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Role of Visuospatial Cognition Assessment in the Diagnosis and Research of Atypical Parkinsonian Disorders

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INTRODUCTION

Visuospatial abilities play a pivotal role in our daily living. Indeed, our survival depends, to a great extent, on our ability to navigate sensory space. This means our ability to use spatial maps dependent on visual, tactile, and auditory information to form and guide motor programs. Visuospatial abilities are complex brain operations requiring integration of occipital, parietal, and frontal lobe function, as well as the contribution of subcortical structures. Consequently, it is not surprising that visuospatial skills are often impaired in diseases with movement disorders—an impairment that depends both on the type and on the stage of the disease in question.

Investigating visuospatial skills is helpful not only for differentiating among various diseases with movement disorders, but also for analyzing the source of patients' everyday life impairment, as this can, in turn, generate useful pointers for the development of remedial strategies.

Also, in the detailed analysis of visuospatial performance in patients with movement disorders, particular care must be taken to separate motor from cognitive components. In the devising of neuropsychological tools that can help us to gain a new insight into cortical and subcortical contributions to these activities, this represents a constant challenge.

The aim of this chapter is to review the contribution of visuospatial assessment in the differential diagnosis of movement disorders. After presenting a classification of visuospatial skills, we will discuss the evidence of visuospatial dysfunction in Parkinson's disease (PD) and in the various atypical parkinsonian disorders. We will then advance our own proposal for visuospatial assessment in this group of patients.

CLASSIFICATION OF VISUOSPATIAL DISORDERS

Visuospatial activities have been classified according to different criteria. O'Keefe and Nadel *(1)* divided them on the basis of the sensorimotor responses of persons moving in their own environment, classifying them as "position (or egocentric) responses" when subjects use their body as a reference, as "cued responses" when movements are guided by external cues, and as "place responses" when movements are guided by relationships between external references. Grüsser *(2)* classified the space around the subject as consisting of three functionally different "subspaces": the *body surface*, the *grasping space*, and the *distal space*. It seems that different brain regions are responsible for directing attention to different regions of space. For example, experimental studies on monkeys have local-

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ized the representation of personal space to parietal area 7a and postarcuate frontal area 6. Peripersonal space seems to be encoded by parietal areas 7a and 7b and frontal areas 6 and 8. Extrapersonal space is represented in frontal area 8, parietal area 7a, and the superior colliculus *(3)*.

For the purpose of this review we present a classification of visuospatial abilities that divides them into spatial perception, visuomotor coordination, visuospatial attention, perception of size, spatial memory, and visuospatial imagery. Although any classification of this sort is somewhat arbitrary, we believe it is useful to list the different domains to be examined during neuropsychological testing. Furthermore, the various parkinsonian disorders can affect some of these skills while leaving others intact.

Spatial Perception

Spatial perception is the ability to analyze the spatial relationships both between the stimulus and the observer and between different stimuli. Visual, tactile, and auditory information can contribute to spatial perception. However, visual-perceptual skills predominate disproportionately over the other perceptual skills. According to current theories *(4,5)* visual information is processed by two distinct pathways: the occipito-temporal (ventral) pathway, which conveys information about shape and patterns, and the occipito-parietal (dorsal) pathway, which is involved in spatial analysis. Three fundamental aspects of spatial perception are stimulus localization, perception of line orientation, and depth perception. All can be impaired after brain damage.

Stimulus Localization

Different methods have been proposed to examine stimulus localization. Warrington and Rabin *(6)* presented two cards, either simultaneously or in succession, and asked subjects to evaluate whether the position of a point was the same or different on the two cards. Hannay et al. *(7)* projected onto a screen one or two dots for 300 ms, then, after a 2-s delay, they presented a display showing 25 numbers in different positions: the subject's task was to read aloud the numbers corresponding to the correct dot positions. The performances of right-posterior brain-damaged patients are typically impaired.

Perception of Line Orientation

The most widely used instrument in the assessment of this component of visuospatial perception is the Benton's Judgement of Line Orientation Test *(8)*. This test requires subjects to identify the orientation of a pair of lines on an 11-line multiple-choice display. A number of studies have used this test to assess visuospatial abilities in PD patients, and given varying results. Boller et al. *(9)* demonstrated that PD patients with a normal IQ are impaired in line orientation judgement. Similar results were obtained by Goldenberg et al. *(10)*. However, Richards, Cote, and Stern *(11)* did not find differences between 14 patients with idiopathic PD and 12 normal controls matched for age and education. Similarly Levin and colleagues *(12,13)* did not identify line orientation abnormalities in their mildly and moderately affected PD patients. In a large sample (76 patients and an equal number of matched normal controls), Montse et al. *(14)* demonstrated that, in line orientation judgment, PD patients make proportionally more complex intraquadrant and horizontal line errors, but fewer simple intraquadrant errors than controls. Girotti et al. *(15)* reported that when PD patients were divided into those with and those without dementia, the line orientation test was one of the few tasks that distinguished the nondemented PD patients from controls, whereas many tasks differentiated the demented PD patients from controls. In conclusion, the line orientation test is often abnormal in PD patients but may be normal in patients in whom the disease is less advanced.

Depth Perception

The perception of depth is based on both monocular and binocular sources *(16,17)*. Monocular cues include apparent size of familiar objects, texture and brightness gradient, linear perspective,

occluding contours, shading, and monocular parallax (i.e., the ability to analyze disparate retinal images successively produced by the same object on the retina). Stereopsis is the ability to discriminate depth on the basis of binocular information. Stereoacuity is commonly tested using the quantitative Titmus stereotest, which requires the subject, who is wearing appropriately polarized lenses, to detect circles that appear on a closer plane with respect to the background. Global stereopsis is tested using Julez's random dot stereograms, geometric forms that can—if viewed stereoscopically—be seen from below or above the background plane.

Both the striate and the peristriate and parietal visual areas play a pivotal role in depth perception based on binocular cues *(18–20)*. To the best of our knowledge, no systematic study of depth perception in patients with parkinsonian disorders has to date been conducted.

Visuomotor Coordination

The impaired ability to reach for visually presented stimuli, not related to motor, somatosensory, visual-acuity, or visual-field deficits, is named *optic (visuomotor) ataxia*. To detect subtle visuomotor ataxia, the subject is asked to reach for an object that requires a precision grip (i.e., true opposition of thumb and index finger). In a clinical setting, the examiner will hold the object (a coin or a paper clip) by its edge while the patient attempts to grasp it between the index finger and thumb. In the most severe cases, the disorder is apparent even when the patient is fixating when reaching for the object. More frequently, the impairment is only apparent when the target is located at the periphery of the visual field, or when the patient is not allowed to look at his reaching arm *(21)*.

Reaching for an object is a movement that can be divided into two components: the proximal component (the reaching or transportation phase) and the distal component (the grasping or manipulation phase). This dichotomy has received particular attention because it reveals the difference between two pathways of visuospatial perception respectively devoted to determining the target coordinates in a body-centered space (the occipito-parietal pathway) and to computing shape, size, and weight of the target object (the occipito-temporal pathway) *(4)*.

Examining in detail the different components of reaching for an object requires frame-by-frame analysis of a video recording of the movement. Studies of visuomotor coordination in PD patients show no deficit in the "transportation" and in the "manipulation" components of the reaching-to-grasp movement *(22)*. On the contrary, PD patients demonstrate some dysfunction when they are required to respond appropriately to modification of object size and location *(23,24)*. Rearick et al. *(25)* demonstrated that global features observed in five-digit grasping are preserved in PD patients. However, more subtle aspects of the coordination between digits, as revealed by frequency domain analysis, are not preserved, possibly owing to action tremor.

Visuospatial Attention

When we move in the environment, we are confronted with a vast array of sensory information that the nervous system cannot deal with on an equal basis. Thus, the brain must select which information to process. Visuospatial attention refers to the processes engaged by the nervous system in the selection of relevant information from the mass of information presented by the visual environment.

The neglect syndrome has been characterized as a failure to report, respond to, or orient attention to novel or meaningful stimuli presented to the side opposite to a brain lesion, when this failure cannot be attributed to either sensory or motor defects *(26)*. In severe neglect, patients may behave as though one-half of the world had suddenly ceased to exist. They may fail to eat the food on the left side of their plate, or omit to shave, groom, and dress the left side of the body. In other patients, the symptoms are much subtler and might not be detected by observation of their spontaneous behavior. In the latter cases, special maneuvers may be needed in order to disclose the presence of neglect.

Cancellation tasks are often used for diagnosis of the syndrome. Albert *(27)* developed the simplest form of these tasks, a test in which subjects are required to cancel each item in an array of 40

scattered lines. In the Bells Test *(28)*, rather than scattered lines, 315 small, silhouetted objects are distributed in a pseudorandom manner on the page, with 35 bells scattered among them. Despite their apparently random positions, the bells are actually arranged in seven columns with five bells to a column. The subjects' task is to circle the bells as quickly as possible. Similarly, Mesulam *(29)*, with the purpose of enhancing the method's sensitivity to inattention to the right as well as to the left side, devised verbal and nonverbal cancellation tasks consisting of four sheets, two (nonverbal) with various shapes, and two (verbal) with randomized letters.

A different technique for investigating unilateral inattention is to ask the patient to bisect a line. In the traditional version, patients are asked to mark the midpoint of a horizontal line drawn on a sheet of paper. Normal subjects tend to bisect the line 1–2 mm left of its true center *(30,31)*. Patients with left hemineglect tend to place their mark rightward of the center. To interpret this finding, both space representation and premotor impairment have been invoked. Assuming perceptual factors are responsible, bisection toward the right would be a result of underestimation of the length of the left part of the line, whereas the influence of premotor factors would result in reduced action toward the left (directional hypokinesia) or in reduced amplitude movement toward the left (directional hypometria). Different modifications of the line bisection paradigm have been devised to disentangle the representational and premotor component of bisecting a line. In the landmark test *(32)*, the subject's task is to point to the shorter side of a correctly prebisected line: when patients choose the left side as the shorter their neglect can be attributed to a representational deficit. In the line extension test *(33)*, patients are requested to extend a horizontal line leftward to double its original length. If premotor factors dominate, they should cause a relative left underextension (compared to the right) because of left hypokinesia-hypometria.

Animal studies have shown a central role of the dopaminergic system in the regulation of directional attention. Some authors believe that these circuits are purely premotor *(34)*, whereas others maintain that dopaminergic circuits also mediate perceptual aspects *(35,36)*. In humans, some case reports have shown significant improvement of patients with chronic neglect syndrome after therapy with dopaminergic drugs *(37,38)*. Asymmetric degeneration of the dopaminergic nigrostriatal pathways is the major mechanism underlying the motor symptoms of PD.

A number of early studies have found that patients with left hemi-PD tend to neglect the left side of space *(13,39–41)*. However, the rightward bias of left hemi-PD is at most mild and some authors *(42,44)* were not able to demonstrate visual neglect in their patients. In a more recent study Lee et al. *(43)* examined PD patients with two line bisection tasks. One was a conventional paper- and pencil-test. In the other, subjects were required to bisect a line presented on a computer screen by adjusting the position of a cursor operated by two pushbuttons, one in each hand. No significant differences were found on the paper-and-pencil test. On the contrary, predominantly left-sided PD patients showed significant rightward bias in their setting of the cursor. The same bias was found when subjects repeated the task with the pushbuttons switched between the hands, so that the cursor was moved to the left by the right hand and vice versa, thus suggesting a perceptual rather than a premotor bias.

Adopting a different approach, Ebersbach et al. *(44)* demonstrated that patients with predominantly right-sided PD, as well as normal controls, were more likely to start visual exploration on the left side of texture arrays requiring attentive oculomotor scanning. On the contrary, PD patients with predominantly left-sided disease showed a rightward directional bias for initial exploration, a behavior similar to that demonstrated by patients affected by visuospatial neglect following cortical lesions of the right parietal lobe.

Work by Posner and colleagues *(45)* has provided a theoretical framework within which the different processes involved in orienting attention might be interpreted. They distinguish between two distinct modes of spatial orienting. "Overt" orienting involves turning the eyes toward a particular location of interest, whereas "covert" orienting requires attention to be shifted to this location while the eyes remain fixated elsewhere. Several studies have examined overt orienting in PD patients, and there is a general consensus that internal control of eye movements through voluntary saccades

(remembered, delayed, and predictive saccades and antisaccades) is deficient in PD patients *(46–49)*. At the same time there appears to be no deficit in PD patients for purely reflexive (or visually guided) saccades *(46,47,50,51)*. Thus, studies in PD patients suggest deficits in voluntary (internal) control, but no deficit in reflexive (external) control of overt orienting of attention. To evaluate covert orienting, subjects, all the time maintaining central fixation, are asked to press a key as soon as a peripheral stimulus appears. At the beginning of each trial subjects are given a visual cue, meant to draw their attention to the side where the stimulus is to appear. In most trials the target is presented where it was cued to appear (valid trials), but in some it appears on the opposite side (invalid trials). As it might be expected, normal subjects are significantly faster on valid than invalid trials. Patients with parietal lesions, even if nearly as good as normal controls on valid trials, are severely impaired on invalid trials, which require them to respond to a stimulus contralateral to the lesion. This impairment indicates defective attentional disengagement from a cued location. A number of researchers have reported conflicting results regarding the performance of PD patients in covert orienting tasks, with some studies reporting small covert orienting effects in PD patients *(52,53)*, and others finding no difference *(54–56)*. It turns out that, as for overt attention, it is important to distinguish between voluntary and reflexive control of spatial attention. Voluntary covert attention is assessed by using symbolic cues (e.g., arrows) presented at a central location. The purpose of these cues is to make the subject shift his or her attention to the intended location. Reflexive covert attention is evaluated by presenting a brief cue stimulus in the visual periphery that automatically draws attention to the location of the cue. A couple of studies *(57,58)* compared voluntary and reflexive covert control of spatial attention in PD patients. Both reported relatively normal cuing effects with voluntary (i.e., internally controlled) cues at short (250 ms) and intermediate (500 ms) intervals between cue and target. However, in PD patients facilitatory effects were eliminated with longer (800–1000 ms) intervals, thus demonstrating defective voluntary control of covert attention. On the contrary, PD patients appear to be significantly faster than control subjects on covert reflexive orienting *(59)*. Progressive supranuclear palsy (PSP) and corticobasal degeneration patients (CBD) can show specific impairments in visual-orienting tasks that will be discussed later in this chapter.

Perception of Size

In human perception theories, it is commonly assumed that size is processed independently of shape. Experimental animal studies in monkeys *(60,61)* have confirmed that object size is processed in the brain independently of other stimulus characteristics. An important consequence of this distinction between form and size concerns our general ability to identify objects of different size as identically shaped. The disorder of size perception of which patients are aware is termed *dysmetropsia* (also called dysmegalopsia or metamorphopsia). Objects can appear either shrunk (micropsia) or enlarged (macropsia), compared to their actual size *(62)*. Size perception can be also distorted in visuospatial neglect *(63)*, but in this case patients are unaware of the symptom.

It has recently been demonstrated *(64)* that predominantly left PD patients, probably because of right-hemisphere impairment, perceive a rectangle presented in the left and upper visual space as smaller compared to rectangles presented in different regions of space. The same authors *(65)* have raised the possibility that perceptual errors might have a causal role in determining PD patients' difficulties in negotiating doorways, narrow corridors, and other confined spaces. They asked PD patients to judge whether or not they would fit through a life-size schematic doorway shown on a large screen. Predominantly left PD patients obtained an increased ratio between the door width for which 50% of the judgments were positive and the width of the participant's body at the shoulders. This finding was interpreted as suggesting that the visual representation of the doorway (or of its relationship to perceived body size) is compressed in left PD. However, the clinical implications of this finding are not yet clear, since the authors could not demonstrate a causal role of these perceptual distortions in freezing episodes experienced by PD patients.

Spatial Memory

Within *spatial memory* it is possible to identify *short-* and *long-term* components.

Short-Term Spatial Memory

According to a widely accepted theoretical model *(66)* short-term memory is viewed as a "working memory," where information can be temporarily stored and accessed for use in a wide range of cognitive tasks. Working memory, on the other hand, is made up of an attentional system of limited capacity (the so-called "central executive") and of at least two "slave" subsystems: the "articulatory loop" and the "visuospatial sketchpad," respectively dealing with phonological and visuospatial items. In this scheme, the visuospatial sketchpad would appear to keep visuospatial information "on line" for subsequent processing by the "central executive." This hierarchical organization could allow the concurrent performance of phonological and visual tasks as long as they remain within the capacity limits of the two "slave" systems, whereas the "central executive" would be called upon should the information to be processed exceed these limits. A series of neuroimaging studies *(67)* has determined that spatial working memory is mediated by a network of predominantly right-hemisphere regions that include posterior parietal (BA 40 and BA 7), anterior occipital (BA 19), and inferior prefrontal (BA 47) sites. It has been hypothesized that the premotor area and the superior parietal area might mediate spatial rehearsal, whereas the inferior posterior parietal area and the anterior occipital area might mediate storage of spatial information *(67,68)*.

A simple way to test the visuospatial short-term memory is to measure its span with the Corsi Block Tapping Test *(69)*. The test consists of nine blocks arranged on a board. The examiner taps the blocks in sequences of increasing length, and after each one the subject is requested to copy the sequence just tapped out. The longest sequence correctly tapped out by the subject constitutes his or her visuospatial memory span. An important limitation regarding use of this task in a clinical setting with parkinsonian patients is the fact that it requires a motor response: the spatial span might be underestimated owing to the presence of bradykinesia. Nonetheless, studies that have used Corsi's test *(70)* failed to find any difference between PD patients and normal controls. On the contrary, Bradley, Welch, and Dick *(71)* found that PD patients are slower that normal controls when performing complex visuospatial memory, but not verbal memory, tasks. Postle et al. *(72)* also found a selective impairment of spatial (but not object) delayed response in PD, indicating a selective disruption of spatial working memory. A selective impairment of spatial working memory was also demonstrated in PD patients by Owen et al. *(73)* using a computerized battery of tests designed to assess spatial, verbal, and visual working memory. In the spatial working memory task, subjects were required to search systematically through a number of boxes to find "tokens" while avoiding those boxes in which tokens had previously been found. In the visual and verbal conditions, the subjects were required to search in exactly the same manner, but through a number of abstract designs or surnames, respectively, avoiding designs or names in which a token had previously been found. Medicated PD patients with severe clinical symptoms were impaired on all three tests of working memory. In contrast, medicated patients with mild clinical symptoms were impaired on the test of spatial working memory, but not on the verbal or visual working memory tasks. Nonmedicated patients with mild clinical symptoms were unimpaired on all three tasks. Further investigations by the same group *(73–76)* focused on the cognitive heterogeneity in PD. Taken together, the results demonstrate that impairment of spatial working memory can occur in the early stages of the disease in a subgroup of PD patients with frontostriatal circuitry involvement.

Using the dual-task paradigm to measure the ability to cope with concurrent task demands, a number of investigators *(77–80)* have hypothesized that the "central executive" is impaired in PD patients. Le Bras et al. *(81)*, using a specifically designed testing procedure, concluded that PD patients are impaired in all steps of executive information processing involved in spatial working memory (stimulus encoding, storage, and response programming). More recently, Lewis et al. *(76)* have found that PD patients performing badly on the Tower of London Test (a standard visuospatial

task of executive functioning) were specifically impaired in manipulating information within verbal working memory.

Recent functional magnetic resonance imaging studies *(82)* have implicated the rostral caudate nucleus in the transformation of spatial information in memory to guide the action. Dorsal premotor cortex *(82)* and premotor cortex (Brodmann's areas 46 and 9) are also involved *(83–85)* in performing spatial memory tasks. PD patients are known to suffer loss of dopaminergic input to the rostral caudate. Extensive two-way connections link the striatum, the premotor, and the dorsolateral prefrontal cortices. It is therefore conceivable that the functional impairment of these brain regions is the basis of spatial working memory impairment in PD patients.

Long-Term Spatial Memory

Memory for location is commonly tested by presenting a sheet showing a number of figures, representing objects, and then asking patients, after various time intervals, to relocate them on another sheet in exactly the same position *(86)*. Using a similar procedure Pillon et al. *(87)* demonstrated that, compared to controls, PD patients show significantly impaired spatial location of pictures, a result that contrasts with their relatively preserved verbal memory and only mildly impaired perceptual visuospatial and executive functions. Subsequently, the same group *(88,89)* carried out a number of experiments specifically aimed at determining the nature of the deficit and its relationship with the dopaminergic depletion that characterizes the disease. Results suggested that the memory deficit for spatial location observed in PD patients is a consequence of a disturbance of strategic processing and of decreased attentional resources, which may be a result of dopaminergic depletion and related striatofrontal dysfunction.

Postle et al. *(72)* examined the performances of PD patients and normal controls on a visual delayed-response test with a spatial condition and a (nonspatial) object condition, equating the perceptual difficulty of the tests for each participant. The stimuli were irregular polygons presented at different locations on a computer screen. Results revealed a disruption of spatial memory unconfounded by sensory processing difficulties. The authors hypothesized that the selectivity of this deficit might reflect the circumscribed nature of pathophysiological change affecting the caudate nucleus in early PD.

Maze learning can also be used to evaluate long-term spatial learning. Wallesch et al. *(90)*, to analyze spatial learning and cognitive processes described as impaired in PD, used a computerized maze task that allowed only partial vision of the maze. Results demonstrated that PD patients require more trials than controls to solve the maze problems. Differences between the performances of patients and controls were interpreted as owing to a response bias in the PD patients that resulted in a tendency to repeat the previous action and in impaired multistep plan generation.

Spatial Imagery

The ability to create and manipulate images plays a central role in many daily activities: from navigation to memory and to creative problem solving. According to Kosslyn *(91)* imagery abilities fall into at least four categories: image generation, image inspection, image maintenance, and image transformation. Several neuroimaging studies *(92–94)* have provided strong evidence that visuospatial imagery activates the same brain areas that are involved in visuospatial processing. In line with this finding Levin et al., on the basis of the double dissociating performance of two patients, demonstrated that the distinction between the "what" and "where" cortical visual systems extends to mental imagery tasks. An open question is whether or not image generation, besides being associated with activation of the same representations that are involved in visuospatial processing, also involves the activation of circuits specifically devoted to mental image generating *per se*. In investigating visuospatial impairments of patients with movement disorders, imagery tasks have the advantage that they do not involve overt motor components liable to interfere with the recording of subjects' responses.

Image generation was investigated by Jacobs et al. *(95)*. These authors demonstrated that PD patients are impaired on a task of emotional facial imagery but not on an object imagery control task. They are also impaired on tasks of perceiving and making emotional faces. Performance on both the perceptual and motor tasks of facial expression correlated significantly with performance on the emotional facial imagery task.

Image transformation was investigated in Brown and Marsden's study *(96)*. They employed a mental rotation task that required subjects to align mentally an arrow with one arm of a Maltese cross and to decide whether a dot was on the left or the right of the arrow. PD patients, although slower than controls, did not perform differentially worse in the conditions that required a greater amount of reorientation (e.g., when the arrow was pointing down), thus demonstrating lack of a generalized visuospatial deficit in PD. However, in a subsequent study, Lee et al. *(97)*, using both two- and three-dimensional visual rotation tasks, demonstrated that PD patients make more errors on mental rotations involving larger rotations in depth (or three-dimensional rotations). Furthermore, when three-dimensional rotation is involved, they showed a pattern of reaction time suggesting a specific impairment with larger rotations, thus indicating that PD patients may indeed have some problems in extrapersonal space image transformation.

Disorders of Topographical Orientation

An individual's successful navigation of the environment depends on his or her ability to establish an integrated viewpoint from which objects are represented spatially in relation to her or himself and to each other. To achieve this, visual inputs have to be processed and the results of visuospatial processing associated with information already stored in long-term memory *(2)*. Disorders at any of these levels may affect route finding. Bowen et al. *(98)* demonstrated that a standardized "route walking test" yields deficiencies in PD patients, especially those with left-sided or bilateral symptoms. However, natural environments usually provide a subject with a much richer supply of external cues, which have been shown to facilitate performance *(99)*. Indeed, there is one report in the literature that may account for the thesis that mild-to-moderate PD patients' object-in-location memory does not show spatial deficits when tested in a natural setting *(100)*. Yet, Montgomery et al. *(101)* compared the ability of mild and moderate PD patients and controls to remain oriented to the starting position after being transported passively in a wheelchair. They examined subjects under the condition of either visual or vestibular processing. The moderate PD group demonstrated the poorest performance in both sensory conditions. The visual condition discriminated between the mild PD group and the controls, but both groups gave similar performances in the vestibular condition. Poor performance in the visual condition correlated significantly with poor performance on judgment of line orientation in the mild PD group. The authors concluded that spatial updating, or maintaining a sense of orientation while being moved in the environment, is impaired in PD. More recently, Leplow et al. *(102)* corroborated the view that PD patients show spatial memory deficits also in real-life settings. They devised a "search through" locomotor task incorporating the basic features of two paradigms (the radial maze and the water maze) widely used to assess spatial behavior in animal research *(103,104)*. The participants had to find and remember 5 out of 20 hidden locations within a completely controlled environment. The performances of PD patients were found to worsen if the starting position was moved by 90° and the proximal cues were deleted simultaneously. The results were interpreted as indicating patients' inability to generate rules that can be used flexibly in changing environments.

VISUOSPATIAL DISORDERS IN PARKINSON DISEASE

Visuospatial abnormalities have often been reported in PD patients. Early in 1964, Proctor et al. *(105)* demonstrated that PD patients have difficulty in determining when a rod is vertical if they are in a darkened room. Later, this abnormality was confirmed both in patients seated in a chair that is

tilted either to the right or to the left *(13)*, and in patients who are upright *(106)*. Subsequently, as we have already documented, a number of authors reported that PD is associated with disproportionate impairments in visuospatial abilities. However, for a long time, consensus on the specificity and significance of experimental data was lacking. Part of the debate stemmed from methodological inadequacies of early studies that did not account for factors such as motor speed, dexterity, and presence or absence of pharmacological treatment. On this basis, it was suggested *(107)* that impaired visuospatial ability in PD patients may be owing to "generic" increase in reaction time or other aspects of attentional disorders.

More refined neuropsychological studies both in *de novo* PD patients *(88)* and using tasks either requiring no motor response or minimizing the dexterity, speed, and coordination, provided insight into the existence of visuospatial disturbances free of such confounding motor factors. In addition, statistical techniques were used to explore relationships between motor and visuospatial deficits and helped to determine whether or not spatial deficits are of the same magnitude as, or in excess of, those attributable to motor abnormalities.

Since degeneration of dopaminergic neurons constitutes the main biochemical abnormality found in PD, dopamine depletion has been considered to account for most of the symptoms, including behavioral abnormalities and cognitive deficits *(89)*. If striatal dopamine deficiency plays a role in PD patients' cognitive deficit, specialized hemispheric functions contralateral to the motor symptoms should be altered in patients with hemiparkinsonism, providing a unique opportunity to study the effect of asymmetrical subcortical degeneration on cognitive functions *(108)*. Yet, the results of these studies have been controversial. A number of studies were not able to demonstrate a specific pattern of difference between patients with predominantly left and right symptoms *(9,109–111)*. However, a number of more recent studies *(43,44)* did find a specific directional bias related to the side of the predominant symptoms. On the other hand, Pillon et al. *(112)* demonstrated that cognitive impairment is poorly correlated with symptoms responding well to levodopa treatment (e.g., akinesia and rigidity) and is strongly related to axial symptoms (such as gait disorders and dysarthria), which respond little if at all to levodopa treatment. This finding was interpreted as suggesting that cognitive impairment in PD patients is, to a great extent, a result of dysfunction of non-dopaminergic neuronal systems. A further suggestion that the visuospatial deficits of PD patients do not always depend on the same mechanisms subserving motor impairments derives from the observation that patients treated with bilateral deep brain stimulation of the subthalamic nucleus, despite obtaining clinical motor benefits, show a significant decline in their ability to encode visuospatial material *(113)*. According to this study, the decline was more consistently observed in patients over the age of 69 yr and it led to a mental state that the authors describe as similar to that observed in progressive supranuclear palsy (PSP) patients.

In conclusion, it is still possible that striatal dopamine deficiency, even if it is not the major determinant of visuospatial deficits, could play a role in determining attentional bias underlying the subtle neglect phenomena that are encountered in predominant left-sided PD patients.

PROGRESSIVE SUPRANUCLEAR PALSY

The most striking feature of PSP patients is the fixity of gaze that, resulting from supranuclear ophthalmoplegia, gives the disease its name. However, far from being a purely oculomotor problem, PSP patients' ocular movement difficulties are accompanied by a severe deficit in orienting attention. Rafal *(114)* has outlined very well the difficulties that PSP patients encounter in everyday life and how these difficulties interact with other components of the disease (gait disorder, dysphagia, and nuchal dystonia). When conversing with others, reaching for objects, eating, or dressing, PSP patients typically tend not to look at what they are doing. This failure to orient spontaneously the lower visual field contributes to gait disequilibrium (the source of falls) and to the ingestion of boluses that are too large to swallow (the source of *ab ingestis*). Loss of spontaneous social orienting is also a striking

feature of PSP and it is kind of unique to this disease. Relatives tend to note this as an early sign and often attribute it to a change of mood or to carelessness.

A further characteristic trait of visuomotor impairment in some PSP patients is, conversely, difficulty in inhibiting orienting responses in situations in which orienting is disadvantageous. One need only think of patients who, as they walk, tend to orient toward the door or a wall mirror or TV set they have just passed, as if they were magnetically attracted to and fixed upon that object in the environment. This visual behavior, also called "visual grasping" by Ghika et al. *(115)*, is associated with repeated backward head movements while walking and is, consequently, a further cause of backward falls *(114)*.

As early as 1981, Kimura et al. *(116)* demonstrated that PSP patients are impaired in visual search and scanning tasks. Subsequently, Fisk et al. *(117)* performed systematic observations in an attempt to relate the performances of PSP patients on visual search and scanning tasks to the pattern of their oculomotor deficits. In one of these tasks, subjects were required to scan lines composed of a variable number of dots and dashes and to report either the number of dashes or the number of dots. Scanning in each of the four directions was measured: left to right, right to left, top to bottom, and bottom to top. PSP patients were less accurate than controls only when scanning along the vertical plane. This confirmed that bradykinesia and psychomotor retardation could not account for impaired performance and that some specific defect of visual search and scanning along the vertical plane had to be assumed.

Impaired performance on a visual search task, as well as on the Benton's Judgement of Line Orientation Test *(8)*, was also demonstrated by Soliveri and coworkers, in comparison with both normal controls *(118)* and PD patients *(119)*. The same authors could not demonstrate any difference on these tasks between PSP and CBD patients *(119)*.

In a detailed study of 25 patients, Esmonde et al. *(120)* confirmed a severe visuo-perceptual deficit in PSP. They found marked differences between patients and controls in two subtests of the Visual Object and Space Perception Battery *(121)*, (the Fragmented Letter and Cube analysis tests) which were explicitly chosen to minimize the effect of oculomotor scanning on performance.

Subsequently, in a series of experiments, Rafal, Posner, and colleagues *(45,122,123)* demonstrated that PSP patients are not only slow in scanning and searching when allowed to move their eyes, but also in covertly shifting their visual attention, especially in the vertical plane. However, unlike PD patients, who demonstrate defective voluntary control of covert attention, PSP patients are especially impaired in reflexive orienting.

The authors came to this conclusion after comparing attentional movements from both endogenous and exogenous cues. In both cases the subjects' task was to press a button upon detecting a target. In these tasks, targets are preceded by cues that may orient the attention to the target location (valid cue) or to another location (invalid cue), or may have only an alerting value and provide no spatial information (neutral cue). For testing voluntary control of attention, the (endogenous) cue is typically an arrow in the center of the display, instructing the subject where to expect the forthcoming target. Reflexive orienting is tested by an exogenous cue, e.g., lighting up of the box where the target might appear. In this case, unlike the case of the central cue paradigm, the cue has no predictive value and the target is equally likely to appear in an uncued as in the cued location. Results demonstrated that PSP patients show no "validity effect" on reflexive orienting of attention along the vertical plane: i.e., they are no faster in responding to a target when it is preceded by a valid exogenous cue. A similar trend for smaller orienting effects in the vertical plane is also seen in endogenous orienting but it is not as dramatic as in reflexive orienting. In other words PSP patients have problems in "shifting" attention, especially in the vertical plane and especially in response to exogenous signals.

Kertzman et al. *(124)* also provided evidence consistent with the conclusion that PSP has little or no effect on endogenous orienting of attention. In their experiment the cue was lighting up of a peripheral box that predicted the location of the forthcoming target. Vertical and horizontal attention

movements were tested in separate blocks, thus giving the subjects maximum opportunity to use the cue to shift attention. Under these conditions the PSP patients did not show a smaller effect of cue validity in the vertical plane. This demonstrated that PSP patients' attentional deficit can be contrasted with that of inferior parietal lobe patients. These latter patients are typically impaired in the presence of endogenous cues, in the horizontal plane, and in the invalid cue condition, i.e., when they have to "disengage" attention that was cued by a central signal to the side opposite the target.

Rafal et al. *(114)* demonstrated quite convincingly that PSP attentional deficit is likely to be a result of the degenerative damage to the superior colliculus and the adjacent tectal nuclei. This part of the midbrain constitutes the phylogenetically older retinotectal pathway, which retains important functions for regulating visual attention and visually guided behavior. The frontal eye fields are also important in controlling saccadic eye movements *(125)*, show dramatic hypometabolism in PSP patients *(126)*, and might also be responsible for visual attention deficits. Nonetheless, patients with lesions restricted to the dorsolateral prefrontal cortex (including the frontal eye fields) perform normally in covert orienting of attention *(127)*, even if they show increased latencies for endogenous saccades to targets contralateral to the lesion *(128)*. Furthermore, converging evidence from normal subjects *(129)* and from hemianopic patients *(130)* demonstrates that the midbrain retinotectal pathway is important in reflexive orienting to exogenous signals and corroborate the view that it is decisive in determining the visuomotor and attentional deficit typically found in PSP patients.

CORTICOBASAL DEGENERATION

Corticobasal degeneration (CBD) is clinically characterized by the combination of motor with cognitive disorders. Neuropathologically, it features circumscribed parietal or frontoparietal atrophy, associated with basophilic and tau-postive inclusions in the neurons of the substantia nigra and basal ganglia.

Reflecting this definite pattern of neuronal damage, neuropsychological deficits of CBD patients most commonly include deficits of executive functions and of retrieval processes (in relation to the damage of the prefrontal cortex and the striatum) and apraxia (owing to the involvement of the parietal cortex). Leiguarda et al. *(131)* described the nature of apraxia in CBD. To minimize the confounding effects of the primary motor disorder, they examined the least affected limb. They found that ideomotor apraxia is the most frequent type of apraxia in CBD patients and they hypothesized that it was because of the dysfunction of the supplementary motor area (SMA). They also examined a subgroup of CBD patients with severe (ideomotor and ideational) apraxia, correlating this with global cognitive impairment, and attributed it to additional parietal or diffuse cortical damage. Several authors have hypothesized that SMA dysfunction underlies limb apraxia in CBD *(132,133)*, but a similar role has also been attributed to the lateral premotor cortex *(133,134)* and to the parietal regions *(135,136)*.

Indeed, the left supplementary motor cortex has been repeatedly implicated in the genesis of apraxia *(137–140)*. However, the role of the left posterior parietal lobe in determining ideomotor *(141,142)* and ideational *(143)* apraxia is well documented. Furthermore, the assumption that ideational apraxia is an extreme form of ideomotor apraxia (a result of brain damage superimposed on that causing the latter form of apraxia) is disproved by the lack of correlation between the two deficits *(144)*.

A couple of studies have tried to determine the origin of apraxia in CBD patients. Blondel et al. *(132)* tried to characterize the different processes underlying apraxic disorders in these patients according to a theoretical framework postulating a two-step system controlling limb gestures: the conceptual system and the production system. The results, extremely similar in the three patients they studied, showed a sparing of the conceptual system and an impairment of the production system with a dramatic deficit in the control of the temporal and spatial aspects of the gestures. The authors interpreted these results as suggesting a dysfunction of the SMA. Similarly, Jacobs et al. *(133)* reported the

results of testing three nondemented CBD subjects on tasks requiring the production of meaningful or meaningless gestures to command, gesture imitation, gesture discrimination, and novel gesture learning. The results suggested that apraxia associated with CBD is initially induced by a production-execution defect with relative sparing of the movement representations. However, combining neuropsychological and neuroimaging investigations, Peigneux et al. *(145)* found that, in CBD patients, the anterior cingulate cortex is involved when visuospatial attention and conflict monitoring is necessary or when task difficulty, motor output, and recent memory requirements must be combined. However, when apraxia is defined according to a more stringent test of the integrity of the components of the praxic system (measuring the patients' ability to correct their errors on a second attempt), hypometabolism is found in the superior parietal lobule and in the SMA. This demonstrates the importance of parietofrontal circuits in the transformation of sensory input into action. Damage to these systems is likely to produce different types of limb apraxia depending on the injured site, the context in which the movement is performed, and the cognitive demands of the action *(146,147)*.

The superior parietal lobule appears to be crucial in visually guided movements *(148)*, mental transformation of the body in space *(149)*, and elaboration and maintenance of working representation of gestures to perform *(150,151)*. It is also involved in successful integration of internal and external representations to direct action *(152)*. In turn, the SMA is most likely to be involved in transcoding stored space-time representations of movement into limb innervatory patterns *(153)*.

Wenning et al. *(154)* have reported that constructive apraxia, possibly demonstrable as a failure to copy drawings, is reported at the first visit in 64% of pathologically confirmed CBD patients. Since constructive apraxia is unlikely to be an early sign in a patient with an asymmetric parkinsonism, drawing copying might be a useful test to corroborate the CBD diagnosis.

Interestingly, in the same study, two patients with onset of motor symptoms on the left side developed left-sided visuospatial neglect, whereas patients with onset of right motor symptoms developed aphasia. A further pathologically confirmed CBD demonstrating left neglect was reported by Rey et al. *(155)*. More recently, Kleiner-Fisman et al. *(156)* reported a single case study of a professional artist in whom presumed CBD was associated with left hemispatial neglect. It led to a complex alteration of his artistic judgment and production. From a clinical standpoint it should be concluded that in the absence of focal lesions (e.g., of vascular or neoplastic origin), the presence of both ideomotor apraxia and left neglect should give rise to suspicion of CBD.

Following bilateral involvement of the parieto-occipital junction, CBD patients can also show a complete Balint–Holmes syndrome *(157)*, consisting of gaze apraxia (defective visual scanning), optical ataxia (defective visual reaching), impaired visual attention, defective estimation of distance, and impaired depth perception. Mendez *(158)* recently described a patient whose illness began with a slow, rigid gait, abnormal postures of his right hand, and retrocollis. As the disease progressed, he developed prominent visuospatial deficits that, after 8 yr, included a Balint–Holmes syndrome. We have personally observed *(159)* a patient with an opposite disease progression: i.e., beginning with the visuospatial symptoms of the Balint–Holmes syndrome and showing signs and symptoms of basal ganglia involvement only 4 yr after disease onset. Examples of Balint–Holmes syndrome can also be found in early stages of Alzheimer's dementia *(160,161)*. There has been some suggestion that cognitive impairment is a common feature of CBD *(162,163)*. According to Grimes, Lang, and Bergeron *(163)* CBD patients fulfilling classical diagnostic criteria might represent a minority of those with a pathologically confirmed diagnosis. They argue that case series emphasizing motor deficits, originating prevalently from movement disorder clinics, might slight the importance of cognitive impairment in CBD. Such a bias would indeed make the differential diagnosis of a patient presenting with Balint–Holmes syndrome particularly challenging, including besides CBD, Creutzfeld–Jakob disease, multifocal progressive leucoencephalopathy, strokes *(164)*, and a progressive posterior atrophy occurring in isolation *(165–168)*.

DIFFUSE LEWY BODY DISEASE

Dementia with Lewy bodies (DLB) is the second most common type of cognitive degeneration after Alzheimer's disease (AD) *(169)*. Clinically, DLB is characterized by spontaneous parkinsonism and progressive dementia associated with fluctuating cognitive functions, and hallucination *(169)*. Parkinsonism and dementia tend to co-occur. A history of Parkinsonism predating dementia by more than 1 yr might be better designated "Parkinson's disease with dementia." Since publication of the clinical and pathological diagnosis criteria *(169)*, several studies have tried to delineate the neuropsychological features that distinguish DLB disease from AD. A number of them have demonstrated that, compared with AD, visuospatial and visuoconstructive abilities are disproportionately impaired in patients with DLB disease *(170–173)*. Compared with AD patients matched for age, sex, education, and Mini Mental State Examination (MMSE) score, DLB patients perform worse on the Raven Colored Progressive Matrices test and on the picture arrangement, block design, object assembly, and digit symbol substitution subtests of the Wechsler Adult Intelligence Scale–Revised *(173)*. They also perform worse on size discrimination, form discrimination, visual counting, and overlapping figure identification *(174)*.

Mori et al. *(174)* also demonstrated that, in the DLB group, patients with visual hallucinations scored significantly lower on overlapping figure identification than those without, whereas patients with television misidentifications gave significantly lower scores on the size discrimination, form discrimination, and visual counting tasks than those without. The underlying assumption is that specific brain regions are involved in the performance of these tests: the occipital visual association cortex for size discrimination, the occipito-temporal visual association cortex for size discrimination, and the occipito-parietal cortex for visual counting.

Similar results were obtained by Simard, Rikum, and Myran *(175)*. These authors compared the performance on the Benton Judgement Line Orientation Test of patients with DLB and predominant parkinsonism, with DLB and predominant psychosis, and with AD. For this purpose they analyzed errors as resulting from visual attention and visuospatial perception failures. The study did not find significant differences on the total score of the Benton Judgement Line Orientation Test. However, error analysis demonstrated that subjects with DLB and psychosis have more severe visual-perception (VH errors) impairments than subjects with DLB and predominant parkinsonian features, and AD subjects.

These results suggest that defective visual input caused by visual-system damage can result in hallucinations from defective visual processing or abnormal cortical release phenomena *(176)*. Indeed, Imamura et al. *(177)* using positron emission tomography, found that visual hallucinations in DLB patients are associated with relatively preserved metabolism in the right temporoparietal association cortex and severe hypometabolism in the primary and secondary visual cortex.

A practical implication of the disproportionate impairment of DLB patients in visuospatial tasks has been demonstrated by Ala et al. *(178)*. These authors analyzed accuracy in copying the interlocking pentagon item of the MMSE in patients with neuropathologically confirmed DLB and AD. They concluded that in patients with MMSE scores $\geq$13 an inability to accurately copy the pentagons suggests that the diagnosis is more likely DLB than AD with a sensitivity of 88% and a specificity of 59%.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) is a term used to describe a progressive neurological condition incorporating a parkinsonian syndrome (striatonigral degeneration), often accompanied by autonomic failure (Shy–Drager syndrome) or cerebellar and/or pyramidal signs (olivopontocerebellar atrophy—OPCA) *(179,180)*.

Cognitive deterioration is not generally considered to be an integral feature of MSA *(181)*. Indeed, lack of dementia throughout the course of the disease has been proposed as a feature that might help to differentiate between MSA and PD premortem *(182)*.

However, routine neuropsychological assessment often reveals multiple cognitive deficits suggesting a prominent involvement of the frontal lobe *(183)*. MSA patients perform normally on tasks of spatial and pattern recognition, which are sensitive to deficits in patients with AD and medicated PD *(183,184)*. On the contrary, Robbins et al. *(183)* demonstrated that MSA patients are impaired in comparison with matched controls on test of visual memory and learning but in specific and unusual ways. Thus on a matching-to-sample test they were significantly impaired at the simultaneous stage, when no memory was involved, but showed normal delayed matching performance. This particular pattern of deficit is distinct from that reported in PD patients *(184)*. Moreover, on the test of visual learning, unlike PD patients *(184)*, the MSA subjects performed surprisingly well at the more difficult levels of the task but were inefficient at the early stages.

Taken together, this pattern of performance is suggestive of problems in attention and orientation rather than of primary visual learning or memory deficits. Visuospatial contrast thresholds are also unimpaired in MSA, unlike PD patients, who normally exhibit a reduction in contrast sensitivity *(185)*. This finding suggests that reduced contrast sensitivity is related to a dopaminergic pathology, possibly at the level of retinal amacrine cells, which might be affected in PD *(186–188)* but not in MSA *(185)*.

CONCLUSION

Abnormalities of visuospatial functions are common in PD and in atypical parkinsonian disorders. They have been described in several domains of visuospatial ability. In some tasks the alteration can reflect the motor disorders. However, in many instances it is possible to demonstrate that the contribution of motor skills to a task is either minimal or absent. Different disorders have different patterns of impairment. For instance, in CBD, apraxia and optic ataxia are most common, whereas PSP patients show a characteristic impairment in shifting their visual attention downward.

To date, no systematic study of atypical parkinsonian syndromes has been performed using a predefined battery of visuospatial tasks aimed at helping the clinician in the differential diagnosis at disease onset. We would propose that such a battery (*see* Table 1) should at least contain a perceptual task such as the Benton's Judgement of Line Orientation Test *(8)*, a task of visuospatial working memory and a task of visuospatial learning. To examine visuospatial working memory we would propose a visuospatial span task as proposed by Le Bras et al. *(81)*. A computerized maze task *(90)* could be used to test visuospatial learning. The Tower of London task *(189,190)* or one of the several versions of the Tower of Hanoi Test *(191)* could be useful to test visuospatial working memory and some aspects of planning. If administered repeatedly, it can also allow exploration of implicit rule learning, which is typically impaired in PD and in Huntington's disease patients *(192)*. Three-dimensional visual rotation tasks *(97)* appear to be most sensitive to test visuospatial transformation in the imagery domain.

In the clinical setting, we have found it extremely useful to test visuomotor coordination by asking patients to reach for an object that requires precision gripping. Patients with damage to the posterior parietal lobe (as in CBD) show early impairment on this task. A standardization of the procedures for testing visuomotor coordination is likely to improve the sensitivity of this procedure.

To test visuospatial attention in this group of patients we prefer to use visuospatial search tasks. For this purpose, it is important to present the stimuli on a screen in front of the subject and to prepare visual displays that can allow exploration of attentional movements in both the horizontal and the vertical direction. Finally, testing visuospatial functions may be extremely useful in the differential diagnosis of disorders associating parkinsonian features and early cognitive damage. For this purpose, a copying drawing task should be included in the test battery. In this case the motor components cannot be eliminated. However, in most cases it is not difficult to separate them from errors owing to faulty organization of the spatial arrangement of the design to be copied.

Table 1
Visuospatial Test for the Assessment of Parkinsonian Disorders

Test	Reason to Include It in the Visuospatial Assessment
Judgement of Line Orientation *(6)*	Can help differentiate demented from nondemented PD patients.
Copying Drawing Task *(154,178)*	Early impaired in CBD and DLB patients.
Optic Ataxia Assessment (*)	CBD patients are particularly impaired at this task
Tower of London *(76)*	A sensitive task to detect visuospatial working memory deficit in early stages of PD.
Tower of Hanoi *(191,192)*	Comparison of repeated performance at this task allows exploration of implicit rule learning, which is typically impaired after basal ganglia damage.
Wilson-Le Bras test *(81)*	It can measure of the visuospatial span without the motor component involved by the Corsi Block Tapping Test.
Posner test *(45,122,123)*	At this task, PD patients demonstrate defective voluntary control of covert attention. PSP patients, on the contrary, are especially impaired in reflexive orienting.
3D mental rotation *(97)*	PD patients are impaired in 3D mental rotation. Little is known about the performance of atypical parkinsonism patients at this task.

*There is no standardized bedside procedure to administer this task.

SPECIFIC ISSUES THAT CAN BE ADDRESSED BY FUTURE RESEARCH OF VISUOSPATIAL COGNITION IN PARKINSON DISEASE AND IN ATYPICAL PARKINSONIAN DISORDERS

1. What is the role of the colliculus and of the dorsal frontallobe damage in the visuospatial impairment of PSP patients?
2. To develop a suitable method for assessing attentional movements both in the horizontal and in the vertical direction in a clinical setting.
3. Does unilateral neglect in CBD patients have a different qualitative pattern than in PD patients?
4. Which is the physiological basis of neglect in unilateral PD patients compared with parietal lobe damaged patients?
5. Which is the role of the dopaminergic system in controlling visuospatial exploration in PD patients? Can dopaminergic drugs improve directional attention deficits in PD patients?
6. Is there any difference in depth perception and in reaching performance between PD and atypical parkinsonian syndromes?
7. Can a careful assessment of visuospatial skill help diagnostic accuracy in the early stage of parkinsonian diseases?
8. Is there any role of impairment in size discrimination in determining "freezing" episodes in PD patients?

REFERENCES

1. O' Keefe J, Nadel L. The Hippocampus as a Cognitive Map. New York: Clarendon, 1978.
2. Grüsser OJ. Multimodal structure of the extrapersonal space. In: Hein A, Jeannerod M, eds. Spatially Oriented Behavior. New York: Springer-Verlag, 1987:327–352.
3. Rizzolatti G, Gentilucci M, Matelli M. Selective spatial attention: One centre, one circuit, or many centres? In: Posner MI, Marin OSM, eds. Attention and Performance IX. Hillsdale, NJ: Erlbaum, 1985:251–265.
4. Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci 1992;15:20–25.
5. Ungerleider LG, Haxby JV. "What" and "where" in the human brain. Curr Opin Neurobiol 1994;4:157–165.
6. Warrington EK, Rabin P. Perceptual matching in patients with cerebral lesions. Neuropsychologia 1970;8:475–487.
7. Hannay HJ, Varney NR, Benton AL. Visual localization in patients with unilateral disease. J Neurol Neurosurg Psychiatry 1976;39:307–313.
8. Benton AL, Varney NR, Hamsher KD. Visuospatial judgment: a clinical test. Arch Neurol 1978;35:364–367.

9. Boller F, Passafiume D, Keefe NC, Rogers K, Morrow L, Kim Y. Visuospatial impairment in Parkinson's disease: Role of perceptual and motor factors. Arch Neurol 1984;41:485–490.
10. Goldenberg G, Wimmer A, Auff E, Schnaberth G. Impairment of motor planning in patients with Parkinson's disease: evidence from ideomotor apraxia testing. J Neurol Neurosurg Psychiatry 1986;49:1266–1272.
11. Richards M, Cote LJ, Stern Y. The relationship between visuospatial ability and perceptual motor function in Parkinson's disease. J Neurol Neurosurg Psychiatry 1993;56:400–406.
12. Levin BE, Llabre MM, Weiner WJ. Cognitive impairment associated with early Parkinson's disease. Neurology 1989;39:557–561.
13. Levin BE. Spatial cognition in Parkinson disease. Alzheimer Dis Assoc Disord 1990;4:161–170.
14. Montse A, Pere V, Carme J, Francesc V, Eduardo T. Visuospatial deficits in Parkinson's disease assessed by judgment of line orientation test: error analyses and practice effects. J Clin Exp Neuropsychol 2001;23.:592–598.
15. Girotti FS, Soliveri P, Carella F, et al. Dementia and cognitive impairment in Parkinson's disease. Neurology 1988;51:1498–1502.
16. Livingston M, Hubel D. Segregation of form, color, movement, and depth: Anatomy, physiology, and perception. Science 1988;240:740–749.
17. Parker AJ, Cumming BG, Johnston EB, Hurlbert AC. Multiple cues for three-dimensional shape. In: Gazzaniga MS, ed. The Cognitive Neurosciences. Cambridge, MA: MIT Press, 1985:351–364.
18. Gulyas B, Roland PE. Binocular disparity discrimination in human cerebral cortex: functional anatomy by positron emission tomography. Proc Natl Acad Sci USA 1994;91:1239–1243.
19. Ptito A, Zatorre RJ, Petrides M, Frey S, Alivisatos B, Evans AC. Localization and lateralization of stereoscopic processing in the human brain. Neuroreport 1993;4:1155–1158.
20. Fortin A, Ptito A, Faubert J, Ptito M. Cortical areas mediating stereopsis in the human brain: a PET study. Neuroreport 2002;3:895–898.
21. Perenin MT, Vighetto A. Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. Brain 1988;111(Pt 3):643–647.
22. Bonfiglioli C, De Berti G, Nichelli P, Nicoletti R, Castiello U. Kinematic analysis of the reach to grasp movement in Parkinson's and Huntington's disease subjects. Neuropsychologia 1998;36:1203–1208.
23. Castiello U, Bennett K, Bonfiglioli C, Lim S, Peppard RF. The reach-to-grasp movement in Parkinson's disease: response to a simultaneous perturbation of object position and object size. Exp Brain Res 1999;125:453–462.
24. Fellows SJ, Noth J, Schwarz M. Precision grip and Parkinson's disease. Brain 1998;121:1771–1784.
25. Rearick MP, Stelmach GE, Leis B, Santello M. Coordination and control of forces during multifingered grasping in Parkinson's disease. Exp Neurol 2002;177:428–442.
26. Heilman KM. Neglect and related disorders. In: Heilman KM, ed. Clinical Neuropsychology. New York: Oxford University Press, 1979:268–307.
27. Albert ML. A simple test of visual neglect. Neurology 1973;23:322–326.
28. Gauthier L, Dehaut F, Joannette Y. The Bells Test: A quantitative and qualitative test for visual neglect. Int J Clin Neuropsychool 1989;11:49–54.
29. Mesulam M-M. Principles of Behavioral Neurology. Philadelphia: Davis, 1985.
30. Bradshaw JL, Nettleton NC, Nathan G, Wilson L. Bisecting rods and lines: effects of horizontal and vertical posture on left-side underestimation by normal subjects. Neuropsychologia 1985;23:421–425.
31. Scarisbrick DJ, Tweedy JR, Kuslansky G. Hand preference and performance effects on line bisection. Neuropsychologia 1987;25:695–699.
32. Milner AD, Brechmann M, Pagliarini L. To halve and to halve not: an analysis of line bisection judgements in normal subjects. Neuropsychologia 1992;30:515–526.
33. Ishiai S, Sugishita M, Watabiki S, Nakayama T, Kotera M, Gono S. Improvement of left unilateral spatial neglect in a line extension task. Neurology 1994;44:294–298.
34. Carli M, Evenden JL, Robbins TW. Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. Nature 1985;313:679–682.
35. Marshall JF, Gotthelf T. Sensory inattention in rats with 6-hydroxydopamine-induced degeneration of ascending dopaminergic neurons: apomorphine-induced reversal of deficits. Exp Neurol l1979;65:398–411.
36. Ljungberg T, Ungerstedt U. Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. Exp Neurol 1976;53:585–600.
37. Fleet WS, Valenstein E, Watson RT, Heilman KM. Dopamine agonist therapy for neglect in humans. Neurology 1987;37:1765–1770.
38. Geminiani G, Bottini G, Sterzi R. Dopaminergic stimulation in unilateral neglect. J Neurol Neurosurg Psychiatry 1998;65:344–347.
39. Villardita C, Smirni P, Zappalà G. Visual neglect in Parkinson disease. Arch Neurol 1983;40:737–739.
40. Gauthier L, Gautheir SG, Joannette Y. Visual neglect in left-, right-, and bilateral parkinsonians. J Clin Exp Neuropsychol 1985;7:145 (abstract).

41. Starkstein S, R Leiguarda R, Gershanik O, Berthier M. Neuropsychological disturbances in hemiparkinson's disease. Neurology 1987;37:1762–1764.
42. Ransmayr G, Schmidhuber-Eiler B, Karamath E. Visuoperception and visuospatial and visuorotational performance in Parkinson's disease. J Neurol 1987;235:99–101.
43. Lee AC, Harris JP, Atkinson E, Fowler MS. Evidence from a line bisection task for visuospatial neglect in left hemiparkinson's disease. Vision Res 2001;41:2677–2686.
44. Ebersbach G, Trottenberg T, Hattig H, Schelosky L, Schrag A, Poewe W. Directional bias of initial visual exploration. A symptom of neglect in Parkinson's disease. Brain 1996;119(Pt 1):79–87.
45. Posner MI, Cohen Y, Rafal RD. Neural systems control of spatial orienting. Philos Trans R Soc Lond B Biol Sci 1982;298:187–198.
46. Briand KA, Strallow D, Hening W, Poizner H, Sereno AB. Control of voluntary and reflexive saccades in Parkinson's disease. Exp Brain Res 1999;129:38–48.
47. Crawford T, Henderson L, Kennard C. Abnormalities of nonvisually guided eye movements in Parkinson's disease. Brain 1989;112:1537–1586.
48. Crevits L, De Ridder K. Disturbed striatoprefrontal mediated visual behavior in moderate to severe Parkinsonian patients. J Neurol Neurosurg Psychiatry 1997;63:296–299.
49. O'Sullivan EP, Shaunak LH, Hawken M, Crawford TJ, Kennard C. Abnormalities of predictive saccades in Parkinson's disase. Neuroreport 1997;8:1209–1213.
50. Carl JB, Wurts RH. Asymmetry of saccadic control in patients with hemi-Parkinson's disease. Investigative Ophthalmology and Visual Science 1985;26:258.
51. Kitagawa M, Fukushima J, Tashiro K. Relationship between antisaccades and the clinical symptoms in Parkinson's disease. Neurology 1994;44:2285–2289.
52. Wright MJ, Burns RJ, Geffen GM, Geffen LB. Covert orientation of visual attention in Parkinson's disease: an impairment in the maintenance of attention. Neuropsychologia 1990;28:151–159.
53. Yamada T, Izyuuinn M, Schulzer M, Hirayama K. Covert orienting attention in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:593–596.
54. Bennett KM, Waterman C, Scarpa M, Castiello U. Covert visuospatial attentional mechanisms in Parkinson's disease. Brain 1995;118:153–166.
55. Rafal RD, Posner MI, J.A. W, Friedrich FJ. Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. Brain 1984;107:1083–1094.
56. Sharpe MH. Patients with early Parkinson's disease are not impaired on spatial orientating of attention. Cortex 1990;26:515–524.
57. Filoteo JV, Delis DC, Salmon DP, Demadura T, Roman MJ, Shults CW. An examination of the nature of attentional deficits in patients with Parkinson's disease: evidence from a spatial orienting task. J Int Neuropsychol Soc 1997;3 :337–347.
58. Yamaguchi S, Kobayashi S. Contribution of the dopaminergic system to voluntary and automatic orienting of visuospatial attention. J Neurosci 1998;18:1869–1878.
59. Briand KA, Hening W, Poizner H, Sereno AB. Automatic orienting in Parkinson's disease. Neuropsychologia 2001;39:1240–1249.
60. Desimone R, Schein SJ. Visual properties of neurons in area V4 of the macaque: sensitivity to stimulus form. J Neurophysiol 1987;57:835–868.
61. Shiller PH, Lee K. The role of the primate extrastriate area V4 in vision. Science 1991;251:1251–1253.
62. Frassinetti F, Nichelli P, di Pellegrino G. Selective horizontal dysmetropsia following prestriate lesion. Brain 1999;122(Pt 2):339–350.
63. Milner AD, Harvey M. Distortion of size perception in visual spatial neglect. Curr Biol 1995;5:85–89.
64. Harris JP, Atkinson EA, Lee AC, Nithi K, Fowler MS. Hemispace differences in the visual perception of size in left hemiParkinson's disease. Neuropsychologia 2003;41:795–807.
65. Lee AC, Harris JP, Atkinson EA, Fowler MS. Disruption of estimation of body-scaled aperture width in Hemiparkinson's disease. Neuropsychologia 2001;39:1097–1104.
66. Baddeley A. Working Memory. London: Oxford University Press, 1986.
67. Smith EE, J. J. Neuroimaging analyses of human working memory. Proc Natl Acad Sci USA 1998;95:12061–12068.
68. Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. Science 1998;279:1347–1351.
69. Milner B. Interhemispheric differences in the localization of psychological processes in man. Br Med Bull 1971;27: 272–277.
70. Orsini A, Fragassi NA, Chiacchio L, Falanga AM, Cocchiaro C, Grossi D. Verbal and spatial memory span in patients with extrapyramidal diseases. Percept Mot Skills 1987;65:555–558.
71. Bradley VA, Welch JL, Dick DJ. Visuospatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:1228–1235.

72. Postle BR, Jonides J, Smith EE, Corkin S, Growdon JH. Spatial, but not object, delayed response is impaired in early Parkinson's disease. Neuropsychology 1997;11:171–179.
73. Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997;35:519–532.
74. Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992;115(Pt 6):1727–1751.
75. Owen AM, Beksinska M, James M, et al. Visuospatial memory deficits at different stages of Parkinson's disease. Neuropsychologia 1993;31:627–644.
76. Lewis SJ, Cools R, Robbins TW, Dove A, Barker RA, Owen AM. Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. Neuropsychologia 2003;41:645–654.
77. Brown RG, Marsden CD. Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. Brain 1991;114(Pt 1A):215-–231.
78. Dalrymple-Alford JC, Kalders AS, Jones RD, Watson RW. A central executive deficit in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1994;57:336–367.
79. Fournet N, Moreaud O, Rouliin JL, Naegele B, Pellat J. Working memory functioning in medicated Parkinson's disease patients and the effect of withdrawal of dopaminergic medication. Neuropsychology 2000;14:247–253.
80. Tamura I, Kikuchi S, Otsuki M, Kitagawa M, Tashiro K. Deficits of working memory during mental calculation in patients with Parkinson's disease. J Neurol Sci 2003;209:19–23.
81. Le Bras C, Pillon B, Damier P, Dubois B. At which steps of spatial working memory processing do striatofrontal circuits intervene in humans? Neuropsychologia 1999;37:83–90.
82. Simon SR, Meunier M, Piettre L, Berardi AM, Segebarth CM, Boussaoud D. Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. J Neurophysiol 2002;88:2047–2057.
83. Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 1993;90:873–877.
84. McCarthy G, Blamire AM, Puce A, et al. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. Proc Natl Acad Sci USA 1994;91:8690–8694.
85. Belger A, Puce A, Krystal JH, Gore JC, Goldman-Rakic P, McCarthy G. Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. Hum Brain Mapp 1998;6:14–32.
86. Smith ML, Milner B. The role of the right hippocampus in the recall of spatial location. Neuropsychologia 1981;19: 781–793.
87. Pillon B, Ertle S, Deweer B, Sarazin M, Agid Y, Dubois B. Memory for spatial location is affected in Parkinson's disease. Neuropsychologia 1996;34:77–85.
88. Pillon B, Ertle S, Deweer B, Bonnet AM, Vidailhet M, Dubois B. Memory for spatial location in "de novo" parkinsonian patients. Neuropsychologia 1997;35:221–228.
89. Pillon B, Deweer B, Vidailhet M, Bonnet AM, Hahn-Barma V, Dubois B. Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on 'strategic' processes? Neuropsychologia 1998;36:1–9.
90. Wallesch CW, Karnath HO, Papagno C, Zimmermann P, Deuschl G, Lucking CH. Parkinson's disease patient's behaviour in a covered maze learning task. Neuropsychologia 1990;28:839–849.
91. Kosslyn SM. Image and the Brain: The Resolution of the Imagery Debate. CAmbridge, MA: MIT Press, 1996.
92. Le Bihan D, Turner R, Zeffiro TA, Cuenod CA, Jezzard P, Bonnerot V. Activation of human primary visual cortex during visual recall: a magnetic resonance imaging study. Proc Natl Acad Sci U S A 1993;90:11802–11805.
93. Kosslyn SM, Thompson WL, Kim IJ, Alpert NM. Topographical representations of mental images in primary visual cortex. Nature 1995;378:496–498.
94. Cohen MS, Kosslyn SM, Breiter HC, et al. Changes in cortical activity during mental rotation. A mapping study using functional MRI. Brain 1996;119(Pt 1):89–100.
95. Jacobs DH, Shuren J, Bowers D, Heilman KM. Emotional facial imagery, perception, and expression in Parkinson's disease. Neurology 1995;45:1696–1702.
96. Brown RG, Marsden CD. Visuospatial function in Parkinson's disease. Brain 1986;109(Pt 5):987–1002.
97. Lee AC, Harris JP, Calvert JE. Impairments of mental rotation in Parkinson's disease. Neuropsychologia 1998;36:109–114.
98. Bowen B, Hoehn MM, Yahr MD. Parkinsonism: alteration in spatial orientation as determined by route walking task. Neuropsychologia 1972;10:355–361.
99. Buytenhuijs EL, Berger HJ, Van Spaendonck KP, Horstink MW, Borm GF, Cools AR. Memory and learning strategies in patients with Parkinson's disease. Neuropsychologia 1994;32:335–342.
100. Stepankova K, Ruzicka E. Object location learning and non-spatial working memory of patients with Parkinson's disease may be preserved in "real life" situations. Physiol Res 1998;47:377–384.
101. Montgomery P, Silverstein P, Wichmann R, Fleischaker K, Andberg M. Spatial updating in Parkinson's disease. Brain Cogn 1993;23:113–126.
102. Leplow B, Holl D, Zeng L, Herzog A, Behrens K, Mehdorn M. Spatial behaviour is driven by proximal cues even in mildly impaired Parkinson's disease. Neuropsychologia 2002;40:1443–1455.

103. Olton DS, Samuelson RJ. Remmebrance of place passe: spatial memory in rats. J Exp Psychol Anim Behav Proc 1976;2:97–116.
104. Morris RGM. Spatial localization does not require the presence of local cues. Learning and Motivation 1981;12:239–260.
105. Proctor F, Riklan M, Cooper IS, Teuber H-L. Judgement of visual and postural vertical by parkinsnonian patients. Neurology 1964;14:287–293.
106. Danta G, Hilton R. Judgment of the visual vertical and horizontal in patients with Parkinsonism. Neurology 1975;25: 43–47.
107. Della Sala S, Di Lorenzo G, Giordano A, Spinnler H. Is there a specific visuo-spatial impairment in Parkinsonians? J Neurol Neurosurg Psychiatry 1986;49:1258–1265.
108. Direnfeld LK, Albert ML, Volicer L, Langlais PJ, Marquis J, Kaplan E. Parkinson's disease. The possible relationship of laterality to dementia and neurochemical findings. Arch Neurol 1984;41:935–941.
109. Bentin S, Silverberg R, Gordon HW. Asymmetrical cognitive deterioration in demented and Parkinson patients. Cortex 1981;17:533–543.
110. Huber SJ, Freidenberg DL, Shuttleworth EC, Paulson GW, Clapp LE. Neuropsychological similarities in lateralized parkinsonism. Cortex 1989;25:461–470.
111. Riklan M, Stellar S, Reynolds C. The relationship of memory and cognition in Parkinson's disease to lateralisation of motor symptoms. J Neurol Neurosurg Psychiatry 1990;53:359–360.
112. Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 1989;52:201–206.
113. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000;123(Pt 10):2091–-108.
114. Rafal RD. Visually guided behavior. In: Litvan I, Agid Y, eds. Progressive Supranuclear Palsy: Clinical and Research Approaches. New York: Oxford University Press, 1992:204–222.
115. Ghika J, Tennis M, Growdon J, Hoffman E, Johnson K. Environment-driven responses in progressive supranuclear palsy. J Neurol Sci 1995;130:104–111.
116. Kimura J, Barnett HJ, Burkhart G. The psychological test pattern in progressive supranuclear palsy. Neuropsychologia 1981;19:301–306.
117. Fisk JD, Goodale MA, Burkhart G, Barnett HJ. Progressive supranuclear palsy: the relationship between ocular motor dysfunction and psychological test performance. Neurology 1982;32:698–705.
118. Soliveri P, Monza D, Paridi D, et al. Cognitive and magnetic resonance imaging aspects of corticobasal degeneration and progressive supranuclear palsy. Neurology 1999;53:502–507.
119. Soliveri P, Monza D, Paridi D, et al. Neuropsychological follow up in patients with Parkinson's disease, striatonigral degenration-type multisystem atrophy, and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2000;69:315–318.
120. Esmonde T, Giles E, Gibson M, Hodges JR. Neuropsychological performance, disease severity, and depression in progressive supranuclear palsy. J Neurol 1996;243:638–643.
121. Warrington EK, James M. Visual object and space perception battery. Bury St. Edmonds, UK: Thames Valley Test Co., 1991.
122. Posner MI, Rafal RD, Choate L, Vaughn J. Inhibition of return: Neural basis and function. Cogn Neuropsychol 1985;2:211–228.
123. Rafal RD, Posner MI. Deficits in human visual spatial attention following thalamic lesions. Proc Natl Acad Sci USA 1987;84:7349–7353.
124. Kertzman C, Robinson DL, Litvan I. Effects of physostigmine on spatial attention in patients with progressive supranuclear palsy. Arch Neurol 1990;47:1346–1350.
125. Schiller PH, True SD, Conway JL. Effects of frontal eye field and superior colliculus ablations on eye movements. Science 1979;206:590–592.
126. D'Antona R, Baron J, Samson Y, et al. Subcortical dementia. Frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. Brain 1985;108 (Pt 3):785–799.
127. Posner MI, Walker JA, Friedrich FJ, Rafal RD. Effects of parietal injury on covert orienting of attention. J Neurosci 1984;4:1863–1874.
128. Henik A, Rafal R, Rhodes D. Endogenously generated and vsually guided saccades after lesions of the human frontal eye fields. Soc Neurosc Abstr 1991;17:803.
129. Rafal R, Henik A, Smith J. Exrageniculate contributions toreflex visual orienting in normla humans: A temporal hemified advantage. J Cogn Neurosci 1991;3:323–329.
130. Rafal R, Smith J, Krantz J, Cohen A, Brennan C. Extrageniculate vision in hemianopic humans: saccade inhibition by signals in the blind field. Science 1990;250:118–121.
131. Leiguarda R, Lees AJ, Merello M, Starkstein S, Marsden CD. The nature of apraxia in corticobasal degeneration. J Neurol Neurosurg Psychiatry 1994;57:455–459.
132. Blondel A, Eustache F, Schaeffer S, Marie RM, Lechevalier B, de la Sayette V. Étude clinique et cognitive de l'apraxie dans l'atrophie cortico-basale. Un trouble sélectif du système de production. Rev Neurol (Paris) 1997;153:737–747.

133. Jacobs DH, Adair JC, Macauley B, et al. Apraxia in corticobasal degeneration. Brain Cogn 1999;40:336–354.
134. Merians A, Clark M, Poizner H, et al. Apraxia differs in corticobasal degeneration and left-parietal stroke: A case study. Brain Cogn 1999;40(2):314–335.
135. Otsuki M, Soma Y, Yoshimura N, Tsuji S. Slowly progressive limb-kinetic apraxia. Eur Neurol 1997;37:100–103.
136. Moreaud O, Naegele B, Pellat J. The nature of apraxia in corticobasal degeneration: a case of melokinetic apraxia. Neuropsychiatry Neuropsychol Behav Neurol 1996;9:288–292.
137. Goldenberg G, Wimmer A, Auff E, Schnaberth G. Impairment of motor planning in patients with Parkinson's disease: evidence from ideomotor apraxia testing. J Neurol Neurosurg Psychiatry 1986;49:1266–1272.
138. Watson RT, Fleet WS, Gonzalez-Rothi L, Heilman KM. Apraxia and the supplementary motor area. Arch Neurol 1986;43:787–792.
139. Yamadori A, Osumi Y, Imamura T, Mitani Y. Persistent left unilateral apraxia and a disconnection theory. Behav Neurol 1988;1:11–22.
140. Marchetti C, Della Sala S. On crossed apraxia. Description of a right-handed apraxic patient with right supplementary motor area damage. Cortex 1997;33:341–354.
141. Pause M, Freund HJ. Role of the parietal cortex for sensorimotor transformation. Evidence from clinical observations. Brain Behav Evol 1989;33:136–140.
142. Freund HJ. The parietal lobe as a sensorimotor interface: a perspective from clinical and neuroimaging data. NeuroImage 2001;14(1 Pt 2):S142–S146.
143. De Renzi E, Lucchelli F. Ideational apraxia. Brain 1988;111(Pt 5):1173–1185.
144. Barbieri C, De Renzi E. The executive and ideational components of apraxia. Cortex 1988;24(4):535–534.
145. Peigneux P, Salmon E, Garraux G, et al. Neural and cognitive bases of upper limb apraxia in corticobasal degeneration. Neurology 2001;57:1259–1268.
146. Leiguarda RC, Marsden CD. Limb apraxias: higher-order disorders of sensorimotor integration. Brain 2000;123(Pt 5): 860–879.
147. Leiguarda R, Merello M, Balej J. Apraxia in corticobasal degeneration. Adv Neurol 2000;82.
148. Decety J, Perani D, Jeannerod M, et al. Mapping motor representations with positron emission tomography. Nature 1994;371:600–602.
149. Bonda E, Petrides M, Frey S, Evans A. Neural correlates of mental transformations of the body-in-space. Proc Natl Acad Sci USA 1995;92:11180–11184.
150. Sirigu A, Daprati E, Pradat-Diehl P, Franck N, Jeannerod M. Perception of self-generated movement following left parietal lesion. Brain 1999;122(Pt 10):1867–1874.
151. Wolpert DM, Goodbody SJ, Husain M. Maintaining internal representations: the role of the human superior parietal lobe. Nat Neurosci 1998;1:529–533.
152. Andersen RA, Snyder LH, Bradley DC, Xing J. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annu Rev Neurosci 1997;20:303–330.
153. Rothi LJ, Ochipa C, Heilman KM. A cognitive neuropsychological model of limb praxis. In: Rothi LJ, Heilman KM, eds. Apraxia: The neuropsychology of action. Hove, UK: Psychology, 1997:29–50.
154. Wenning GK, Litvan I, Jankovic J, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. J Neurol Neurosurg Psychiatry 1998;64:184–189.
155. Rey GJ, Tomer R, Levin BE, Sanchez-Ramos J, Bowen BB, J.H. Psychiatric symptoms, atypical dementia, and left visual field inattention in corticobasal ganglionic degeneration. Mov Disord 1995;10:106–110.
156. Kleiner-Fisman G, Black SE, Lang AE. Neurodegenerative disease and the evolution of art: the effects of presumed corticobasal degeneration in a professional artist. Mov Disord 2003;18:294–302.
157. De Renzi E. Disorders of Space Exploration and Cognition. New York: Wiley, 1982.
158. Mendez MF. Corticobasal ganglionic degeneration with Balint's syndrome. J Neuropsychiatry Clin Neurosci 2000;12:273–275.
159. Leone M, Budriesi C, Molinari MA, Nichelli P. Progressive biparietal atrophy: A case report and a review of clinico-pathological correlations of focal (lobar) atrophy. Neurol Sci 2002;23:117.
160. Mendez MF, Turner J, Gilmore GC, Remler B, Tomsak RL. Balint's syndrome in Alzheimer's disease: visuospatial functions. Int J Neurosci 1990;54:339–346.
161. Furey-Kurkjian MI, Pietrini P, Graff-Radford N, et al. Visual variant of Alzheimer disease: Distinctive neurospychlogical features. Neuropsychology 1996;10:294–300.
162. Bergeron C, Davis A, Lang AE. Corticobasal ganglionic degeneration and progressive supranuclear palsy presenting with cognitive decline. Brain Pathol 1998;8:355–365.
163. Grimes DA, Lang AE, Bergeron CB. Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology 1999;53:1969–1974.
164. De Renzi E. Disorders of spatial orientation. In: Frederiks JAM, ed. Handbook of Clinical Neurology, Vol. 45: Clinical Neuropsychology. Amsterdam: Elsevier Science, 1985:405–422.

165. Goethals M, Santens P. Posterior cortical atrophy. Two case reports and a review of the literature. Clin Neurol Neurosurg 2001;103:115–119.
166. Mendez MF. Visuospatial deficits with preserved reading ability in a patient with posterior cortical atrophy. Cortex 2001;37:535–543.
167. Papagno C. Progressive impairment of constructional abilities: a visuospatial sketchpad deficit? Neuropsychologia 2002;40:1858–1867.
168. Suzuki K, Otsuka Y, Endo K, et al. Visuospatial deficits due to impaired visual attention: investigation of two cases of slowly progressive visuospatial impairment. Cortex 2003;39:327–341.
169. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.
170. Gnanalingham KK, Byrne EJ, Thornton A. Clock-face drawing to differentiate Lewy body and Alzheimer type dementia syndromes. Lancet 1996;347:696–697.
171. Gnanalingham KK, Byrne EJ, Thornton A, Sambrook MA, Bannister P. Motor and cognitive function in Lewy body dementia: comparison with Alzheimer's and Parkinson's diseases. J Neurol Neurosurg Psychiatry 1997;62:243–252.
172. Walker Z, Allen RL, Shergill S, Katona CL. Neuropsychological performance in Lewy body dementia and Alzheimer's disease. Br J Psychiatry 1997;170:156–158 .
173. Shimomura T, Mori E, Yamashita H, et al. Cognitive loss in dementia with Lewy bodies and Alzheimer disease. Arch Neurol 1998;55:1547–1552.
174. Mori E, Shimomura T, Fujimori M, et al. Visuoperceptual impairment in dementia with Lewy bodies. Arch Neurol 2000;57:489–493.
175. Simard M, van Reekum R, Myran D. Visuospatial impairment in dementia with Lewy bodies and Alzheimer's disease: a process analysis approach. Int J Geriatr Psychiatry 2003;18:387–391.
176. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain 1998;121(Pt 10):1819–1840.
177. Imamura T, Ishii K, Hirono N, et al. Visual hallucinations and regional cerebral metabolism in dementia with Lewy bodies (DLB). Neuroreport 1999;10:1903–1907.
178. Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;70:483–488.
179. Quinn N. Multiple system atrophy—the nature of the beast. J Neurol Neurosurg Psychiatry 1989;Special Suppl:78–89.
180. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Auton Nerv Syst 1998;74:189–192.
181. Litvan I, Bhatia KP, Burn DJ, et al. SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. Mov Disord 2003;18:467–486.
182. Wenning GK, Ben-Shlomo Y, Hughes A, Daniel SE, Lees A, Quinn NP. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;68:434–440.
183. Robbins TW, James M, Lange KW, Owen A, Quinn NP, Marsden CD. Cognitive performance in multiple system atrophy. Brain 1992;115(Pt 1):271–291.
184. Sahakian BJ, Morris RG, Evenden JL, et al. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 1988;111(Pt 3):695–718.
185. Tebartz van Elst L, Greenlee MW, Foley JM, Lucking CH. Contrast detection, discrimination and adaptation in patients with Parkinson's disease and multiple system atrophy. Brain 1997;120(Pt 12):2219–2228.
186. Bodis-Wollner I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. Trends Neurosci 1990;13:296–302.
187. Haug BA, Kolle RU, Trenkwalder C, Oertel WH, Paulus W. Predominant affection of the blue cone pathway in Parkinson's disease. Brain 1995;118(Pt 3):771–778.
188. Djamgoz MB, Hankins MW, Hirano J, Archer SN. Neurobiology of retinal dopamine in relation to degenerative states of the tissue. Vision Res 1997;37:3509–3529.
189. Shallice T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 1982;298:199–209.
190. Keith Berg W, D. B. The Tower of London spatial problem-solving task: enhancing clinical and research implementation. J Clin Exp Neuropsychol 2002;24:586–604.
191. Goel V, Grafman J. Are the frontal lobes implicated in "planning" functions? Interpreting data from the Tower of Hanoi. Neuropsychologia 1995;33:623–642.
192. Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain 1988;111(Pt 4): 941–959.