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**CRITICAL REVIEW**

# Frontal-striatal circuit functions: Context, sequence, and consequence

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**Abstract**

The exact role of the basal ganglia in both the motor and non-motor domains has proven elusive since it is virtually impossible to refer to its function in isolation of cortical, and especially frontal cortical circuits. The result is that we often speak of frontal-striatal circuits and functions but this still leaves us in the dark when trying to specify basal ganglia information processing. A critical review of the data from both basic science and clinical studies suggests that we should break down processing along a temporal continuum, including the domains of context, sequential information processing, and feedback or reinforcement (i.e., the consequences of action). This analysis would cut across other theoretical constructs, such as attention, central executive, memory, and learning functions, traditionally employed in the neuropsychological literature. Under specified behavioral constraint, the basal ganglia can then be seen to be involved in fundamental aspects of attentional control (often covert), in the guidance of the early stages of learning (especially reinforcement-based, but also encoding strategies in explicit paradigms), and in the associative binding of reward to cue salience and response sequences via dopaminergic mechanisms. Parkinson's disease is considered to offer only a limited view of basal ganglia function due to partial striatal depletion of dopamine and the potential involvement of other structures and transmitters in its pathology. It is hoped that the present formulation will suggest new heuristic research strategies for basal ganglia research, permitting a closer link to be established between neurophysiological, functional imaging and neuropsychological paradigms. (*JINS*, 2003, *9*, 103–127.)

**Keywords:** Basal ganglia, Parkinson's Disease, Neuropsychology, Neurophysiology, Neuroanatomy, Frontal lobes, Review

## INTRODUCTION

A functional association between the basal ganglia (i.e., caudate nucleus {Cd}, putamen {Put}, globus pallidus {GP}) and frontal lobe functions has been well-established since the pioneering studies of Rosvold and his colleagues (Rosvold, 1972). Rosvold even demonstrated that there existed a topographically congruent coupling between localized and functionally distinct areas of the prefrontal cortex and the head of the caudate nucleus (Cd) (Johnson et al., 1968); anticipating the landmark anatomical studies of Kemp and Powell (1970). The general view at that time was that the basal ganglia acted in parallel to the pyramidal system (hence, the extrapyramidal system), in agreement with traditional neurological formulations (Denny-Brown, 1962). Only the voice of Brodal (1963) rose against this dogma, pointing out that the major direction of outflow from the pallidum (i.e., globus pallidus) was redirected to the frontal cortical motor areas via the thalamus, a view entirely endorsed today both anatomically and neurologically (Alexander et al., 1990; Parent & Hazrati, 1995a).

Previous formulations of overall basal ganglia functions have followed two general trends: first there are the anatomically-based physiological models which focus on

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(Albin et al., 1989; Wichmann & DeLong, 1996). Conceptually, these models attempt to predict either impoverished or excessive movement as seen clinically in classical Parkinson's Disease (PD), Huntington's Disease (HD) and ballismus. Second, at the systems level, a variety of basal ganglia circuits in receipt of a wide array of cortical inputs, are functionally classified according to behavioral disruption caused by focal lesions (Saint-Cyr et al., 2002). Each of these approaches have their merits, predictive power, and both clinical and experimental support. However, the exact manner in which information is processed within basal ganglia circuits in order to produce behavior remains elusive. Furthermore, although motor impairment has been characterized in detail, the picture is far from clear when attempts are made to precisely define the role of the basal ganglia with regard to neuropsychological deficits.

The study of human basal ganglia function has been dominated by the analysis of cognitive deficits seen in patients with degenerative diseases such as PD and HD (see Dubois et al., 1991 and Saint-Cyr et al., 1995 for reviews). As opposed to the consequences of focal lesions, in which case behavioral change is the consequence of whole system adaptation to the absence of basal ganglia function, the above disease states may permit us to see the effects of poorly functioning, yet still engaged, basal ganglia circuitry (cf. Dubois et al., 1995; Marsden & Obeso, 1994). This approach is perhaps most fruitful in the study of PD patients, since we can be fairly certain that early stage pathology is confined to the depletion of dopamine (DA) from striatal circuits (especially involving the putamen), and that the cortex remains relatively spared. However, Lewy bodies are not uncommon in the cortex and these aged patients may also be prone to other forms of cortical pathology (e.g., vascular or degenerative) (Weiner & Lang, 1989). In comparison, although early degeneration of the caudate is the neuropathological hallmark in HD, pathology inevitably progresses to directly involve the cortex (especially the frontal and parietal lobes) (Lawrence et al., 1998).

Studies predicated on the division of cognitive functions into traditional domains such as attention, memory, or the supra-ordinate executive category have yielded more phenomenological data than comprehensive models. Attempts to reductionistically propose a single underlying deficit to explain cognitive impairment in PD (e.g., attentional deficit, dysexecutive syndrome) have failed to capture the scope of the actual neuropsychological profile, have imputed functions to the basal ganglia at least largely shared with other structures such as the frontal lobes, and are not easily reconcilable with concepts of motor control by similar circuits.

In this review, an alternate functional grouping of data is proposed, avoiding the conceptual constraints of traditional neuropsychological formulations. The three domains labeled *Context*, *Sequence* and *Consequence* were chosen because these appear to be the main correlates of unit recordings in basal ganglia (see Rolls & Treves, 1998, as well as Schultz & Dickinson, 2000 and Wise et al., 1996 for comprehensive reviews). Operations in these functional domains are viewed as working in parallel, rather than serially, although a temporal progression is implicit in the concepts, and can be reflected in functional imaging studies. By regrouping experimental data under these headings, it is hoped that fundamental basal ganglia processes can be more clearly inferred. Before venturing into the details of this analysis, let us first set the anatomical stage.

It should first be recalled that almost the entire cortical mantle sends topographic (by proximity) and longitudinal projections (from association cortical areas) into the striatum (caudate, putamen and nucleus accumbens) as illustrated in Figure 1 (see Parent & Hazrati, 1995a for a review). Clearly, such widespread inputs cannot enlighten us about the functions of the basal ganglia. However, if one follows the motor circuit components, originating in the motor and somatosensory cortical areas, and funneling through the putamen, one can begin to appreciate the complexity and final destination of the basal ganglia output, namely, focusing on the supplementary motor area in this case. Simplified circuit diagrams, taking into account the neurotransmitters used by the different pathways, are typically used to define the anatomical skeleton onto which our current understanding is imposed. The following is a brief review of the current model.

## Functional Neurological Models of Basal Ganglia Function: An Update

The major model of the basal ganglia, which inspires current neurological and neurosurgical treatment strategies, proposes that the overall function of the basal ganglia can be reduced to a pair of direct and indirect pathways. The direct outflow pathway from the striatum to the globus pallidus, pars interna/substantia nigra, pars reticulata (GPi/SNr), is thought to be counterbalanced by an indirect pathway from the striatum to the globus pallidus, pars externa (GPe), and then to the subthalamic nucleus (STN), which in turn, projects to the GPi/SNr (Wichmann & DeLong, 1996). The striatal output neurons of the direct pathway co-localize gamma aminobutyric acid (GABA) and substance P and dynorphin, and act to inhibit the GPi/SNr. The indirect striatal output pathway neurons co-localize GABA and enkephalin and excite the GPe. The latter output is also GABAergic and inhibits the STN. STN neurons use the transmitter glutamate to excite the GPi/SNr. In this way the two routes are in some sort of harmonic balance, with the direct proposed as being responsible for the initiation of action and the indirect for braking or switching from one action to the next. Since the final outflow from the GPi/SNr is also GABAergic and targets the thalamic relay nuclei ventralis anterior (VA, pars parvocellularis) and portions of ventralis lateralis (VL, pars oralis) (to mainly supplementary motor and adjacent areas) and regions of medialis dorsalis (MD, pars parvocellularis) (largely to the frontal eye field and prefrontal areas), the basal ganglia circuits are poised to control the excitability of (or to provide input to) the frontal lobes (see Wise et al., 1996, for details).

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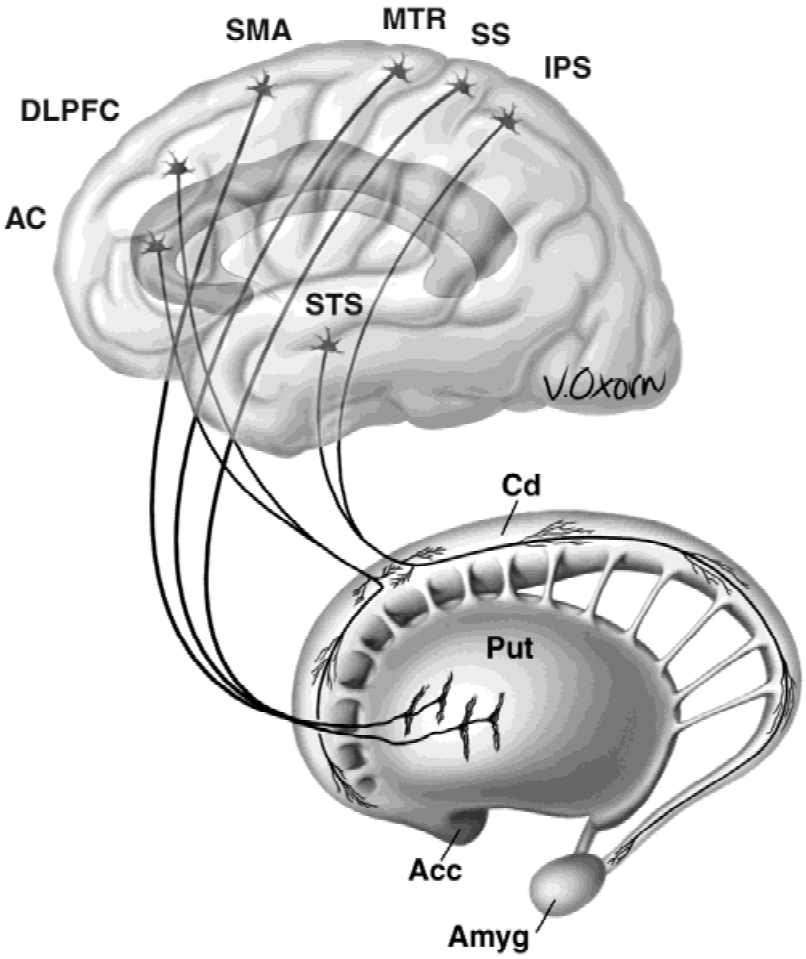



**Fig. 1.** Cortico striatal projections. Two principles of organization of cortico-striatal projections are that of proximity, shown as the motor and somatosensory cortical projections to the putamen, and longitudinal trans-striatal, shown as the cingulate, prefrontal, intraparietal and superior temporal projections to the caudate. Abbreviations: AC, anterior cingulate cortex; Acc, nucleus accumbens; Amyg, amygdala; Cd, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; IPS, intraparietal sulcus; MTR, Motor cortex; Put, putamen; SMA, supplementary motor area; SS, somatosensory cortex; STS, superior temporal sulcus.

In PD or its experimental counterpart, the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkey model, reduction of the DA innervation due to cell loss in the substantia nigra, pars compacta (SNc) leads to the disinhibition of the direct pathway via D1 receptors on the striatal path neurons. Per contra, there is loss of facilitatory action on the striatal indirect path neurons via D2 receptors. This leads to excessive activity in the STN and GPi/SNr which has been demonstrated both in the MPTP monkey and in human PD patients (Bergman et al., 1994; Hutchison et al., 1994; Wichmann et al., 1999). This, in turn, would overly dampen the thalamus, leading to decreased movement, expressed as hypokinesia. Such is the success of this model that it has been used to instruct neurosurgical interventions (e.g., lesions of the posterolateral GPi, or blocking of STN via chronic deep brain stimulation) to treat PD patients with significant success (Krack et al., 1998; Lang & Lozano, 1998a; 1998b; Starr et al., 1998). Elaborations of this model also account reasonably well for hemiballismus (due to STN lesions) and to chorea in HD (due to selective loss of the striatal indirect path neurons) (Albin et al., 1989).

## Revisions of the Classical Basal Ganglia Model

Several complications have arisen to haunt the DeLong and Albin et al. model (Bar-Gad & Bergman, 2001; Chesselet & Delfs, 1996; Parent & Cicchetti, 1998; Wichmann & DeLong, 1996). Both the GPe and SNr have been shown to project directly to the reticular nuclear shell of the thalamus (nucleus reticularis thalami, RT) (Paré et al., 1990; Parent & Hazrati, 1995a). Those shell neurons are GABAergic and can control the excitability of the relay nuclei directly, thereby possibly influencing vigilance (Steriade, et al., 1986). It has recently been shown that, in the cat, the RT also projects to the nucleus centranum medianum (CM) (Kayahara & Nakano, 1998) and that this can control excitability of both basal ganglia and cortex (Schneider & Rothblat, 1996).

Parent and Cecchetti (1998) argue that the projection of the GPe to the STN falls into a region which may not project to the GPi/SNr, although there are contrary opinions (Wichmann et al., 1994). Single neurons from the STN can project not only to the GPi/SNr, but also back to the GPe (strongly),

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as well as to the striatum and even as far as the cortex (Parent & Hazrati, 1995b). In addition, the STN also receives direct input from motor cortical areas (Künzle, 1978), while the SNr is also modulated by cortical input from motor and prefrontal regions via the STN and striatum (Kitano et al., 1998).

Although the model predicts that GPe firing rates should be diminished in PD (also in the MPTP monkey model), this has not been found (Hutchison et al., 1994). The model does not predict or explain tremor, one of the cardinal signs of PD, and is hard pressed to account for either dopa-induced dyskinesias or gait and postural problems. The latter may be related to another descending basal ganglia projection, from the GPi/SNr to the pars compacta of the tegmento-pedunculopontine nucleus (TPC), which may be functionally linked to the mesencephalic locomotor region (Garcia-Rill et al., 1987). In addition, it has been suggested that the TPC may also form part of the centrencephalic arousal system (Reese et al., 1995). Most projections from the TPC reascend to terminate in the SNc, STN and pallidum (Parent & Hazrati, 1995a). Recent unit studies of the TPC have revealed context-dependent and reinforcement-related activity in the cat (Dormont et al., 1998) and relationships to voluntary arm movements in the monkey (Matsumura et al., 1997). Lesions of the TPC have also been shown to induce akinesia in the monkey (Munro-Davies et al., 1999).

The model does not take into consideration a major thalamic input to the basal ganglia, arising from the posterior intralaminar nuclei, CM and parafascicularis (Pf). Both of these nuclei receive inputs from the GPi/SNr, as well as from the cerebellum. CM also receives a projection directly from the motor cortex. Different sectors of the Pf project to the striatum and STN (Sadikot et al., 1992), and bilateral lesions of the CM/Pf lead to a state of akinetic mutism (Heilman et al., 1993). Therefore, we could expect general arousal level to be controlled through this relay, long associated with Penfield's centrencephalic system (Steriade & Llinás, 1988). Recently, electrophysiological (Schneider & Rothblat, 1996) as well as functional imaging data (Kinomura et al., 1996), confirmed the role of this link in arousal and attentional control.

## FIRST PRINCIPLE: CONTEXT

In both human neuropsychological assessments and behavioral studies with subhuman primates, context, or behavioral set is an underlying and axiomatic condition. Patients are asked to focus and to do their best to solve problems, answer questions, learn or perform, while monkeys in a testing environment are always performing conditionally, in anticipation of rewards. Thus, it is clear that a conscious mental set is present and this is generally held to be under the aegis of the prefrontal cortex (Fuster, 1997; Mishkin, 1964). It has been argued that set, goals, rules, and expectations are then imposed on the basal ganglia by the cortex (Rolls & Treves, 1998; Wise et al., 1996) and this is in keeping with a long history of studies comparing the consequences of frontal lobe and basal ganglia lesions on a variety of tasks (Rosvold, 1972). We will now examine the neuroanatomical organization of this influence.

### Cortico-Striatal Projections: Cortex Provides the Context, but does Anatomy Ensure Functional Segregation?

In general, most cortical areas (apart from the primary visual cortex) project to the striatum, which then funnels projections down through the pallidum and nigra and back to the thalamus for a final return loop specifically targeting the frontal lobes (Parent & Hazrati, 1995a).

In general terms, the funneling of output from the striatum to the pallido-nigral complex falls into a tripartite pattern. Rostral to the anterior commissure, associative inputs dominate Cd, Put, and the GPe. There is also a subcommissural portion of the GP called the ventral pallidum; this belongs to the accumbens-limbic circuit, projecting to the habenula. Caudal to the anterior commissure, the dorsal-medial third of the GP is dominated by associative projections, the ventral-lateral two-thirds is sensorimotor, and only the caudal tip is considered limbic.Within the STN, the dorsal two-thirds is considered to be sensorimotor dominated, while the ventral third is associative and a small caudal-medial tip is limbic (Parent & Hazrati, 1995a). Indeed, one sometimes hears reference to the neurologist's, the psychologist's, and the psychiatrist's basal ganglia (Saint-Cyr et al., 1995). Neurologists study movement disorders, psychologists focus on cognitive operations, and psychiatrists examine behavioral and emotional disorders (e.g., psychosis, obsessive compulsive disorder, Tourette's syndrome, abulia).

According to the principle of proximity, enunciated by Kemp and Powell (1970) on the basis of degeneration techniques, there is a topologically congruent pattern of projection from cortical areas directly to the nearest regions of the striatum. Thus, frontal projections dominate the head of the Cd, motor, and somatosensory cortical areas project to the Put, while parietal cortex projects to the body and genu of the Cd, and temporal cortex is related to the tail of the Cd and ventral Put. This conceptual organization has been partly retained but expanded in several important aspects. Yeterian and van Hoesen (van Hoesen et al., 1981; Yeterian & Pandya, 1998; Yeterian & van Hoesen, 1978) showed association areas of the cortex that were themselves closely linked (in the monkey, sulcus principalis, intraparietal sulcus, superior temporal sulcus, anterior cingulate gyrus), projected to common strip-like regions of the Cd.

Second, Selemon and Goldman-Rakic (1985) revealed that all cortically originating projections had long axonal arborizations which coursed longitudinally through the striatum, not in overlapping, but in adjacent, or interdigitating, strips. The cortical inputs from the polymodal association areas identified by Yeterian and van Hoesen, however, proved to give rise to the longest terminal fields, coursing through virtually the entire length of the striatum, especially in the

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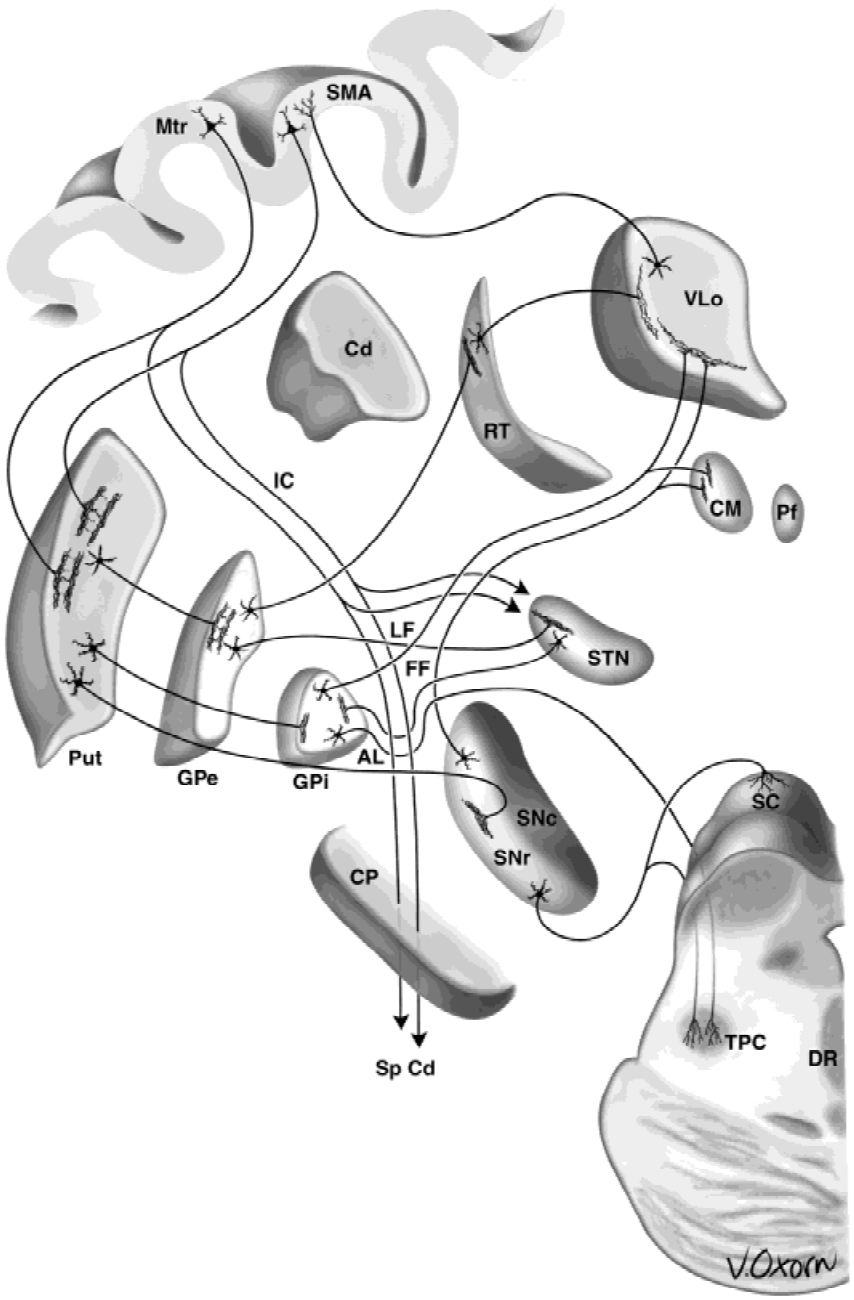



**Fig. 2A.** Principal components of the striatal circuitry: the direct and indirect pathways and projections to the thalamus. The so-called direct pathway involves a projection from the putamen to the GPi/Snr, while the so-called indirect pathway is from the putamen to the GPe, and thence to the STN, which projects back to the GPi. Both the GPi and SNr project to the thalamus via both the lenticular fasciculus and the ansa lenticularis and through the fields of Forel. In addition, the GPi/SNr also project to the brain stem. An additional link to the thalamus arises from the GPe, influencing the thalamo-cortical projections via the reticular shell. Abbreviations for Figures 2 and 3: AL, ansa lenticularis; Assoc, association cortical areas; Cbl, cerebellum; Cd, caudate nucleus; CM, centre médian; CP, cerebral peduncle; Ctx, cortex; D1, D1 dopamine receptor; D2, D2 dopamine receptor; DR, dorsal raphé nucleus; FF, fields of Forel; GPe, globus pallidus, pars externa; GPi, globus pallidus, pars interna; IC, internal capsule; Mtr, motor cortex; Pf, parafascicular nucleus; RT, reticular shell nuclei; SC, superior colliculus; SMA, supplementary motor area; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; Sp Cd, spinal cord; STN, subthalamic nucleus; TPC, nucleus tegmento-pontinus, pars compacta; Vlo, nucleus ventralis lateralis, pars oralis; 5HT, 5-hydroxytryptamine (serotonin).

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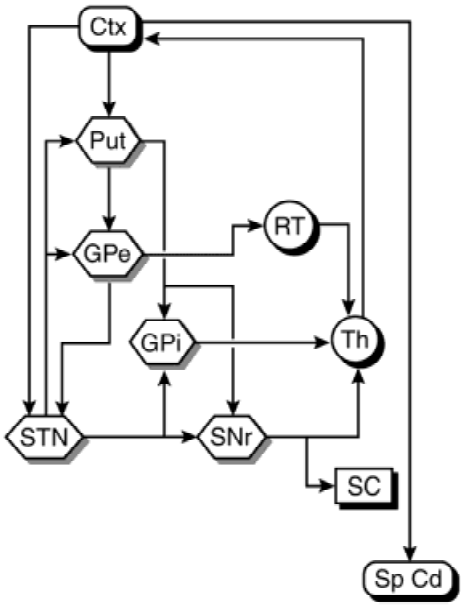



**Fig. 2B.** Schematic diagram of Figure 2A.

caudate (Saint-Cyr et al., 1990). Graybiel's group pursued these studies and showed that there were both overlapping and non-overlapping terminations from functionally related cortical areas in striatal matrisomes (Flaherty & Graybiel, 1995; Parthasarathy et al., 1992).

These studies raise important questions about the viability of a seminal conceptual model described in the mid-1980s by Alexander et al. (1986). They proposed that there were as many as five anatomically and functionally separate circuits coursing through the basal ganglia and subserving different functions. These were: 1) the motor, 2) oculomotor, 3) complex or cognitive, 4) lateral frontal (possibly lexical-grammatical), and 5) emotional, orbito fronto-cingulate loops. Should we then consider the existence of five contextually segregated sets, or could some of these be activated in parallel?

Within the sensorimotor corticostriatal system, studies with transneuronal virus tracers have revealed the existence of multiple somatotopic representations (Middleton & Strick, 1997). A fractionation of the prefronto-Cd projections has also been demonstrated (Yeterian & Pandya, 1991). Evidence for somatotopic representation within the motor circuit has been demonstrated, both anatomically and physiologically (Alexander & Crutcher, 1990a; Kitano et al., 1998; Strick et al., 1995) through all levels of the system including the pallidum and STN. Hikosaka and Wurtz (1989) described a functional circuit from the frontal eye fields through the Cd and SNr, which controls memory-driven saccades via the superior colliculus. Thus, despite the anatomical convergence or overlap described above, subsets of connections may nevertheless have a certain degree of functional autonomy.

While seductive in its conceptualization and simplicity, the multiple parallel loop model suffers when scrutinized anatomically (see Wise et al., 1996). In view of the findings concerning the organization of cortico-striate projections, cited above, we cannot define totally segregated circuits on the basis of cortical inputs. Similarly, the return portion of the circuit from the thalamus to cortex also provides opportunity for overlapping projections (Ilinsky et al., 1997), such that one cannot say that there is a cortically originating purely motor circuit which influences purely sensori-motor regions of the frontal lobes. It is also the case that one cannot define an executive cortical system which would gather all relevant cortical associative information to funnel it back uniquely to the dorsolateral prefrontal cortex, especially since Middleton and Strick (2000) have demonstrated a temporal cortical target for basal ganglia outflow, namely area TE, which brings traditional memory processing structures directly into the sphere of striatal influence.

### *Anatomical basis for integration of information and associative learning*

We may become even less enthralled by the lure of anatomical segregation when considering that the axonal arborizations of the striatofugal fibers ramify extensively in the medio-lateral plane (Parent & Hazrati, 1995a) and cascade through both the GPe and GPi as well as into SNr. Elegant Golgi studies by Percheron and his colleagues (Percheron et al., 1984; Yelnik et al., 1997) have revealed that the pallidal neurons have large discoidal dendritic domains which intersect with at least 2–3 of the so-called parallel circuits within the pallidum. Similarly large dendritic domains are also found in the STN (Parent & Hazrati, 1995b). Projections from the STN are not only widespread within the pallidum and striatum, but the axonal arborizations also are large enough to span more than one parallel circuit. Coupling between adjacent circuits may also be modulated at the level of the striatum via cholinergic and GABAergic interneurons (Gerfen, 1992).

Physiologically, loss of DA in the striatum, due to MPTP or PD, has a remarkable effect on the specificity of encoding of the neurons. Whereas in the intact animal, single pallidal neurons fire in relation to a single (contralateral) limb moving in a particular direction, loss of DA, after MPTP treatment, results in a defocusing with single cells firing in relation to more than one limb (even ipsilaterally) moving in a variety of directions (Filion et al., 1988). Thus, the anatomical intersection of axonal arborizations and large dendritic trees of pallidal neurons described above, provides the basis for this loss of focus, putting the DA system in a key position to influence the selection of specificity of encoding in these circuits (Filion et al., 1994; Percheron & Filion, 1991). A similar defocusing has been documented during surgery in PD patients (Hutchison et al., 1994).

The general model also emphasizes cortical projections uniquely into the striatum at the beginning of the circuit. It has also been shown that motor cortical areas from primary motor, through the premotor and including the supplemen-

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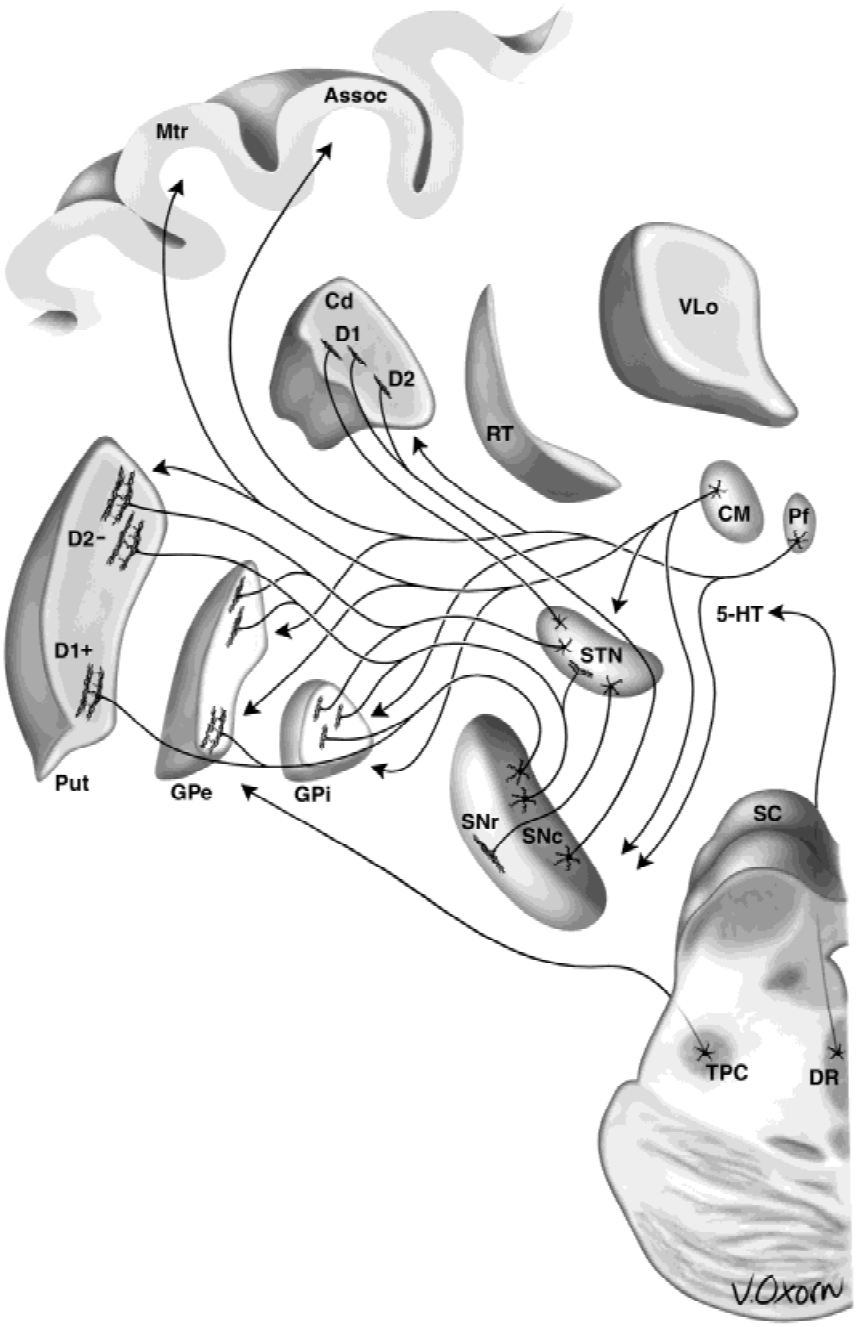



**Fig. 3A.** Major ascending inputs to the basal ganglia. It should be noted that the dopaminergic input to the striatum from the SNc is both excitatory (D1 receptors into the direct pathway) and inhibitory (D2 receptors into the indirect pathway). Furthermore, the STN projects to all levels of the striatal circuits (Cd, Put, GP, SN). The major TPC efferents, re-ascend to terminate in the pallidum. The posterior midline nuclei CM and Pf, project back into the basal ganglia as well as to the cortex. Note the reciprocal connections between the thalamus and cortex. The cerebellum projects to both the posterior thalamus and the TPC, thus indirectly influencing the basal ganglia. The DR is the source of serotoninergic input to the striatum.

tary motor, project directly to the STN (Inase et al., 1999; Nambu et al., 1997), as well as to the CM in thalamus (Künzle, 1978), recalling that the latter nucleus projects directly to all levels of the basal ganglia circuitry, including the STN (Sadikot et al., 1992). Prefrontal and motor areas also indirectly influence the SNr (Kitano et al., 1998). Clearly, these glutamatergic cortical projections would be expected to exert a powerful modulatory action on basal ganglia outflow.

Cortico-striate projections also do not terminate in a homogeneous neuropil. A complex chemical neuroanatomical compartmentation has been defined within the striatum (Ger-

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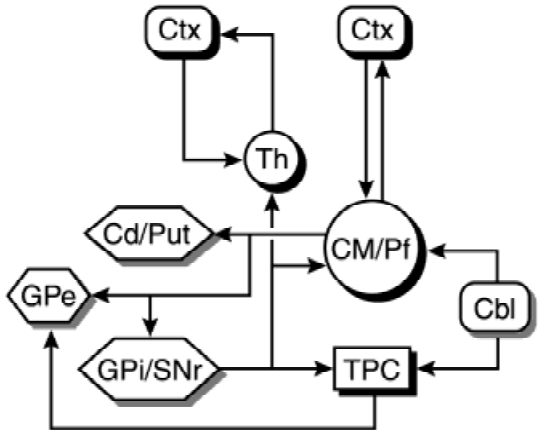



**Fig. 3B.** Schematic diagram of Figure 3A.

fen, 1992; Goldman-Rakic & Selemon, 1990; Graybiel, 1990; Holt et al., 1997). Thus, a striatal mosaic pattern is described in which striosomes, rich in DA and opiate receptors, stand out from the surrounding matrix (matrisomes), rich in acetylcholinesterase (AChE). The prefrontal, insular and amygdalar afferents target the striosomes, while the other cortical regions preferentially target the matrisomes (Eblen & Graybiel, 1995). Moreover, it is from the matrix that most of the projection neurons arise, sending their axons into the pallidum and nigra. Within the matrix are also found cholinergic and GABAergic interneurons (Gerfen, 1992). There have been numerous studies of the chemical anatomy of the striatum, with a rich variety (at least 30) of putative transmitter or neuromodulatory substances having been identified (Graybiel, 1990; see also Parent et al., 1995). Calcium binding proteins (calbindin and parvalbumin) appear to have complementary distributions in the basal ganglia, although their functional significance has not been established. Calbindin may be associated with DA and neuroprotective mechanisms while parvalbumin appears to be closely related to GABAergic neurons (Parent et al., 1995).

In the striatum, there are tonically active neurons (TANs) (possibly cholinergic) which may bridge striosomes and matrix and their capacity to encode changes due to learning is DA dependent (Aosaki et al., 1994b, 1995). In addition, neighboring GABAergic interneurons appear to be electrotonically coupled and may profoundly inhibit GABAergic projection neurons (Koos & Tepper, 1999). While these findings have not been formally integrated into the clinically-applied models of basal ganglia function, the potential role of interneurons is significant. It has been speculated that the excitatory glutamatergic cortical input may preferentially activate these interneurons, rather than the more numerous projection neurons (Graybiel, 1995; Graybiel et al., 1994). This could represent a mechanism for the coordination of the direct and indirect pathways, or at least link DA-driven striosomes with GABAergic path neurons. If this were so, another revision of current models of basal ganglia function would be required. To further complicate matters, the ventral striatum may be organized differently than the dorsal with regard to histochemical compartmentation (Holt et al., 1997) and circuitry (Haber et al., 1995; see also Nakano et al., 2000). These ventral striatal regions are also specifically labeled by monoclonal antibodies to limbic system associated proteins (Parent et al., 1995), and those circuits appear concerned with the encoding of appetitive reward (Blackburn et al., 1992; Bowman et al., 1996; Everitt et al., 1999; Schultz & Dickinson, 2000; see review by Rolls, 2000). In addition, ventral striatal circuits and their connections have long been associated with preparatory behavior in relation to DA (Blackburn et al., 1989).

In conclusion, while there does appear to be anatomical (Middleton & Strick, 2000) and physiological (Alexander & DeLong, 1985; Mink, 1996) evidence for functionally segregated processing within the cortico-striatal pathways, there is also clearly ample anatomical opportunity for significant overlap of information channels. It would appear that DA plays a crucial role in the focusing of information within these circuits (Filion et al., 1994).

## Neurophysiological Studies: Preparatory Activities

Recalling that virtually all studies correlating unit activity to behavior in the basal ganglia require that animals be in a reinforcement-constrained environment, and that their responses are conditionally performed according to reward contingencies, it is not surprising that movements made spontaneously without such constraints are poorly, if at all, correlated with unit activity. Nevertheless, some degree of encoding of posture and limb movements has been proposed (e.g., Anderson, 1978; see Rolls & Treves, 1998, for a review). In a number of studies, the intended direction of movement as well as the preparatory phases of movement were shown to be multiply encoded at cortical and putamenal levels (Alexander & Crutcher, 1990b; 1990c; Crutcher & Alexander, 1990). Thus, the anticipation of reward (i.e., set) appears to establish the neural tone necessary for the emergence of cue, response or reinforcement-locked correlations. The preparatory phases of neural operations leading up to operant responses are therefore generated by the testing milieu and focused by a cue such as a ready signal. We can refer to the testing environment and behavioral set of the animal as the context within which interaction with the environment can influence basal ganglia activity.

Rolls and Treves (1998) have argued that it is the cortex which imposes patterns on the underlying striatum (behavioral set, according to Hikosaka, 1993; state space according to Graybiel, 1998) and that we should not mis-attribute functions that have been computed at the cortical level to the basal ganglia. Both premotor cortical areas and basal ganglia are involved in attentional processes related to preparatory activities leading up to movement execution (Boussaoud & Kermadi, 1997; Kermadi & Boussaoud, 1995). Wise et al. (1996) emphasized this point in suggesting that the context recognized by the cortex may be the cue used

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by the basal ganglia to evoke DA-potentiated, but cortically-determined, rules.

Within the sensorimotor sphere, numerous studies have demonstrated that the basal ganglia are preferentially involved in encoding the preparatory phases of action (Alexander & Crutcher, 1990b, 1990c; Crutcher & Alexander, 1990; Mink & Thach, 1991). Units selectively encode attention to task-related cues and activity changes which precede the initiation of responses. Furthermore, units encode both the limb selected for the response as well as its direction of movement. Recently, SNr neurons in monkeys have been shown to differentially encode reinforced saccadic eye movements (Handel & Glimcher, 2000), suggesting that behavioral set or context modulates these responses.

Clearly, attentional mechanisms cannot be divorced from the notions of set and context. While consciously selected goals and awareness of the environment and identification of salient cues must be attributed to the cortex, context may also be implicitly encoded subcortically, possibly by the basal ganglia. This leads us to examine what is known about attentional control in basal ganglia disease, notably PD.

## Attentional Mechanisms: Supervisory, Focusing and Shifting

Supervisory attentional functions can be broadly conceptualized as overseeing all conscious activities, cf. Supervisory Attentional System (SAS) of Shallice (1988), but tasks designed to probe this domain are typically more focused. Brown and Marsden (1988, 1990) proposed that one of the fundamental cognitive impairments of PD is a diminished capacity to control attention. They have demonstrated that PD patients are impaired in carrying out dual tasks, as well as in self-monitoring while generating strings of random numbers (Brown & Marsden, 1991; Brown et al., 1998). In addition, Taylor et al. (1986) demonstrated that PD patients were impaired in their capacity to carry out simultaneous motor actions. Similar findings have also been reported by Malapani et al. (1994) and Brown and Marsden (1991). Downes et al. (1993) provided support for the attentional dysfunction theory of cognitive impairment in PD using an alternating fluency paradigm.

Another paradigm in this domain has involved a type of attentional priming, which can be done overtly (Downes et al., 1989) or covertly (Bennett & Castiello, 1996). In both cases, deficits were observed in PD patients.

Partiot et al. (1996) showed that PD patients had difficulty re-engaging their attention after a shift, and then maintaining it focused on the required cues. Set-shifting is a capacity known to be impaired in PD (Hsieh et al., 1996; Owen et al., 1993). In Petrides' Self Ordered Pointing task (Petrides & Milner, 1982), patients have to engage in self-monitoring of response choices in order to avoid repeating prior selections. While Petrides showed that patients with frontal lobe lesions are deficient in this task, a similar impairment has also been shown with PD patients (West et al., 1998) Finally, the argument has been made that attentional capacity in PD is limited in terms of amount of information ($7 \pm 2$ units) which can be conceptually grasped and utilized by working memory (Taylor et al., 1986).

In sum, there does appear to be good evidence for an attentional deficit in PD, and this would certainly be expected to interfere with executive functions such as working memory. The deficit involves the selective focusing of attention, either implicitly (covertly) or explicitly (worse with multiple ambiguous stimuli) the ability to engage in dual processing, extradimensional shifting, and self-monitoring. Clearly, there is a continuum of complexity from attentional priming to functions considered as part of the central executive. To explain this range of deficit, one could invoke several levels of neural dysfunction. The nigro-tectal (visual grasp reflex and memory driven saccadic control, see Hikosaka & Wurtz, 1983), and TPC (context-dependent activity, see Dormont et al., 1998) could play a role at an almost reflexive level. However, there are both thalamic and intrinsic basal ganglia mechanisms which may be central to these functions.

The fundamental attentional control deficit in PD may be due to disruption of thalamo-cortical functions, under the control of the posterior midline (i.e., CM/Pf) since those thalamic centers are in turn subject to pallido-nigral control (see below). In addition, the direct projection from GPe to the reticular shell nuclei of the thalamus may be critical since this provides a mechanism for the control of the excitability of specific thalamic relay nuclei and may modulate the signal to noise ratio of information transmission (cf. Steriade & Llinás, 1988). Also, ambiguity of encoding in the striatum, due to DA loss, may make the selection of salient cues unstable. These latter two mechanisms may be additive. Finally, recent studies have suggested that NA plays a critical role in the control of attention in PD (Bédard et al., 1998). Therefore, we cannot attribute all of the attentional deficits seen in PD to a single pathological mechanism residing entirely within the basal ganglia.

There is little debate that impaired attentional control is expected to lead to poor encoding of information since ambiguity of attentional focus implies ambiguity of encoding. There are therefore several mechanisms at work in PD contributing to poor memory, namely, an attentional deficit, poor strategic establishment, selection or application, and deficient reinforcement.

## Memory Dysfunction: Encoding Strategies and Working Memory

The domain of memory cannot be ascribed to any one of the concepts proposed in this review; it is too broad and distributed over time. For this reason, it may be best to discuss memory under our most encompassing category, *Context*, since this also varies over time and specifies the goals of the task. The memory profile in PD is usually fairly normal (especially in the early phases of the illness), but in roughly half of the patients studied by Filoteo, it was either comparable to that seen in HD or Alzheimer patients (Filoteo et al., 1997). In these and other studies, care must

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always be taken to rule out co-morbidity with cortical dementias (cf. Saint-Cyr & Trépanier, 2000). It has been suggested that memory dysfunction may be due to either a prospective or declarative deficit or both, rather than being explained by the dysexecutive model (Tröster & Fields, 1995). Malapani et al. (1998) have proposed that DA is required to form temporal associations, a concept entirely in keeping with the current formulation. While deficits in prospective memory fit well with the frontal-striatal model (Choudhry & Saint-Cyr, 2000), a large body of research (Cooper & Sagar, 1993; Heindel et al., 1989; Knoke et al., 1998; Pillon et al., 1993; Taylor et al., 1986; 1990a) has consistently shown that initial encoding is disrupted in PD and that this can lead to poor free recall and intact recognition. In spatial working memory, deficits in all processing stages (encoding, resistance to interference, and response production) have been demonstrated in PD patients (Le Bras et al., 1999; Owen et al., 1997). PD patients, however, do not appear to be excessively vulnerable to proactive interference (Moscovitch & Winocur, 1995; Sagar et al., 1991). A short-term spatial representational memory deficit has been demonstrated after either frontal or striatal pathology (Partiot et al., 1996). These functions have classically been the exclusive dominion of the prefrontal cortex (Goldman-Rakic, 1987). PD patients are also very poor at spatial conditional associative learning (Canavan et al., 1989; Shahakian et al., 1988; Taylor et al., 1990a), a task also disrupted after lesions of the dorsolateral prefrontal cortex (Petrides, 1985).

Most authors agree that the type of declarative memory deficit typically seen in PD is qualitatively similar to that associated with frontal dysfunction (Taylor et al., 1990a). The deficit can be characterized by poor strategies for supraspan information processing, and reduction of free recall and partially cued retrieval (Knoke et al., 1998). One interesting phenomenon has been called the incubation effect, wherein free recall improves after a delay. This may be due to inefficient associative encoding of the material (e.g., clustering strategies, Berger et al., 1999) or to slowed consolidation (Taylor et al., 1986; 1990a).

Working memory involves aspects of supervisory attention (i.e., self-monitoring), short term memory, delayed response capacity, and problem-solving (Baddeley, 1986). PD patients have been shown to be impaired in many exemplars of working memory paradigms such as paced serial addition (Trépanier et al., 1998, 2000), self-ordered pointing (West et al., 1998), conditional associative learning (Canavan et al., 1989; Sahakian et al., 1988; Taylor et al., 1990a; Vriezen & Moscovitch, 1990), some types of procedural-cognitive learning (Saint-Cyr et al., 1988, 1992), spatial and nonspatial working memory (Owen et al., 1997) and cognitive planning (Owen, 1997).

There is therefore evidence that memory processes, especially encoding and working memory, are impaired in PD. This is consistent with both the evidence from attentional limitations and also suggests that there is poor implicit establishment and instantiation of strategies for supraspan encoding.

## SECOND PRINCIPLE: SEQUENCING

Putting actions in the proper order is fundamental to many adaptive processes such as motor control, skill learning, grammar, and problem-solving. The general neurological model of basal ganglia function posits that the direct and indirect pathways control the initiation, switching, modulation and termination of actions, that is, aspects of serial processing. An examination of recent findings reveals that the evidence for sequential processing by the basal ganglia is fairly robust (Brown, 1999).

### Behavioral Studies

At a behavioral level, studies in PD patients have demonstrated an impairment of sequential motor performance (Martin et al., 1994) and learning (Harrington et al., 1998; Roy et al., 1993), in sequencing within scripts (Choudhry & Saint-Cyr, 1999; Zalla et al., 1998) and in temporal coupling (Malapani et al., 1998). Impairments in the temporal ordering of information (Sagar et al., 1988) as well as source amnesia (may involve temporal tagging) have also been shown in PD (Taylor et al., 1990a). Harrington et al. (1998) have shown that PD patients are impaired in timing, while Rammsayer and Classen (1997) demonstrated that deficits in temporal discrimination are dependent on DA. Harrington and Haaland (1999) and Brown (1999) have both emphasized sequence learning deficits in PD patients, as has Dominey (Dominey et al., 1995a, 1996; Dominey & Jeannerod, 1997). Beatty and Monson (1990) have demonstrated a deficit in picture and motor sequencing in PD patients while externally cued movement sequences are also disrupted (Georgiou et al., 1994). Sequencing deficits have also been compared across patient groups including PD, HD and dystonia (Agostino et al., 1992).

Recently, Graybiel (1998) has proposed that chunking of action sequences is carried out by the basal ganglia. That conceptual formulation may be compared to Grafman's (1994) concept of Managerial Knowledge Units, supposedly under frontal cortical control. Models of basal ganglia function have also focused on the sequential processing of information (Beiser & Houk, 1998; Berns & Sejnowski, 1996; Hikosaka et al., 1999) as well as on sequence learning (Dominey et al., 1995b; 1995c; Dominey & Jeannerod, 1997).

### Neurophysiological Studies

Not surprisingly, the role of prefrontal cortex in serial order memory has also been emphasized by Petrides in monkeys (Petrides, 1994). In the prefrontal, supplementary and premotor cortical areas, neurons encode the forward planning of sequences of movement (Gerloff et al., 1997; Tanji, 1994, 2001). Lee et al. (1999) demonstrated a temporal sequence of unit discharge within the preSMA and SMA. Anterior to posterior shifts in activation paralleled the transition from preparatory to execution stages of tasks. This may be related to the observation that injections of carbachol into the

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anterior caudate and putamen in monkeys have been shown to disrupt the learning of new sequences of movement, while similar injections more caudally, in the middle-posterior putamen, caused a disturbance in the execution of well-learned sequences (Miyachi et al., 1997).

In sensorimotor processing, pallidal units may signal the termination of one action, and the start of the next (Brotchie et al., 1991a, 1991b). Other studies have convincingly shown a specific role for the fronto-striatal circuits in the encoding of sequential actions (Barone & Joseph, 1989; Kermadi & Boussaoud, 1995; Mushiake & Strick, 1995). Matsumoto et al. (1999) showed that monkey striatum and its nigral afferents encode the initial learning of movement sequences and are also involved in the retrieval of that information. However, after MPTP lesions, relearning was still possible, suggesting the recruitment of compensatory circuits (perhaps cortically based as shown in functional imaging studies, see below). These studies illustrate the neurophysiological bases of serial action in behavior, the encoding of sequential actions, and the distributed nature of processing within the frontal-striatal system. As recently reviewed by Tanji (2001), numerous studies (Brotchie et al., 1991b; Kermadi & Joseph, 1995; Kimura & Matsumoto, 1997; Mushiake & Strick, 1995) have shown that basal ganglia units may fire selectively to spatial sequences of target-reaching arm or saccadic actions (sequence-selective). In addition, units may also encode serial position sequences of actions (rank-order-selective or phase-selective), while in the ventral striatum, units encode progress through predictable sequences (Shidara et al., 1998).

At the level of motor control, inappropriate timing of muscular action can lead to both tremor and rigidity (agonist-antagonist co-contraction). Sequential, as opposed to simultaneous recruitment of motor neurons leads to delayed initiation of action. These are classical clinical deficits in PD (Weiner & Lang, 1989). It is assumed that similar errors in sequential coding and execution are found with respect to cognitive processing at the neuronal level in the associative striatum, and that these underly the documented cognitive-behavioral problems in PD outlined above.

## THIRD PRINCIPLE: CONSEQUENCES

Given a goal, and having emitted a behavioral response, there must be some feedback through the environment about the consequences of that action. If the goal is approximated, then a reinforcement mechanism should be activated indicating that attention had been appropriately focused on salient cues and that the choice of action was at least good enough to register progress. In a novel situation, recursion or reiteration of such a sequence is the mechanism of learning habits, procedures or skills, by trial-and-error.

### Habits, Procedures, and Rules: Non-Declarative System

Since Corkin (1965) demonstrated the ability of patient HM to learn a pursuit rotor task normally despite his inability to consciously recall the experience, a second memory system has been proposed. This theme has been taken up by various authors (Cohen & Squire, 1980) and termed procedural or non-declarative learning, including phenomena such as implicit learning (see Nissen & Bullemer, 1987). Differentiation of the so-called non-declarative domain (cf. Gabrieli, 1998; Squire et al., 1993) is under theoretical scrutiny, but it seems clear that the basal ganglia are essential for certain types of skill, implicit, or procedural operations (Butters et al., 1985; Doyon et al., 1996; Haaland et al., 1997; Harrington et al., 1998; Knowlton et al., 1996; Owen et al., 1995; Saint-Cyr et al., 1988). Gabrieli (1998) has proposed that the basal ganglia are involved in open-loop learning.

In a series of papers (Mishkin et al., 1984; Mishkin & Petri, 1984), Mishkin and his colleagues proposed that the basal ganglia are responsible for stimulus-response (S-R) learning or the establishment of response habits. Since monkeys were able to perform concurrent visual discrimination learning with a 24-hour inter-trial interval, despite complete elimination of the hippocampal-diencephalic structures essential for the performance of declarative or representational memory, Mishkin deduced that the only remaining route for information from the critical TE temporal region to support this response habit was the basal ganglia. The organization of that projection has been well documented (Saint-Cyr et al., 1990; Yeterian & Pandya, 1998). Furthermore, neurotoxic lesions of the tail of the Cd (a TE recipient area), resulted in impaired performance of the 24-hour concurrent discrimination learning task (Fernandez-Ruiz et al., 2001).

Wise (1996) has criticized this model severely. He has argued that there is no case wherin striatal lesions (whether ablative or neurotoxic) have completely eliminated animals' ability to perform learning tasks. In his opinion, reductions of learning efficiency by as much as 50%, do not validate Mishkin's concept. However, this may only indicate that partial lesions lead to partial deficits, as is certainly the case when examining the medial temporal-diencephalic memory system (cf. Squire & Zola-Morgan, 1991).

#### *Implicit, procedural, and skill learning*

Subsequent to Mishkin's proposals, Saint-Cyr et al. (1988) was the first to demonstrate a double dissociation between the declarative and procedural systems with the latter being associated with basal ganglia dysfunction. This was later confirmed by Knowlton et al. (1996). There have been numerous studies demonstrating impairment in skill acquisition or procedural tasks in patients with basal ganglia dysfunction, usually PD or HD (Bondi et al., 1993; Frith et al., 1986; Haaland et al., 1997; Harrington & Haaland, 1999; Heindel et al., 1989; Jackson et al., 1995; Westwater et al., 1998).

Other studies have shown that PD patients have difficulty in the maintenance of new programs until completion and automatization of a routine (Partiot et al., 1996)

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and have deficits in automatic processing (Faglioni et al., 1997). However, artificial grammar and category learning have been shown to be normal in PD (Reber & Squire, 1999). Recent positron emission tomography (PET) studies have revealed that other neural systems, particularly the cerebellum, may very well contribute to skill and implicit as well as to visuo-motor learning (see Doyon et al., 1997; Gabrieli et al., 1996; Jueptner & Weiller, 1998; Pascual-Leone et al., 1994).

Mishkin has stressed the non-conscious nature of basal ganglia operations, thus reserving all reference to cognition and cognitive operations for cortically based functions. However, the essential participation of the basal ganglia in some stages of these operations suggests that a useful concept might be the term *protocognitive*, when referring to basal ganglia contributions to the type of task typically employed in neuropsychological studies. Of course skill and implicit learning are not plagued by these semantic distinctions. The use of the term *habit* may be too broad, since this would possibly include other mechanisms such as sensitization, habituation and orientation, which may operate without the involvement of the basal ganglia (Squire et al., 1993).

Based on Norman and Shallice's (1980) Supervisory Attentional System model (Shallice, 1988) and Anderson's (1983) work, the acquisition of skills can be broken down into 5 phases, namely, Phase I: internalization of task rules and constraints; Phase II: incremental filtering of salient cues and approximation of cue-reward temporal contingencies; Phase III: optimization of successful strategies; Phase IV: option for conscious conceptualization of task, hypothesis testing and encephalization; Phase V: automatization of the task with conscious monitoring and predictive planning. It can be suggested that the basal ganglia are involved in the first 3 of these phases, and perhaps in the automatization component of Phase V.

## Neurophysiological Studies: Dopamine, Reinforcement and Learning

Tasks such as detour reaching (Diamond, 1990; Moll & Kuypers, 1977), known to be sensitive to lesions of prefrontal and supplementary motor cortical areas, are also impaired in the MPTP monkey (Schneider et al., 1992; Schneider & Pope-Coleman, 1995; Taylor et al., 1990c). Certain conditional oculomotor tasks (delayed anti-saccades and memory driven saccades), (Briand et al., 1999; Funahashi et al., 1993; Goldman-Rakic, 1996; Guitton et al., 1985; O'Driscoll et al., 1995; Slovin et al., 1999), also seem to be dependent on the fronto-striatal oculomotor loop (Hikosaka & Wurtz, 1989). Chronic recording with multiple electrode arrays in the striatum of rats learning new habits (i.e., T-maze learning) has shown large and widely distributed changes in neuronal activity patterns during acquisition of the task (Jog et al., 1999). These patterns were most marked for the beginning and end of automatized procedures and were stable for weeks. In the unilateral MPTP monkey model, Matsumoto et al. (1999) have demonstrated an impairment in the learning of sequential motor tasks, in the limb contralateral to the DA loss. While this could reflect defocusing of processing at the pallidal level (cf. Filion et al., 1994), the presence of DA is also crucial at a more molar level.

Wise et al. (1996) have proposed a reformulation of basal ganglia function. In their model, the basal ganglia would provide a DA-based mechanism for rule potentiation and the learning of context. Thus, rules determined by the frontal cortex would be potentiated if behaviorally successful and eliminated if not (through lack of reinforcement), via the action of the direct pathway. Schultz and his colleagues have in fact simulated delayed response task learning, using the known physiological actions of DA in the striatum (Contreras-Vidal & Schultz, 1999; Schultz et al., 1998; Suri & Schultz, 1998). The indirect pathway in the Wise et al. model would encode behavioral context such that previous exposures to a given paradigm would facilitate the evocation of the potentiated rules in the future. This is the most comprehensive model to date, which accounts for known frontal cortical operations, as well as basal ganglia information processing. Recently, Bar-Gad and Bergman (2001) have proposed that the DA-dependent reinforcement signals and local competition learning rules reduce the dimensionality of information arriving into the basal ganglia from the cortex. This is proposed to be the basis for response selection and adaptive learning. In the pathological PD state, loss of DA would lead to reduced lateral inhibition (i.e., defocusing), persistent negative reinforcement and, hence inefficient reduction of dimensionality. Behaviorally, this would cause inability to select appropriate responses due to ambiguity of undifferentiated choices.

Schultz and his colleagues (Hollerman et al., 1998; Schultz et al., 1998; Tremblay et al., 1998) have proposed a dual role model for the action of DA in the striatum, based on extensive single unit studies. First, there would be a fundamental, tonic facilitatory action by DA, relatively uninfluenced by phasic environmental or behavioral events. Thus, loss of DA in PD would entail a general poverty of processing and loss of neurophysiological tone. While DA replacement therapy would correct this to a certain extent, the phasic encoding role of the DA system would not be reinstated. This second, phasic role is of more interest here. DA would be responsible for the imbuing of incentive value to environmental cues which are novel (transiently) and task-related in a reward-predictive sense. Other studies of the firing repertoirs of tonically active neurons (TANs) are concordant with this view (Aosaki et al., 1994a; Apicella et al., 1998).

In the ventral striatum, neuronal activity appears to monitor the progress of learning a task in relation to anticipated reward (Shidara et al., 1998). Studies by Rolls and his colleagues (Rolls et al., 1983; Rolls & Treves, 1998) as well as from Schultz's (Tremblay & Schultz, 1999) and Richmond's labs (Bowman et al., 1996), have also shown that reward, or expectation of reward is coupled to unit activity in the ventral striatum. The potential role of nucleus accum-

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bens and the amygdala in behavioral activation and reward has a long history (e.g., Blackburn et al., 1992; Everitt et al., 1999), especially in relation to the orbitofrontal cortex (Rolls, 2000). An extensive analysis of the role of DA in incentive salience, reward learning, and other associated concepts has recently been published (Berridge & Robinson, 1998).

In this way, DA plays a critical role in adaptive learning, at least in its early stages. This has been called *procedural mobilization* in relation to skill or implicit learning (Saint-Cyr & Taylor, 1992) and *protocognitive operations* in relation to conscious learning and problem-solving (Saint-Cyr et al., 1988; Taylor & Saint-Cyr, 1995; Taylor et al., 1990b). Similar formulations of the role of the basal ganglia in the control of behavior have also been proposed by other authors (Hikosaka, 1993; Kimura & Matsumoto, 1997; Watanabe & Kimura, 1998; Wise et al., 1996).

## TESTING THE MODEL

The question now arises as to whether the effects of an experimentally produced focal lesion, or stimulation-induced disruption to the basal ganglia circuitry, are congruent with the present formulation.

### Outcome of Neurosurgical Interventions in PD

The rationale for surgical interventions in PD is that reduction of the excessive inhibitory output from the GPi to thalamus should release thalamocortical systems and thus facilitate cortically-based motor function. Consequently, in the surgical treatment of PD, lesions in the posteroventral pallidum (PVP) have been shown to ameliorate the dyskinesias experienced as adverse effects of DA replacement therapy, although there were no changes in medication or in underlying symptoms (Lang et al., 1997; Lozano et al., 1995).

To the extent that the basal ganglia in these patients are still participating in processing information in cognitive operations, one might expect performance to suffer post operatively. This was in fact observed by Trépanier et al. (1998) as well as by Stebbins et al. (2000). Both hemisphere-specific functions (recently reviewed by Green & Barnhart, 2000) as well as executive functions (specifically working memory, Stebbins et al., 2000) were affected. Thus, we have seen a further deterioration in cognitive functions already established as being at risk due to PD. Some centers have reported only mild, if any, cognitive changes after surgery (i.e., Ghika et al., 1999; Green et al., 2002; Soukup et al., 1997), but factors such as the long-term clinical effectiveness (perhaps related to size of lesion), adequacy of neuropsychological assessment and location of lesion within the pallidum may be critical in this regard. The location of lesions made within the GPi has been shown to be predictive, not only of motor outcome (Gross et al., 1999), but also in terms of impact on cognition (Lombardi et al., 2000). In the latter study, anterior PVP lesions led to poorer working memory and proactive interference, while caudal lesions marginally improved attentional resource utilization. The latter effect may be secondary to decreased motor symptoms such as rigidity, thus liberating attentional resources to focus on cognitive tasks. These observations suggest that it is possible to demonstrate a functional segregation within the pallidal circuits, at least at a gross resolution (cf., Parent & Hazrati, 1995a).

In cases of simultaneous, or staged bilateral pallidal lesions, all too often, outcome is characterized by catastrophic declines cognitively and also in loss of behavioral control, with a full-blown frontal syndrome being induced (Scott et al., 1998; Trépanier et al., 1998, 2000), with many of the features described by Lhermitte (1986).

Referring back to the basic anatomical model of striatal dysfunction in PD, surgeons have also attempted to rebalance the circuit by applying high frequency electrical stimulation (deep brain stimulation or DBS) to either the GPi or, in preference, to the STN.

In a large series of carefully selected PD patients, GPi or STN-DBS caused little change in cognitive functions on a group basis (Ardouin et al., 1999). Furthermore, neither presence nor absence of stimulation appeared to alter global cognitive function (Pillon et al., 2000). Further studies on these patients, focusing on executive functions, have shown a marginal improvement with STN-DBS and a decline with GPi DBS (Jahanshahi et al., 2000).

However, in older PD patients, STN-DBS was shown to reduce cognitive resources (Saint-Cyr et al., 2000; Trépanier et al., 2000). Specifically, decreased attentional capacity and alertness, reminiscent of that seen in Progressive Supranuclear Palsy (cf. Dubois et al., 1988), as well as impaired memory and verbal fluency were prominent. Behavioral changes of a frontal nature were also observed (Saint-Cyr et al., 2000; Trépanier et al., 2000). It has become clear that outcome of DBS is therefore predicted by age at surgery, extent of response to DA replacement therapy, and successful elimination of patients at cognitive or psychiatric risk as shown by rigorous neuropsychological screening (cf. Ardouin et al., 1999; Trépanier et al., 2000). The cognitive impact of DBS within the basal ganglia has been interpreted as evidence both for the facilitation of cortically-based functions and the interruption of striatally-based processing.

These studies suggest that cortical reserve and the preservation of non-DA systems, in particular the cholinergic (Bédard et al., 1999; Dubois et al., 1990), may play a major role in the cognitive capacity of PD patients with and without surgical treatment.

Unfortunately, the assessment of patients, especially those undergoing surgery, cannot be encyclopaedic. Interpretation of findings is complicated by clinical management (e.g., post STN-DBS, medications are often reduced by at least 50%), improved motor clinical status (resulting in liberation of attentional resources on a behavioral basis), and often altered mood (initial transient euphoria and isolated

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cases of severe depression) (Saint-Cyr, 2002). While some mood changes have been shown to be instantly induced by the onset of DBS (Bejjani et al., 1999), more chronic changes may also occur (Saint-Cyr et al., 2000).

Nevertheless, the profile of impaired cognitive function in these patients, when present, is entirely concordant with current formulations of basal ganglia contributions to behavior. In the series showing little or no cognitive change, it may be the case that cortically-based processing has taken over even those functions normally subserved by the basal ganglia. In some instances, notably for verbal fluency, this supposed compensation is less than perfect since all studies report post-surgical impairment (Saint-Cyr, 2002). Studies have yet to be done examining attentional capacity, sequential processing per se, or efficiency of reinforcement based learning in surgical patients. Abstracting these domains from the current studies, one is left with the impression that some tasks, such as spatial conditional associative learning, may already have been at floor levels (e.g., Saint-Cyr et al., 2000; Trépanier et al., 1998; but see Jahanshahi et al., 2000), while cortical compensation, as indicated with regard to improved motor control, may be responsible for maintained or restored function (cf. Limousin et al., 1997).

Since the study of PD patients, with and without surgery, may be far more complex than our functional models suggest, another way of testing the proposed conceptual framework is to exploit functional imaging paradigms, especially in intact subjects.

## Functional Imaging of Fronto-Striatal System Operations

The most integrative approach to visualizing the domain of operations of the basal ganglia is functional imaging in health and disease (Brooks, 2000; Bucher et al., 1995; Eidelberg, 1998; Grafton et al., 1998; Jueptner & Weiller, 1998; Owen & Doyon, 1999). Kinomura et al. (1996) showed blood flow changes in the reticular formation and thalamus in relation to attentional control. Normal subjects performing antisaccade tasks had regional blood flow changes throughout an oculomotor circuit which included the frontal eye fields and putamen (O'Driscoll et al., 1995).When normal subjects attended to directional cues to detect visual targets, regional blood flow was shown to increase in the putamen (Koski et al., 1999). Long interval cue-target orienting of foveal attention has been shown to engage the basal ganglia (Coull et al., 2000). Recent studies have also shown that the prefrontal cortex-caudate circuit is critical for response selection within prior and current contextual space (Peigneux et al., 2000). These results tie in with the attentional deficits observed in PD behaviorally, although we do not have an imaging correlate for postulated dysfunctional brain stem and thalamic contributions in PD.

Ceballos-Baumann and his colleagues (1999; Ceballos-Baumann & Brooks, 1997) have demonstrated that the anterior supplementary motor area (SMA) is active in the early phases of motor sequence learning, and that the focus of activation moves caudally toward the primary motor cortex as the task becomes automatized. A similar sequence moves through the basal ganglia from rostral to caudal (Boecker et al., 1998). Repeated sequence visuo-motor learning tasks activate the right striatum as well (Doyon et al., 1997, 1998). Thalamic deactivation has been shown in the early phases of implicit sequence learning (Rauch & Savage, 1997), possibly signaling striatal inhibitory influences.

Using activation paradigms in normal subjects, it has now been shown that the basal ganglia are involved in spatial problem-solving (Owen et al., 1996), set shifting, and reversal learning (Rogers et al., 2000), usually on the right side. However, reversal learning of intra- *versus* extra-dimensional sets may recruit the left caudate (Rogers et al., 2000). This may be a reflection of the instantiation of a conscious top-down strategy to self-monitor the set shift. In a spatial forward planning task, complexity of the problem sets was correlated with activation of the right dorsal caudate (Dagher et al., 1999). Using a 4-dimensional conceptual reasoning task, Rao et al. (1997) demonstrated the activation of a circuit involving the right dorsolateral prefrontal cortex, head of the caudate and GPi (inter alia).

In a problem-classification task requiring probabilistic classification, bilateral frontal cortex and right caudate activation has been demonstrated, while there was deactivation of the left hippocampal complex (Poldrack et al., 1999). By comparison, spatial navigation through a virtual reality environment requires the interaction of both the hippocampal formation, to identify place location, and the basal ganglia, to plan a rapid route (Maguire et al., 1998). In normal subjects engaged in a video game, requiring both vigilance and rapid visuo-motor responses, striatal DA was released (Koepp et al., 1998) (supposedly in relation to progressive success).

A study with bilingual subjects indicated activation in the left putamen during silent rehearsal of their secondary language (Klein et al., 1994), suggesting that this was due to greater effort and non-automatized activation of articulatory sequences. In addition, it has been shown that sentence processing requires mesial frontal and left caudate function, while grammatical processing relies on bilateral dorsolateral prefrontal cortical function (Grossman et al., 1993).

In intact monkeys, Levy et al. (1997) reported spatial delayed response induced changes in the head of the caudate, while nonspatial delayed response tasks activated other portions of the caudate. This again echoes the coupled relationship of frontal cortex and striatum. The question arises as to whether this coupling is also seen in PD. One might imagine a redistribution of processing or shift of anatomical locus of control when the basal ganglia become dysfunctional.

In idiopathic PD, frontal, as well as subcortical hypometabolism and decreased blood flow have traditionally been reported (Brooks, 1997; Eidelberg et al., 1994). In PD there is a greater cortical activation as a compensation in

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sequential finger movement learning (Catalan et al., 1999). Samuel et al. (1997) have also described overactivation of premotor and parietal cortical areas in PD patients, while they performed sequential motor tasks.

The acquisition of explicit finger sequences in PD patients engages the right dorsolateral prefrontal cortex, the premotor, posterior parietal and precuneus cortices bilaterally, without the additional activation of the left preSMA and caudate-putamen seen in control subjects (Nakamura et al., 2001). After PVP, increases in both the previously underactivated SMA and premotor cortices are seen with PET (regional cerebral blood flow) during voluntary movements (Grafton et al., 1995; Samuel et al., 1997).

Limousin et al. (1997) have shown that SMA activations, induced by performance of a visuo-motor joystick task, are normally depressed in idiopathic PD but that this is partially reversed by STN-DBS. Pallidal DBS, in the PD patient at rest, can alter blood flow in the motor, SMA, anterior cingulate, and rostromedial area 25 cortical regions (Davis et al., 1997).

These studies reveal the functional coupling of the fronto-striatal circuits and implicate those circuits in adaptive motor control, sequence learning, and spatial problem-solving tasks. There is some evidence that specific circuits can be activated, according to laterality and within the cortico-striatal loops. It is also clear that disconnection or stimulation-induced alteration of basal ganglia actions (by pathology or surgical intervention) is reflected in cortical compensatory changes. This leads to the conclusion that the performance of patients with basal ganglia pathology (e.g., PD or HD) is determined by both information processing errors within striatal circuits and also is a reflection of cortically-based compensatory strategies.

## Is the Cognitive Deficit in PD Uniquely due to Loss of Dopamine (DA)?

If PD pathology is considered to be uniquely due to loss of striatal DA, then one might expect DA replacement therapy to ameliorate cognitive function in a manner analogous to its effects on motor control. Some studies (Gotham et al., 1988; Lange et al., 1992) found impaired performance as a consequence of l-dopa withdrawal. In problem-solving, selected tasks do show improvement with l-dopa (Owen et al., 1995) but these effects are difficult to separate from a non-specific improvement in attentional capacity. A dopa toxicity effect has also been noted for certain tasks (see Gotham et al., 1988). Kulisevsky et al. (1996) also showed that l-dopa may have adverse effects on neuropsychological tests, but may otherwise only speed up response times. Malapani et al. (1994) have demonstrated impairment in *de novo* PD patients, as well as in patients in the off state, in their ability to perform concurrent tasks. In sum, studies of PD patients on and off medication either show little cognitive impact or occasionally, a toxic high dose effect. The supposed cognitive benefits of dopa replacement may be due to improved attentional resources (secondary to motor improvement) or speeded response times. This may reflect the extraordinary capacity of cortical compensatory mechanisms and the reserve capacity of the basal ganglia to process some useful information (recall that the loss of DA in the caudate is limited in PD, cf. Kish et al., 1988).

Pullman et al. (1988) were able to show a negative impact of fluctuation of blood levels of DA in a motor control task. It must be realized that withdrawing patients from DA medication for 12 hours (the usual method) is not equivalent to the neurological status of *de novo* patients (Quinn, 1998). This might in fact create a more dysfunctional state and artificially indicate that the test in question was DA state-dependant (not the same as DA withdrawal). DA instability might be expected to thwart the establishment of compensatory strategies since the basal ganglia would not become "off-line" consistently. That being said, many patients who experience fluctuations in their response to these medications (typically candidates for surgery), have a cognitive profile which is the same as for other patients with more stable response (Taylor et al., 1987). However, loss of benefit of dopaminergic medication is associated with more profound fronto-striatal cognitve dysfunction, and also predicts failure to respond to neurosurgical interventions (Benabid et al., 2000; Taylor et al., 1987).

Future studies may need to employ convergent clinical assessments to improve accuracy of differential diagnosis, since disease subtype (Graham & Sagar, 1999; Huber et al., 1991), as well as stage (Huber et al., 1989; Owen et al., 1992) may be associated with differential cognitive performance and response to treatment. It has even been suggested that PET studies of receptor availability and distribution may have some predictive power (Eidelberg et al., 1998).

Kish et al. (1988) have shown that in the striatum, outside of the putamen, only the dorsomedial head of the caudate has significant loss of DA. Although loss of DA at the frontal cortical level is usually considered too minor in PD (c. 17%) to be of any global functional consequence (Agid, 1991), Williams and Goldman-Rakic (1995) demonstrated that local DA loss can impair saccadic control mechanisms in the frontal eye field. Focal loss of prefrontal cortical DA may enhance extradimensional shifting or impair spatial delayed response functions (Roberts et al., 1994), or may impair extradimensional set shifting when the change is to a previously reinforced dimension (Collins et al., 2000). This latter effect is accompanied by long term adaptive changes in DA release in the caudate. Thus, if the loss of prefrontal DA is actually localized in PD this too could contribute to performance impairment in selected tests.

Finally, other sources of monoamine transmitters, namely serotonin (5-hydroxytryptamine or 5-HT, arising from the nuceus raphé dorsalis), and noradrenalin (NA, arising from the locus coeruleus), are known to innervate the basal ganglia, and to undergo degeneration in PD (Agid, 1991; Hornykiewicz, 1998). Other mesencephalic sources of DA, which may eventually also succumb to PD, arise from the ventral tegmental area of Tsai (VTA or A10) and the retro-

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rubral group (A8) (Braak et al., 1995; Forno, 1996). These project, in part, to the basal ganglia but also to the basal forebrain, amygdala, nucleus accumbens, anterior cingulate gyrus and to the frontal lobes (Williams & Goldman-Rakic, 1998). This raises the possibility that extra-striatal dysfunction may contribute to cognitive impairment or to altered adaptive capacity in PD patients.

Thus, PD may not represent as pure a model of basal ganglia dysfunction as previously thought, and inferences drawn from the study of PD patients must be tempered by the recognition of the underlying pathology and likely neural reorganization of circuits involved, especially at the cortical level.

## SUMMARY AND CONCLUSIONS

The integration of basic neuroscience data with clinical neuroscience observations in studies of basal ganglia function may be viewed along a temporal continuum. From an initial behavioral state space or *Context*, which defines conditional reward contingencies, the basal ganglia appear to be primed by frontal cortical instruction to process incoming signals. These signals are selected and shaped through experience to encode *Sequences* of action or response. Finally, the *Consequences* of both selective attention (identification of task-salient cues) and choice of goal-seeking actions, are differentially facilitated through a DA-based reward system which eliminates error. Basal ganglia efferents provide the cortex with an attentional and domain specific focus in preparation for action, and also instruct the evolving behavioral pattern according to the outcome.

Studies of PD patients provide only a partial view of basal ganglia functions since the pathology does not involve all circuits and the slow evolution of the disease may also permit the establishment of cortically-based compensatory mechanisms. Per contra, pathological processes outside the basal ganglia may also be contributory to cognitive impairment in these patients. Nevertheless, functional imaging studies in both normal subjects and PD patients confirm a central role for the basal ganglia in attentional and preparatory functions, implicit learning, the establishment of response habits, procedural learning (or mobilization), skill learning, rule learning, and associative learning, and even some aspects of cognitive skill acquisition.

Although DA is the key to reinforcement (phasic mode), it is also responsible for overall neural tone in the frontal-striatal system (tonic mode). Ach is suspected of being critical for cortically-based processes, especially when striatal functions are weakened by disease or lesions (see Bédard et al., 1999; Dubois et al., 1990), but it may also have a direct role within the striatum in encoding new learning (cf. TANs activity patterns shown by Graybiel during learning, Aosaki et al., 1994a; 1995). Roles for other neurotransmitters (e.g., NA, 5-HT, opioids and GABA inter alia) in processing information employed in cognitve functions have yet to be defined.

## Conclusion

The conceptual model proposed here suggests a decomposition of tasks into different supraordinate domains than those traditionally utilized in neuropsychology. However, under the umbrella of *Context*, one can still find attention, set (including establishment and switching), problem-solving, strategies (building, selecting, and instantiation), encoding of information, and retrieval, as well as preparatory phases of movement and task execution. This long list emphasizes that we cannot be overly zealous in the fractionation of behavior. The *Context* label may remind us that behavioral control is a constant process, continuously being updated in the light of experience via environmental feedback. Thus *Context* does change over time as cue salience is modified, subgoals are reached and new ones chosen with different cues and strategies being needed. At the micro-structure level of behavior, we find motor control being tuned, while at a macro-level, there is the opportunity for top down conscious cortical intervention to define hypothesis-driven courses of action. It is axiomatic that cortical processes are inextricably bound with the striatum in these functions.

Both the micro and macro-structure of *Sequences* (timing, selection, temporal order) represents the gears controlling the mechanics of action. Most of this occurs automatically and outside of conscious awareness, and has traditionally been at the core of formulations of basal ganglia function. Specific signalling of sequential processing is also found to be distributed at cortical and subcortical levels.

The essential role of DA for reinforcement-based learning, as well as for the focusing of information processing is now recognized (the so-called phasic and tonic components). Clearly, this represents the mechanism underlying *Consequences* of action. Again, a distributed model involving the ventral striatum and associated mesolimbic system, with its own cortical components is central.

It would be artificial to attempt to entirely divorce the above processes either anatomically or temporally. These systems must function in parallel and continuously although there is a temporal recursive quality to the present formulation.

In closing, with regard to our understanding of the basal ganglia, we must always consider interactions with anatomically linked structures from brain stem, through thalamus to cortex. Trying to abstract an unique role for the basal ganglia is akin to Hughlings Jackson's adage that the concept of the motor system without sensory input is a myth and not a very useful one. Nevertheless, there is overwhelming evidence that the basal ganglia play a central role in the processing of attentional and preparatory activities, that sequential marker events are encoded and that reinforcement based learning is central to basal ganglia functions. The conceptual regrouping suggested here may encourage the design of experiments which bridge the gap between unit recording, neuropsychology and functional imaging, by isolating the various phases of information processing in time.

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