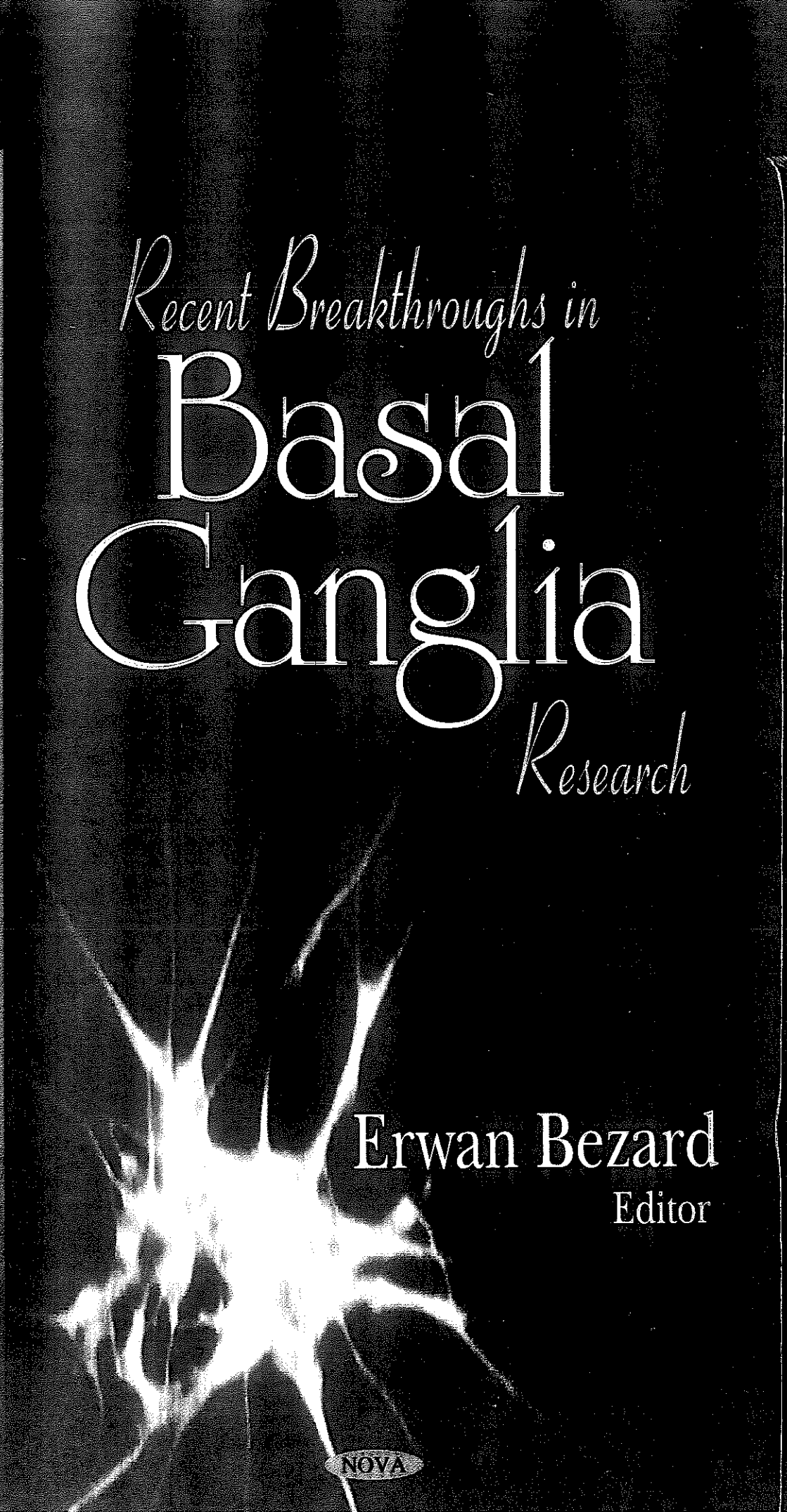
Nova Biomedical

Recent Breakthroughs in Basal Ganglia Research



Erwan Bezard
Editor

NOVA

In: Recent Breakthroughs in Basal Ganglia Research
Editor: Erwan Bezard, pp. 227-239
ISBN: 1-59454-880-3

Chapter 18

CONVERGING EVIDENCE OF THE BASAL GANGLIA S ROLE IN FOCUSED ACTION SELECTION AND INHIBITION OF COMPETING INFORMATION

Elizabeth A. Franz*
University of Otago, Otago – New Zealand

ABSTRACT

At any given time, we are faced with a number of potential actions and we somehow select one to be carried out over other possible competitors. This problem of action selection is of fundamental importance to studies of cognition. The present chapter highlights a recent cognitive approach to research on basal ganglia function that supports earlier cognitive models of inhibition and a more recent model that amalgamates anatomical and neurophysiological findings. Evidence from these different domains strongly supports models that link competing inhibitory processes and focused selection of action to operations of the basal ganglia.

INTRODUCTION

At any given time, we are faced with a number of potential actions and somehow select one to be carried out over other possible competitors. This problem of action selection is of fundamental importance in studies of cognition. The present chapter highlights a recent cognitive perspective on basal ganglia function. Experimental findings from patients with Parkinson's disease (PD) support the view that a basic operation of the basal ganglia is related to activation and deactivation (inhibition). According to the present author's view, this basic operation occurs on different types of information processing and is captured in earlier cognitive models on action selection and more recent anatomical-physiological models of basal ganglia function. The present aim is to present a persuasive argument that cognitive and neurophysiological models have run a parallel course in their development, and that the two have converged on a coherent framework for understanding the processes of action selection and the role of the basal ganglia.

In an earlier cognitive account of action selection, Neumann, (1987) raised the puzzling question: How does a person selectively reach for an apple from a tree that contains many apples? As Neumann suggested, a cognitive approach might consider why one apple is selected over the others that surround it. Perhaps the target apple becomes the focus of attention because it is bigger and brighter than the others. A cognitive approach might also consider how the brain organizes the goal-directed action of reaching the target apple by selecting one hand rather than the other to perform the reach. Or, it may consider the principles of organization and initiation of an appropriate sequence of movements necessary to bring the selected hand in contact with the apple. Few cognitive approaches generally deal with the possibility that the brain might

* Correspondence to Liz Franz: Action, Brain, and Cognition Laboratory, Department of Psychology, University of Otago, Box 56, Dunedin, New Zealand. E-mail address: Lfranz@psy.otago.ac.nz. Phone: 64-3-479-5269, Fax: 64-3-479-8335

not be focused solely on the goal to reach the apple, as there might be myriad other goals or subgoals (or candidate actions) that are at least partially activated simultaneously. In contrast, a cognitive approach is much less likely to be concerned with the body's maintenance of an appropriate posture to support the reaching arm so that the action can be effectively carried out. Neurophysiological approaches consider this aspect in more detail, however.

As the above example suggests, the problem of action selection entails more than initiating a reaching movement with a particular arm and hand; rather, action selection might occur on numerous levels, from properties related to the motor movements themselves, to those related to the maintenance of goals. I begin the development of the present framework with a description of some basic properties of reaction time (RT), the standard measure used in studies of cognition. RT, or the latency to respond to a stimulus to which a response is mapped, is typically viewed as a measure of cognitive processing. As shown in early seminal studies, reaction time (RT) tends to increase with the number of stimulus-response choices and is therefore often regarded as a measure of task complexity or difficulty (Hick, 1952; first documented in German by Merkel, 1885). A common interpretation is that RT reflects time taken to program a movement, which includes events preceding movement initiation (Klapp, 1975).

In what follows, I will first briefly review some early investigations that applied RT paradigms to examine performance of patients with Parkinson's disease in an attempt to elucidate whether RT effects reflect basal ganglia operations involved in response planning and preparation. I will then present an overview of recent work conducted by my colleagues and me that sheds a different light on the operations of the basal ganglia, suggesting instead that these nuclei are critically involved in activation and inhibition more generally. Following this, I will build on selected studies in the cognitive literature that view behavioral activation and inhibition as central to processes of action selection. Finally, I will argue that activation and inhibition deficits are the outcome of basal ganglia impairments and that these basic operations are captured in recent anatomical-physiological models of focused selection and inhibition of competing responses.

1 Early Investigations of RT in People with Parkinson's Disease

The literature on RT in PD patients reveals mixed findings, perhaps due to the differences in methodologies and severity of symptoms of the patients tested (King, 1959; Angel et al., 1970; Heilman et al., 1976). Some studies reported that PD patients were slower than controls on simple RT tasks (where all response information is known prior to the stimulus to move), whereas the two groups were not reliably different on choice RT tasks (Evarts et al., 1981; Bloxham et al., 1984; Sheridan et al., 1987). A corollary finding common across these studies- that simple and choice RT are not reliably different within the patient group- has led to the interpretation that PD patients are impaired in utilizing advanced information that is provided in the simple RT case (i.e., Sheridan et al., 1987; but see Rafal et al., 1984). However, it is equally plausible that the benefit of advanced information appears to be lost in PD patients because they cannot effectively hold planned information in store prior to movement initiation (Bloxham et al., 1984; see also Klapp, 1976). For example, basal ganglia dysfunction might cause the program for movement to degrade quickly due to noise in the system and to interference that arises due to an inability to inhibit the programming of other potential responses (see Sheridan et al., 1987). As suggested above, due to the broad range of methodologies employed in these studies, it has been difficult to weigh one possibility against the others.

2 A Recent Demonstration that Sheds a Different Light on the Basic Cognitive Deficits Related to Parkinson's Disease

Taking a very different approach, Franz and Miller, (2002) recently examined whether a basic function of the basal ganglia relates to activation and inhibition. Rather than using RT as a measure of task difficulty or complexity, RT was measured from analogue force profiles to examine the effects of high and low response readiness using a go no-go task. Specifically, each block of trials was equally divided into trials

with color cues that corresponded to either high or low probability events. Cues in either of two colors flooded the computer screen just prior to presentation of a stimulus that signaled the subject to respond (go trial) or to withhold responding (no-go trial). To reinforce the manipulation on response readiness, participants were instructed prior to performance of each block that one color cue indicated high probability that a response is likely on that trial and the other color indicated low probability that a response is likely on that trial. Following the color cue, an arrow pointing in the direction of the response key was presented on 80 % of trials for high response readiness blocks, and an '=' was presented on the remaining 20 %. All trials with an arrow required a response (go trials), whereas trials with the '=' required withholding of the response (no-go). The opposite probability-to-response mapping was used for low probability trials (low response readiness conditions), with 80 % 'no-go' stimuli and only 20 % 'go' stimuli. Force output was measured on each trial, and RT was computed using a force threshold criterion. It was previously unknown how patients with PD would respond on high versus low readiness conditions, and the primary issue of interest was in whether they would reveal deficits in response activation, following logic provided by studies on healthy control subjects.

Previous studies on healthy control participants demonstrated that faster RTs occur with high probability compared to low probability events (i.e., Mattes et al., 1997, 2002). Mattes et al., (2002) extended similar findings to the force domain, demonstrating that high probability trials resulted in a smaller peak force than low probability trials. This latter effect, in particular, motivated the study by Franz and Miller, (2002) who noted that impairments associated with PD appear to range from too little activation (i.e., akinesia, bradykinesia) to too much activation (i.e., festination, chorea). Franz and Miller also noted that the common observation, that Parkinson's patients have difficulty stopping an ongoing movement, might be a marker of a deficit associated with inhibition (deactivation).

To capture properties of response activation in healthy controls, Mattes et al., (2002) elaborated on a framework proposed earlier by Näätänen, (1971). Specifically, Näätänen, (1971) found that mean RT lengthened with systematic increases in the interval that separates stimuli that are used to cue responses in a simple RT task. According to Näätänen, response readiness is high with expectancy of a short interval compared to expectancy of a long interval. He further asserted that with a high response readiness, only a small additional amount of response activation is required to reach a 'motor action limit', whereas with a low response readiness, a larger amount of activation is required to reach that limit. This relationship between expectancy and response activation was later elaborated by Mattes et al., (2002) to account for the effects on force that were demonstrated using direct manipulations on response readiness (described above). Franz and Miller, (2002) therefore raised the question of whether PD patients would produce different patterns of force output than controls under manipulations of response readiness, and if so, whether these patterns on force could be interpreted as deficits in response activation (and deactivation). A group of mild to moderate PD patients and age-matched controls were among the participants tested in that study.

Of primary interest, Franz and Miller, (2002) learned that the effects of response readiness on RT were similar in the patient group and their age-matched controls, although the patients showed abnormal force profiles compared with the matched controls. For the controls, peak force and force integral were smaller for high probability trials compared to low probability trials, whereas the opposite pattern was apparent in the patients. The average values of these variables collapsed across blocks performed by the left and right hands can be seen in Table 1 (see also Franz and Miller, 2002; Table 2). Note that variables for the responding hand only are shown in Table 1, although force output was concurrently measured for both hands (a point I will return to later). Further analyses revealed that, on average, the rate of force output was faster on low compared to high response readiness trials in control participants, whereas the rate of response output was approximately the same for the two conditions in the patients. Force output also occurred for a longer duration in the PD group compared to the controls, and a longer average duration for larger impulses occurred in the patients despite the lack of differences in rate. Franz and Miller, (2002) interpreted this pattern of results as reflecting an inability of the patients to modulate response activation according to the internal level of response readiness. In other words, the patients produced a constant increment of activation regardless of the level of internal readiness. It was concluded that a primary deficit of the patients is related to response activation.

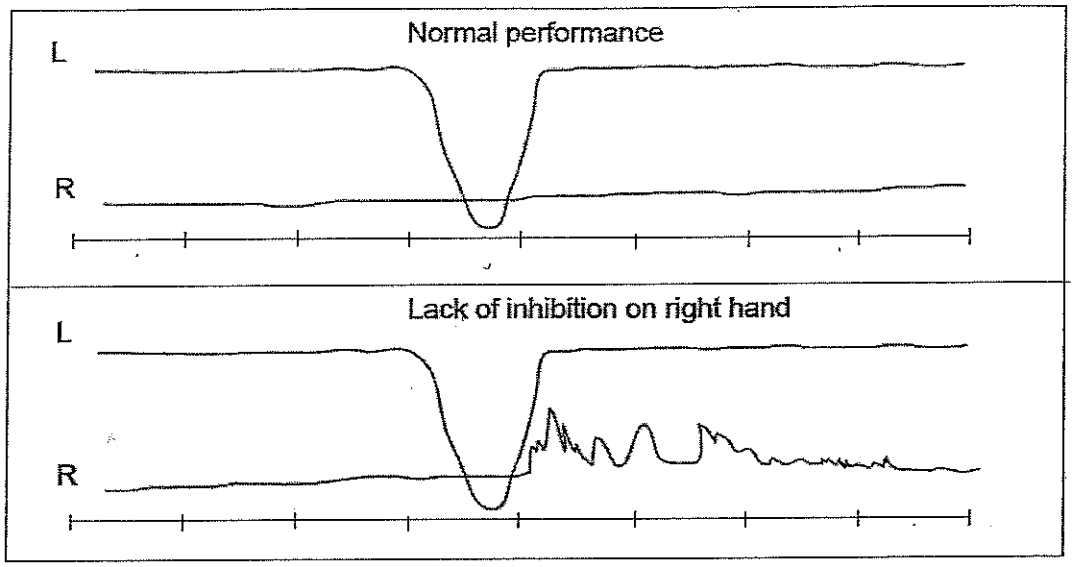


Figure 1. One representative trial of a normal 'go' response with high response readiness (top panel), and one representative trial of a response from the same condition showing evidence of a lack of inhibition (lower panel). Tick marks occur each second. L means left hand, and R means right hand. Adapted from data of (Franz and Miller, 2002).

Table 1. Mean measures of force for PD patients and age-matched (AM) controls for the responding hand on go trials with high or low readiness. Values are collapsed across the two hands.

	Peak Force (cN) Readiness condition		Impulse size (cN) Readiness condition	
	High	Low	High	Low
Group				
PD	**567**	556	27,784	26,802
AM	512	526	17,594	18,035

Adapted from Franz and Miller, (2002, Table 2).

Other related research is consistent with an inability in people with PD to appropriately modulate response activation. For example, electromyographical activity (EMG) in healthy subjects shows the characteristic triphasic pattern of agonist and antagonist activity with a normal limb movement to a target, but it has been shown that PD patients often do not generate sufficient EMG activity in the initial agonist burst to obtain the force necessary for large and fast movements (Hallett and Khoshbin, 1980). Marsden, (1984) suggested that while the selection of muscles and the sequential timing of their activations are not impaired in PD patients, perhaps the number and frequency of activated motor neurons is not adequate. It has also been suggested that the diminution of letter size known as micrographia, and a similar type of effect in continuous drawing tasks might be a manifestation of an inability to sustain an appropriate level of response activation through time (see Figure 2).

In addition to response activation, Franz and Miller, (2002) proposed that response deactivation (or inhibition) would also be impaired in the PD patients. At least two aspects of the findings of the study supported this hypothesis. First, although interest was primarily in the responding hand on each trial, force output was also measured continuously throughout each trial for the hand that was not supposed to respond (given all trials involved only a unimanual go versus no-go response, there was always one uninvolved hand). For the uninvolved hand, at least some level of force output was found on some temporal epochs following stimulus presentation, and this significant level of force occurred somewhat sporadically for control participants. In contrast, for the PD patients a significant level of force output occurred for the uninvolved hand quite often on temporal epochs that surrounded the time at which RT would normally occur (see Figure 1). In other words, response inhibition of the hand that was not supposed to respond was

somewhat impaired in the PD group. Second, illustrating a possible impairment in response inhibition, the PD group also produced a larger mean force level than the control group on no-go trials, or those trials in which no response was required. Collectively, these findings are suggestive of problems in inhibiting or deactivating responses (Franz and Miller, 2002). Of additional note, given that the effects on force output were incidental (or implicit) rather than being explicit requirements of the task (subjects were instructed to press the key on 'go' trials, without any mention of force), it would seem that any explanation of response activation/deactivation deficits would have to apply both for explicit as well as implicit force demands (Franz and Miller, 2002).

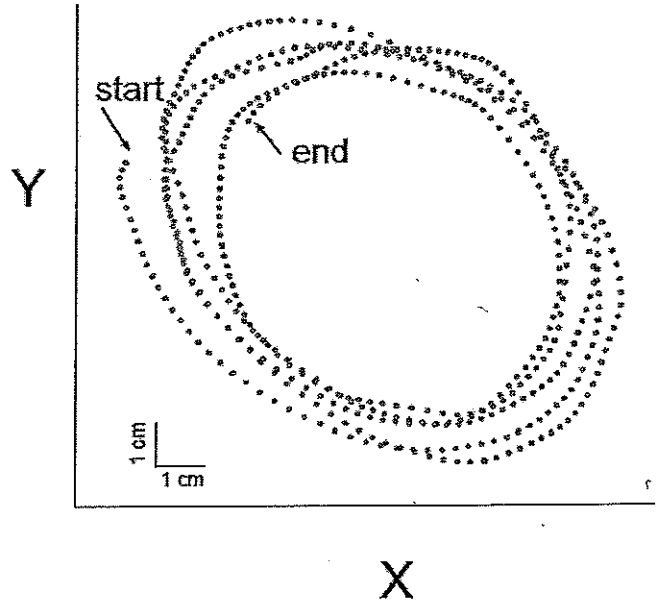


Figure 2. One representative trial of a PD patient drawing continuous circular trajectories through 10 seconds of time. Position data are plotted for the x and y dimensions for the trial. Note that the circles are getting slightly smaller through time, and that there is some evidence of variability along the trajectory. Franz data (unpublished).

With the aim of clarifying how impairments in response activation using a go no-go task might reveal a more general deficit of basal ganglia function, I now take a small leap of faith, which is to suggest that force output is an expression of a rudimentary form of cognition. By this view, the activation and inhibition deficits demonstrated in the force output profiles of Franz and Miller, (2002) reveal basic operations of abstract information processing, and these operations rely on basal ganglia motor loops. These operations, in my view, need not be different from those that operate on other forms of cognitive information, whether activating and inhibiting certain perceptual cues, cognitive sets, memories for action, or goals. It follows that, along with the operations of activation and inhibition on force output, which implicate basal ganglia motor loops, similar deficits should be revealed for cognitive processes mediated by other basal ganglia loops. To support this argument, I now refer to some elegant accounts in earlier literature on cognition that form the basis of this type of framework for action selection. I then attempt to link features of these cognitive accounts to models based on anatomy and physiology that suggest that the cognitive processes of action selection rely on the integrity of basal ganglia operations.

3 Earlier Cognitive Accounts of the Inhibition of Competing Responses

In an earlier cognitive account of action selection in the normal brain, Allport, (1980) proposed that one form of task difficulty might occur due to the demand to keep specific goals active and others inhibited. Accordingly, inhibition of specific goals or subgoals to enable activation of other more pertinent goals

might entail a competitive process (Neumann, 1987). According to Allport, (1980) and echoed by Neumann, (1987), one set of inputs must be decoupled from potential command of actions, a problem of action selection that humans are extremely efficient at solving. This type of view casts a slightly different light on earlier issues examined in RT literature. Notably, it leaves open the possibility that RT increases reflect both the processes associated with response selection in the face of alternatives, and the operation of inhibitory processes on potentially active competing responses. Interestingly, a parallel development of models of action selection in the face of competing alternatives can be traced in the neurophysiological literature. What follows is an outline of that development.

4 A Parallel Development in Neurophysiology

Perhaps one of the earliest direct examples of behavioral inhibition comes from von Holst and his colleagues' work on the functional organization of drives (Von Holst and Von St. Paul, 1963; see also Mink, 1996). These researchers presented elegant examples of the competing drives in the behavior of the domestic fowl, which, due to their central internal relationships, are overcome by those behaviors that dominate in particular situations. Although Von Holst and Von St. Paul, (1963) did not specify precisely what neural mechanisms are involved in the form of behavioral inhibition they demonstrated, neurophysiological evidence in the last decade or so has converged to make a strong case that in humans, these operations are a primary function of the basal ganglia.

In this section, I will focus primarily on the work of Mink and Thach, (1991a, 1991b, 1991c), and a model of focused selection and competing inhibition that emerged from those and other related studies (Mink, 1996). For purpose of illustration, I will once again refer to the example described by Neumann, (1987), which is also cited in the opening paragraph of the present chapter—that of reaching for an apple from a tree. To perform this task, a person interrupts his locomotion by stopping and assuming a steady posture that supports the body while one arm reaches for the apple (Mink, 1996). Some of the cognitive considerations were noted above. Here, I elaborate on some of the issues that anatomico-physiological models might also consider. First, how is posture controlled so that a volitional action, such as a reach to an object, can be performed? Wilson, (1928), in his early investigations of patients with basal ganglia damage, noted that while syndromes associated with damage to the pyramidal system were not apparent, numerous problems associated with the phylogenetically-older extrapyramidal motor system could be readily observed. These included muscular rigidity, tremor, and weakness which could be associated with bradykinesia, symptoms that are now commonly associated with Parkinson's disease (see this volume). According to Wilson, the extrapyramidal system operates somewhat automatically to control posture, whereas, the pyramidal system is involved in voluntary, phasic movements. Mink, (1996) further proposed a framework based on anatomical-neurophysiological evidence that nicely captures complex tasks that involve focused selection of action and inhibition of competing responses. Central to the assumptions of this model is the time course of activation of the different structures involved during motor preparation, particularly with reference to the basal ganglia.

Since the pioneering work of DeLong, (1971), it has been known that basal ganglia activity occurs with movement. However, there has been considerable debate as to the precise role performed by the basal ganglia, and whether its nuclei actually code parameters of movement (Crutcher and DeLong, 1984). A significant amount of movement-related activity in the putamen (part of the input nuclei to basal ganglia) has been found to occur after rather than before the onset of muscle activity (Ibid), and activity of output nuclei (globus pallidus) also has been found to occur later than motor cortex activation (Anderson and Horak, 1985; Mink and Thach, 1991a, 1991b). Some have suggested that late activity occurs in more posterior portions of the striatum, whereas anterior portions might mediate earlier set-related activity (see Mink, 1996).

As Mink, (1996) describes (also using Neumann's example of reaching for an apple), multiple mechanisms involved in maintaining an upright posture (presumably extrapyramidal), both prior to the reach and during the reach, are also involved in supporting the posture of the reaching arm to perform a volitional action. These mechanisms must remain active for the rest of the body but must be selectively deactivated for the reaching arm during the reach so that the reaching action can be produced. Viewed in this way, competing motor pattern generators (MPGs: Mink's term) must be turned off so that they don't interfere with the voluntary (reaching) movement. This process of selectively inhibiting the competing

MPGs so that the MPGs for the required volitional action can be activated, is central to Mink and Thach's model of focused selection and inhibition of competing motor mechanisms (summarized in Figure 3).

As Mink, (1996) elaborates, the pattern of activity from basal ganglia circuits would result in inhibition of a large portion of thalamic and brainstem nuclei receiving projections from GPi, and disinhibition of a smaller portion of GPi nuclei, resulting in the opposite effect on their thalamic and cortical targets. According to Mink, (1996), GPi activity increases occur earlier than GPi decreases, which is consistent with excitatory STN-GPi connections being faster than the inhibitory Striatum-GPi connections (see Figure 3). Consistent with this model, studies using electrical stimulation to individual neurons in prefrontal and motor cortical regions have demonstrated that initial excitation is followed by inhibition (Nambu et al., 1990). In sum, Mink and colleagues conjectured that set-related and movement-related activity originate in the cerebral cortex and not the basal ganglia, thus calling into question the earlier-held views that the function of the basal ganglia is in movement initiation. Instead, they suggested that the basal ganglia are involved in focused selection of actions, and inhibition of competing programs.

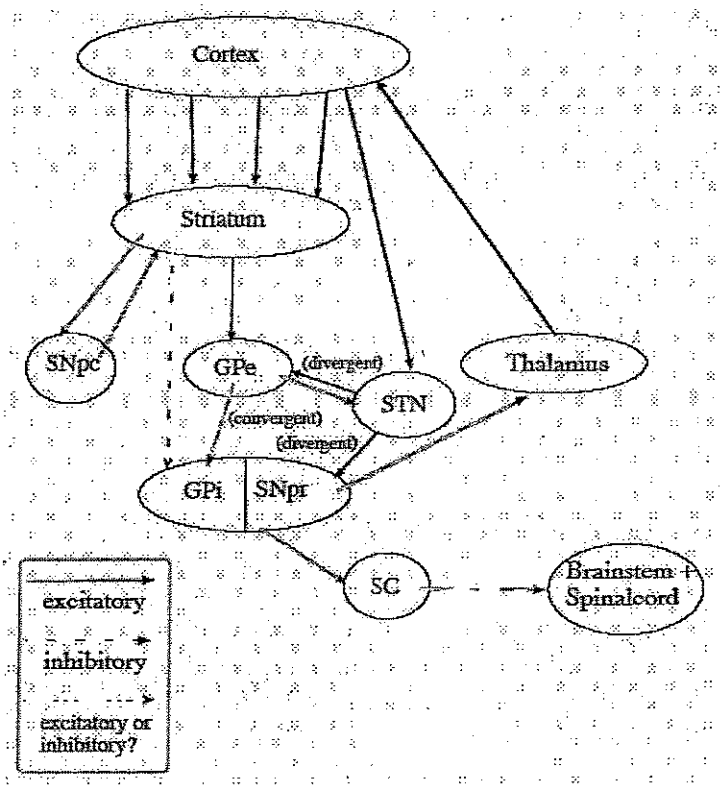


Figure 3. The striatum is one primary input that receives excitatory input from diffuse areas of the cerebral cortex. Inhibitory projections from the striatum to Gpi and on to thalamus (direct loop) and ihhibitory projections from the striatum to GPe, which in turn inhibits Gpi (referred to as part of the indirect loop) result in focused input to Gpi (and also SNpr). These projections onto Gpi are believed to be convergent, thus producing focused selection. A second input from motor and premotor areas (A4, 6) and frontal eye fields (A8) is excitatory on STN. Through divergent projections, STN is excitatory on GPe and GPi. STN also receives inhibitory input from GPe. This loop is also referred to as indirect. Importantly, the focused input from striatum to Gpi is purportedly slow, whereas the STN input to GPi and SNpr is fast. This results in fast divergent excitation and a slower focused inhibition on specific output neurons of GPi and SNpr. Note that the mechanisms intrinsic to the striatum are proposed to integrate the input from cortex and focus the output to other nuclei of the basal ganglia. A third loop involves inhibitory input from the striatum to SNpc, which in turn projects back to the striatum in either an inhibitory or excitatory manner depending on the receptors. This loop likely modulates cortical inputs to the striatum (Mink, 1996). Terminology used throughout this article: GPi (internal segment of the globus pallidus), GPe (external segment of the globus pallidus), SNpr (substantia nigra pars reticulata), STN (subthalamic nucleus), SNpc (substantia nigra pars compacta).

With respect to findings of a simple go no-go task involving reaching movements in monkeys, Romo and Schultz, (1992) found that of the neurons that responded to the instruction (approximately one fifth of the total), about half responded with sustained activity only in the "go" condition, whereas the other half responded transiently in relation to the instruction. The so-called 'late activity' changes in the basal ganglia are also consistent with the problems of deactivation reported by Franz and Miller, (2002) using their go no-go task in PD patients.

5 Integrating Cognitive and Neurophysiology Research

Is it possible that the impairments in the force profiles of PD patients on a go no-go task (Franz and Miller, 2002), the cognitive models of Neumann, (1987) and Allport, (1980), and the anatomic-physiological model of Mink and colleagues (Mink, 1996) converge on a coherent framework of action selection in which the basal ganglia play a central role? I will now attempt to fill in some of the missing pieces that hopefully will make this proposed framework more persuasive.

First, the findings of Franz and Miller, (2002) are based on the use of one of the simplest types of motor tasks, that consisting of a go versus inhibit response task (go no-go), under conditions of high or low response readiness. As suggested above, the force output on such a task might be regarded as the expression of a rudimentary form of cognition. One might assume, for example, that when preparing to make a response under high readiness, the motor system is in a state of high preparation, and therefore the initial level of internal activation is higher than in the situation in which the system is not prepared to respond (low readiness condition). Echoing a model elaborated by Mattes et al., (2002) based on an earlier proposal by Näätänen, (1971): under high readiness, the system requires only a small increase in activation to produce the response, whereas, under low readiness, much more activation is necessary. In addition to this effect on the activated responses, those responses that were to be inhibited also displayed a larger than appropriate level of force output in the PD patients (see above description). If these force output processes reflect the operation of a rudimentary form of cognition, and the basal ganglia are responsible for activation (focused selection) and inhibition (inhibition of competing actions) more generally, then similar deficits should be demonstrated in patients with basal ganglia damage on other types of cognitive tasks.

6 Other Cognitive Phenomena that Can Be Captured by this Integrated Framework: Set Switching

Another example of a fundamental task of cognition is the ability to switch from one task to another (Jersild, 1927; Allport et al., 1994; Rogers and Monsell, 1995; Hayes et al., 1998). This can be viewed in simple form as a switch between perceptual dimensions, such as color and shape. Take, for example, a task similar to that of Hayes et al., (1998), in which subjects are presented with two response keys, each labeled with a shape (circle or square) and a color (pink or yellow). On a given trial, subjects are instructed to respond on the basis of a cue word that occurs at the same time as the stimulus, with the cue word indicating to respond to "shape" or "color". One can then consider pairs of trials as Hayes et al., (1998) did, in which two "color" cues occur in succession for consecutive trials, or two "shape" cues occur in succession for consecutive trials. These trials would be considered 'no switch' trials, given the perceptual dimension is the same for both. Compare this to the pair of trials in which a "shape" cue occurs on trial 1, and a "color" cue occurs on trial 2 (or vice versa). In this case, a switch is necessary between one perceptual dimension and the other, in order to respond correctly. Hayes et al., (1998) demonstrated an increase in RT for switch compared to no switch trials of this type in healthy control subjects, and a significantly larger switch cost in patients with Parkinson's disease. Our laboratory recently replicated these findings, with further examinations of patients tested both during their normal medication cycle and with their levodopa medication withheld for approximately 12 hours (Shook et al., Under revision). The results for switching costs are shown in Figure 4. Clearly, there are increases in cognitive switch times for the patients compared to the controls. Moreover, these switch costs are exacerbated when the patients' medication is withheld, indicating that switching is dopamine-dependent.

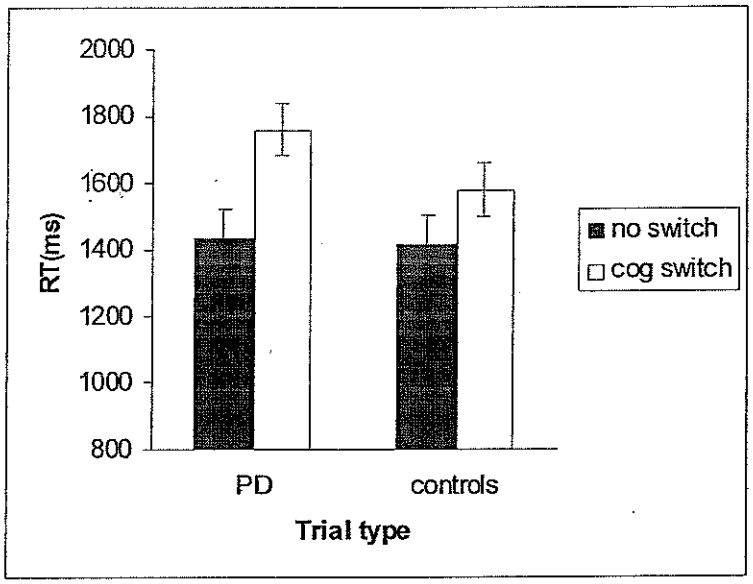


Figure 4. Cognitive switch costs (cog) compared to no switch trials, where the switch is between perceptual dimensions on consecutive trials. These data are averages from all control subjects, and all PD patients in the 'off' medication state. Standard error bars for each group are shown. Adapted from Shook et. al., 2004.

How can these findings be reconciled with the earlier-reported findings on force output? As a start point, one might consider that the perceptual cues of color and shape trigger different perceptual sets. When responding on the basis of the color cue, one's perceptual set of color is activated, and one's perceptual set of shape is deactivated (or inhibited). The reverse argument holds for processes associated with the shape cue. Thus, rather than operating on the level of force output as in the simple go no-go task of Franz and Miller, (2002), the basal ganglia operations of focused selection (activation) and inhibition of competing surround would be operating on perceptual sets. Given perceptual sets might involve vast cell assemblies in the cortex, it seems reasonable that switching from one to another would result in an increase in RT. In other words, if activation and inhibition are general deficits with PD, one might expect them to be manifest in deficits of force output on the simplest forms of motor tasks that are cued by basic perceptual shapes. However, when the task demands instead require discrimination between one perceptual dimension and another (color versus shape), these operations might reflect different cognitive loops of the basal ganglia: activating the perceptual dimension that is appropriate to responding while inhibiting the dimension that is not appropriate. In a similar manner, selecting the appropriate perceptual dimension on which to respond illustrates the process of focused selection, and inhibiting the inappropriate dimension illustrates the process of inhibiting competing responses (according to Mink's 1996 terminology).

7 Anatomical Models of Parallel Circuits within the Basal Ganglia Suggest that Similar Cognitive Operations Occur in the Different Segregated Circuits

What is required for this type of model to apply generally across numerous cognitive domains, is that different loops within the basal ganglia-cortical circuits operate in a similar manner. A remarkable feature of the basal-ganglia-cortical circuitry that has been elegantly described by neurologists, neuroscientists, and physiologists, is that there are numerous circuits that are functionally segregated and organized in parallel (Alexander et al., 1986). Figure 5 is adapted from Alexander et al., (1986), showing the different structures involved in five parallel circuits of the basal ganglia.

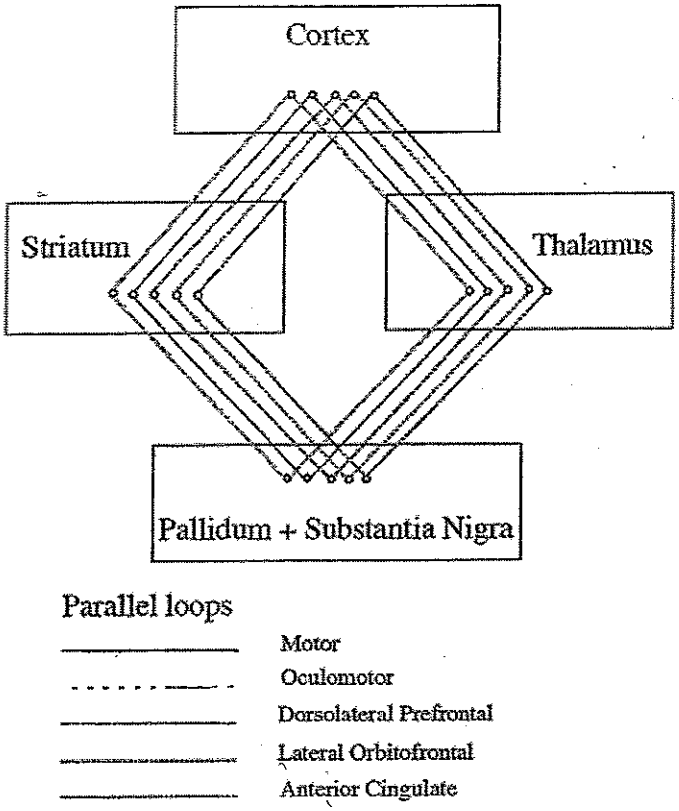


Figure 5. Schematic of parallel segregated loops involving cortical-basal ganglia-thalamic circuits. Specific nuclei at each structure are not shown. See text for details. Adapted from (Alexander et al., 1986).

Indeed, there are likely to be many more such circuits. Note that the motor circuit involves the supplementary motor area's input to the putamen (of the striatum), through the basal ganglia circuitry to the GPi and SNpr output nuclei, and back to the cortex via the VLo and VLm of the thalamus (for simplicity, the present figures do not depict specific nuclei but only general structures). As can be seen in Figure 5, the other parallel circuits are organized in a similar manner, each engaging specific regions of the structures involved. If we can imagine, therefore, that the circuits producing focused selection and inhibition of competing programs (as shown in Figure 4) also characterize each of the other functionally segregated and parallel cortical-bg-thalamic-cortical circuits, then it seems reasonable that the activation-inhibition functions that might characterize the motor loop extend to similar functions mediated by the other loops. Indeed, a number of researchers have suggested that the existence of a parallel organization of these circuits is strongly suggestive of similar basic functions occurring in all of them (Alexander et al., 1986; Hayes et al., 1998; Shook et al., Under revision).

8 Relating this Model to Symptoms Commonly Seen in Parkinson's Disease

As suggested earlier, the symptoms of PD often appear to reflect either too little or too much activation, as though the balance between activation and inhibition is awry (Franz and Miller, 2002). I now point out some of the more obvious PD symptoms that can easily be captured by the type of model described herein. Dyskinesia, or the rapid flailing movements of the limbs, might appear to be characterized by an inappropriate sequence of unwanted movements, as though some components of movement are inappropriately activated while others are inappropriately inhibited. Impairments in either the focused selection component or the inhibition component of the basal ganglia circuitry could account for these observed symptoms. Increased visual distraction is also often observed in people with PD, as though

competing information is not appropriately inhibited. Indeed, as can be seen in Figures 3 and 5, one loop of the frontal-basal-ganglia circuitry comprises the frontal eye fields, caudate nucleus of the basal ganglia, and superior colliculus, which, together describe a system for eye movements that might be similar to that described above for limb movements. It is therefore plausible that symptoms such as chorea reveal similar properties as the type of distraction associated with eye movement saccades.

9 Can we Extrapolate beyond the Mink (1996) Model on the Basis of Other Cognitive Research ?

I will now briefly attempt to extrapolate beyond the model proposed by (Mink, 1996), to consider one possible function of the dopaminergic projections from the substantia nigra pars compacta on the striatum (see Figure 3). As suggested by the model of Mink, (1996), dopaminergic projections from the substantia nigra pars compacta to the striatum and back might mediate increases or decreases in striatal activity, which is also influenced by cortical projections. The model described above seems to capture activation and inhibition processes within basal ganglia circuitry, but it is somewhat undefined precisely how those circuits 'know' to focus attention on events that are significant, while inhibiting activation to those that are not.

Recent years have witnessed a rapid proliferation of findings and perspectives on the precise role of dopamine in the context of the complex frontal-basal-ganglia-thalamic circuitry described. While it seems generally accepted that dopamine plays a role in motivation and reward, the precise nature of what dopamine is doing remains debatable. Whereas early views suggested a role of dopamine as a pleasure mediator (Wise, 1996), more recent findings have led to the idea that dopamine signals that something significant is occurring, even if the stimuli these neurons responded to were not in themselves rewarding (Schultz et al., 1997). A related account holds that dopamine is involved in an attention-getting system, in which novel or unpredictable events attract the organism's attention (Horvitz et al., 1997). Although the precise role of dopamine is not yet known, an intriguing possibility is that the dopamine system is involved in both signaling significant events for action, and in maintaining current action sets until they are completely carried out. In a sense, dopamine would 'juice the system' for actions that should receive (possibly sustained) focused attention. The finding that cognitive switching costs are exacerbated when regular application of dopamine precursors are withheld temporarily from the patients, seems to be consistent with this possibility (Hayes et al., 1998; Shook et al., Under revision). Thus, although speculative, it seems possible that the dopaminergic inputs to the set-related neurons in the striatum assist in the maintenance of a particular set so that a current action can be carried out completely and without intrusion by other action selection processes. This system would enable sustained activation of networks within the striatum so that other operations of the basal ganglia loops can be carried out before another selected input goes through these loops.

Summary

The present paper was an attempt to synthesize data from recent cognitive experimentation on patients with Parkinson's disease with models of the anatomy and neurophysiology of the basal-ganglia-frontal circuitry and intrinsic circuits within the basal ganglia. One main point is that the focused selection and competing inhibition model of Mink, (1996) reflects a similar cognitive view espoused by Neumann, (1987) and others (see Allport, 1980); and these process models can account for recent findings in cognition that identify activation and inhibition as a basic function of the basal ganglia. Activation and inhibition on a force output task are proposed to reflect a rudimentary form of cognition, and a similar deficit is proposed to operate on different forms of information processing. I propose that these approaches are all converging on the same basic model of basal ganglia function, and that this basic function has already gained support from other cognitive domains. In sum, the conjecture is that the basal ganglia complex performs a function of selection on many different levels of the cognitive system (via parallel operations on segregated circuits) by focused selection (activation) and inhibition of competing information (inhibition). It is my belief that deficits of bimanual coordination, switching, focused selection, and

sequencing all can be captured by basal ganglia operations involved in focused selection and inhibition of competing information.

ACKNOWLEDGEMENTS

I am grateful to Professor Jeff Miller and Professor Karen Sigvardt for their invaluable lessons and discussions on issues related to this work. Thanks also to Reuben Fischer for drawings.

REFERENCES

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* **9**:357-381.

Allport DA (1980) Attention and Performance. In: Cognitive psychology-new directions. (Claxton G, ed). London: Routledge & Kegan Paul.

Allport DA, Styles EA, Hsieh S (1994) Shifting intentional set: Exploring the dynamic control of tasks. In: *Attention and performance* (C. Umilta MM, ed), pp pp. 421-452. Hillsdale, NJ: Erlbaum.

Anderson ME, Horak FB (1985) Influence of the globus pallidus on arm movements in monkeys. III. Timing of movement-related information. *J Neurophysiol* **54**:433-448.

Angel RW, Alston W, Higgins JR (1970) Control of movement in Parkinson's disease. *Brain* **93**:1-14.

Bloxham CA, Mindel TA, Frith CD (1984) Initiation and execution of predictable and unpredictable movements in Parkinson's disease. *Brain* **107** (Pt 2):371-384.

Crutcher MD, DeLong MR (1984) Single cell studies of the primate putamen. II. Relations to direction of movement and pattern of muscular activity. *Exp Brain Res* **53**:244-258.

DeLong MR (1971) Activity of pallidal neurons during movement. *J Neurophysiol* **34**:414-427.

Evarts EV, Teravainen H, Calne DB (1981) Reaction time in Parkinson's disease. *Brain* **104**:167-186.

Franz EA, Miller J (2002) Effects of response readiness on reaction time and force output in people with Parkinson's disease. *Brain* **125**:1733-1750.

Hallett M, Khoshbin S (1980) A physiological mechanism of bradykinesia. *Brain* **103**:301-314.

Hayes AE, Davidson MC, Keele SW, Rafal RD (1998) Toward a functional analysis of the basal ganglia. *J Cogn Neurosci* **10**:178-198.

Heilman KM, Bowers D, Watson RT, Greer M (1976) Reaction times in Parkinson disease. *Arch Neurol* **33**:139-140.

Hick WE (1952) On the rate of gain of information. *Quarterly Journal of Experimental Psychology* **4**:11-26.

Horvitz JC, Stewart T, Jacobs BL (1997) Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. *Brain Res* **759**:251-258.

Jersild AT (1927) Mental set and shift. Archives of Psychology 89.

King HE (1959) Defective psychomotor movement in Parkinson's disease: exploratory observations. *Perceptual and Motor Skills* **9**:326.

Klapp ST (1975) Feedback versus motor programming in the control of aimed movements. *J Exp Psychol Hum Percept Perform* **104**:161-169.

Klapp ST (1976) Short-term memory as a response preparation state. *Memory and Cognition* **4**:721-729.

Marsden CD (1984) Which motor disorder in Parkinson's disease indicates the true motor function of the basal ganglia? In: *Functions of the Basal Ganglia.* (M.O'Connor. DEa, ed), pp 225-237. London: Pitman.

Mattes S, Ulrich R, Miller J (1997) Effects of response probability on response force and simple RT. *Quarterly Journal of Experimental Psychology* **50***A*:405-420.

Mattes S, Ulrich R, Miller J (2002) Response force in RT tasks: isolating effects of stimulus probability and response probability. *Visual Cognition* **9**:477-501.

Merkel J (1885) Die Zeitlichen Verhältnisse der Wiellensthätigkeit. *Philosophische Studien* **2**:73–127.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* **50**:381-425.

Mink JW, Thach WT (1991a) Basal ganglia motor control. I. Nonexclusive relation of pallidal discharge to five movement modes. *J Neurophysiol* 65:273-300.

Mink JW, Thach WT (1991b) Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. *J Neurophysiol* 65:301-329.

Mink JW, Thach WT (1991c) Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. *J Neurophysiol* 65:330-351.

Näätänen R (1971) Non-aging fore-periods and simple reaction time. *Acta Psychologica (Amst)* 35:316-327.

Nambu A, Yoshida S, Jinnai K (1990) Discharge patterns of pallidal neurons with input from various cortical areas during movement in the monkey. *Brain Res* 519:183-191.

Neumann O (1987) Beyond capacity: A functional view of attention. In: *Perspectives on Perception and Action* (Sanders HHaA, ed), pp 361-394. Hillsdale, NJ: Erlbaum.

Rafal RD, Posner MI, Walker JA, Friedrich FJ (1984) Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. *Brain* **107** *(Pt 4)*:1083-1094.

Rogers RD, Monsell S (1995) The cost of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General* **124**:207-231.

Romo R, Schultz W (1992) Role of primate basal ganglia and frontal cortex in the internal generation of movements. III. Neuronal activity in the supplementary motor area. *Exp Brain Res* 91:396-407.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. *Science* 275:1593-1599.

Sheridan MR, Flowers KA, Hurrell J (1987) Programming and execution of movement in Parkinson's disease. *Brain* **110** *(Pt 5)*:1247-1271.

Shook S, Franz EA, Higginson CI, Sigvardt KA (Under revision) Dopamine dependency of intradimensional and extradimensional switching operations in Parkinson's patients. Neuropsychologia.

Von Holst E, Von St. Paul U (1963) On the functional organization of drives. *Animal Behavior* **11**:1-20.

Wilson SAK (1928) Modern problems in neurology. London.

Wise RA (1996) Neurobiology of addiction. *Curr Opin Neurobiol* 6:243-251.