretation of some of their data. Specifically, they suggested that the performance of HD patients in the second task reflects difficulties in switching between motor segments,¹³⁸ and that the disproportionate difficulty of HD patients in performing the first task with the nonpreferred hand reflects difficulties in suppressing unwanted activity.¹³⁶

In summary, we suggest that in the early stages of HD, both chorea and bradykinesia result from disruption of the connections between the associative striatum and the motor circuit which normally subserve the sequencing of movements of a motor program by beginning/ending the movements of the program (the open indirect pathway) and by suppressing inappropriate movements of the current and of competing motor programs (the closed indirect pathway of the open associative pathway). Bradykinesia may result in addition from disruption of the closed indirect pathway of the motor circuit, which assists in the suppression of unwanted muscle activity during performance of single movements.

Cognitive symptoms

HD patients undergo a gradual loss of cognitive functions, often preceding the appearance of the movement disorder by many years, which invariably leads to the development of dementia. The early stages of the disease, however, are characterized by a specific pattern of cognitive deficits,^{51,155,156} which are very similar to those observed in patients with dorsolateral prefrontal

cortex lesion.^{70,95,96} It is widely accepted that these symptoms reflect dysfunction of the "complex" loops (which correspond to the closed associative circuit in the present scheme) resulting from pathology at both striatal and cortical levels.^{61,69,81,82,96,97,152,156,157} However, the specific circuit dysfunction subserving these symptoms has not been delineated.

We suggest that the disrupted functioning of the closed associative circuit in HD is due to the degeneration of its direct (associative striatal projections to SNR) and closed indirect (associative striatal projections to the associative GPe) pathways as well as to pathology of the prefrontal cortex.^{74,77,80-82,97,58} Degeneration of the direct pathway is expected to result in underactivity of the prefrontal cortex, further contributing to prefrontal dysfunction due to direct prefrontal pathology. Loss of functions normally subserved by the prefrontal cortex is expected to follow. In contrast, degeneration of the indirect pathway is expected to lead to "disinhibition" of functions.

The distinction between these two groups of symptoms, one reflecting underactivity of the prefrontal cortex (resulting directly from prefrontal pathology and indirectly from degeneration of the direct pathway) and the other reflecting underactivity of the indirect pathway, is best exemplified by comparing the cognitive symptoms exhibited by patients with early HD to those exhibited by patients with mild to moderate PD. In both diseases there is a prefrontal pathology^{154,156,158,159} as well as an underactivity of the direct pathway of the closed associative circuit (resulting from different pathologies, degeneration of striatal neurons in HD versus loss of striatal dopaminergic input in PD). Therefore, in both diseases, the prefrontal cortex is expected to be underactive. However, in contrast to HD, in PD there is overactivity of the indirect pathway, due to loss of striatal dopaminergic input.^{1,5,16}

The similarity of the cognitive deficits in HD and PD, considered to reflect frontal underactivity, has been repeatedly recognized.^{95,156,160-163} In both conditions, several "executive" functions are impaired, such as, planning, selecting, initiating and sequencing motor programs, mental flexibility, and set shifting.^{49,51,82,95,154,156,159,160,164} Both patient groups have memory impairments, which although more pronounced in HD, are thought to result from impairment in the strategic aspects of memory function.^{49,51,95,125,126,154-156,158,160,162-164} Finally, HD and PD patients are impaired on "frontal" neuropsychological tests, such as the stylus maze, verbal fluency, Tower of Toronto, and the Wisconsin Card Sorting Test.^{49,70,81,95,155-157,161,165-171}

There are, however, some differences between the

cognitive deficits in HD and PD, although these are often overlooked. HD but not PD patients are reported to have concentration difficulties.¹⁶² HD patients are more impaired on the arithmetic, digit span, and digit symbol subsets of the Wechsler Adult Intelligence Scale (WAIS),^{95,162} which comprise a concentration and "freedom from distraction" factor.⁹⁵ In a study of cognitive flexibility and complex integration, both HD and PD patients had decreased solution fluency, but HD patients showed, in addition, impulsive responding to partial information and difficulties in set maintenance and shifting,¹⁷² which can also be attributed to inability to suppress a dominant cognitive set. Similarly, in a study investigating attention in HD and PD patients, both groups were slower than matched controls, but only HD patients exhibited a specific impairment in inhibiting inappropriate responses and in responding in the face of conflicting information.^{152,173}

According to the present scheme, these cognitive symptoms, characterized by impaired ability to suppress interfering information, reflect "cognitive disinhibition" which results from underactivity of the indirect pathway of the closed associative circuit.

In addition to its involvement in cognitive functions, the associative circuit has an important role in the control of eye movements. Therefore, examination of the specific pattern of eye movement abnormalities in HD allows further analysis of the deficits arising from abnormal functioning of the associative circuit.

Descriptions of abnormal eye movements appeared already in early reports on HD, but have received more attention in the last two decades.¹⁷⁴ The main ocular motor abnormalities in the early stages of HD include difficulties in initiating the more voluntary types of saccades and in suppressing unwanted reflexive saccades. The former is reflected in increased latency in the initiation of volitional (i.e., on command), remembered and predictive saccades, which is often accompanied by head movements or blinking. The latter is reflected in abnormal fixation and smooth pursuit, which are disrupted by extraneous saccades which take the eye off the target, as well as in the "antisaccade" task, in which patients are required to generate a saccade to the mirror location of a suddenly appearing target. Most HD patients have marked difficulty in suppressing the reflexive saccade to the target.¹⁷⁵⁻¹⁸⁰ The ocular motor abnormalities of early HD have been attributed to disruption of the basal ganglia circuitry involving the SNR and frontal eye fields, in particular, their projections to the superior colliculus.^{127,174-176,178-180}

According to current schemes of the neural mechanisms subserving saccade generation, more reflexive saccades are triggered by parietal regions, while more vol-

untary saccades are generated by frontal regions. The production of both types of saccades is dependent on the superior colliculus, and can be gated by its tonic inhibitory input from the SNR.^{174,176,180} Furthermore, facilitation of the generation of voluntary saccades is dependent on excitatory frontocaudal projections, which disinhibit the superior colliculus, i.e., the direct pathway of the associative circuit, whereas the suppression of unwanted reflexive saccades and the termination of saccades are subserved by the indirect pathway of this circuit.^{118,124,174,176,181} In view of the above, it is likely that deficits in the initiation of voluntary saccades and in the suppression of unwanted saccades in the early stages of HD reflect frontal eye field (FEF) pathology combined with degeneration of the direct pathway of the associative circuit, and degeneration of the indirect pathway of the associative circuit, respectively.

The above suggestion receives support from a comparison between eye movement abnormalities in early HD and in mild to moderate PD. Thus, like HD patients, parkinsonian patients exhibit difficulties in the initiation of several types of voluntary saccades (i.e., predictive and remembered). These difficulties, which are reflected in increased latency and decreased amplitude (i.e., hypometric saccades),^{176,182–185} are not identical, however, to those of HD patients, who show increased latency and decreased, normal or increased amplitude with greater within-subject variability than normal.^{177,178,180} In addition, HD, but not PD patients,^{182,186–188} have great difficulties in the antisaccade task, in which they cannot suppress reflexive saccades to the target. The increased latency in the initiation of voluntary saccades in HD and PD as well as the deficits of HD but not PD patients in the antisaccade task, are in line with our suggestion that the former reflects underactivity of the direct pathway whereas the latter reflects underactivity of the indirect pathway. The differences in saccade amplitude may also reflect the opposite nature of dysfunction of the indirect pathway in the two diseases.

The brain regions subserving the control of eye movements have been implicated also in the control of spatial attention.^{189–191} Therefore, the different mechanisms underlying eye movement dysfunction in HD and PD are expected to be reflected also in different patterns of spatial attention deficits in these diseases.

In reaction time tasks which assess both motor and attentional processes, both HD and PD patients show behavioral slowness. However, whereas HD patients show profound difficulties in shifting attention, particularly when no external guidance is provided,^{97,141,192} and a milder deficit in the ability to maintain attention in the absence of an external cue,¹⁴¹ PD patients have difficul-

ties in maintaining attention, particularly when no external cue is available, but not in shifting attention.^{141,173,185}

Better performance of both patient groups when external guidance is available may reflect intact passive (exogenous) orienting of attention, which is dependent on posterior cortical regions (Posner's posterior attention system), together with deficient internal control of attention, which is thought to depend on regions of the frontal cortex and basal ganglia (Posner's anterior attention system).^{97,189–192} HD and PD patients have difficulties, however, with relatively distinct aspects of the internal control of attention. We suggest that difficulties in self-generated attention shift, which are observed only in HD patients, result from difficulties in inhibiting or terminating selective attention to a current target, and reflect underactivity of the indirect pathway of the closed associative circuit. These difficulties in shifting attention may be analogous to the difficulties of HD patients in shifting cognitive set, which were also attributed to an inability to suppress a dominant cognitive set as a result of underactivity of the same indirect pathway (see above). The difficulties in maintaining attention found in both patient groups (although more pronounced in PD patients), are suggested to reflect an inability to maintain a sufficient level of activity in a subgroup of prefrontal or collicular neurons, due to underactivity of the direct pathway of the closed associative circuit.

The attentional deficits of HD and PD patients are reminiscent of their eye movement abnormalities in that both saccadic eye movements and the control of attention are particularly impaired when external information is unavailable and performance is internally generated. This probably reflects the fact that in both diseases there is dysfunction of the prefrontal cortex rather than of posterior cortical regions. However, the specific pattern of attentional deficits in HD and PD may seem inconsistent with that of their eye movements abnormalities. Thus, HD but not PD patients exhibit an inability to suppress unwanted saccades as well as difficulties in shifting attention, whereas both patient groups exhibit difficulties in saccade initiation as well as difficulties in maintaining attention. This inconsistency may be resolved when considering the mechanisms underlying attention as described in Rizzolati's premotor theory of attention.¹⁹¹

According to Rizzolati's theory, spatial attention to a specific location is a consequence of activation of collicular neurons resulting from the preparation to perform a saccade to that location. The reorientation of attention to a new location is dependent on a change in the saccade program. It follows that the ability to initiate a saccade or to maintain attention is dependent on activation (by disinhibition) of a group of collicular neurons or on main-

taining the activity of a group of collicular neurons, respectively, whereas the ability to suppress unwanted saccades or to shift attention is dependent on the prevention of activation of a group of collicular neurons or on inhibition of currently active collicular neurons, respectively. Thus, the difficulties exhibited by both patient groups in initiating saccades and maintaining attention is suggested to reflect the disruption of the direct pathway of the closed associative circuit, which is involved in initiating and maintaining activity in a subset of frontal (or collicular) neurons. Complementarily, the finding that HD but not PD patients show difficulties in inhibiting unwanted saccades and in the volitional termination of attention to a current target is suggested to reflect disruption of the indirect pathway of the closed associative circuit, which is involved in the suppression and termination of activity in a subset of frontal (or collicular) neurons.

Finally, although it is difficult to compare motor impairments to cognitive impairments, it should be noted that both the eye movement and cognitive abnormalities in HD patients are characterized by a similar pattern, i.e., difficulties in initiating and facilitating wanted activity (motor or cognitive) coupled with difficulties in suppressing unwanted activity. These difficulties are suggested to originate from a common mechanism, i.e., underactivity of the direct and indirect pathways of the closed associative circuit.

Emotional symptoms

Affective and psychiatric symptoms appear in many HD patients, and may precede the appearance of the movement disorder by many years,^{50,51,95,125,126,193} although their systematic assessment is relatively scarce. The most prevalent behavioral disturbances associated with HD include: (1) personality and behavioral changes, which include on the one hand impulsive and erratic behavior, increased irritability, aggressiveness and labile mood, and on the other hand, reduced spontaneity and initiative,^{49,50,125,126,193} and (2) definable psychiatric disorders, namely, depressive and manic-depressive mood disorder, schizophreniform psychosis, and less commonly, obsessive compulsive disorder.^{50,51,125,126,171,193-197}

Since damage to the frontal cortex or basal ganglia can lead to symptoms similar to those outlined above,^{96,198-200} the emotional disturbances in HD were suggested to reflect disturbed frontostriatal functioning.^{96,201} As noted above, Litvan et al.¹⁰¹ suggested that the symptoms of agitation, irritation, and euphoria in HD are secondary to underactivity of the indirect pathways which arise from the ventromedial caudate and ventral striatum, respec-

tively. However, these two striatal regions are not involved in the early stages of HD. According to the split circuit scheme, psychopathological symptoms in HD reflect dysfunction of the limbic circuit resulting from underactivity of the open indirect pathway connecting the associative striatum to the limbic circuit.

Dysfunction of the limbic circuit has been implicated in the pathophysiology of schizophrenia, depression, and obsessive compulsive disorder.^{7,17,96} One of the most influential and detailed models of basal ganglia-related psychiatric disorders is that of Swerdlow and Koob.¹⁷ This model is similar to the present one in maintaining that striatal projections to the limbic pallidum (the direct pathway) serve to promote the activity of a set of cortical neurons. In Swerdlow and Koob's model, however, inhibition of ongoing thalamocortical activity is attributed to the dopaminergic input to the striatum, which is presumed to inhibit striatal neurons projecting to the limbic pallidum, and thus disinhibit the latter, whereas in the present scheme this function is attributed to indirect pathways. Swerdlow and Koob suggested that schizophrenic and manic psychoses result from increased dopaminergic input to the striatum which leads to "inability to filter inappropriate cognitive or emotional processes at the accumbens level and similarly to select and maintain appropriate processes among corticothalamic interactions" (p. 204). Since, according to current models of basal ganglia circuitry, dopamine is considered to inhibit striatal neurons of the indirect pathway,^{1,93} increased dopaminergic input to the striatum may be analogous to a functional lesion of the indirect pathway. Therefore, degeneration of the indirect pathway connecting the associative striatum to the limbic circuit in HD is expected to result in a circuit dysfunction similar to the one hypothesized to subservise schizophrenic and manic psychoses according to Swerdlow and Koob.¹⁷

Swerdlow and Koob¹⁷ further suggested that depression may result from underactivity of the dopaminergic system. The latter results in an inability to inhibit corticothalamic activity by limbic pallidal input, and this "excess of corticothalamic positive feedback would be accompanied by an inability...to switch or initiate new 'cognitive sets'" (p. 205). This mechanism is reminiscent of the one we propose to underlie the difficulties of HD patients in cognitive set shifting and in self-generated attention shift, i.e., inability to terminate or suppress the current cognitive or attentional set, which results from underactivity of the closed indirect pathway of the closed associative circuit. Therefore, the depression of HD patients may reflect difficulties in suppressing a dominant cognitive or emotional state, resulting from underactivity of the closed indirect pathway of the closed associative

circuit and of the open indirect pathway connecting the associative and limbic circuits, respectively. Similar difficulties may also underlie the obsessions and compulsions reported in some HD patients, i.e., inability to suppress a dominant thought or action.

Underactivity of the open indirect pathway connecting the associative striatum to the limbic circuit may also lead to emotional “disinhibition” analogous to the cognitive and motor “disinhibition” seen in HD patients, which, as detailed above, also reflect degeneration of indirect pathways. This emotional disinhibition is evident in a subgroup of emotional symptoms exhibited by HD patients, including aggression, increased irritability, impulsivity, erratic behavior, and emotional outbursts. Interestingly, in line with our view, these symptoms have been suggested to be striatal “release” symptoms analogous to the motor “release” symptoms of this disease.²⁰²

Lesion of the Associative GPe: A Potential Treatment for HD?

The pathological mechanism suggested here to underlie the symptomatology of HD raises a possibility of a treatment for this disease. According to the present model, in the early stages of the disease, associative striatal pathology results in overactivity of the associative GPe which leads, via the resultant underactivity of STN, to motor, cognitive, and emotional abnormalities. We have suggested that lesion of the overactive associative GPe could ameliorate some of these symptoms.²¹ The rationale for this treatment is similar to the rational underlying lesion of the overactive motor GPi in order to ameliorate hypokinetic symptoms in Parkinson’s disease.^{5,13} There is some evidence that stereotaxic pallidal lesions can ameliorate hyperkinetic movements in affected patients.²⁰³

We have begun to investigate this possibility in one of the leading rat models of HD, namely, quinolinic acid (QA) striatal lesion.^{131,204–206} We showed that bilateral electrolytic lesions to the rat globus pallidus (GP, the rat analog of the primate GPe) ameliorated the deleterious effects of bilateral QA striatal lesion on several behavioral measures (postsurgery weight, activity level, and performance in a water maze task).²⁰⁷ We have recently found that an excitotoxic (axon sparing) lesion of the rat GP has the same ameliorating effect as an electrolytic GP lesion, and that this ameliorating effect is obtained both when the GP is lesioned simultaneously with the striatum and when it is lesioned 1 month following the striatal lesion; moreover, this ameliorating effect is also obtained when the GP is inactivated by intrapallidal injection of muscimol (manuscript in preparation). While these results are promising, future studies are needed, particu-

larly in nonhuman primates, to further evaluate the potential of GPe lesion for the treatment of HD. Moreover, even if the suggested treatment is found to be effective in alleviating HD symptoms at the early stages of the disease, it may not lead to long-lasting positive effects, since the pathological process in HD is progressive, ultimately leading to a degeneration of extensive regions of the brain.

Conclusion

The present work has provided a detailed account of HD symptomatology based on the open interconnected model of basal ganglia-thalamocortical circuitry and the known pathophysiology of HD. We have suggested that specific motor, cognitive, and emotional symptoms of HD are related to specific disturbances in the functioning of the motor, associative, and limbic circuits which result from the degeneration of a direct pathway and of several indirect pathways arising from the associative striatum.

This analysis highlights the advantages of the open interconnected model for explaining neuropathological mechanisms, namely, its capacity to account for the co-existence of symptoms as a result of damage to one station within one of the circuits, as well as its utility in explaining how disruption of different types of connections (e.g., direct versus indirect pathways) leads to qualitatively different types of symptoms (e.g., difficulties in initiation versus suppression) within each symptom domain. The latter further enables the delineation of analogies between symptoms from different domains (e.g., motor, cognitive, and emotional disinhibition).

With regard to HD, the present approach has allowed a more comprehensive delineation of HD symptomatology by drawing attention to symptoms which were postulated to exist according to the model, but are usually overlooked, such as those reflecting “cognitive disinhibition.” Likewise, it has enabled a better differentiation between HD and PD, particularly in the cognitive domain, by directing attention to types of symptoms which were expected according to the model to be manifested differently in the two patient groups.

In general, it is suggested that a model-driven analysis of symptoms of individual basal ganglia-related disorders, and in particular a comparison between the symptomatology of two such disorders with related but different underlying pathologies (such as HD and PD), may lead to a better understanding not only of each disorder but also of the normal functioning of the circuits, their subcomponents and their connections.

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