PD is a progressive neurodegenerative disease with a relatively high prevalence, afflicting approximately 1/1,000 individuals uniformly throughout the world (McDowell et al. 1978). Onset is usually between the ages of 50 and 65 years, and the average duration is around 8 years. The cause is unknown, but it may reflect an inherited susceptibility to certain environmental or endogenous toxins (Jenner et al. 1992). Clinical diagnosis is based upon the presence of two or more of the following motor symptoms:

1. Rhythmic tremor (3-6 beats/sec) involving the hands and lower legs and most prominent at rest.
2. Increase in muscle tone or rigidity that often has a cogwheel- or ratchet-like effect.
3. Slowness in executing movement (bradykinesia) and/or difficulty in initiating movement (akinesia).
4. Stooped, unstable posture with lowered shoulders and flexed elbows and knees.

Additional clinical signs include a "masked" facial expression with a blank stare and reduced rate of eyeblink (hypominia), tiny handwriting (micrographia), impaired articulatory capacities (dysarthria), lowered volume of speech (hypophonia), problems swallowing (dysphagia), oily skin with dry, flaky patches (seborrheic keratitis), dizziness after standing up (orthostatic hypertension), and constipation.

In An Essay on the Shaking Palsy, James Parkinson (1817) reported that in this disease "the senses and intellect are uninjured." Half a century later, however, several researchers recognized that this was clearly false (Trousseau 1861; Charcot 1872). Still, very little in the way of sophisticated neuropsychological investigation of PD took place until the beginning of the "L-DOPA era" in the 1970s. Since then, research on cognitive deficits in PD has been steadily accumulating. Overall, this research indicates that PD
patients fall into three broad categories (DuBois et al. 1991; Ebmeier et al. 1991; Mayeux et al. 1988, 1992). First, roughly 20% of patients develop global intellectual deterioration severe enough to be considered dementia.¹ Second, another 20% of patients are intellectually not significantly different from age-matched healthy control subjects. Finally, the remaining 60% of patients exhibit a variable "mix" of specific cognitive deficits that are similar to those found in patients who have suffered lesions to the prefrontal cortex.

This chapter has two main goals. The first is to review the underlying neuropathology of PD. PD is one of many disorders that directly affect the basal ganglia and indirectly affect the frontal lobes; other such disorders include Tourette's syndrome, Huntington's disease (HD), progressive supranuclear palsy (PSP), schizophrenia, and obsessive-compulsive or addictive disorders. In section 2.1 I will discuss the anatomy, physiology, neurochemistry, and cortical connections of the basal ganglia as well as the nature of the disturbance that occurs in PD. The second goal of this chapter is to review the major cognitive deficits that are found in PD patients. I will focus on nondemented patients because they are the ones whose syntactic comprehension abilities will be of central concern later in the thesis. Most of the neuropsychological research with this group of patients has concentrated on deficits of executive function that are manifested in several cognitive domains specifically, visuospatial processing, memory, and the regulation of mental "sets." In section 2.2 I will discuss each of these domains of mental impairment.

¹ According to the widely used "Clinical Dementia Rating Scale" (Hughes et al. 1982), dementia consists of memory loss, temporal and spatial disorientation, impaired judgement and problem-solving ability, and an impaired ability to carry out daily tasks involving social interactions and personal care.
2.1 Neuropathology

2.1.1 The Basal Ganglia

2.1.1.1 Anatomy

The basal ganglia consist of six extensively interconnected subcortical structures: the caudate, the putamen, the ventral striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra (Figure 1). The caudate and putamen develop from the same telencephalic structure, and as a consequence they are composed of identical cell types and are fused anteriorly. Together they are referred to as the striatum. Two additional structures located beneath the striatum—namely, the nucleus accumbens and the olfactory tubercle—are very similar to the striatum in terms of both connections and histological features, and for this reason they are referred to as the ventral striatum. The globus pallidus (a.k.a. pallidum) is derived from the diencephalon and lies directly medial to the putamen. It is divided into two segments, referred to simply as the internal and external segments. The subthalamic nucleus is located under the thalamus at its junction with the midbrain. Finally, the substantia nigra is embedded in the midbrain and has two zones, one ventral and the other dorsal. The ventral zone, which is called the pars reticulata, has cell types similar to those in the internal segment of the globus pallidus, and for this reason the two structures are sometimes considered to be a single structure which is arbitrarily divided, much like the caudate and putamen. The dorsal zone, which is called the pars compacta, is comprised of dopaminergic cells that contain neuromelanin, a dark pigment that gives the substantia nigra its name—literally "black substance."

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2 Most of the research that I will review in this section is based on studies of nonhuman primates, typically macaque monkeys.
In highly simplified form, the major features of the connectional architecture of the basal ganglia are as follows (Figure 2). Input is received by the striatum. This input comes from the entire cerebral cortex, including sensory, motor, association, and limbic areas; additional but less significant input comes from the thalamus. Output is sent by the internal pallidum and substantia nigra reticulata (not shown in Figure 2) to several nuclei in the thalamus, which in turn project to the frontal cortex. There are two pathways through the basal ganglia, one direct and the other indirect. The direct pathway goes straight from the striatum to the internal pallidum and substantia nigra reticulata, whereas the indirect pathway goes from the striatum to the internal pallidum and substantia nigra reticulata via the external pallidum and subthalamic nucleus.

Figure 2: Schema of information flow between the cerebral cortex, the thalamus, and several subdivisions of the basal ganglia. "Pallidum" indicates the internal portion of the globus pallidus. (From Houk 1995)

2.1.1.2 Physiology
It is interesting to look at this connectional architecture in a bit more detail (Figure 3). The input structures receive very dense excitatory connections from widespread
areas of the cortex—indeed, each cell receives approximately 10,000 different afferent fibers, a degree of convergence which is second only to that found in the cerebellum (Houk 1995). All of the connections in the two pathways through the basal ganglia are inhibitory except for those extending from the subthalamic nucleus to the output structures. The direct pathway operates in a very straightforward manner: when the cortex activates the input structures, this causes them to suppress the output structures. By contrast, the operation of the indirect pathway is more complicated: when the cortex activates the input structures, this causes them to suppress the external pallidum; this releases the subthalamic nucleus from inhibition; as a result, the subthalamic nucleus activates the output structures. It is apparent, then, that the two pathways are constantly involved in a push-pull tug-of-war for control over the output structures. The effects of these competing forces depend on the following additional features of the architecture: the output structures exert a tonic inhibitory influence on their target nuclei in the thalamus, but the subsequent connections from the thalamus to the frontal cortex are excitatory. Thus, when the direct pathway suppresses the output structures, this disinhibits specific thalamic nuclei, thereby gating or facilitating specific activity patterns in the frontal cortex. Conversely, when the indirect pathway activates the output structures, the thalamus is suppressed, which in turn prevents the thalamus from activating specific cell assemblies in the frontal cortex.

How do the basal ganglia contribute to motor control, cognition, and affect? Although no single, comprehensive theory of basal ganglia function is currently available, research in this area is progressing rapidly and a number of sophisticated hypotheses have been proposed in recent years (Cools et al. 1995; DuBois et al. 1995; Taylor & Saint-Cyr 1995; Partiot et al. 1996; see especially the papers in Houk et al. 1995). Perhaps the most well-established point is that the basal ganglia are crucially involved in regulating
the selection of appropriate responses to both exogenous and endogenous stimuli. Cells in the caudate, putamen, and ventral striatum recognize activation patterns in their cortical inputs that represent familiar contexts. When such a context is detected, concurrent transmission through the direct and indirect pathways leads to the competitive selection of activation patterns in the output structures, and these activation patterns ultimately serve to facilitate processing routines in the frontal cortex that have been rewarding in similar contexts in the past. Thus the basal ganglia are probably involved in regulating much of our habitual, routine thought and behavior. For instance, the basal ganglia may be in the driver's seat, literally, when we find ourselves in that eerie situation of skillfully negotiating the traffic on a highway while simultaneously daydreaming about something completely different. Another function that has been attributed to the basal ganglia is to coordinate the operations of the posterior, perception-related cortical areas with the operations of the anterior, decision-related cortical areas. On this view, the basal ganglia construct transient working memories that are useful for monitoring the flow of perceptually guided behavior. Finally, the basal ganglia may play a role in the initiation of internally generated movements and ideas. This view is consistent with the akinesia of PD and the hyper-kinesia (i.e., excessive involuntary movements) of HD, as well as with the reports by Tourette's and schizophrenic patients of unwilled, alien thoughts invading their consciousness.

2.1.1.3 Dopaminergic Projection Systems

The basal ganglia contain two dopaminergic projection systems, both of which originate in the pars compacta of the substantia nigra (Figure 4). The first and heaviest of these is the nigrostriatal system, which projects dopaminergic fibers from one part of the compacta to the putamen and caudate. The second is the mesocortical (a.k.a. meso-limbic) system, which projects dopaminergic fibers from another part of the compacta
(specifically, the ventral tegmental area, or VTA) to the ventral striatum, amygdala, medial temporal regions, and cortical mantle. The cortical projections are diffuse but

Figure 4: Dopaminergic projection systems. The nigrostriatal system originates in the pars compacta of the substantia nigra and terminates in the striatum. The mesocortical system originates in the ventral tegmental area of the substantia nigra and terminates in the ventral striatum, amygdala, frontal lobe, and some other basal forebrain areas. A third projection system which is shown here but not discussed in the text is the tubero-
infundibular system. It innervates the intermediate lobes of the pituitary and the nearby median eminence. (From Heimer 1983)

nonetheless somewhat region-specific—they are stronger in the frontal lobes than in the parietal and temporal lobes (Levitt et al. 1984; Lewis et al. 1987), stronger dorsally than laterally and mesially (Williams & Goldman-Rakic 1993), and stronger in the left than the right hemisphere (Glick et al. 1982).

Dopamine is a member of the class of modulatory neurotransmitters called catecholamines (Foote & Morrison 1987; Cooper et al. 1991). There is substantial evidence that it functions as a reinforcement signal that guides both the learning and the maintenance of adaptive behaviors (Wickens & Kötter 1995). This is illustrated most clearly in the striatum. In order for cells in the striatum to recognize behaviorally relevant contexts in their massive cortical inputs, a training mechanism is required that adjusts synaptic weights in the right directions. Current evidence suggests that the basal ganglia contain their own specialized training mechanism which involves not only unique cellular compartments within the striatum (viz., the striosomal or patch compartments), but also the nigrostriatal dopaminergic projection system (Houk et al. 1995). Physiologically, these dopaminergic fibers serve to reduce the potency of excitatory corticostriatal and thalamostriatal inputs to a moderate degree (Freund et al. 1984; Schultz et al. 1995). This has the effect of enabling only the strongest, most task-relevant inputs to pass through to the impulse-generating mechanism at the cell body; the weakest, most task-irrelevant inputs are filtered out. This has been referred to as a "focussing" effect (Schultz et al. 1995) or an enhancement of the "signal-to-noise ratio" of the cell's inputs (Foote et al. 1975; Robbins & Brown 1990). The contribution of dopamine as a reinforcer of critical inputs is important for learning as well as for maintaining the proper synaptic weights. This is reflected in the fact that dopamine cells always fire with a brief burst discharge that is time-locked to either an event that provides a primary reward or an
event that, through learning, has become associated with a subsequent reward (Houk et al. 1995). The overall influence of dopamine on corticostriatal synapses is shown in Figure 5.

Figure 5: The influence of dopamine on striatal information processing (from Schultz et al. 1995). "Suppose that inputs from different cortical origins converge in an ordered manner on single striatal neurons. The different strengths of these inputs reflect the differential activation of cortical neurons by the current behavioral situation . . . (Top) In the absence of dopamine, cortical inputs would influence striatal neurons in a poorly contrasted manner. (Middle) Dopamine has an immediate focusing effect which non-linearly enhances the strongest inputs occurring at the time of the dopamine signal relative to weaker inputs which are suppressed. (Bottom) In a hypothetical learning
mechanism, dopamine facilitates long-term changes at hebbian-modifiable synapses. Arrow width represents the relative synaptic influences on postsynaptic impulse activity, consisting in a combination of presynaptic influence and synaptic strength." (Schultz et al. 1995: 244).

One could say that the basic function of dopaminergic modulation is to ensure that the signals that are allowed to activate striatal cells represent the most behaviorally significant features of the situation that the individual is facing. This in turn enables the basal ganglia to process the cortical input in such a way as to endorse an appropriate response to the situation and feed this recommendation up to the frontal lobes, where it may strongly influence the decision that is ultimately made. Taylor and Saint-Cyr (1995) have suggested that dopamine is especially useful for the learning and main-tenance of adaptive behavior in situations where several optional responses are available. Dopaminergic focussing or, as they put it, "boosting" helps the striatum learn which responses are rewarding and which aren't, so that over time some signals gain greater meaning than others, gradually shaping a "habit pattern" through which performance becomes expert:

Given the potential of dopamine to modify signal-to-noise ratios within the striatum, the constant application of practice, enhanced by signal boosting, could facilitate reduction of options. In other words, through approximation, the range of choices shrinks, the basal ganglia serving to establish the best "ballpark" of action (Taylor & Saint-Cyr 1991). Ultimately, over time, the optimal response becomes the one with the highest valence and a habit is established. This habit, or set, can be stored as an algorithm, ready to be executed when the stimulus appears. (Taylor & Saint-Cyr 1995: 289-90)

On this view, striatal boosting of the most favorable option serves to augment selective attention, which is under cortical control, thereby facilitating the choice of that option. Although Taylor and Saint-Cyr do not mention it, I should emphasize that selective attention and decision-making in the prefrontal cortex are also influenced by direct
dopaminergic reinforcement through the mesocortical projection system (Brozoski et al. 1979; Clark et al. 1987b). If the nigrostriatal system is compromised, the prefrontal cortex is left to reason its way through the available options without striatal boosting, relying solely on the weaker mesocortical innervation for guidance. And if the latter system is also compromised, the prefrontal cortex is completely on its own. As we shall see later in this chapter, both dopaminergic projection systems are damaged in PD, and as a result patients can suffer considerable cognitive deficits.

2.1.1.4 Basal Ganglia-Thalamocortical Circuits

So far I have spoken of the basal ganglia-thalamocortical circuit as if it was unitary. In fact, however, five distinct circuits linking the basal ganglia and the frontal cortex have been identified, and additional ones are likely to exist (Alexander et al. 1986, 1990a, 1990b). All of these circuits have parallel but segregated routes through the basal ganglia and thalamus, and there are even multiple subsets of parallel channels within each circuit. Each of these specialized circuits is named according to its cortical focus (Figure 6).

Two of the circuits are devoted to motor programming. The first is referred to simply as the motor circuit. It includes the following structures: within the cortex, the supplementary (BA\(^3\) 6, medial), premotor (BA 6, lateral), and primary motor (BA 4).
areas; within the basal ganglia, the putamen and specific regions of the pallidum, substantia nigra (pars reticulata), and subthalamic nucleus; and within the thalamus, the ventrolateral nucleus. Several lines of research—computational analysis, neural network computer modeling, neuroimaging studies, and lesion studies—converge on the view that the three cortical areas participating in the motor circuit contribute to the planning and execution of actions in unique ways that are hierarchically organized (Kosslyn & Koenig 1992). At the top of the hierarchy, the supplementary motor area computes, for a given voluntary movement such as reaching for a glass, the path through space (i.e., the "via points") that one's limb must traverse in order to arrive at the desired position. At the next level, the premotor cortex computes the joint angles (kinematic information) that are necessary for moving one's limb along the trajectory specified by the higher-
level area. Finally, the primary motor cortex computes the muscle forces (dynamic information) needed to achieve the appropriate joint angles. Within the basal ganglia, single-cell recording studies have revealed distinct neuronal channels that represent the same three types of information specified in the three cortical areas; in addition, it is well-known that disruption to the basal ganglia impairs motor control, albeit in different ways depending on which structures are affected (Albin et al. 1989).

The second circuit involved in motor programming is called the oculomotor circuit. It includes the following structures: within the cortex, the supplementary and frontal eye fields (BA 8); within the basal ganglia, the body of the caudate nucleus and specific regions of the pallidum, substantia nigra (pars reticulata), and subthalamic nucleus; and within the thalamus, the ventroanterior and mediodorsal nuclei (Figure 6). Studies drawing on lesion analysis as well as single-cell recordings indicate that this circuit is dedicated to the planning and execution of eye movements for visual search (Alexander et al. 1990).

The other three circuits are specified in terms of three gross divisions of the prefrontal cortex—namely, the dorsolateral, orbital, and anterior cingulate regions. Much less is known about the functional anatomy of these circuits; however, recent investigations
making use of both deficit-lesion correlations and functional neuroimaging techniques have begun to shed some light on the different roles these circuits play in high-level cognition. The literature on the cortical regions involved in these circuits is very large and is rapidly becoming larger (recent anthologies include Uylings et al. 1990; Levin et al. 1991; Boller & Grafman 1994; Thierry et al. 1994; and Grafman et al. 1995); consequently, the following review is quite selective and limited in coverage.

To begin with the dorsolateral circuit, it includes the following structures: the dorsolateral prefrontal region (BA 46, 9), the dorsal part of the caudate nucleus, specific sectors of the pallidum, substantia nigra, and subthalamic nucleus, and the ventroanterior and mediodorsal nuclei of the thalamus (Figure 6). Cummings (1993, 1995) brings together a great deal of data indicating that damage to either the dorsolateral prefrontal cortex or the dorsal part of the caudate nucleus impairs a broad range of so-called executive functions; moreover, he notes that a few cases have been reported of similar impairments following damage to the pallidum or thalamus. The behavioral syndrome is characterized by depression, together with a reduced ability to "generate hypotheses and flexibly maintain or shift sets as required by changing task demands on such tests as the Wisconsin Card Sort Test [WCST]" (Cummings 1993: 874). In this test, subjects must sort cards according to one criterion (color, form, or number of items depicted) which they must infer solely from the pattern of correct and incorrect responses provided by the examiner. After ten consecutive correct responses, the examiner shifts the sorting principle without warning, forcing subjects to abandon the old principle and infer the new one. In addition to performing poorly on the WCST, patients with damage restricted the dorsolateral circuit exhibit a variety of other executive deficits, including impaired verbal and graphic fluency (i.e., spontaneous word-list and design generation), disrupted organizational strategies for learning tasks, and motor programming disturbances in tasks that require alternating or sequencing actions in complex ways.
Within the past few years, a large number of neuroimaging studies have provided convergent evidence for the view that the dorsolateral prefrontal cortex is crucial for executive functions. First of all, several studies have shown that this brain region is activated when subjects perform the WCST (PET: Weinberger et al. 1986; SPECT: Rezai et al. 1993) as well as when subjects are tested for verbal fluency (PET: Frith et al. 1991a); in both cases the activation is stronger in the left hemisphere than in the right. This brain region is also activated when subjects perform tasks that emphasize completely self-generated or "willed" responses as opposed to purely stimulus-driven responses. For instance, in a PET study Frith et al. (1991b) compared the blood flow maps from two conditions that involved stimulus-driven responses (repeating a spoken word, or lifting a touched finger) with the blood flow maps from two conditions that involved random selection of a response from a repertoire (hearing a letter and generating a word that begins with that letter, or feeling a finger being touched and then lifting one of two fingers). They found activation of the left dorsolateral prefrontal cortex in the condition requiring random word generation and bilateral activation of this region in the condition requiring random finger movements. Another cognitive process that elicits strong activity in the left dorsolateral prefrontal cortex is the controlled manipulation of semantic information, e.g., generating verbs that are semantically related to nouns (PET: Petersen et al. 1988), monitoring a list of words for items that designate dangerous animals (PET: Petersen et al. 1988), and discriminating between words designating man-made and natural objects (PET: Frith & Grasby 1995). Finally, two very elegant PET studies conducted by Petrides and coworkers have shown that the dorsolateral prefrontal cortex contributes to working memory tasks that require comparing responses that have already been made to those still remaining to be carried out (Petrides 1995; Petrides et al. 1993a, 1993b). The first study focused on the visual modality (Petrides et al. 1993a). Subjects were presented with sequences of eight abstract figures, and on each trial the sequence was ordered differently. The subjects' task was to select a different stimulus on each trial.
until all had been selected—a task that requires keeping track of previous responses. When the blood flow map from this condition was compared to that for a baseline condition (one that involved the same stimuli and motor responses but lacked the working memory component), significant activation in the dorsolateral prefrontal cortex was found, especially in the right hemisphere. The second study focused on the verbal domain but was designed in a manner similar to the first study (Petrides et al. 1993b). In one condition the subjects had to randomly generate numbers from 1 to 10, avoiding repetition of any number until all of them had been produced. In another condition the subjects were presented with random sequences of nine numbers between 1 and 10 and had to identify which number was missing. When the blood flow maps from these conditions were compared to that from a baseline condition (one that simply involved counting forwards from 1 to 10), it was found that, once again, the dorsolateral prefrontal cortex was activated, except this time predominantly in the left hemisphere. Petrides et al. suggest that the major functional specialization of the dorsolateral prefrontal cortex is to monitor and manipulate information being held on-line in working memory; in addition, they suggest that this large brain region is subdivided not according to functional differences but rather according to the type of information that is operated on. This general characterization of the functional anatomy of the dorsolateral prefrontal cortex appears to be consistent with the other studies described above; however, it must be acknowledged that the representational and computational details of the processes described by Petrides et al. remain to be clarified. While it is true that considerable progress has been made in understanding executive functions at both cognitive and neural levels of description, it is also true that we have a long way to go before research in this area becomes as sophisticated as, say, research on low-level visual processing. Grafman (1995) expresses the same point by saying, rather sardonically, that current theorizing about executive functions is comparable to Broca's theorizing about linguistic functions.
Moving on now to the orbitofrontal circuit, it includes the following structures: the lateral orbitofrontal cortex (BA 10, 11), the ventral part of the caudate nucleus, specific regions of the pallidum, substantia nigra, and subthalamic nucleus, and the ventro-anterior and mediodorsal nuclei of the thalamus (Figure 6). As with the dorsolateral circuit, evidence about the functions subserved by the orbitofrontal circuit comes from both deficit-lesion correlations and neuroimaging studies. Cummings (1993, 1995) summarizes a wide range of data indicating that damage to either the lateral orbitofrontal cortex or the ventral caudate nucleus produces mania together with irritability, disinhibition, tactless social behavior, and obsessive-compulsive disorder (see also Damasio 1994; Damasio et al. 1990, 1991, 1994, 1995). Patients with lesions to this circuit have difficulty with set-shifting on the WCST. They also tend to perseverate on delayed alternation tasks, which require shifting back and forth between stimuli after brief delay periods. Very few neuroimaging studies have reported task-related activation in the orbitofrontal cortex, perhaps because activity in this rather low-lying region of the brain is sometimes not recorded due to the narrow field of view of current PET cameras (Frith & Grasby 1995). Still, two PET studies have obtained results which are consistent with the picture of lateral orbitofrontal function gleaned from clinical data. First, Alexander et al. (in press) found activation in this region when subjects were required to fixate on an unchanging point for the duration of the scan. Frith and Grasby (1995: 392) comment on this study as follows: "Although this is often used as a 'control' condition, subjects sometimes report that it is quite taxing and requires considerable concentration. It is interesting to note that [lateral orbitofrontal] lesions in man are observed to impair central gaze fixation maintenance (Paus et al. 1991). It is possible then that this area is involved in the suppression of prepotent responses." Second, Jaeger et al. (in press) found activation in the left lateral orbitofrontal cortex when subjects were presented with English verb stems that have irregular past tense forms and had to generate the appropriate past tense form of each one (e.g., hold - held, swim - swam, see - saw). They
suggest that this activation may reflect the need to suppress inappropriate responses such as overregularizations (e.g., *hold - holded*) or false analogies (e.g., *fling - flang*).

The last basal ganglia-thalamocortical circuit that has been documented is referred to as the anterior cingulate circuit. It includes the following structures: the anterior cingulate cortex (BA 24, 32), the ventral striatum, specific sectors of the pallidum, substantia nigra, and subthalamic nucleus, and the mediodorsal nucleus of the thalamus (Figure 6). According to Cummings (1993, 1995), damage to either the anterior cingulate cortex or the ventral striatum produces apathy, withdrawal, and loss of motivation. Severe lesions of the anterior cingulate and the adjoining areas cause a very strange disorder known as akinetic mutism. Such patients seem to be in what Damasio (1994: 71) calls a state of "suspended animation." They lie peacefully in bed, motionless and speechless, with open eyes but a blank facial expression. They answer questions in monosyllables if at all and display no emotion or concern about their circumstances, even when in pain. In general, they appear not to attend to either external stimuli or internal representations. After one patient had gradually emerged from this state and was asked why she had never been inspired to communicate, she answered quite simply: "I really had nothing to say" (Damasio 1994: 73).

A large number of neuroimaging studies have found activation of the anterior cingulate cortex. In fact, in all of the studies that I mentioned in the discussion of the dorsolateral prefrontal cortex, activation also appeared in the anterior cingulate. This makes sense in light of Posner's (1994) view that this brain region is involved in controlled or focused attention, i.e., attention that serves to amplify processing efficiency within a specific domain of interest, whether it be perceptual, cognitive, emotional, or action-related. Further support for the idea that the anterior cingulate contributes to attention comes from a study conducted by Corbetta et al. (1991). Across three conditions, subjects were shown sequences of two pictures containing objects which could vary along the dimensions of shape, color, and speed of movement. In the first condi-
tion, the subjects just passively viewed the stimuli; in the second, they had to detect a change in a single, predetermined dimension; and in the third, they had to detect a change in any of the possible dimensions. In comparison to the baseline condition, the anterior cingulate was not activated in the second condition but was activated in the third condition, which suggests that this brain area comes into play when attentional demands are especially high. Other neuroimaging studies have indicated that the anterior cingulate also contributes to response selection, particularly when the subject must inhibit a routine response and facilitate a nonroutine response; it may be the case, however, that this kind of operation is simply another manifestation of controlled attention (Devinsky et al. 1995; Stuss et al. 1995). For instance, several recent studies have demonstrated that the anterior cingulate is activated when subjects perform the Stroop task (Pardo et al. 1990; Bench et al. 1993; George et al. 1994). Although there are many versions of this task, in the most common one subjects are presented with a succession of color words printed in a color other than the one referred to by the word, and are asked to name the color of the ink as quickly as possible. The task is challenging because the subject must inhibit the strong tendency to read the word. The contribution of the anterior cingulate is apparently very important for this task, because one study found that behavioral performance is positively correlated with activation in this region of the brain (George et al. 1994). It is noteworthy that although response selection is a key function of the dorsolateral prefrontal cortex, no activation was found in this brain area in any of the neuroimaging studies of the Stroop task. It must also be noted, however, that response selection was critical for many of the previously mentioned studies in which activation was found in both the dorsolateral prefrontal cortex and the anterior cingulate cortex. This raises the question of what unique roles these two brain areas play in executing response selection. In considering this question, Frith and Grasby (1995: 392) suggest that the anterior cingulate "is involved when responses are speci-fied, but their selection is not routine. In such cases, close attention to the eliciting stimulus is required. In
contrast, [the dorsolateral prefrontal cortex] is involved only when the particular response
to be selected is not fully specified." Another question that is worth asking is why the
lateral orbitofrontal cortex is not activated when subjects perform the Stroop task; after
all, this area is also reputed to be involved in response selection, especially when it is
necessary to suppress an automatic behavior. The answer to this question is not clear at
the present time, but hopefully future research will shed some light on it.

I have now completed my review of the functional anatomy of the five established
basal ganglia-thalamocortical circuits. Before going on to summarize the nature of the
neuropathology that occurs in PD, however, there are two final issues that I want to
address. First, although the preceding discussion of the three circuits that involve pre-
frontal cortical sites emphasized the distinctive functional properties of each one, it is
important to make explicit the functional properties that they have in common. Based on
a thorough survey of the clinical literature, Cummings (1995) has observed that damage
to any of these circuits causes, on the one hand, impaired behaviors that are self-
generated and, on the other hand, preserved behaviors that are guided by features of the
external environment (see also Lhermitte et al. 1986; Lhermitte 1986; and especially
Noack 1995). Thus, patients with the dorsolateral syndrome show the following
behavioral contrasts: they may achieve set on the WCST but perseverate when required
to change set; they have intact recognition memory but impaired recall; they have intact
confrontation naming but impaired verbal fluency; they can understand concrete lan-
guage but have difficulty with abstract or figurative language; and they can execute a
stereotyped motor program but cannot reverse the sequence of component actions.
Patients with the orbitofrontal syndrome display similar contrasts: although they are able
to learn instructions, they respond to the environment on impulse; and although they
seem to have at least some degree of personal control, they imitate the actions of others
and are tempted to use objects that are within reach (utilization behavior). Finally,
extreme envirnomental dependency is exhibited by patients with the anterior cingulate
syndrome: they can respond to questions but are otherwise apathetic; they can maintain
induced postures but are otherwise catatonic; and last of all, they can repeat words that
they hear but otherwise have virtually no spontaneous verbal output (trans-cortical motor
aphasia).

Finally, Alexander et al. (1986, 1990a, 1990b) pointed out that additional basal
ganglia-thalamocortical circuits are likely to exist, and one candidate is a circuit that has
the ventrolateral prefrontal region (BA 45, 47, inferior 46) as its cortical focus. Petrides
(1995) argues that this cortical region subserves executive functions that are less compli-
cated than those carried out by the dorsolateral prefrontal cortex. In particular, he claims
that this region is devoted to the active selection (i.e., encoding or retrieval) and judg-
ment of information held in short-term or long-term memory stores in the posterior
association cortices. This view is supported by lesion studies in nonhuman primates and
by two recent PET studies; I will focus on the latter. In the first study, which concerned
the visual modality, subjects were scanned under three conditions: passively observing
familiar stimuli, passively observing novel stimuli, and making explicit recognition
judgements between familiar and novel stimuli (Petrides 1995). When the blood flow
maps from the first two conditions were subtracted from that from the third condition,
activation was found in the ventrolateral prefrontal cortex (but not, interestingly enough,
in the dorsolateral prefrontal cortex). The second study emphasized verbal working
memory (Paulesu et al. 1993). In one condition, passive storage of a simple list of words
was required but not active articulatory rehearsal; in another condition, rehearsal was also
necessary. Inspection of the blood flow maps revealed that the storage comp-onent of
verbal working memory is implemented in the left inferior parietal cortex (BA 40) and
that the rehearsal component, which involves strategic retrieval of information held in the
short-term store, is implemented in the ventrolateral prefrontal cortex (for convergent
data from functional neuroimaging research, see Awh et al. 1995, and for convergent
2.1.2 Disruption in PD

The central pathology in PD is progressive degeneration of the pars compacta of the substantia nigra. This has several deleterious effects. First, disruption of the nigrostriatal dopaminergic projection system causes massive dopamine depletion in the striatum. This loss of dopaminergic innervation follows a gradient such that the putamen is affected more severely than the caudate. Postmortem studies, for instance, have revealed only 5% or less of normal values in the putamen, compared to 15 or 20% in the caudate (Agid et al. 1987). Furthermore, while all patients suffer dopamine depletion in the putamen, only around half of patients exhibit dopamine depletion in the caudate (Martin et al. 1986). As more nigrostriatal dopaminergic neurons die, the surviving neurons become increasingly overactive in order to compensate for the loss (Agid et al. 1973). It is thought that when this compensatory mechanism ceases to be effective and the first parkinsonian symptoms appear, at least 70% of the nigrostriatal system is already damaged (Bernheimer et al. 1973; Riederer & Wuketich 1976; Scherman et al. 1989). The reduced dopamine supply to the putamen and caudate interferes with the information processing capacities of these nuclei, and as a result the multiple circuits linking the basal ganglia and the frontal lobes no longer function normally. Because the putamen participates in circuits with the supplementary, premotor, and primary motor cortices, all PD patients develop motor disorders, most notably tremor, rigidity, akinesia, bradykinesia, and gait abnormalities (Delwaide & Gonce 1988). These motor impairments progress in severity and are often measured according to a five-stage scale proposed by Hoehn and Yahr (1967). Moreover, because the caudate participates in circuits with regions of the prefrontal cortex, around half of all patients
also develop cognitive disorders similar to those exhibited by patients with lesions in these cortical areas (DuBois et al. 1991; Wolters & Scheltens 1995).

Another consequence of the degeneration of the pars compacta of the substantia nigra is that the mesocortical dopaminergic projection system is disrupted. A significant proportion of dopaminergic neurons in the VTA die, thereby reducing the supply of dopamine to the ventral striatum as well as to cortical and limbic sites; this reduction in dopamine, however, is not as severe as in the striatum – levels in the ventral striatum, frontal lobes, and hippocampus are approximately 40% of normal, while levels in the cingulate cortex, amygdala, and hypothalamus are closer to 50% of normal (Javoy-Agid & Agid 1980; Scatton et al. 1982; Agid et al. 1987; Shinotoh & Calne 1995). Still, this dopamine depletion is severe enough to contribute to the cognitive deficits of PD patients; in fact, the degree of mesocortical impairment correlates positively with the degree of intellectual impairment (Torack & Morris 1988; German et al. 1989; Rinne et al. 1989).

Although the loss of dopaminergic neurons in the pars compacta of the substantia nigra is the central pathology in PD, it is not the only pathology. There is also mild degeneration of three other modulatory neurotransmitter projection systems – specifically, the cholinergic, noradrenergic, and serotonergic systems (for reviews see DuBois et al. 1991, 1992). Like the two dopaminergic systems, each of these systems originates in the midbrain and projects rather diffusely to cortical and limbic sites. Reduction of these neurotransmitters may be implicated in the cognitive and affective changes observed in PD patients. For instance, demented patients tend to have more severe damage to the cholinergic system than nondemented patients (Whitehouse et al. 1983; Perry et al. 1985), and depressed patients tend to have more severe damage to the serotonergic system than nondepressed patients (Mayeux et al. 1984). Finally, alterations of neurons in the cerebral cortex, especially in the temporal and parietal lobes, have been found in some patients, predominantly in those with dementia (Ruberg & Agid 1987). These
alterations consist of senile plaques, neurofibrillary tangles, and Lewy bodies similar to those that occur in Alzheimer's or Cortical Lewy Body Disease.

2.2 Neuropsychology

Given that the neuropathology of PD involves disruption of not only the basal ganglia-thalamocortical circuits but also the direct dopaminergic projection to the prefrontal cortex, it is not surprising that a substantial proportion (around 50%) of patients who are nondemented still suffer from cognitive deficits that are similar to those found in patients with lesions of the prefrontal cortex (for reviews see Brown & Marsden 1990, 1995; Rashkin et al. 1990; Dubois et al. 1991, 1995; Levin et al. 1992; Taylor & Saint-Cyr 1995). In general, the vast neuropsychological research that has been done on PD indicates that such patients have difficulty with the following broad categories of tasks: (1) when the cognitive system does not have a well-learned line of thought or action for the current context and hence must formulate and evaluate hypotheses; (2) where it is necessary to suppress a strong habitual response or resist a temptation; and (3) when attentional control is needed to keep the cognitive system focused on the appropriate stream of information processing. Although it is undoubtedly an oversimplification, these broad categories of tasks seem to map, at least in a rough manner, onto the three basal ganglia-thalamocortical circuits that involve prefrontal cortical sites: the first category corresponds mainly to the dorsolateral circuit; the second category corresponds mainly to the orbitofrontal circuit (although the other two circuits may also contribute); and the third category corresponds mainly to the anterior cingulate circuit. Despite this rough mapping of tasks onto circuits, however, most of the neuropsychological research with nondemented PD patients has concentrated on various cognitive domains independent of anatomical considerations. The cognitive domains that have
been investigated most intensively are visuospatial processing, memory, and set regulation. I will review some of the major findings in each of these domains, and then I will conclude by returning to the issue of how the cognitive deficits can be related to the underlying neuropathology.

2.2.1 Visuospatial Processing

Visuospatial processing involves appreciating the relative positions of visually represented objects in space, integrating these objects into a coherent spatial framework, and performing mental operations that actively transform one's internal representation of the visual world, in some cases through imagery. The visuospatial processing abilities of PD patients are controversial because a number of seemingly inconsistent results have been reported. Some researchers have found that PD patients are normal in this domain, others have obtained mixed results, and still others have found that PD patients are impaired on a variety of tasks.

Some of the tasks that do not seem to cause difficulty for PD patients include the following: left-right and above-below discrimination (Brown & Marsden 1986), mentally rotating an object to match it with an item in a sample (Ransmayr et al. 1987; Heitanen et al. 1990), calculating rebound angles (Della Sala 1986), extrapolation of the intersections between a target and a baseline (Della Sala 1986), and judgement of spatial displacement (Stelmach et al. 1989).

By contrast, some of the tasks that do cause trouble for PD patients are as follows. First of all, a large number of studies have shown that PD patients perform poorly at discriminating line orientation (Boller et al. 1984; Goldenberg et al. 1986; Hovestadt et al. 1987; Lavernhe et al. 1989; Wasserstein et al. 1990). Many patients are also impaired at drawing complex figures (DuBois et al. 1991). A third finding is that patients have trouble with visuospatial tasks that require complex planning and sequencing (Ogden et al. 1990). In addition, patients perform poorly on a test where they are shown
drawings of angular figures and asked to make a line indicating how each figure could be divided into two parts such that these parts could form a square (Ransmayr et al. 1987). Finally, although patients are able to walk along a given route when there are explicit signposts marking directions, they have difficulty walking along a route when they are forced to generate their own mental map or to use their own body as a constantly changing reference point for movement through space (Bowen et al. 1972). This impairment is captured in an anecdote from a patient: "I used to walk alone in the woods, fog or no fog, but when the symptoms of Parkinson's disease appeared, I noticed that I could not orient myself any more, and in case of fog, I got lost" (Hovestadt et al. 1987).

Although these conflicting results about the visuospatial processing abilities of PD patients suggest that the population is quite heterogeneous, several researchers have been able to make at least some degree of sense out of the data. For instance, DuBois et al. (1995) point out that, except for line discrimination, the tasks that elicit poor performance demand mental flexibility and the generation of strategies without guidance from external cues. This is clear in the last example where route-walking with signposts is intact but route-walking without such overt directional markers is impaired. It can also be seen if we compare using mental rotation to match an object against a sample—a preserved ability—with using mental rotation to determine how a figure should be divided so that its parts form a square—an impaired ability. As Brown and Marsden (1990) point out, in the former task the correct solution is present in the sample array, whereas in the latter task the patient's response is completely self-generated. In sum, it is reasonable to suppose that the majority of visuospatial deficits exhibited by PD patients are not specific to this domain but rather arise from a disruption of more generalized executive or control processes.

2.2.2 Memory
A similar mixture of good and poor performance has been found in the domain of memory. I begin by considering short-term memory (STM). There are numerous content-specific STM systems, but most of the research with PD patients has focused on just two of them: the articulatory loop, which permits rehearsal of verbal information, and the visuospatial scratchpad, which enables temporary storage and manipulation of visuospatial material (Baddeley 1986, 1992). The articulatory loop appears to be intact in PD patients, since they are not deficient at rehearsing sequences of digits such as telephone numbers (Hietanen & Tervinen 1988; Cooper et al. 1991). The visuospatial scratch-pad also seems to be preserved, since patients are able to retain a representation of a configuration of objects in visual STM during a delay period (Morris et al. 1988; Sullivan & Sagar 1989).

Difficulties emerge, however, when interfering stimuli are introduced into STM tasks. An example is the Peterson and Peterson (1959) paradigm, in which three letters are presented and immediately followed by a distractor task, intended to prevent subjects from focusing exclusively on rehearsing the items to be remembered. PD patients perform significantly worse than control subjects on this test (Tweedy et al. 1982; Huber et al. 1989). Another such case is the Sternberg (1975) paradigm, in which subjects must decide if probe digits correspond to a set of digits being held in verbal STM. PD patients display normal accuracy on this test, but their reaction times are significantly slower than those of control subjects (Wilson et al. 1980; Ransmayr et al. 1986). These results suggest that PD patients are only impaired on STM tasks when they require the strategic use of control processes.

I turn now to long-term memory, which can be divided into implicit and explicit memory (Graf & Schacter 1985; Schacter 1996). There are several forms of implicit memory. One of the most important is motor skills and cognitive routines that have been acquired through multiple exposures and that are not accessible to conscious inspection. Another is lexical priming, in which the occurrence of a word facilitates the response to a
semantically or phonologically related word. PD patients have been shown to perform normally on tasks requiring implicit memory (Heindel et al. 1989; Spicer 1994).

Explicit memory consists of declarative knowledge that is available for conscious recollection. It can be measured through both recognition and recall tasks. Recognition tasks are generally passive insofar as subjects need only make a decision about a fixed set of alternatives. A large number of studies have demonstrated that PD patients have normal recognition memory for verbal as well as visuospatial material (Lees & Smith 1983; Boller et al. 1984; Flowers et al. 1984; Weingartner et al. 1984; Taylor et al. 1986; El-Awar et al. 1987). However, recognition performance declines when the task requires the patients to mentally manipulate the material or actively organize a response. For example, in a word-list paradigm Tweedy et al. (1982) asked patients to signal whether a word was a repetition or a synonym of a previously presented one. The patients recognized fewer repetitions than control subjects, but they were most impaired at detecting synonyms.

Recall tasks are inherently more effortful than recognition tasks, since the response must be completely self-generated. PD patients are often impaired at story and paired associate recall, both immediately and after a delay period (Bowen et al. 1976; Halgin et al. 1977; Pirozzolo et al. 1982; Stern et al. 1984; Pillon et al. 1986; El-Awar et al. 1987). Moreover, their performance is especially poor when the material is not semantically organized at presentation, as in word-list acquisition (Tweedy et al. 1982; Villardita et al. 1982; Weingartner et al. 1984; Globus et al. 1985). Many patients are also deficient at recall in the visuospatial domain (Boller et al. 1984; Sullivan et al. 1989; Growdon et al. 1990). Finally, it is important to note that performance on recall tasks improves dramatically when explicit cues are provided to trigger efficient access of the appropriate knowledge (Pillon et al. 1993).

Taken together, these findings concerning long-term memory function in PD patients suggest that the memory stores themselves are intact; the deficit appears to reside in the
higher-level control processes that are necessary for actively retrieving and manipulating
the information.

### 2.2.3 Set Regulation

A substantial amount of neuropsychological research on PD has been concerned with
a cognitive ability referred to as set regulation. The notion of set that is used in
neuropsychology bears many similarities to the notions of schema, frame, and script that
are used in cognitive science. Buchwald et al. (1975) define set as "the relatively
persisting predisposition to behave in a particular way on the occurrence of a given
stimulus," and Flowers and Robertson (1985) define it in a related fashion as "a state of
brain activity which predisposes a subject to respond in one way when several alterna-
tives are available." These operational definitions are quite broad, but this breadth is
altogether fitting as an initial characterization of the phenomenon, since set effects are in
fact a pervasive feature of much adaptive behavior. The information processing systems
of humans and other animals must be able to benefit from the redundancies in past
experience by using such redundancies to assemble and store stimulus-response strate-
gies, i.e., sets, of varying degrees of hierarchical complexity, and they must also be able
to use their inventory of sets in an efficient way by selecting one among a number of
competing sets for coping with a given situation. In order to accomplish this selection
process, attentional control is sometimes needed to maintain the selected set in the face of
interference from alternatives and, when necessary, to shift from an inappropriate set to
an appropriate one.

An example should help to make this more concrete. If you are working in your
office and the phone rings, this stimulus is directly associated with the response to answer
the call. This stimulus-response strategy, or set, is (ceteris paribus) immediately selected
as opposed to alternatives, such as ignoring the call or walking out of the room, because
it has been reinforced in the past and because it is part of our more general cultural
knowledge of the responsibilities of office workers. Such set selection does not require the intervention of attentional control because it is automatic. By contrast, if you are a visitor in someone else's office and the phone rings, this stimulus activates not just the previously described knowledge about the positive consequences of answering phone calls, but also conflicting knowledge about the social rule dictating that a visitor in someone else's office should defer answering the phone. In this case, set selection does require the intervention of attentional control, since the automatic, or default, response of answering the call must be actively inhibited and the alternative response of not answering it must be selected (Grafman 1995).

A large number of studies have demonstrated that PD patients are impaired at shifting from one set to another. A good example is the Wisconsin Card Sorting Test (WCST), which I described earlier in the discussion of the dorsolateral prefrontal cortex. PD patients reliably make numerous perseverative errors on this test, revealing difficulty in "getting out" of one sorting principle and shifting to a new one; it is remarkable that patients may verbalize the correct sorting principle but still perseverate in their behavior (Lees & Smith 1983; Brown & Marsden 1988a, 1988b; Caltagirone et al. 1989a, 1989b). Another example is the Trail Making Test, part B, which requires subjects to connect consecutively numbered and lettered circles, thus continuously shifting from one category (numbers) to another (letters). Again, PD patients are impaired on this test, providing further evidence for a set shifting deficit (Reitan & Boll 1971; Pirozzolo et al. 1982; Hietanen & Tervinen 1986; Taylor et al. 1986). A third case involves tests of category alternation fluency, e.g., generating animal names and then shifting to the names of professions, or sorting blocks first by form and then by size. In general, PD patients are disproportionately impaired on the second phase of such tests, when they have to stop thinking in terms of the first category and redirect their attention to the new one (Lees & Smith 1983; Cools et al. 1984; Pillon et al. 1986; Taylor et al. 1986; Goldenberg et al. 1989; Downes et al. 1993).
The hypothesis that PD patients have difficulty shifting between sets was refined by two important studies conducted by Brown and Marsden. In one study (Brown & Marsden 1988a), they required PD patients to shift between two modes of processing a visual stimulus. First, the patients had to make a simple left-right discrimination, and second, they had to mentally rotate the stimulus 180 degrees before making the same left-right discrimination. The patients received alternating blocks of the two tasks, with each block consisting of ten trials; cues indicating how the stimulus was to be processed were given on every trial. The results showed that both PD patients and control subjects had increased reaction times (RTs) and error rates when required to shift, followed by a reduction in RTs and error rates as each block progressed. However, these measures were not significantly greater for the PD patients in the shifting phase compared to the baseline phase. This finding implies that although PD patients are impaired on many tasks that require shifting between different sets, they are not impaired on all such tasks.

In a subsequent study, Brown and Marsden (1988b) sought to determine what distinguishes the shifting tasks that elicit poor performance in PD patients from those that elicit good performance. This study employed a version of the Stroop test. They presented PD patients with sequences of color words printed in noncorresponding colors of ink–either red printed in green ink or green printed in red ink. After the presentation of each word, the patients had to push an appropriate button, according to either the meaning or the color of the word. The relevant dimension, meaning or color, remained fixed for ten trials, and then the command to "switch" was given, indicating that the relevant dimension had changed. Twelve switches of this kind were required. In addition, there were two different conditions. In one condition, an explicit cue about the relevant dimension was provided on every trial, and in another condition, a cue was given for just the first trial of the first block, thereby forcing the patients to remember the relevant dimension for the rest of the trials. The results showed that in the first condition, both PD patients and control subjects had increased RTs and error rates when required to
switch, followed by a reduction in these measures as each block progressed. The effects were not significantly different for the two groups. By contrast, in the second condition the performance of the two groups diverged: while the control subjects had the same pattern of RTs and error rates as they did in the first condition, the PD patients had significantly greater RTs and error rates, especially for the trials immediately following switches. Brown and Marsden interpret this finding as evidence that PD patients are only impaired at shifting between sets when doing so requires internal attentional control. Furthermore, they argue that such a view is consistent with the other studies on set shifting. The shifting tasks that elicit poor performance—i.e., the WCST, the Trail Making Test, part B, the fluency alternation tests, and the noncued Stroop test—demand that the patients use internal attentional control to regulate which sets are active and which are inhibited, whereas the tasks that elicit good performance—i.e., "rotated" left-right discrimination of a visual stimulus (where cues were given on every trial), and the cued Stroop test—provide external guidance for how the material should be processed and hence do not rely so strongly on high-level control processes.

Several other studies have shown that PD patients are also impaired at maintaining a given set in the face of strong interference from competing ones. For instance, on the WCST, patients make not only perseverative errors but also nonperseverative errors, which indicates difficulty "staying in" a particular sorting principle and avoiding being distracted by others (Bowen et al. 1975; Gotham et al. 1988). Additional evidence for a deficit in maintaining set comes from the performance of PD patients on the Odd Man Out Test, which is similar to the WCST insofar as subjects have to apply a particular sorting principle consistently before switching to a different one. After making the first shift, patients tend to revert to the previous response pattern, suggesting difficulty in keeping their attention focused on the relevant stimulus attribute (Flowers & Robertson 1985). A third example of a set maintenance impairment is the finding that PD patients exhibit abnormally rapid disengagement of visual attention from a target stimulus when
measured in Posner’s (1980) attentional orienting paradigm (Wright et al. 1990). In some contexts such rapid disengagement may facilitate efficient shifting of attention to a new target and hence have positive implications for cognitive processing, but in other contexts it may reduce the ability to keep attention locked on a specific target and hence have negative implications for cognitive processing (Filoteo et al. 1994). For instance, PD patients have been reported to experience an unusually high rate of spontaneous reversal of perspective when viewing ambiguous visual figures such as the Necker cube (Talland 1962).

To summarize, a considerable body of evidence suggests that PD patients have a deficit in using control processes to regulate the activation levels of sets. Not only do they perform poorly on tasks that require using such processes to shift between different sets; they also have difficulty on tasks that require using such processes to maintain the appropriate sets in the face of interference from alternatives.

2.2.4 Relating the Cognitive Deficits to the Underlying Neuropathology

2.2.4.1 Hypotheses

A number of recurrent themes can be discerned in the preceding review of the patterns of performance that PD patients exhibit in different cognitive domains. On the one hand, patients generally perform well on tasks that are passive, automatic, provide organized stimulus material, provide explicit solutions to choose from, or provide external cues for regulating set. On the other hand, they generally perform poorly on tasks that are active, effortful, require that the patient organize the stimulus material, require the spontaneous generation of a response, or require internal attentional control to regulate set. How can these behavioral contrasts be related to the underlying neuropathology of PD?
At present, no single, well-developed answer to this question is available; however, it is still possible to develop several hypotheses that are based on the information at hand and pitched at a fairly general level of description (for some recent proposals, see Cools et al. 1995; DuBois et al. 1995; Taylor & Saint-Cyr 1995; and Partiot et al. 1996). Recall that PD is essentially a neurochemical disorder that affects the dopamine supply in the brain. As I mentioned in section 2.1.1.3 (pp. 6-8), the primary function of this modulatory neurotransmitter is to serve as a reinforcement signal for the learning and maintenance of adaptive behaviors. In particular, in the striatum and ventral striatum, dopamine increases the signal-to-noise ratio of cortical and thalamic inputs by allowing only the strongest, most task-relevant inputs to get through; in other words, it has a "focusing" or "boosting" effect that enables the target cells to accurately recognize the most behaviorally significant features of the current situation. This in turn enables the basal ganglia to select, by means of competitive processing in the direct and indirect pathways, the most appropriate response to the current situation and then relay this information up to the frontal lobes in the form of a recommendation for thought or action. It is worth adding that the direct dopaminergic innervation of the frontal lobes also contributes to the efficient functioning of these brain areas by facilitating the most task-relevant activation patterns.

There is substantial evidence that the dopaminergic projection systems and the circuits linking the basal ganglia with the prefrontal cortex are more important for tasks that require attentional control and self-generated responses than they are for tasks that provide environmental support (Cummings 1993, 1995). The reason for this may be that when environmental support is available, appropriate responses can be made through more or less direct perceptual-motor linkages without the intervention of the special "biasing" mechanisms of dopamine and the basal ganglia-thalamocortical circuits; however, when environmental support is lacking, these mechanisms are necessary to guide the elaborate decision-making system in the prefrontal cortex toward adaptive
behavior. If I may indulge in a convenient metaphor, the dopaminergic projection systems and the basal ganglia-thalamocortical circuits function as a compass that helps the prefrontal cortex navigate through the world of cognitive challenges. This compass is only needed, however, when there aren't clear signposts in the environment that indicate one's position and which direction one should take.

Turning now to PD, when the dopamine supply in the striatum and ventral striatum is significantly reduced, the cells in these nuclei are no longer able to filter out "noisy," irrelevant inputs and hence cannot accurately recognize the most important features of the current situation. As a result, the basal ganglia have difficulty determining the most appropriate strategy for dealing with the situation and cannot send a confident recommendation up to the frontal lobes via the multiple specialized circuits. To use an expression coined by DuBois et al. (1991: 227), the aberrant basal ganglia-thalamocortical signals lead to "cortical demodulation" (as opposed to deafferentation, which occurs when the cortex is completely deprived of subcortical input). Furthermore, because the mesocortical dopaminergic projection system is also moderately compromised, the prefrontal cortex cannot fall back on it for reinforcement and guidance in working out the most adaptive response to the current situation. The overall effect is that the prefrontal cortex is forced to "think through" difficult problems that are normally handled much more quickly and easily by virtue of dopaminergic boosting of the most appropriate course of information processing. To continue with the metaphor introduced earlier, when the compass is damaged, navigation is no longer such a straightforward process; in fact, it can only be accomplished by resorting to more laborious and unreliable ways of determining one's position and the right direction to take to get to one's destination.

From this perspective, then, it is possible to make some sense of the general finding that PD patients have the most trouble with tasks that are not environmentally supported but rather depend on internal attentional control and self-generated responses. For
instance, to take a case that fits nicely with the navigation metaphor, the fact that patients perform poorly on route-walking tasks when there aren't any explicit cues available may be explained in terms of insufficient facilitation of visuospatial working memory by the relevant basal ganglia-thalamocortical circuits (probably the dorsolateral circuit is most important here—see Goldman-Rakic 1987, 1995) and by the mesocortical dopaminergic system. Similarly, good performance on recognition tasks may occur because the stimulus primes the appropriate response, whereas poor performance on recall tasks may be due to a lack of basal ganglia-thalamic and mesocortical-dopaminergic enhancement of cell assemblies in the prefrontal cortex that are involved in actively retrieving information stored in long-term memory (the right ventrolateral prefrontal cortex and its putative circuit with the basal ganglia may be especially important here—see Kapur et al. 1995 and Schacter et al. 1996). Finally, problems with set shifting and set maintenance, especially when there aren't any explicit cues available, could derive from the noisiness of signal processing in the striatum and ventral striatum and the resultant loss of precision in how the direct and indirect basal ganglia pathways operate to determine which response strategy, or set, is recommended to the prefrontal cortex (as I mentioned earlier—see p. 20—the anterior cingulate, dorsolateral, and orbitofrontal cortices are probably all involved in set regulation).

2.2.4.2 Further Evidence about the Role of Dopamine

Support for the importance of dopamine in attentional control and working memory comes from experimental studies involving both animals and humans. First of all, studies with rats, cats, and monkeys have shown that the integrity of dopaminergic projections is critical for the attentional control that underlies the selection of appropriate responses to stimuli. Disruption of these projections causes spatial neglect, diminished orienting capacity, stereotypic behavior, abnormal search and exploratory behavior, and impaired switching of attentional focus (Clark et al. 1987a). With regard to working memory,
Fuster (1980), Goldman-Rakic (1987), and others have found cells in the dorsolateral prefrontal cortex of the rhesus monkey that are specific to a particular visuospatial stimulus-response set and that remain active during a brief delay period between presentation of the stimulus and execution of the response. Not only does ablation of this cortical area destroy the animal's ability to carry out such delayed response tasks (Diamond & Goldman-Rakic 1989), but so does pharmacological blocking of the dopamine receptors in this cortical area (Brozoski et al. 1979). It is notable that although nondemented PD patients are not impaired at simple visuospatial delayed response tasks, demented PD patients are (Freedman & Oscar-Berman 1986). Apparently the reduction of prefrontal cortical dopamine in nondemented patients isn't severe enough to cause significant difficulty with this kind of task (Brown & Marsden 1990).

In humans, evidence about the functions of the dopaminergic projection systems has come not only from research on PD but also from research on schizophrenia. One of the most enduring biological accounts of schizophrenia (Carlsson 1988) maintains that the positive symptoms (e.g. hallucinations and delusions) are due to dopamine overactivity in the basal ganglia and prefrontal cortex, whereas the negative symptoms (e.g., flattening of affect, various cognitive deficits, impaired social functioning, etc.) are due to dopamine underactivity in these brain regions. Prominent among the cognitive disturbances observed in schizophrenic patients are, first, problems with a variety of tests that measure the ability to select one "train of thought" or behavioral response in the face of multiple competing ones, and second, poor performance on tests that are sensitive to working memory (Cohen & Servan-Schreiber 1992).

Additional evidence for the view that dopamine is important for both attentional control and working memory comes from recent studies that investigated the effects of dopamine agonists and antagonists on the cognitive abilities of normal human subjects. Looking first at attentional control, Clark et al. (1987b) assessed the performance of subjects on a target detection task that involved monitoring a list of words for predeter-
mined items. One group was given a placebo while another group was given droperidol, an antipsychotic drug that temporarily blocks dopamine receptors in the brain. The results showed that the drug decreased the accuracy and reduced the speed of word detection. In addition, when the subjects were not being tested, they were withdrawn and unwilling to attend to external events—a state resembling the akinetic mutism that follows damage to the most anterior sector of the cingulate gyrus (see 2.1.1.4, pp. 13-14). The researchers interpreted these findings as suggesting that dopamine blockade disrupts the allocation of attentional resources and reduces responsiveness to the environment.

Turning now to working memory, two studies have demonstrated that a significant improvement in performance on tests of this capacity may occur when normal subjects are given drugs that increase dopamine levels in the brain (Luciana et al. 1992; Kimberg et al. 1994). Moreover, the study by Kimberg et al. (1994) showed that improvement is dependent on the subject's baseline capacity. While subjects with a low baseline capacity displayed improvement under conditions of dopamine supplementation, subjects with a high baseline capacity worsened under such conditions. The same pattern has been observed in single-cell studies of dopamine metabolism in the dorsolateral prefrontal cortex of rhesus monkeys as the animals performed tasks requiring working memory (Williams et al. 1995). Also, these findings are consistent with the "hyper-dopaminergic" model of the positive symptoms of schizophrenia (Carlsson 1988; Hoffman et al. 1995).

2.2.4.3 Effects of Medication

The preceding discussion of pharmacological studies with normal subjects leads naturally to the question of how levodopa treatment affects the cognitive abilities of PD patients. Of the handful of studies that have addressed this question, perhaps the most interesting is the one conducted by Gotham et al. (1988). These researchers assessed the performance of PD patients on four tests that are known to be sensitive to prefrontal cortical dysfunction: (1) the WCST; (2) two measures of verbal fluency, one with a
single category and another with alternation between two categories; (3) a self-ordered pointing task in which 12 cards were presented in sequence, each bearing 12 different abstract figures randomly arranged, and the patient's task was to point to a different figure on each card; and (4) a conditional associative learning task which involved learning to match abstract figures with particular colors. The patients were tested with these materials under two conditions—first while "on" levodopa medication, and then while "off" it.

The results were as follows. Performance on the WCST was significantly impaired regardless of whether the patients were on or off their medication. Performance on the verbal fluency test varied depending on both the version of the test and the patients' medication status. Thus, the patients had normal verbal fluency with a single category in both on and off conditions; however, their verbal fluency with alternating categories was good while on levodopa but poor while off it. For the remaining two tests—self-ordered pointing and conditional associative learning—an unexpected pattern was found. The patients showed largely normal performance while off levodopa, but they were significantly impaired while on it.

These findings indicate that the effect of levodopa treatment on cognitive abilities supported by the prefrontal cortex is quite variable: sometimes it has no positive effect at all, sometimes it has a normalizing effect, and sometimes it has an adverse effect. Such variability also emerges when other studies are compared with one another. Thus, while some studies report an improvement in frontal lobe function when PD patients are on levodopa medication (Perry et al. 1985; Mohr et al. 1987; Taylor et al. 1987; Jahan-shahi et al. 1992), other studies have not found a positive change (Girotti et al. 1986; Pullman et al. 1990). Gotham et al.'s (1988) discovery that levodopa can have adverse effects is not completely new (see, e.g., Parkes et al. 1972), and it can be explained by considering the neuropathology of PD. As I mentioned in section 2.1.2 (p. 18), dopamine depletion is always more severe in the putamen than in the caudate, ventral stria-
tum, and prefrontal cortex, and in some patients the degree of dopamine depletion in the latter structures is negligible. Given this background, Gotham et al. (1988: 316) suggest that "levodopa doses necessary to remedy the dopamine lack in the putamen may 'over-dose' any area where dopamine regions are relatively intact . . ." Gotham et al. conclude their article by pointing out that studies of cognitive function in PD patients are required which use neuroimaging techniques to initially classify patients according to their levels of dopamine in various brain areas.

### 2.3 Summary

The basal ganglia are a set of subcortical nuclei that receive massive input from throughout the cortex and project output to the frontal lobes via a number of distinct circuits: the motor circuit, which is involved in bodily movements; the oculomotor circuit, which is involved in eye movements; the dorsolateral prefrontal circuit, which is involved in executive processes; the lateral orbitofrontal circuit, which is involved in impulse control; and the anterior cingulate circuit, which is involved in selective attention (there may also be a ventrolateral prefrontal circuit involved in executive processes). The role of the basal ganglia in these circuits appears to be to identify the most task-relevant features of the current situation and use this information to bias the appropriate prefrontal areas toward the most adaptive decision-making routines. The basal ganglia also contain two dopaminergic projection systems: the nigrostriatal system, which projects to the putamen and caudate; and the mesocortical system, which projects to the ventral striatum, the frontal lobes, and several limbic structures. Dopamine serves to increase the signal-to-noise ratio of the inputs to a given cell. This has a "focusing" or "boosting" effect that enables the cell to be influenced by the most pertinent inputs while
filtering out the less important ones, thereby increasing the efficiency of information processing.

PD is a progressive neurodegenerative disease which primarily involves deterioration of the dopaminergic projection systems of the basal ganglia. The nigrostriatal system is affected most strongly, causing severe dysfunction in the putamen in 100% of patients and less severe dysfunction in the caudate in around 50% of patients. The dopamine reduction in the putamen and caudate prevents these structures from processing their cortical and thalamic input in the normal fashion, and this in turn leads to "demodulation" of the areas in the frontal lobe with which these structures interact. Since the putamen participates in the motor circuit, all patients develop the motor disorders that are the most salient characteristics of PD; and since the caudate participates in the dorsolateral and orbitofrontal circuits (and perhaps also a ventrolateral circuit), about half of patients develop cognitive disorders as well. The mesocortical dopaminergic projection system is also affected, albeit less severely than the nigro-striatal system. This leads to moderate dopamine depletion in the ventral striatum, which is involved in the anterior cingulate circuit, as well as directly in the frontal lobes. Hence, the degeneration of this dopaminergic system contributes to the cognitive deficits found in PD patients.

Neuropsychologically, around 50% of nondemented PD patients display cognitive deficits that are similar to those exhibited by patients who have suffered lesions to the prefrontal cortex. In a variety of mental domains, including visuospatial processing, memory, and set regulation, they perform well on tasks that provide explicit cues for response selection, but perform poorly on tasks that require them to rely entirely on internal attentional and working memory resources in order to formulate and select the appropriate response. More generally, they appear to depend far more than healthy age-matched subjects on environmental guidance for the control of thought and behavior. As a consequence, they have difficulty concentrating and flexibly shifting among different trains of thought.