Studies of patients with Parkinson’s disease (PD) suggest that the characteristic clinical symptoms of bradykinesia, rigidity, and resting tremor are frequently accompanied by impairments in cognitive function. Between 15% and 20% of PD patients develop a frank dementia (Brown and Marsden 1984), and less severe cognitive impairment is a well-recognized feature early in the disease that has been shown to be an important predictor for quality of life (Karlsen and others 1998; Schrag and others 2000). The pattern of cognitive impairments seen in the early stages of PD resembles that produced by frontal lobe damage and includes deficits of executive functions. Executive processes are cognitive mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different processes (Baddeley 1986). Executive functioning is required, therefore, when sequences of responses must be generated and scheduled and when novel plans of action must be formulated and conducted. The frontal lobes have long been known to play an important role in executive functioning, although the fact that the dysexecutive syndrome may be observed in patients with damage to other brain regions (e.g., Morris and others 1990) suggests that an equivalence between the prefrontal cortex and executive functioning cannot be assumed.

In PD, several aspects of executive dysfunction have been shown to be extremely sensitive to the effects of controlled L-Dopa withdrawal (Lange and others 1992), suggesting a predominantly dopaminergic substrate for the deficits observed. Dopaminergic neuronal loss represents the primary neuropathology in PD and occurs predominantly in the nigrostriatal tract and to a lesser extent in the mesocortical pathway where neurons project from the ventral tegmental area and the medial substantia nigra pars compacta (Jellinger 2001). Recent functional neuroimaging studies exploring the executive deficits in PD have provided supporting evidence for a role in disruption in both the nigrostriatal (Owen, Doyon, and others 1998; Dagher and others 2001) and mesocortical (Cools and others 2002; Mattay and others 2002) pathways. Although these models are not mutually exclusive, emerging evidence suggests that this mixed pattern of results across studies may reflect, in part, differential involvement of discrete components of frontostriatal circuitry in subgroups of patients with PD.

Heterogeneity in Parkinson’s Disease

The identification of clinical subgroups is important for understanding the neuropathological basis of cognitive deficit in PD because different disease types probably involve different pathological processes and foci (Brooks 1999; Jellinger 1999). For example, the akinesic-rigid symptoms of PD relate to striatal dopamine deficiency (Morrish and others 1995), a failure to activate the cortical motor areas (Playford and others 1992), and also possibly abnormalities in the pedunculopontine nucleus (Nandi and others 2002). In contrast, tremor in PD probably reflects abnormalities in the corticocerebellar pathways (Parker and others 1992) and the serotonergic system (Doder and others 2003).
There have been many attempts to classify subgroups of patients with PD using a variety of approaches. In general, classification is based on predetermined patient attributes, such as age (Aarsland and others 1996), age of disease onset (Gibb and Lees 1988; Diamond and others 1989; Jankovic and others 1990), medication (Lange and others 1992; Owen and others 1992), cognitive performance (Lewis, Cools, and others 2003; Woods and Troster 2003), motor phenotype (Hoehn and Yahr 1967), dominant motor symptom (Zetuky and others 1985; Jankovic and others 1990), the presence of depression (Mayeux and others 1984; Santamaria and others 1986), disease severity (Hoehn and Yahr 1967; Owen and others 1992; Owen, Beksinska, and others 1993; Owen, Roberts, and others 1993), or motor symptom laterality (Direnfeld and others 1984; Tomer and others 1993). However, all such approaches suffer from limitations that are inherent in the a priori assumptions that have been made in defining these criteria and in assigning patients to subgroups based on them. Furthermore, inconsistencies between inclusion criteria and assessment techniques limit the extent to which results can be compared across studies. An alternative approach to classification requires a methodology that avoids the need for prospective definition and is capable of assessing variables of interest in conjunction with one another, rather than independently. One such technique is cluster analysis (Everitt 1993), by which patients are divided into discrete clusters, such that any one individual belongs to one cluster only and the complete set of clusters contains all the patients. In one recent study, three PD clusters were identified from a cohort of patients at all stages of the disease and were defined as motor only, motor and cognitive, or rapidly progressive (Graham and Sagar 1999). The inclusion of patients with advanced disease in such a study is, however, problematic, as it may mask some of the more subtle clinical (and cognitive) variance that is observed only in the early stages of disease as well as being associated with significant comorbidity (Hughes and others 1993). To address this issue, Lewis, Foltynie, and others (forthcoming) collected data on demographic, motor, mood, and cognitive measures from 120 PD patients in the early stages of disease. Four main subgroups of patients were identified: one group with younger disease onset who had a slow rate of disease progression and no cognitive impairment, a second tremor-dominant subgroup who were not cognitively impaired, a third non-tremor-dominant subgroup with mild depression who showed executive impairments, and a fourth subgroup with a rapid rate of disease progression but no cognitive impairment.

Using these descriptive criteria as a basis for subdivision of patients for further study, Lewis, Cools, and others (2003) were able to generate two subgroups of patients, one executively impaired and one executively unimpaired, who were nevertheless perfectly matched on all other neuropsychological, clinical, and demographic variables, including age, disease duration, medication, disease severity, and depression. These results suggest that there are at least two distinct cognitive subgroups of patients with PD who may be best characterized in terms of their impaired or unimpaired performance on tests of executive function.

**Psychological Basis of Executive Deficits in Nondemented PD**

In recent years, a number of studies have assessed executive function in nondemented groups of patients with PD (Gotham and others 1988; Morris and others 1988; Bradley and others 1989; Cooper and others 1991; Singh and others 1991; Owen and others 1992; Cooper and others 1993; Owen, Beksinska, and others 1993; Owen, Roberts, and others 1993; Owen and others 1995; Postle and others 1997). A central model for much of this work has been the concept of cortico-striatal loops (Alexander and others 1986), which emphasizes the functional interrelationships between the neocortex and the striatum. Of particular interest is the fact that the principal target of basal ganglia outflow appears to be the frontal lobes. Furthermore, different sectors of the striatum project to specific premotor regions such as the supplementary motor area or to discrete regions within dorsal and ventral regions of the frontal cortex, which have been implicated in specific higher cognitive functions (Middleton and Strick 2000a, 2000b). Although methodological differences preclude direct comparisons between studies, in general, the results lend support to the notion that deterioration of executive processes in PD progresses in parallel with the degeneration of motor functions that characterizes the disorder. For example, although nonmedicated patients with mild clinical symptoms have been repeatedly shown to be unimpaired on a test of spatial working memory (Morris and others 1988; Owen and others 1992), deficits on the same task have been observed in medicated patients and particularly in those with severe clinical symptoms (Owen and others 1992). Further comparisons between studies also suggest that some aspects of executive function may be affected earlier in the course of PD than in others. For example, Bradley and others (1989) found that patients with mild to moderate PD were impaired on a test of visuospatial working memory, whereas performance on an analogous test of verbal working memory was unaffected. Similarly, both Postle and others (1997) and Owen and others (1997) have demonstrated that although spatial working memory is impaired in medicated patients with mild PD, working memory for visual shapes is relatively preserved. Although this pattern of impairments may simply reflect a disproportionate involvement of spatial processing deficits in PD (Le Bras and others 1999), an alternative possibility is that the spatial tasks used in these studies differ from the nonspatial tasks in terms of their underlying executive requirements.

Several recent studies have investigated this possibility directly by comparing the performance of groups of patients with PD on spatial memory tests that are known to tap demonstrably different aspects of executive function (Morris and others 1988; Lange and others 1992; Owen and others 1992; Robbins and others 1994). For

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example, one cross-sectional study of patients with PD clearly demonstrated that L-Dopa medicated and nonmedicated patients at different stages of the disease can be differentiated in terms of their performance on a test of spatial span (Owen and others 1992). In this task, patients are required to remember sequences of color-changing boxes on a computer screen. After each successful trial, the number of boxes changing in the next sequence is increased, from two up to a maximum of nine boxes. Performance is scored according to the highest level at which the patient successfully recalls the sequence of boxes. A significant impairment was observed in patients who were medicated and had severe clinical symptoms but not in patients who were either medicated or nonmedicated with mild disease (Owen and others 1992). It is unlikely that dopaminergic medication contributed significantly to this deficit as a parallel study of 10 patients with severe PD has demonstrated that L-Dopa improves, rather than impairs, performance on the spatial span task (Lange and others 1992).

This pattern of impaired spatial span performance in severe PD and intact spatial span in early PD contrasts markedly with the performance of these same groups on a more complex spatial search task (Owen and others 1992). This test is essentially a modification of a task used by Passingham (1985) to examine the effects of prefrontal cortex lesions in primates and is conceptually similar to the radial arm maze, which has been successfully used to assess working memory in rats (Olton 1982). Subjects are required to search through a number of colored boxes presented on a computer screen (by touching each one) to find blue tokens that are hidden inside. The object is to avoid those boxes in which a token has already been found. Like the span task described above, this test places a significant load on memory for spatial information, although unlike that test, it also requires the active reorganization and manipulation of information within working memory and the development of an efficient and organized searching strategy, factors that interact closely with the more fundamental mnemonic requirements to affect performance. Medicated PD patients with both mild and severe clinical symptoms made more errors than did matched controls, and a nonsignificant trend toward impairment was observed even in a nonmedicated PD group of patients with extremely mild disease (Owen and others 1992; Owen, Beckinska, and others 1993). Again, it is unlikely that dopaminergic medication contributed to this deficit as L-Dopa improves, rather than impairs, performance on this task in patients with severe PD (Lange and others 1992).

These results clearly demonstrate that patients at different stages of PD can be differentiated in terms of their performance on two tests of spatial memory that make different demands of executive processes. Among the patients with PD, there is an apparent increase in severity and broadening of spatial memory impairments as patients show increasing clinical disability. Thus, when the task simply involved the retention and recall of a spatial sequence within working memory, deficits were observed only in a subgroup of patients with severe clinical symptoms. By contrast, when the task required the active manipulation of spatial information within working memory and the identification and implementation of organizational strategies, deficits were observed in medicated patients with both mild and severe clinical symptoms. Because of the controlled nature and design of these tests, these differences cannot simply be explained in terms of the concurrent deterioration of motor function in these patients. The results do, in fact, concur fully with more extensive neuropsychological evaluations of these same patient groups that suggest that the pattern of cognitive impairment in PD emerges and subsequently progresses according to a defined sequence that evolves in parallel with the motor deficits that characterize the disorder (Owen and others 1992; Owen, Beckinska, and others 1993). This apparent “progression” on tests that are known to emphasize different aspects of executive function could simply reflect a global difference in cognitive capacity between patients with mild and severe PD. This seems unlikely, however, because similar groups of patients cannot be distinguished in terms of their performance on nonfrontal tests of visual recognition memory (e.g., Owen, Beckinska, and others 1993).

**Neuroanatomical Basis of Executive Deficits in Nondemented PD**

Although no consensus has been reached regarding the fractionation of functions within the prefrontal cortex, it is widely accepted that this region plays a critical role in many aspects of working memory (Goldman-Rakic 1987; Fuster 1997). A number of relevant studies have suggested that the manipulation of information within working memory and the identification of strategies for facilitating performance in such tasks involve the mid-dorsolateral frontal cortex, whereas more basic mnemonic functions such as encoding and retrieval preferentially involve more ventral regions (Owen, Evans, and others 1996; Bor and others 2003; for review, see Owen 2000). On the basis of this and related evidence, a general theoretical framework regarding the role of these different regions of the lateral frontal cortex in executive processing has been described (Petrides 1994; Owen 2000). According to this view, there are two distinct systems within the lateral frontal cortex (Fig. 1) that mediate different aspects of executive processing through reciprocal connections to modality-specific posterior cortical association areas. The ventrolateral frontal cortex (areas 45 and 47) constitutes the first level of interaction between posterior cortical regions and the entire lateral frontal cortex and in this capacity is assumed to be critical for various low-level control processes, such as comparisons between or judgments about the occurrence or nonoccurrence of remembered stimuli and the initiation of explicit (i.e., intentional) retrieval of information from long-term memory. By contrast, the mid-dorsolateral frontal cortex (dorsal area 46 and area 9) is...
assumed to constitute a higher level of executive control and is recruited only when the active manipulation and monitoring of information within memory is required or when organizational strategies are required to facilitate performance by reducing the load on memory. This two-stage model of lateral frontal cortical function, by which two anatomically and cytoarchitectonically distinct regions of the frontal lobe are linked with different aspects of executive processing, describes how information is both retained and organized within working memory to optimize performance on a variety of tasks.

Broadly speaking, the tests of spatial span and spatial search described above map directly on to the two frontal lobe (ventrolateral and dorsolateral) executive systems proposed by Petrides (1994), emphasizing the short-term retention and execution of sequences of responses, on one hand, and active, “online” strategic organization of remembered information on the other. Moreover, the functional architecture subserving performance on these tasks has been confirmed using positron emission tomography (PET) in healthy volunteers (Owen, Evans, and others 1996; Owen and others 1999). For example, when healthy volunteers performed a version of the spatial span task, a significant region of increased cerebral blood flow (CBF) was observed in the ventrolateral frontal cortex (area 47) in the right hemisphere. No significant changes were observed in the dorsolateral frontal cortex. In the same study, significant changes in CBF were clearly observed in the right middorsolateral frontal cortex (areas 46 and 9) when subjects performed a version of the spatial search task described above (Owen, Evans, and others 1996).

On this basis, a model of frontostriatal cognitive degeneration in PD has been formulated (Owen, Sahakian, and others 1998) that suggests that higher-level executive functions such as manipulation, strategies, and planning, which are assumed to depend critically on the integrity of the dorsolateral frontal cortex, may be more susceptible than basic mnemonic functions such as maintenance and recall, which are assumed to depend on more ventral frontal regions (Petrides 1994; Owen 2000).

One further question that arises is how this pattern of cognitive degeneration relates to the pattern of heterogeneity observed in subgroups of patients with PD. To address this issue, Lewis, Cools, and others (2003) recently developed a novel verbal working memory task that assessed both dorsolateral (e.g., manipulation) and ventrolateral (e.g., retrieval) components of executive control within the same general paradigm. Specifically, patients were required to hold a sequence of four letters in memory (maintenance) across a variable delay period and then, in separate trials, either recall that sequence (retrieval) or reorder it (manipulation) according to a previously learned rule. By directly comparing performance on recall-only trials with performance on manipulation trials, this task allows the separate assessment of ventral and dorsal components of frontal lobe function, respectively, while all potentially confounding factors such as sensory and motor requirements of the task remain constant. Moreover, unlike previous studies, two groups of nondemented patients with PD were recruited, one executively impaired and one executively unimpaired, who were nevertheless perfectly matched on all other neuropsychological, clinical, and demographic variables, including age, disease duration, medication, disease severity, and depression. In terms of “thinking” times (corrected for baseline difference in motor reaction time), patients in the executively impaired subgroup were significantly slower but only in those conditions in which they were required to manipulate information within memory (Fig. 2). Thus, although thinking times were not different from controls when the patients were required simply to retrieve a previously maintained sequence of four letters, they were significantly prolonged when they were required to reorder those letters according to either of the two previously learned rules. These results provide further evidence that in mild PD, the functions of the dorsolateral frontal cortex are more susceptible to impairment than are the functions of the ventrolateral frontal cortex, which remains relatively intact. Moreover, this pattern of cognitive degeneration is evident only in a subgroup of patients with predefined executive impairment.

**Neurochemical Basis of Executive Deficits in Nondemented PD**

In PD, the primary neuropathology is loss of dopaminergic neurons in the nigrostriatal tract and the resultant depletion of dopamine throughout the striatum. The main output of the dorsomedial projection of the nigrostriatal tract is to the head of the caudate nucleus (Bernheimer and others 1973), and a correlation between the loss of dopaminergic neurons in this region and the degree of dementia in PD patients has been reported (Rinne and others 1989). Animal lesion experiments also suggest that the caudate nuclei may play a specific role in cognition. For example, damage to different regions of the caudate nucleus produces deficits that resemble the effects of damage to their corresponding targets of projection within the prefrontal cortex (Divac and others 1967). In addition, 18F-dopa PET studies in PD patients have shown a correlation between dopaminergic depletion of the caudate nucleus and neuropsychological performance (Marie and others 1999; Bruck and others 2001), although these findings have not been universally reported (Broussolle and others 1999; Rinne and others 2000). Research in nonhuman primates (Middleton and Strick 2000a, 2000b) has confirmed that prefrontal cortical regions receive fibers in a highly ordered topographical fashion from distinct regions of the basal ganglia (Alexander and others 1986). Thus, the pattern of executive deficits in PD may not arise through frontal lobe pathology per se but rather as a result of striatal dopamine depletion, which effectively interrupts the normal flow of information through frontostriatal circuitry. If this is the case, then recent anatomical and neuropathological evidence suggests that the evolving pattern of executive impairments in PD...
described above may be best explained in terms of what is known about the spatiotemporal progression of dopamine depletion within the striatum in relation to the terminal distribution of its cortical afferents. This is highlighted by a detailed postmortem neurochemical analysis that shows uneven patterns of striatal dopamine loss in patients dying with idiopathic PD (Kish and others 1988). The study confirms the well-documented finding that the putamen is more severely depleted than the caudate nucleus and extends the analysis to show that the caudal putamen is more affected than the more rostral portions. However, in view of anatomical and electrophysiological evidence, the putamen is generally implicated in the motor deficits associated with PD. Dopamine levels in the caudate nucleus, which appears to be a more serious candidate for mediating the cognitive sequelae of PD, are also substantially depleted. This depletion is greatest (to a maximum of about 90%) in the most rostromedial extent of the head of this structure, an area that is heavily connected with dorsolateral regions of the frontal lobe (Yeterian and Pandya 1991). It seems likely, therefore, that these rostromedial regions of the caudate nucleus are subjected to greater disruption by the disease and probably at an earlier stage of its progression. By contrast, ventral regions of the caudate, which are preferentially connected with more ventral regions of the frontal lobe (including the ventrolateral and orbitofrontal cortices) (Yeterian and Pandya 1991), are relatively spared in early PD, which may leave functions that are maximally dependent on this neural circuitry relatively intact.

However, PD is also characterized by dopamine depletion within the frontal cortex itself (Scatton and others 1983), and degeneration of the mesocortical dopamine system, which projects to the frontal lobes and other cortical areas, may also play a significant role in the pattern of executive deficits observed. It has been suggested that dopamine acting within the frontal cortex enables a focusing of activity of glutamatergic output neurons that, as a result, respond more efficiently (Mattay and others 1996; Goldman-Rakic 1998). However, this system is known to be less severely affected (50% depletion) than the nigrostriatal dopamine system in PD (Agid, Ruberg, and others 1987) and possibly at a later stage of the disease process.

Nondopaminergic forms of pathology, including noradrenergic, serotoninergic, and cholinergic deafferenta-
tion of the cortex, also occur in PD (Agid, Javoy-Agid, and others 1987) and may play a significant role in some of the cognitive deficits observed. Similarly, cortical Lewy bodies, which may occur even in the early stages of PD, may play a contributory role (Byrne and others 1989; Gibb and others 1989).

In patients, so-called on/off studies have been used to demonstrate a relationship between cognitive deficits and dopaminergic pathology (e.g., Gotham and others 1988; Lange and others 1992). L-Dopa, a precursor primarily affecting levels of dopamine (Maruyama and others 1996), typically ameliorates the motor symptoms of PD, although the effects on cognition are more variable. Thus, deleterious as well as beneficial effects have been reported (Gotham and others 1988; Lange and others 1992; Kulisevsky 1996; Swainson and others 2000). For example, Gotham and others (1988) observed beneficial effects of dopaminergic medication on some cognitive tasks but detrimental effects on others and speculated that the L-Dopa dose necessary to restore normal levels of dopamine to the striatum may “overdose” any area where dopamine depletion is less severe, such as the prefrontal cortex. Swainson and others (2000) explored this issue directly using tasks that have been differentially associated with specific components of frontostriatal circuitry. Nonmedicated PD patients were impaired on a spatial recognition memory task that has been shown to involve the dorsolateral frontal cortex (Owen, Milner, and others 1996) but performed significantly better than medicated patients on a test of reversal learning that appears to depend more on ventral frontal and striatal regions (Dias and others 1996). It was suggested that the medication dose sufficient to restore function to dorsal frontostriatal circuitry effectively overdoses and impairs function in the less affected ventral frontostriatal circuitry (Fig. 3). This important result was followed up by Cools and others (2001) who demonstrated both beneficial and deleterious effects of dopaminergic medication in the same group of patients with PD on cognitive tasks that were selected according to their known dependence on different components of frontostriatal circuitry. Thus, whereas withdrawal of L-Dopa in PD impaired task-set shifting, which is assumed to involve the dorsolateral frontal cortex and dorsal sectors of the caudate nucleus, it improved performance on probabilistic reversal learning, which is assumed to involve orbitofrontal and ventral regions of the frontal cortex and the ventral striatum (e.g., Dias and others 1996). Because the effect of L-Dopa stems mainly from its ability to elevate dopamine levels (Maruyama and others 1996) in the striatum (Hornykiewicz 1974), the authors suggested that the observed effects on task-set shifting and reversal learning are most likely due to effects of dopamine in the dorsal and ventral striatum, respectively (Cools and others 2001). However, given the role of the mesocortical dopamine projection in PD, by which neurons project from the ventral tegmental area and the medial substantia nigra pars compacta, a direct effect on the frontal lobe cannot be ruled out.

Lewis, Slabosz, and others (forthcoming) recently assessed a group of patients with mild PD both on and off L-Dopa on the novel verbal working memory task described above that assessed both dorsolateral (e.g., manipulation) and ventrolateral (e.g., retrieval) components of executive control within the same general paradigm. L-Dopa selectively improved performance deficits on those trials that required manipulation while leaving other aspects of executive function, such as maintenance and retrieval, unaffected.

Together, these studies clearly suggest that dopaminergic medication improves or impairs cognitive performance in PD depending on the nature of the task and the basal level of dopaminergic functioning in underlying corticostriatal circuitry. The fact that both the spatial span task and the spatial search task described above are extremely sensitive to the effects of controlled L-Dopa withdrawal in a group of patients with severe PD (Lange and others 1992) is broadly consistent with this conclusion. In severe PD, both dorsal and ventral sectors of frontostriatal circuitry are significantly impaired (Owen and others 1992; Owen, Beksinska, and others 1993), and so dopaminergic medication might be expected to have a beneficial effect on both types of task.

**Frontal versus Striatal Contributions to Executive Deficits in Nondemented PD**

Given the involvement of both the mesocortical dopamine system and the nigrostriatal system in the pathology of PD, together with the evidence described above for clear cognitive subgroups of patients with distinct neuropathological profiles, it is simply not possible to delineate the separate contributions of frontal and striatal dysfunction on the basis of behavioral studies in patients alone. In recent years, PET and, more recently, functional magnetic resonance imaging (fMRI) have provided a new opportunity for addressing such questions by assessing human brain function in vivo. PET activation studies require block designs, usually of between 60 and 90 sec duration, and throughout this period, participants perform a cognitive or sensory-motor task of interest. Critically, however, the PET activation method does not allow for the decomposition of this lengthy acquisition time into more psychologically meaningful temporal units. Thus, the derived estimates of local cortical blood flow represent the total accumulative effect of all of those cognitive, motor, and perceptual processes taking place within the broad acquisition period. fMRI does not suffer the same limitations, and with event-related designs, signal changes can be correlated with cognitive task performance on a trial-by-trial basis; in this way, differential time courses of activation within specific anatomical regions of interest may be examined and compared. Moreover, the increased effective power of high-field fMRI over PET activation studies means that such questions can be asked within an individual subject, allowing single-subject studies, group designs, or a mixture of the two to be implemented.
In terms of investigating frontostriatal dysfunction in PD, this approach is very much in its infancy, and the few functional neuroimaging studies that have been conducted have produced conflicting results. Thus, some findings support a disturbance of the mesocortical projection (Cools and others 2002; Mattay and others 2002) whereas others identify a crucial role for disruption within the nigrostriatal circuitry (Owen, Doyon, and others 1998; Dagher and others 2001). For example, Owen, Doyon, and others (1998) observed abnormal blood flow in the basal ganglia in patients with PD during performance of the Tower of London planning task and a related test of spatial working memory, both of which are known to recruit the dorsolateral frontal cortex as well as the caudate nucleus in healthy volunteers (Owen, Doyon, and others 1996). This blood flow change in patients was accompanied by a performance deficit, similar to that seen in patients with frontal lobe damage, although no abnormalities in regional CBF were observed in the prefrontal cortex (Fig. 4).

A more recent study (Dagher and others 2001) has replicated this pattern of abnormal blood flow in the basal ganglia, but normal blood flow in the cortex, again using the Tower of London task in patients with PD.

Together, these data suggest that in PD, dopamine depletion disrupts basal ganglia outflow and consequently affects the expression of prefrontal functioning by interrupting frontostriatal circuitry (Alexander and others 1986). In keeping with this notion, previous pathological (Rinne and others 1989; Paulus and Jellinger 1991) and 18F-dopa PET studies have confirmed a correlation between caudate dopamine loss and neuropsychological performance in PD patients (Marie and others 1999), suggesting a preferential role for this system in cognitive impairment (Ito and others 2002).

However, a rather different conclusion was reached by Cools and others (2002), who used PET to examine the critical locus of the effect of dopaminergic medication on high-level cognitive functioning in patients with PD (Fig. 5). Patients were scanned on two occasions during performance of the same two executive tasks used previously by Owen, Doyon, and others (1998). On one occasion, patients were asked to take their dopaminergic medication as usual, and on the other, they were asked to abstain from taking any medication for at least 18 h prior to their visit to the imaging center. L-Dopa normalized relative blood flow levels in the right dorsolateral prefrontal cortex in patients with PD by decreasing cerebral blood flow during both the spatial working memory and the planning tasks relative to the control task. Contrary to expectations, no significant changes were observed in the basal ganglia, raising the possibility that L-Dopa may modulate cognitive deficits in patients with PD by acting directly on the dorsolateral prefrontal cortex.

This task-specific, L-Dopa–induced neuromodulation of the dorsolateral prefrontal cortex is broadly consistent with both animal studies (Brozoski and others 1979; Glowinski and others 1984; Mogenson and Yim 1991;
Sawaguchi and Goldman-Rakic 1991; Goldman-Rakic 1992; Roberts and others 1994; Williams and Goldman-Rakic 1995; Zahrt and others 1997; Arnsten 1998) and imaging studies in humans (Daniel and others 1991; Friston and others 1992; Grasby and others 1992; Mattay and others 1996; Mattay, Callicott, and others 2000; Mattay, Tessitore, and others 2000; Mehta and others 2000). The physiological mechanisms underlying the observed L-Dopa–induced blood flow changes in PD patients are, however, not clear. One possibility is that these changes reflect a direct vasodilatory effect on cerebral blood vessels (Leenders and others 1985; Sabatini and others 1991; Krimer and others 1998). However, a direct vascular effect would be expected to produce global and not regionally specific changes. It was suggested, therefore, that the blood flow changes observed reflected the neuromodulatory effects of dopamine on the prefrontal cortex, resulting from local changes in neuronal firing (Cools and others 2002). Previous studies (Foote and others 1975; Johnson and others 1983; Robbins and Everitt 1987; Sawaguchi and others 1990) have demonstrated that catecholamines may act by enhancing the signal-to-noise ratio of local neuronal firing patterns, that is, suppressing spontaneous background neural firing while enhancing cortical neural responses to the stimulus. Daniel and others (1991), Mattay and others (1996), and Mattay, Callicott, and others (2000) have demonstrated that in humans, dextroamphetamine increases the signal-to-noise ratio in task-relevant neural regions, increasing blood flow in areas most relevant to a task and decreasing blood flow in areas less relevant for that task. However, in the study by Cools and others (2002), relative drug-induced decreases were observed in the right dorsolateral prefrontal cortex. Although these results might seem at odds with existing data (e.g., Daniel and others 1991; Mattay and others 1996; Mattay, Callicott, and others 2000), they are consistent with other imaging studies using dopaminergic agents in healthy volunteers (Friston and others 1992; Grasby and others 1992; Mehta and others 2000) and patients with PD (Mattay, Tessitore, and others 2000). For example, Mehta and others (2000) also showed drug (methylphenidate)-induced task-related decreases in the dorsolateral prefrontal cortex using a self-ordered spatial working memory task. Similarly, Friston and others (1992) showed apomorphine-induced attenuation of

**Fig. 4.** When patients with Parkinson’s disease perform the Tower of London test of planning, activation is observed in the dorsolateral frontal cortex (*top right*) at a location very similar to that observed in healthy elderly volunteers (*top left*). However, a significant peak in the center on the internal segment of the globus pallidus during the same task in healthy volunteers (*bottom left*) is not observed in the patients with PD (*bottom right*).
memory-related activation in the dorsolateral prefrontal cortex. Together, these findings cast some doubt on the suggestion that dopaminergic agents consistently increase blood flow in task-relevant areas and decrease blood flow in task-irrelevant areas (Daniel and others 1991; Mattay, Callicott, and others 2000). An alternative suggestion supported by the results of Cools and others (2002) and Mehta and others (2000) is that the blood flow reduction in the dorsolateral prefrontal cortex is related to increased efficiency, that is, increased signal-to-noise ratio within the prefrontal cortex. In keeping with that suggestion, Cools and others (2002) reported a significant correlation between the L-Dopa–induced blood flow change in the right dorsolateral prefrontal cortex in PD and the L-Dopa–induced change in performance on the planning task.

In one very recent study, the neural basis for cognitive heterogeneity in PD was explored using event-related fMRI (Lewis, Dove, and others 2003). Patients with mild disease who were well matched on a range of clinical and neuropsychological measures but differed in terms of their executive impairments underwent event-related fMRI during the novel working memory task described above that assesses both dorsolateral and ventrolateral executive systems within the same general paradigm (Lewis, Dove, and others 2003). On the basis of the mixed imaging results described above, it was hypothesized that cognitive dysfunction in theexecutively impaired subgroup of patients with PD would be accompanied by underactivity in the basal ganglia and/or in their frontal cortical targets, whereas no such effects were predicted in the executively unimpaired group. The results revealed selective impairments in manipulation that were associated with reduced activity in the ventrolateral and dorsolateral prefrontal cortices in the executively impaired subgroup but not in the executively unimpaired group (Fig. 6). Reduced activity in the caudate nucleus was also observed in the executively impaired subgroup of patients with PD, although this effect occurred during both manipulation and retrieval conditions, suggesting that this structure plays a more general role in cognition.

These findings may explain why inconsistent results have been found previously in functional neuroimaging studies of PD and suggest clear strategies for future research in this area. For example, the results suggest that dopamine depletion in early PD specifically affects manipulation, but not retrieval, within working memory and that these deficits may be related to dysfunction of circuitry involving the middorsolateral and/or the midventrolateral frontal cortices. This conclusion, however, depends on the spatial, temporal, and psychological resolution that is afforded only by event-related, high-resolution fMRI. Thus, the fact that most previous studies using PET have reported regional CBF abnormalities in the basal ganglia of patients with PD may reflect the relative spatial and temporal insensitivity of that technique relative to fMRI and the fact that, at best, PET allows

Fig. 5. The average positron emission tomography image is shown as sagittal, coronal, and transverse sections superimposed on a standard template brain for the drug by memory task interaction contrast (spatial working memory task-related blood flow changes modulated by L-Dopa). A significant peak was observed in the right dorsolateral prefrontal cortex (at coordinates x, y, z = 38 28 22 (left); this image was rendered using an uncorrected threshold of P < 0.005). Blood flow was increased during the working memory task relative to the visuomotor control task in the “off L-Dopa” condition, but blood flow did not differ between the tasks in the “on L-Dopa” condition. Post hoc comparisons with baseline voxel values, extracted from healthy volunteers, revealed that the blood flow pattern in the “on” state was similar to that in control subjects, whereas the pattern in the “off” state was not. The pattern of results during the Tower of London task was almost identical. PD = Parkinson’s disease.
rather general associations to be made between cognitive tasks and changes in activation. In keeping with this notion, in the fMRI study described above (Lewis, Dove, and others 2003), significant signal-intensity changes were observed in the basal ganglia but were not specifically related to any particular executive aspect of task performance. Similarly, previous “on/off” studies in PD patients using PET have reported significant changes related to L-Dopa medication in the frontal lobe but not in the basal ganglia (Cools and others 2002), which may simply reflect the relative insensitivity of this technique to detecting the effects of neuropharmacological modulation in smaller, subcortical regions. It remains to be seen whether event-related fMRI can reveal the precise mechanisms by which dopamine acts on specific sectors of frontal and striatal circuitry to improve or impair cognitive performance in patients with PD.

Finally, the two patient groups in the event-related fMRI study of Lewis, Dove, and others (2003) were well matched with respect to many demographic and clinical measures, including age, disease duration, medication, disease severity, and depression (Lewis, Dove, and others 2003). Thus, unlike in all other studies of this type, the apparent difference between the two subgroups of patients is not confounded by potential generalized differences in disease processes. Neither does the heterogeneity represent a global difference in cognitive capacity because the patient subgroups could not be differentiated in terms of their performance on other cognitive tests with less executive loading (e.g., visual recognition memory). The results, therefore, highlight the need for a better characterization of patient groups and their impairments, both motorically and neuropsychologically. Such an approach, when combined with novel approaches in cognitive psychology, clinical neuropsychology, psychopharmacology, and functional neuroimaging, may lead ultimately to a more complete understanding of the specific roles played by the sectors of the frontal cortex and the striatum in the operation of the functional circuits defined by Alexander and others (1986).
References


