

# The role of executive deficits in memory disorders in neurodegenerative disease

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## INTRODUCTION

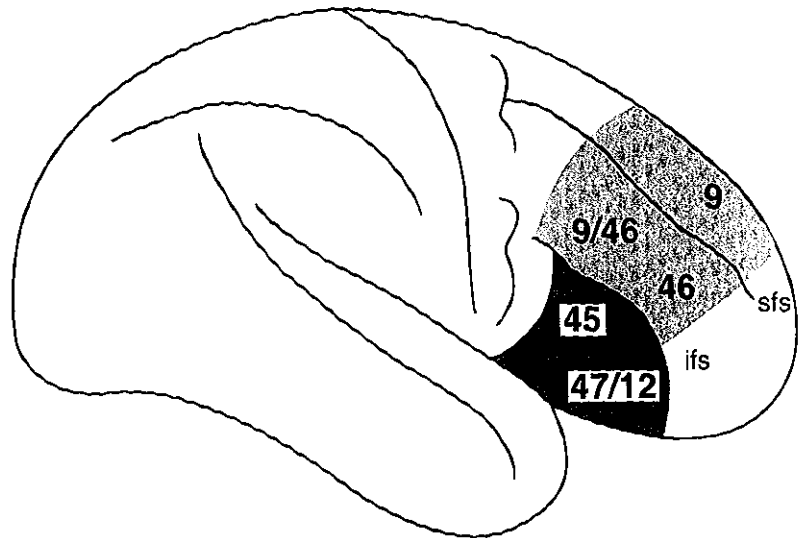
There is now overwhelming evidence that patients with neurodegenerative disorders, including Parkinson's disease (PD), Huntington's disease (HD), progressive supranuclear palsy (also known as Steele-Richardson-Olszewski syndrome), multiple system atrophy, Alzheimer's disease (AD), Korsakoff's syndrome and fronto-striatal dementia exhibit diverse patterns of cognitive impairment that can include deficits of 'executive function'. The term 'executive function' generally refers to those mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different cognitive 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 carried out. 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 (Morris et al. 1990), suggests that an equivalence between the prefrontal cortex and executive functioning cannot be assumed. In addition, much of the research on executive deficits in neurodegenerative groups has focused on broad descriptions of individual patient groups and how their behaviour might best be characterized using standard clinical neuropsychological tools. For example, impairments on the Wisconsin Card Sorting Test (Grant and Berg 1948), a classic test of executive function, have been described in many neurodegenerative groups including PD (Lees and Smith 1983), progressive supranuclear palsy (Pillon et al. 1986) and HD (Josiassen et al. 1983). Tasks such as the Wisconsin Card Sorting Test place significant demands on many different aspects of cognitive

function some, or all, of which may be impaired in a given patient and performance is ultimately determined, therefore, by a complex interaction between multiple dysfunctional processes. In recent years, however, improved methods of assessment combined with a theory-driven approach to task design has led to great advances in our understanding of the fundamental mechanisms which mediate these higher-order cognitive processes. As a direct result, it has been possible to define impairments of executive function in neurodegenerative diseases more precisely, in terms of the specific neuropsychological mechanisms involved.

## FUNCTIONAL ANATOMY OF EXECUTIVE FUNCTION: WORKING MEMORY

One aspect of executive function that has received much attention in recent years is working memory. The term 'working memory' was introduced into the experimental psychology literature by Baddeley (1986) to replace the existing concept of a passive short-term memory store and to emphasize, within a single model, both the temporary storage and the 'on-line' manipulation of information that occurs during a wide variety of cognitive activities. Since then, considerable evidence has accumulated to suggest that the lateral surface of the frontal-lobe plays a critical role in certain aspects of working memory. This evidence comes from the study of patients with excisions of frontal cortex (Petrides and Milner 1982; Owen et al. 1990, 1995a, 1996c; for a review, see Petrides 1989), from lesion and electrophysiological recording work in nonhuman primates (Goldman-Rakic 1987; Petrides 1994) and more recently, from functional neuroimaging studies in humans

Figure 8.1. Schematic drawing of the lateral surface of the human brain to indicate the location of the dorsolateral frontal cortex (areas 9, 46 and 9/46), and the ventrolateral frontal cortex (areas 45 and 47/12). The numbering scheme is taken from the recent cytoarchitectonic reparation of the human frontal cortex by Petrides and Pandya (1994). ifs: inferior frontal sulcus; sfs: superior frontal sulcus.



(Jonides et al. 1993; Petrides et al. 1993a,b; McCarthy et al. 1994; Smith et al. 1995, 1996; Courtney et al. 1996; Gold et al. 1996; Goldberg et al. 1996; Owen et al. 1996a,b; Sweeney et al. 1996). In the monkey it has been shown that lesions confined to one part of the dorsolateral frontal cortex, namely the cortex lining the sulcus principalis (i.e. area 46) result in severe impairments on tests of spatial working memory, such as spatial delayed alternation and delayed response (Goldman-Rakic 1987; Fuster 1989; Chapter 1). Similarly, monkeys with lesions limited to the mid-dorsal part of the lateral frontal cortex are severely impaired on certain nonspatial working memory tasks (Petrides 1988, 1991, 1994). On the basis of this and related evidence, a general theoretical framework regarding the role of the different regions of the lateral frontal cortex in working memory processing has recently been described (Petrides 1994). According to this view, there are two executive processing systems within the lateral frontal cortex which mediate different aspects of working memory through reciprocal connections to modality specific posterior cortical association areas. The first stage of interaction between these posterior association areas and frontal regions occurs primarily within the ventrolateral frontal cortex (i.e. areas 45 and 47). Thus, these areas (see Figure 8.1) are concerned primarily with the active organization of sequences of responses based on conscious, explicit retrieval of information from short-term memory. By contrast, the mid-dorsolateral frontal cortex

(dorsal area 46 and area 9) is assumed to constitute a second level of interaction of executive processes with memory and is recruited only when the active manipulation and monitoring of information within working memory is required (Figure 8.1). This two-stage model of lateral frontal cortical function, by which two anatomically and cytoarchitecturally distinct regions of the frontal lobe are linked with different aspects of executive processing, describes how information is both retained and manipulated within working memory to optimize performance on a variety of tasks.

While the human and animal studies described above support the view that different regions of the prefrontal cortex play distinct roles in working memory, this involvement appears to depend critically on reciprocal connections with more posterior neural structures. Goldman-Rakic (1990) has described several multisynaptic connections between the prefrontal cortex and the hippocampal formation and has speculated that these connections imply a reciprocal functional relationship in working memory (Goldman-Rakic et al. 1984). In keeping with this suggestion, it is well established that damage to the hippocampus and related structures in rats produces severe and enduring deficits in spatial working memory tasks (Olton et al. 1978; Olton and Papas 1979; Rawlins and Olton 1982; Rawlins and Tsaltas 1983; Aggleton et al. 1986; Sziklas and Petrides 1993). Thus, contemporary accounts view working memory as a distributed process that critically

depends on a close functional interaction between regions of the lateral frontal cortex and more posterior cortical structures (including the hippocampus).

#### WORKING MEMORY AND NEURODEGENERATIVE DISEASE: AN OVERVIEW

In recent years, a number of studies have assessed working memory in patients with PD (Gotham et al. 1988; Morris et al. 1988; Bradley et al. 1989; Cooper et al. 1991, 1993; Singh et al. 1991; Owen et al. 1992, 1993, 1995b; Postle et al. 1993). Although methodological differences preclude direct comparisons between studies, in general the results lend support to the notion that deterioration of working memory processes in these patients progresses in parallel with the degeneration of motor functions that characterizes this disorder. For example, while nonmedicated patients with mild clinical symptoms have been repeatedly shown to be unimpaired on a test of spatial working memory (Morris et al. 1988; Owen et al. 1992), deficits on the same task have been observed in medicated patients and particularly in those with severe clinical symptoms (Owen et al. 1992). Further comparisons between studies also suggest that some aspects of working memory may be affected earlier in the course of PD than others. For example, Bradley et al. (1989) found that patients with mild to moderate PD were impaired on a test of visuospatial working memory, whilst performance on an analogous test of verbal working memory was unaffected. Similarly, Postle et al. (1993) and Owen et al. (1997) have demonstrated that, while spatial working memory is impaired in medicated patients with mild PD, working memory for visual shapes is relatively preserved.

Working memory performance has also been investigated in HD using a variety of spatial (Orsini et al. 1987; Lange et al. 1995; Lawrence et al. 1996), visual (Orsini et al. 1987; Rich et al. 1996) and verbal (Orsini et al. 1987), tasks. For example, Rich et al. (1996) have shown that HD patients perform significantly worse than controls on all versions of the self-ordered pointing task devised by Petrides and Milner (1982), making more returns to pictures or abstract designs that have already been selected. Polymodal deficits were also observed by Orsini et al. (1987), who demonstrated that both spatial span and digit span were similarly impaired in HD. In addition, on both

tasks the HD patients performed more poorly than a group of patients with PD.

Deficits have also been described in other neurodegenerative groups, including patients with AD (Baddeley et al. 1986) on a variety of executive tasks that could be said to involve working memory. The results of cross-sectional comparisons between such studies or between different neurodegenerative groups are difficult to evaluate in terms of the likely neuropathological mechanisms underlying the deficits observed, for a number of reasons. Principally, many different tasks have been employed which vary, both in terms of the modality of the stimuli used and in terms of the relative emphasis on different executive processes. Given the theoretical and anatomical arguments outlined above, such tasks are likely to depend on different components of a widely distributed neural system. Second, the different neurodegenerative groups studied often differ markedly in terms of their clinical characteristics such as age of onset, illness duration, rates of cognitive decline and medication regimes. Third, many of the standard clinical neuropsychological tasks that have been employed to test executive function in elderly neurodegenerative groups have not been adequately validated in a normal ageing population. Executive functions such as working memory appear to be particularly vulnerable to the effects of normal ageing (van Gorp and Mahler 1990), a pattern which may reflect the disproportionate reduction in neuron density in the prefrontal cortex and basal-ganglia (Haug and Eggers 1991).

#### TOWARDS A THEORETICALLY DRIVEN APPROACH

In recent years, some of these issues have been addressed directly in a series of studies that have attempted to use a standardized battery of computerized tasks (The Cambridge Neuropsychological Test Automated Battery: CANTAB), including test of executive function, to assess a broad range of neurodegenerative groups (Sahakian et al. 1988, 1990; Lange et al. 1992, 1995; Owen et al. 1992, 1993; Robbins et al. 1992; Lawrence et al. 1996). Two of these tests, which assess different aspects of spatial memory, are of particular relevance to the subject of this chapter as they can be related directly to contemporary accounts of working memory. Thus, broadly speaking, they map directly onto the two frontal lobe (ventrolateral and dorsolateral), executive systems proposed by Petrides (1994),

emphasizing the short-term retention and execution of sequences of spatial responses on the one hand and active, 'on-line' manipulation of spatial information within a spatial search task on the other. Moreover, the functional architecture subserving performance on these tasks has been investigated using positron emission tomography (PET) (Owen et al. 1996b), the results of which concur fully with the findings from comparisons between groups of neurosurgical patients with frontal lobe or temporal lobe excisions (Owen et al. 1990, 1995a). Finally, standardization studies using large samples ( $N > 340$ ) of healthy volunteers have provided important information about the effects of normal ageing on task performance (Robbins, 1996).

The first of these two tasks, is a computerized version of the block tapping test devised by Corsi (described in Milner 1971). Each trial begins with the same arrangement of nine squares, presented on the screen in a pseudo random pattern. Subjects are instructed to observe the boxes because some will change color, one after the other. Their task is to remember the location and the sequential order of the boxes that change. During each series, one box changes color for three seconds and then returns to white before the next in the sequence changes to the same color. The subject is then prompted by a tone to repeat the sequence by touching the boxes in the same order. 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 subject successfully recalls the sequence of boxes. Clearly, this task emphasizes the short-term retention and reproduction of spatial information within working memory but requires little manipulation of that information and, in this sense, is likely to involve ventrolateral frontal areas according to the model proposed by Petrides (1994). A recent functional imaging study combining both PET and magnetic resonance imaging (MRI) has verified that this is the case (Owen et al. 1996b). When normal volunteer subjects performed a modified version of this computerized task, a significant region of increased cerebral blood flow (CBF) was observed in ventrolateral frontal cortex (area 47) in the right hemisphere. No significant changes were observed in more dorsolateral areas of frontal cortex, even when subjects were required to learn and reproduce a 'supra-span' sequence of eight boxes.

In terms of the absolute measure of spatial span, this task is not sensitive to unilateral temporal lobe damage, or

amygdalo-hippocampectomy (Owen et al. 1995a). Patients with frontal lobe damage are also unimpaired according to this gross measure (Owen et al. 1990), although deficits are observed when one considers the number of trials required to reach maximum span.

The second test of frontal executive function 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) in order to find blue 'tokens' which are hidden inside by the computer. 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, factors which interact closely with the more fundamental mnemonic requirements to affect performance. Thus, control subjects often adopt a search strategy which involves retracing a systematic 'route' and 'editing' or 'monitoring' those locations where tokens have been found previously. This searching strategy can be captured by an index which is demonstrably uncontaminated by overall mnemonic performance (Owen et al. 1990, 1996c) and yet which correlates highly with such performance (Robbins 1996). This strategy, which has been described in detail elsewhere (Owen et al. 1990, 1997), is illustrated in Figure 8.2.

The emphasis on 'strategy' in this task clearly implicates the dorsolateral frontal executive processing system according to the model proposed recently by Petrides (1994). It is important to note, therefore, that in a recent PET study, significant changes in CBF were clearly observed in the right mid-dorsolateral frontal cortex (areas 46 and 9), when subjects performed a slightly modified version of this task (Owen et al. 1996b). In addition, as in the spatial span task, the ventrolateral frontal cortex was also activated, confirming that more basic mnemonic factors also contribute to overall performance on this test. Thus, the spatial search appears to be governed by two major factors, one related to short-term spatial memory and the other to strategic processes, which depend upon ventrolateral and dorsolateral regions of the frontal cortex, respectively. The possibility that these two levels of exec-

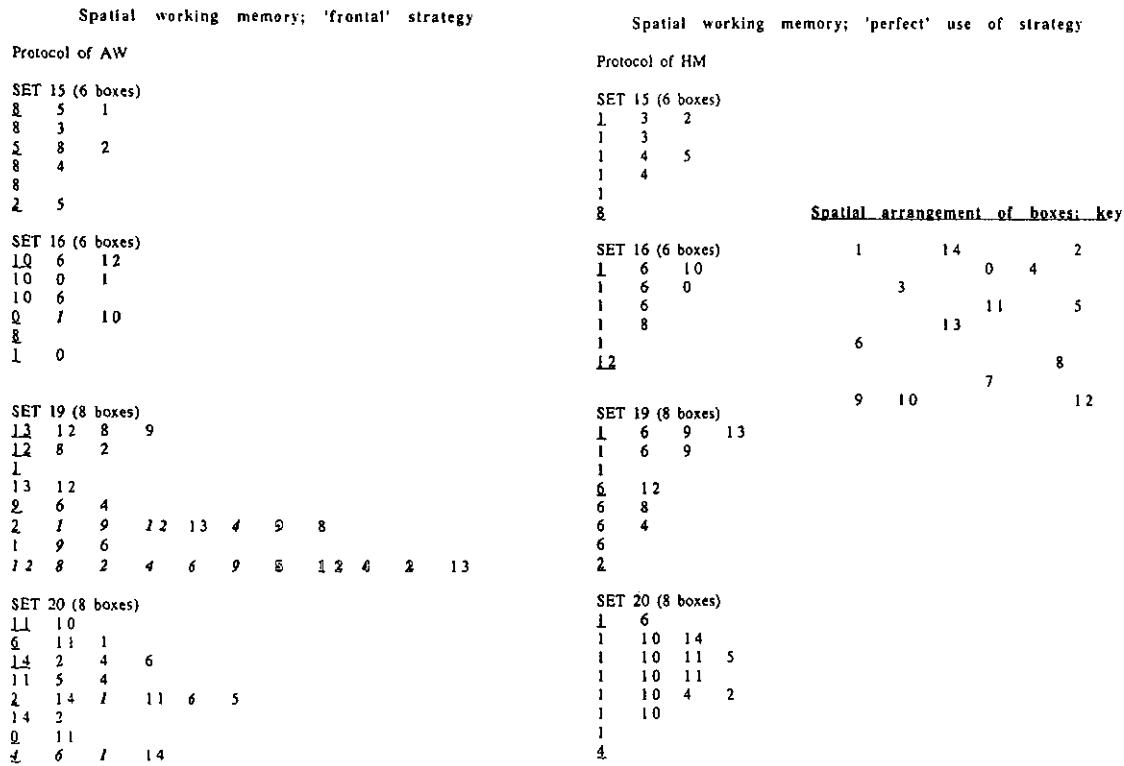


Figure 8.2. Left: a typical response pattern from one of the frontal lobe patients (AW), illustrating how the 'strategy' score is calculated. Right: corresponding normal response pattern from a typical healthy control subject (HM). On the right hand side, the spatial arrangement of boxes as they appear on the screen is illustrated schematically. For each subject, four example trials ('sets') are shown. Horizontal rows represent the choices (boxes) made during each search through the array and vertical columns represent the total

number of searches made during each problem. The strategy score is estimated by totalling the number of novel boxes used to initiate a search sequence (all such boxes are underlined). In this example the strategy scores for the patient and for the control are 18 and 9, respectively. Numbers in bold represent 'between search' errors. Numbers in outline represent 'within search' errors. For a full description, see Owen et al. 1990; 1992; 1993; 1995; 1997.

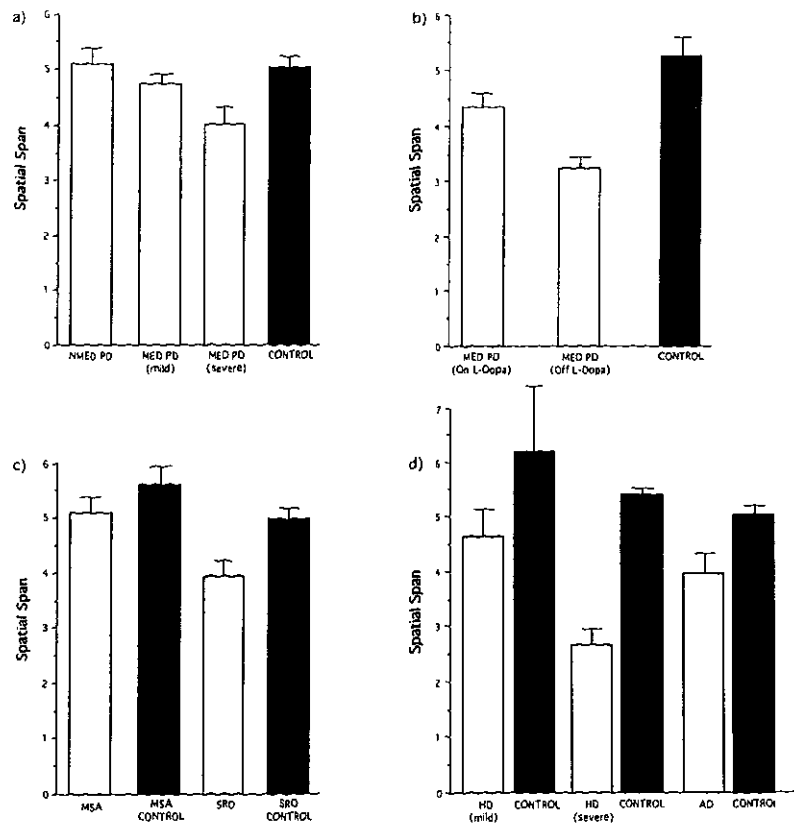
utive processing constitute distinct functional systems which are differentially involved in these two tasks is suggested further by a recent large-sample factor analysis of normal control performance which has identified separate mnemonic and strategic factors in performance (Robbins 1996).

Neurosurgical patients with frontal lobe damage are significantly impaired on this 'strategic' spatial searching task and make more returns to boxes in which a token has previously been found ('between search' errors) even at the simplest levels of task difficulty (Owen et al. 1990, 1995a). In addition, these patients are less efficient in the use of the repetitive searching strategy described above, confirming that at least some of their impairment in spatial working

memory may arise secondarily from a more fundamental deficit in the use of organizational strategies. A typical response pattern from one of the frontal lobe patients is presented in Figure 8.2 (left), along with the corresponding normal response pattern from a typical healthy control subject (Figure 8.2, right). This task is also sensitive to deficits in patients with temporal lobe damage and in patients with selective amygdalo-hippocampectomy (Owen et al. 1995a, 1997), although only at the most extreme level of task difficulty (i.e. eight boxes). Moreover, unlike the frontal lobe patients, the temporal lobe groups utilize a normal and effective searching strategy.

In recent years, these two tasks have been used to draw theoretically driven comparisons between groups of

Figure 8.3. Performance on the spatial span task for the (a) non medicated PD patients with mild clinical symptoms (NMED PD), medicated PD patients with mild clinical symptoms (MED PD (mild)) and medicated PD patients with severe clinical symptoms (MED PD (severe)) (from Owen et al. 1992). (b) Medicated patients with severe clinical symptoms tested both 'on' and 'off' levodopa medication (from Lange et al. 1992). (c) Patients with MSA and PSP (SRO) (from Robbins et al., 1994). (d) Patients with mild HD (from Lawrence et al. 1996), and patients with severe HD or AD matched for severity of dementia (from Lange et al. 1995). Bars represent standard error of the mean (s.e.m.)



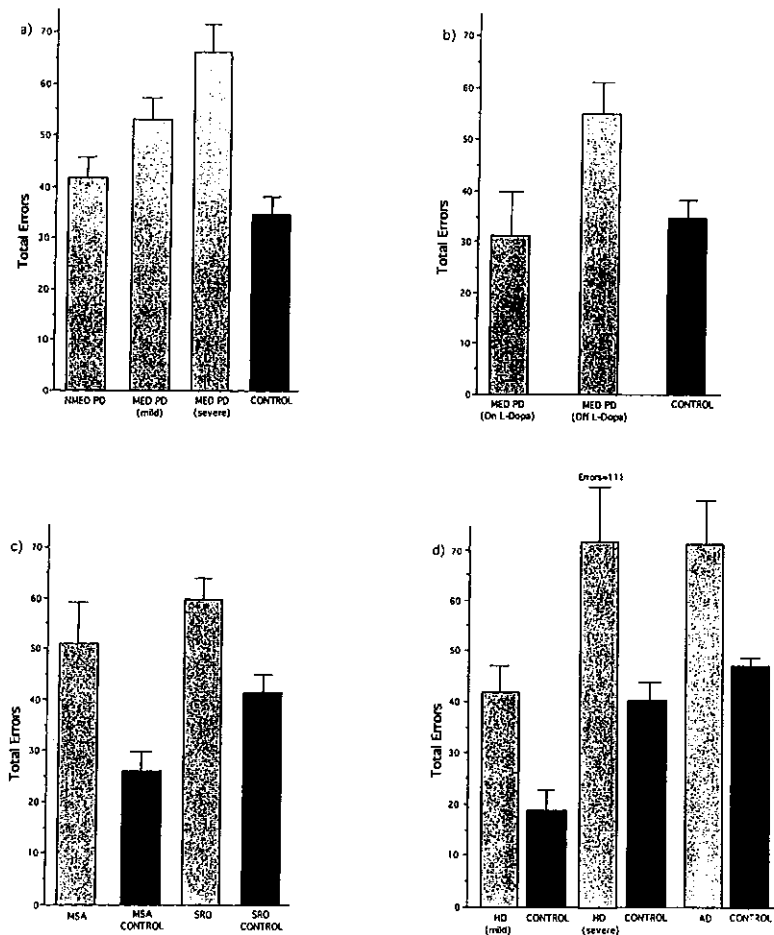
patients at different stages of PD (Owen et al. 1992, 1993), between patients with PD, progressive supranuclear palsy and multiple system atrophy (Robbins et al. 1992, 1994) and between groups of patients with HD and AD matched for degree of dementia (Lange et al. 1995).

#### WORKING MEMORY IN PARKINSON'S DISEASE: THE EFFECTS OF DISEASE SEVERITY

Several recent studies have compared the performance of different groups of patients with PD on these two spatial memory tests which tap demonstrably different aspects of executive function (Morris et al. 1988; Lange et al. 1992; Owen et al. 1992; Robbins et al. 1994). A central model for much of this work has been the concept of cortico-striatal loops (Alexander et al. 1986), which emphasizes the functional inter-relationships between the neocortex and the striatum. Of particular interest is the fact that the princi-

pal 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 higher cognitive functions. A cross-sectional study of patients with PD clearly demonstrated that levodopa medicated and nonmedicated patients at different stages of the disease can be differentiated in terms of their performance on the test of spatial span (Owen et al. 1992) that is known to involve regions of the ventrolateral frontal lobe (Owen et al. 1996b). Thus, a significant impairment was only observed in a subgroup of patients who were medicated and had severe clinical symptoms (Figure 8.3a). This effect was relatively specific as none of the three PD groups was impaired on a test of pattern recognition memory known to be sensitive to temporal lobe, but not frontal lobe, damage (Owen et al. 1995a). It is also unlikely that high doses of dopaminergic medication adversely affect performance in this group as a parallel study of 10

Figure 8.4. Performance on the Self-Ordered Spatial Search task for (a) non-medicated PD patients with mild clinical symptoms (NMED PD), medicated PD patients with mild clinical symptoms (MED PD (mild)) and medicated PD patients with severe clinical symptoms (MED PD (severe)) (from Owen et al. 1992). (b) Medicated patients with severe clinical symptoms tested both 'on' and 'off' levodopa medication (from Lange et al. 1992) (c) Patients with MSA and PSP (SRO) (from Robbins et al. 1994) (d) Patients with mild HD (from Lawrence et al. 1996), and patients with severe HD or AD matched for severity of dementia (from Lange et al. 1995). Bars represent standard error of the mean (s.e.m.)



patients with severe PD has demonstrated that levodopa withdrawal severely disrupts performance on the spatial span task (Figure 8.3b) but does not affect pattern recognition memory (Lange et al. 1992).

In general, patients with PD are more impaired on the strategic searching task (Figure 8.4a) which emphasizes functions known to involve dorsolateral regions of the frontal cortex (Owen et al. 1996b). Thus, like the frontal lobe group, medicated PD patients with both mild and severe clinical symptoms made more errors than matched controls and a non-significant trend towards impairment was observed in the nonmedicated PD group (Owen et al. 1992, 1993). Unlike the frontal lobe patients however, none of the three PD groups was significantly impaired on the measure of task strategy when assessed independently, although subsequently when the same two medicated PD groups were combined for matched comparisons with

other basal ganglia groups (see Robbins et al. 1994), 'frontal like' strategic deficits were suggested. Again, it is unlikely that dopaminergic medication plays any detrimental role in the performance of the medicated PD groups on this spatial self-ordered searching task because controlled withdrawal of levodopa results in a twofold increase in the total number of errors made (Lange et al. 1992; Figure 8.4b).

The results of these studies clearly demonstrate that patients at different stages of PD can be differentiated in terms of their performance on two tests of spatial memory known to involve different regions of the frontal lobe. 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

only observed in a subgroup of patients with severe clinical symptoms. By contrast, when the task required the active manipulation of spatial information within working memory, deficits were observed in medicated patients with both mild and severe clinical symptoms. These differences cannot simply be explained in terms of the concurrent deterioration of motor function in these patients because of the controlled nature and design of these tests. The results do, in fact, concur fully with more extensive neuropsychological evaluations of these same patient groups which suggest that the pattern of cognitive impairment in PD emerges and subsequently progresses according to a defined sequence which evolves in parallel with the motor deficits that characterize the disorder (Owen et al. 1992, 1993). This apparent 'progression' on tests which are known to emphasize different aspects of executive function and appear to depend critically on different regions within the lateral frontal cortex could simply reflect a global difference in cognitive capacity between patients with mild and severe PD. This seems unlikely, however, as the three PD groups could not be distinguished in terms of their performance on a test of pattern recognition memory. This test is not sensitive to frontal lobe excisions, although significant deficits have been observed in patients with temporal lobe lesions (Owen et al. 1995a) and with both mild and moderate dementia of the Alzheimer type (Sahakian et al. 1990; Sahgal et al. 1991). Furthermore, in the series of studies described here, the PD patients were clinically diagnosed as nondemented and were screened for dementia using both the Mini Mental State Examination (Folstein et al. 1975) and the Kendrick Object Learning Test (Kendrick 1985). The possibility that concomitant depression in PD may play a significant role in the progressive pattern of deficits observed can also be discounted because clinical measures of depression did not correlate with performance on either of the spatial memory tests (Owen et al. 1992). In addition, a quite distinct pattern of deficits on these and other tests of cognitive function, has been reported recently for a population of clinically depressed subjects (Elliot et al. 1996).

The question therefore arises as to whether a plausible neural account might be formulated for this progressive sequence of working memory deficits in patients with PD. Nondopaminergic forms of pathology, including noradrenergic, serotonergic and cholinergic deafferentation of the cortex (Agid et al. 1987), may play a significant role in

some of the cognitive deficits observed (Chapters 3 and 4). Similarly, cortical Lewy bodies, which may occur even in the early stages of PD, may play a contributory role (Byrne et al. 1989; Gibb et al. 1989). The fact that both tasks are extremely sensitive to the effects of controlled levodopa withdrawal in a group of patients with severe PD (Lange et al. 1992) suggests a predominantly dopaminergic substrate for both deficits. Moreover, recent anatomical and neuropathological evidence suggests that this evolving pattern of impairments may be linked to what is known about the likely 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 which shows uneven patterns of striatal dopamine loss in patients dying with idiopathic PD (Kish et al. 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. 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 appear 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 rostradorsal extent of the head of this structure, an area which is heavily connected with dorsolateral regions of the frontal lobe (Yeterian and Pandya 1991). It seems likely, therefore, that these rostradorsal 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 (Yeterian and Pandya 1991), are relatively spared in early PD, which may leave functions which are maximally dependent on this neural circuitry relatively intact.

PD is also characterized by dopamine depletion within the frontal cortex itself (Scatton et al. 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 apparent progressive deterioration of 'frontal' working memory deficits in PD. This system however, is known to be less severely affected (50% depletion) than the nigrostriatal dopamine system in PD (Agid et al. 1987) and possibly at a later stage of the disease



process. It may therefore contribute to the more global pattern of frontal lobe deficits observed in patients with severe PD.

#### A COMPARATIVE STUDY OF MEMORY IN PARKINSON'S DISEASE, PROGRESSIVE SUPRANUCLEAR PALSY AND MULTIPLE SYSTEM ATROPHY

A recent comparative study of patients with PD, progressive supranuclear palsy and multiple system atrophy has demonstrated that these patients can also be differentiated in terms of their performance on these two spatial memory tasks. The latter group of patients are particularly interesting because, unlike PD and progressive supranuclear palsy, relatively few studies have specifically investigated the nature of cognitive deficits in multiple system atrophy. In addition to the intrinsic striatal (caudate plus putamen) pathology, damage to the nigrostriatal dopamine pathway in multiple system atrophy is at least equal to, or even greater than, that seen in PD. Like patients with severe PD, a group of patients with progressive supranuclear palsy were significantly impaired, compared to a matched control group, on the test of spatial span, while normal performance was observed in a group of patients with multiple system atrophy (Robbins et al. 1994; Figure 8.3c). The progressive supranuclear palsy patients also made significantly more errors on the spatial search task, although unlike the PD patients, this deficit was quite clearly related to the inappropriate use of the repetitive search strategy, a pattern that is known to characterize the performance of patients with frontal lobe damage (Owen et al. 1990, 1997). In the multiple system atrophy patient group, deficits were also observed in terms of errors (Figure 8.3c), although, unlike the progressive supranuclear palsy group, the strategic element of task performance was preserved (Robbins et al. 1992, 1994).

Thus, like the PD group, the progressive supranuclear palsy patients were significantly impaired on both of the spatial memory tasks, implicating both dorsal and ventral regions of the lateral frontal cortex (Petrides 1994; Owen et al. 1996b). In addition, these patients showed some impairment in a measure of the efficient use of a strategy for mediating the spatial search task, similar to that observed in frontal lobe patients. Together, these findings suggest a profound frontal lobe involvement in progressive

supranuclear palsy, a pattern that is maintained when other frontal lobe tasks are considered (Robbins et al. 1994). They also concur, in a general sense, with the findings of other behavioral (Dubois et al. 1988; Grafman et al. 1990) and neuroimaging (Blin et al. 1990) studies. For example, in the latter PET study, the frontal-like cognitive impairments in patients with progressive supranuclear palsy were found to be correlated with frontal metabolic activity rather than activity in the caudate nucleus.

The fact that performance on the spatial search task was severely impaired in the multiple system atrophy group, while performance on the spatial span task was largely intact, also suggests some similarities between these patients and the neurosurgical group with circumscribed frontal lobe damage, although in general, this pattern is rather less consistent than in the patient group with progressive supranuclear palsy. This general pattern is maintained across a broad range of neuropsychological tasks (Robbins et al. 1992, 1994). The fact that these patients were only impaired on the mnemonic and not the strategic, aspect of task performance on the spatial search test suggests that the deficit observed cannot simply be explained in terms of high level executive dysfunction and may reflect additional deficiencies of spatial memory capacity that are dependent on posterior cortical and subcortical systems.

#### COMPARATIVE STUDIES OF MEMORY IN ALZHEIMER'S AND HUNTINGTON'S DISEASES

It seems likely that striatal dysfunction, as occurs in both PD and HD, would lead to a similar pattern of executive deficits, given the functional inter-relationship that exists between different parts of the frontal cortex and the basal ganglia described above (Alexander et al. 1986). Of particular significance for HD, in view of the primary site of its striatal neuropathology, may be the anatomical and functional relations that exist between the caudate nucleus and the prefrontal cortex.

Lawrence et al. (1996), assessed 18 patients with early HD on tests of executive and mnemonic function, including the two spatial memory tasks of interest here. At this stage of the disease, damage is thought to be restricted primarily to the caudate nucleus and the putamen (Vonsattel et al. 1985; Chapter 3). The HD group had significantly

shorter spatial spans than a matched control group (Figure 8.3d), but performance on this task was far superior to that of a group of patients with more severe clinical symptoms (Lange et al. 1995). Although the deficit in spatial span observed in the mild HD patients reached significance, it is notable that their performance, unlike that of the severe HD group, was relatively good compared to other patient groups who are impaired on this task (see Figure 8.3). The mild HD cases were also significantly impaired in terms of the number of errors committed on the spatial search task (Lawrence et al. 1996; Figure 8.4d) and this group also made significantly less use of the efficient searching strategy, known to improve performance on this task. This pattern of deficit is similar to that observed in neurosurgical patients with frontal lobe damage. In the more severe HD group, deficits on the spatial search task (errors), were far greater than in any other group that has been assessed on this test (Figure 8.4d). In addition, this group showed a tendency to make a very high number of within search errors, i.e. to make repeated, incorrect responses within a given search. This severe impairment in basic mnemonic processing was not observed in the more mildly affected HD patients and is consistent with increased ventrolateral frontal lobe and/or medial temporal lobe involvement late in the course of HD. Together, these findings may suggest a similar pattern of functional degeneration in HD to that observed previously in PD (Owen et al. 1992), by which functions of the dorsolateral frontal cortex are affected at an earlier stage of the disease process than functions of either the ventrolateral frontal cortex or the medial temporal lobe structures. This functional similarity fits with what is known about the neuropathological progression of HD in which neuronal loss begins with the striosome compartment of the head of the caudate nucleus and progresses in a dorsal-to-ventral direction (Hedreen and Folstein 1995). Striosomes in the dorsal regions of the caudate nucleus are connected primarily with the dorsolateral frontal cortex, while those in ventral regions of the caudate nucleus receive input from limbic-related areas. Importantly, however, unlike patients with mild PD, the patients with mild HD studied by Lawrence et al. (1996), were also impaired on a test of visual pattern recognition memory which is known not to involve the frontal lobe, but rather, the temporal lobe and medial temporal lobe structures (Owen et al. 1995a). Connections from the inferotemporal cortex project heavily to the ventrocaudal striatum (ventral putamen and

tail of the caudate nucleus) (Yeterian and Pandya 1995), which has important implications for the pattern of deficits observed in HD, because, unlike PD, some of the earliest neuropathological changes in HD have been reported to occur in the tail of the caudate nucleus (Vonsattel et al. 1985). Thus, it seems likely that the additional impairment in pattern recognition memory in early HD is a result of damage to the ventrocaudal striatum.

Like patients with HD, patients with AD can be expected to be impaired in tests of executive function as the disease progresses, although both neuroimaging and neuropsychological evidence supports the hypothesis that anterior cortical functions are relatively more immune to disruption in this disease (Parks et al. 1993). Sahgal et al. (1991, 1995) have reported spatial span to be impaired in patients with both mild and moderate AD, with the moderate group being significantly more impaired than those with mild AD. Both groups were also impaired on the spatial search task, but not differentially and strategic deficits of the type seen following frontal lobe damage were not evident.

Lange et al. (1995) compared performance in patients with mild to moderate AD and HD matched for level of clinical dementia on these, and other tests of executive function, in order that any differences in specific cognitive functions could not be attributed simply to nonspecific intellectual deterioration. Patients with HD had considerably shorter spatial span scores than patients with AD (Figure 8.3d), although both groups were impaired relative to control subjects matched for age and premorbid IQ. In addition, the HD group made more errors on the spatial search task than the AD group, particularly at more extreme levels of task difficulty (Figure 8.4d). The results clearly demonstrate that, when matched for level of dementia, patients with HD are significantly inferior to patients with AD on the two spatial memory tests that are known to be sensitive to frontal lobe damage and basal ganglia dysfunction. In fact, this general pattern of deficit was maintained across a range of tests of executive function (Lange et al. 1995) and in this sense, the findings are consistent with the existence of greater fronto-striatal pathology in HD than in AD (Berent et al. 1988; Weinberger et al. 1988; Starkstein et al. 1992). It is important to note, however, like patients in the later stages of PD, the deficits in the HD group were not limited to tests clearly requiring executive function. This suggests that the entire pattern of cognitive deficits in HD cannot be

explained by a fronto-striatal hypothesis and may include impairments arising from additional pathology which affects cortical regions other than the prefrontal cortex, such as the temporal lobe. The results are consistent, therefore, with the hypothesis that the neural substrates of many of the cognitive deficits in HD are centered on the caudate nucleus (Berent et al. 1988; Weinberger et al. 1988; Starkstein et al. 1992), but that additional cortical atrophy may also be significant (Berent et al. 1988).

#### EXECUTIVE FUNCTION AND NEURODEGENERATIVE DISEASE: FUTURE DIRECTIONS

The studies described above clearly demonstrate how neuropsychological models of working memory function, developed largely through animal lesion studies and tested using sophisticated functional neuroimaging techniques, have led directly to a marked reappraisal of the status of cognitive deficits in neurodegenerative disease. Much of this work has sought to verify the 'frontal' nature of cognitive deficits in neurodegenerative groups, such as PD and HD and, on the whole, experimental results have supported such a model; however, that is not to say that cognitive impairments resulting from striatal dysfunction are identical to those seen following damage to associated frontal regions. In fact, the studies reported here demonstrate quite clearly that when task demands are subjected to a careful process analysis, subtle but important differences emerge between frontal lobe patients and patients with various neurodegenerative diseases. For example, the deficit in 'strategic' aspects of task performance, which is central to the pattern of impairment observed in patients with frontal lobe damage, is clearly present in patients with HD and progressive supranuclear palsy, but less obvious in PD and markedly absent in multiple system atrophy. Future studies should seek to investigate these potentially important functional differences further by relating them to what is known about the differential neuropathology in each condition.

In drawing comparisons both within and between groups of patients, it is also important to consider the possibility that other 'nonfrontal' aspects of cognitive function may be affected. For example, in some respects, the pattern of deficits observed on the spatial search task in patients with severe PD is similar to that observed in

patients with temporal lobe excisions who make more errors than controls, but exhibited no deficit in task strategy (Owen et al., 1997). This observation is consistent with recent cross-sectional studies which have demonstrated that, while cognitive deficits in early PD are predominantly 'frontal like', performance on tasks which depend preferentially on the medial temporal lobe structures is also affected in the later stages of the disease process (Owen et al. 1992, 1993).

Finally, the majority of studies that have investigated executive processes in neurodegenerative disease in recent years have concentrated on patients with PD and this presumably reflects greater patient availability in this group and the fact that the underlying neuropathology of PD is relatively well established. Future studies, however, should seek to make more direct comparisons between groups of patients with different neurodegenerative disorders including PD, multiple system atrophy, progressive supranuclear palsy and HD and, wherever possible, match across groups for the severity of clinical symptoms. In addition, increasingly sophisticated functional imaging techniques such as functional MRI and PET (Chapter 6) may supplement such comparisons and provide a mechanism by which the neural underpinnings of some of the deficits described above can be more clearly defined. For example, a recent blood flow activation study using PET in patients with PD has demonstrated normal changes in regional cerebral blood in the prefrontal cortex during two tests of executive function involving planning and spatial working memory (Owen et al. 1996a). In contrast, abnormal blood flow in the internal segment of the globus pallidus was observed during both tasks suggesting that striatal dopamine depletion in PD may affect the expression of frontal lobe functions in PD by disrupting the normal pattern of basal ganglia outflow to this region.

Such investigations, when combined with information derived from cognitive psychology, clinical neuropsychology and neurobiology should certainly provide a significant focus for future research and may lead ultimately to a better understanding of the distinctive roles played by the frontal cortex and the striatum in the operation of the 'fronto-striatal' functional loops (Alexander et al. 1986).

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