Title
Visuospatial and visual object cognition in early Parkinson's disease

Permalink
https://escholarship.org/uc/item/08k9p45w

Author
Possin, Katherine L.

Publication Date
2007

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Visuospatial and Visual Object Cognition in Early Parkinson's Disease

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Katherine L. Possin

Committee in charge:

University of California, San Diego

     J. Vincent Filoteo, Chair
     Dean C. Delis
     David P. Salmon

San Diego State University

     Sarah N. Mattson
     Scott C. Roesch

2007

The dissertation of Katherine L. Possin is approved, and it

is acceptable in quality and form for publication on

microfilm:

_____

_____

_____

_____

_____
Chair

University of California, San Diego

San Diego State University

2007

ACKNOWLEDGEMENT

I feel very fortunate to have learned from several exceptional professors during my graduate training. Foremost, I would like to sincerely thank my research advisor and chair of my committee, Professor Filoteo, for his mentorship and generous support. I also gratefully acknowledge all the members of my committee who each made invaluable contributions to my graduate school training and to this dissertation.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

VITA

1993 – 1997 B.A., Tufts University
              Major: Psychology, Magna cum laude with thesis honors

1997 – 1998 M.S., Pacific Graduate School of Psychology
              Major: Psychology

1999 – 2001 Research Analyst, Stanford University and SRI International

2001 – 2007 Ph.D., University of CA, San Diego / San Diego State University
              Major: Clinical Psychology, Specialty Track: Neuropsychology

2006 – 2007 Clinical Internship, University of California, San Francisco

PUBLICATIONS

Possin, K. L., Cagigas, X. E., Strayer, D. L., & Filoteo, J. V. (2006). Lack of impairment in patients with Parkinson's disease on an object-based negative priming task. *Perceptual and Motor Skills,* 102(1), 219-230.

Zizak, V. S., Filoteo, J. V., Possin, K. L., Lucas, J. A., Rilling, L. M., Davis, J. D., Peavy, G., Wong, A., & Salmon, D. P. (2005). The ubiquity of memory retrieval deficits in patients with frontal-striatal dysfunction. *Cognitive and Behavioral Neurology, 18*(4), 198-205.

Possin, K. L., Filoteo, J. V., Roesch, S. C., Zizak, V., Rilling, L. M., & Jennifer D. Davis. (2005). Is a perseveration a perseveration? An evaluation of cognitive error types in patients with subcortical pathology. *Journal of Clinical and Experimental Neuropsychology, 27*(8).

Nordahl, T. E., Salo, R., Possin, K., Gibson, D. R., Flynn, N., Leamon, M., Galloway, G. P., Pfefferbaum, A., Spielman, D. M., Adalsteinsson, E., Sullivan, E. (2002). Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependant subjects: A preliminary proton MRS study. *Psychiatry Research: Neuroimaging, 116*(1-2), 43-52.

Salo, R., Nordahl, T. E., Possin, K., Leamon, M., Gibson, D. R., Galloway, G. P., Flynn, N. M., Henik, A., Pfefferbaum, A., & Sullivan, E. V. (2002). Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Research, 111*(1), 65-74.

Silverberg, G. D., Heit, G., Huhn, S., Jaffe, R. A., Chang, S.D., Bronte-Stewart, H., Rubenstein, E., Possin, K. & Saul, T. (2001). The cerebrospinal fluid production rate is reduced in dementia of the Alzheimer's type. *Neurology, 57*(10), 1763-1766.

ABSTRACT OF THE DISSERTATION

Visuospatial and Visual Object Cognition in Early Parkinson's Disease

by

Katherine L. Possin

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2007

San Diego State University, 2007

Professor J. Vincent Filoteo, Chair

Recent evidence suggests that Parkinson's disease (PD) may be associated with greater impairment in visuospatial working memory as compared to visual object working memory. The nature of this selective impairment is not well understood, however, in part because successful performance on working memory tasks requires numerous cognitive processes. For example, the impairment may be limited to either the encoding or maintenance aspects of spatial working memory. Further, it is unknown at this point whether PD patients' selective impairment in spatial working memory generalizes to other tasks of spatial cognition.

The present study investigated these issues by comparing the performance of nondemented patients with PD and normal control participants on a series of experiments that were designed to independently evaluate visuospatial and visual object cognition. Experiment 1 was composed of working memory conditions that

differed only in what the participant was instructed to remember: locations or shapes. Encoding and maintenance aspects of performance were investigated by measuring accuracy over variable delays. Experiment 2 used an inhibition of return (IOR) task that has been demonstrated to measure spatial- and object-based components of inhibitory attention. Experiment 3 was composed of analogous location and shape discrimination conditions that did not have a working memory component. Group differences on the individual experiments were analyzed using repeated measures analysis of variance designs to test the overarching hypothesis that spatial-based cognition is more impaired than object-based cognition in PD. In Experiment 1, the patients demonstrated impairment in the encoding of spatial-based information, but were able to normally maintain that information over a 10-second delay. The reverse pattern was observed on the object working memory condition in that only maintenance processes were impaired. In Experiment 2, the patients also demonstrated a selective spatial impairment in that they showed reduced spatial-based IOR, while object-based IOR was intact. The results of Experiment 3 revealed that spatial-based visual discrimination was not more impaired than object-based visual discrimination, indicating that selective spatial deficits on higher-level visuocognitive tasks cannot be entirely attributed to a general impairment in spatial cognition. Rather, the selective spatial deficit appears to be limited to encoding and inhibitory attentional processes.

I. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder defined by a clinical triad of motor symptoms, namely bradykinesia, resting tremor, and rigidity. This disorder is widely recognized to also disrupt non-motor cognitive function over multiple domains, including aspects of executive functioning, attention, visuospatial skills, and working memory. Recent evidence suggests that PD may be associated with greater impairment in visuospatial working memory as compared to visual object working memory (e.g., Postle, Jonides, Smith, Corkin, & Growdon, 1997). The nature of this selective impairment is not well understood, in part because successful performance on working memory tasks requires numerous cognitive processes. For example, the impairment may be limited to either encoding or maintenance aspects of spatial working memory. Further, it is unknown at this point whether this selective impairment in spatial working memory generalizes to other types of spatial cognition, such as basic visual processes or specific aspects of attention.

Visuospatial and visual object cognition are functionally and neuroanatomically segregated in the normal brain. This segregation has been demonstrated at brain regions important for executive and mneumonic control functions, such as the prefrontal cortex and the caudate nucleus (Levy, Friedman, Daviachi, & Goldman-Rakic, 1997; Postle & D'Esposito, 1999; Smith and Jonides, 1999; Wilson, O'Scalaidhe, and Goldman-Rakic, 1993), as well as early visual areas important for basic visuoperceptual processes, from the retina to posterior cortex (Courtney, Ungerleider, Keil, & Haxby, 1996; Livingstone & Hubel, 1988; Rockland & Pandya, 1979; Underleider & Miskin, 1982). Past research on both neural changes in PD and

visual processing systems in the normal brain (which will be reviewed in Chapters II and IV) suggest that a selective visuospatial impairment in PD could result from changes at several different points, including within the network of caudate connections with prefrontal cortex or with posterior cortex, or within the earliest visual processing areas (e.g., the retina and lateral geniculate). Thus, research on the nature and extent of visuospatial impairments may be useful for determining which of these possible loci is likely to underlie PD patients' visuospatial dysfunction. For example, if PD impacts only higher aspects of visuospatial processing such as working memory, this pattern of impairment is likely to result from damage to the caudate nucleus and its connections with prefrontal cortex. In contrast, if PD patients are impaired at more basic levels of functioning, it may be due to dysfunction within more posterior cortical regions or within the geniculostriate system.

The present set of studies compared the performance of nondemented patients with PD and normal control (NC) participants on a series of tasks that are designed to independently evaluate visuospatial and visual object cognition. Experiment 1 was composed of separate visuospatial and visual object working memory tasks that differed only in what the participant was instructed to remember: locations in the spatial task or shapes in the object task. Encoding and maintenance aspects of performance were investigated by measuring performance accuracy over variable delays. Experiment 2 used an inhibition of return task that has been demonstrated to measure spatial and object components of inhibitory attention. Experiment 3 was composed of visuospatial and visual object discrimination tasks that differed only in what the participant is instructed to compare: locations or shapes. Based on a review

of the literature, it was hypothesized that PD would be associated with greater impairments in spatial encoding and attentional inhibition, as compared to analogous object-based processes. In contrast, it was predicted that PD would not be associated with selective impairments in spatial maintenance or visuoperceptual processes.

In order to provide the reader with an appropriate background for these studies, the dissertation will begin with an overview of the clinical and neural features of PD. Following this overview, a review of research findings on executive functions, attention, learning and memory, and language in nondemented PD will be provided. Then, theories and research on visuospatial and visual object cognition in normal subjects will be presented to lay the groundwork for the proposed set of studies. Lastly, theory and research on the constructs of working memory, inhibition of return, and visual processing in PD will be presented to directly introduce each of the three experiments.

II. CLINICAL AND NEURAL FEATURES OF PARKINSON'S DISEASE

Clinical Features of Parkinson's Disease

Idiopathic Parkinson's Disease (PD) is one of the most common neurological

illnesses among elderly persons, with a lifetime risk of about 2% (Elbaz, Bower, &

Maraganore, 2002). Most cases begin after age 50, and there is a rapid increase in age-

related prevalence until 80 years (Tanner, Ottoman, Goldman, et al., 1999). PD is

characterized clinically by an insidious onset of slowly progressive symptoms, with

motor symptoms dominating the clinical picture and defining the syndrome. Patients

experience combinations of resting tremor, bradykinesia, rigidity, abnormal posture,

"freezing," and loss of postural reflexes (Fahn, 2003; McPherson & Cummings, 1996).

The resting tremor consists of alternating movements of antagonistic muscles that may

stop during movement and sleep, and can increase during times of stress (Bergman &

Deuschl, 2002; Fahn, 2003). Bradykinesia manifests as slowness of movement,

difficulty initiating movement, slower and smaller handwriting, decreased leg stride

while walking, masked facies, and decreased voice amplitude (Fahn, 2003). Rigidity,

or gradual stiffness of the muscles and joints, can manifest as smooth resistance or

jerky, unsteady movement (Ridenour & Dean, 1999). Clinical features vary among

patients, and there is evidence that there may be neuropathological differences

between patients with primarily tremor versus patients with primarily

rigidity/bradykinesia (Grafton, 2004; Jankovic & Kapadia, 2001; Jellinger, 1999;

Louis et al., 1999; Paulus & Jellinger, 1991).

Although motor symptoms dominate the clinical picture and were once thought to

be the only sequelae of the disease, it is now understood that PD is also associated

with changes in mood and cognition. Depression is the most common psychiatric complication of PD, and is estimated to occur in approximately half of patients (McDonald, Richard, & DeLong, 2003). Depression is more common in patients with PD than in age-matched physically disabled patients, suggesting that the high prevalence is not simply a reaction to increased disability or psychosocial stress caused by the disease, but instead may be secondary to the underlying neuroanatomical degeneration (Ehmann, Beninger, Gawal, & Riopelle, 1990; Menza & Mark, 1994). Another common psychiatric complication in PD is apathy, which appears to be closely associated with cognitive impairment but not to personality traits or depression (Pluck & Brown, 2002). Anxiety has also been reported, although most reports suggest that it is induced by dopamine replacement therapy or related to depression (McPherson & Cummings, 1996). Cognitive changes include selective impairments in executive functions and inhibitory attention, and will be discussed in detail below. The primary focus of the present work involves changes in visual cognition, which have been observed on tests of working memory, attention, and basic visual processing.

<div align="center">Neural Features of Parkinson's Disease</div>

The basal ganglia, the primary area of pathology in PD, are composed of the caudate nucleus, the putamen, the globus pallidus, and the substantia nigra. The caudate nucleus and the putamen together are referred to as the striatum. These basal ganglia structures are highly connected with other brain regions and create multiple circuits with the cerebral cortex. At least five primary circuits connecting the frontal lobes to the basal ganglia have been identified (Alexander, DeLong, & Strick, 1986;

Middleton & Strick, 2000). These frontal-subcortical (FSC) circuits originate in the frontal lobes and project to the striatum before splitting into "direct" and "indirect" pathways. The direct pathway connects the striatum to the globus pallidus interna / subtrantia nigra pars reticulata complex. The indirect loop also originates in the striatum, but then travels sequentially to the globus pallidus externa, subthalamic nucleus, and globus pallidus interna / substantia nigra pars reticulata complex. From there, both pathways project to the cortex via the ventrolateral thalamus. The five circuits share this common structure but are anatomically segregated at both cortical and subcortical levels (Cummings, 1993; Lichter & Cummings, 2001).

Following is a listing of the five circuits, where they originate, and a brief description of their function (for a more detailed review, see Alexander et al., 1986; Lichter & Cummings, 2001). The motor circuit, originating in the supplementary motor area, is involved in preparatory premovement activity and serial processing of movements. The oculomotor circuit, originating in the frontal eye field, is involved in eye-movement. The dorsolateral prefrontal circuit (DLPFC), originating from the lateral surface of the anterior frontal lobe, mediates executive functions. The anterior cingulate circuit (ACC) originates in the anterior cingulate and is involved in motivational mechanisms. The orbitofrontal circuit (OFC) originates in the lateral orbital gyrus and the medial inferior frontal gyrus and integrates limbic and emotional information into contextually appropriate behavioral responses or social behavior. Although these circuits maintain functional and anatomical segregation at cortical and subcortical levels, some "cross-talk" may occur (Lichter & Cummings, 2001).

Dopamine-containing axons from the subtantia nigra pars compacta synapse directly on striatal output neurons, thereby innervating the striatum and influencing all of the FSC circuits. The direct loop is excited by D1 class dopamine receptors whereas the indirect loop is inhibited by D2 class dopamine receptors, although some researchers claim that these receptor classes are expressed at both loops in the striatum (Graybiel, 2000). The basal ganglia are thought to regulate normal behavior through a balance between the direct and indirect loops (Lichter & Cummings, 2001). For example, researchers have suggested that we select movements by inhibiting unintended movements and promoting desired ones, and that the direct and indirect loops mediate such selection and inhibition (Graybiel, 2000).

The primary neuropathological feature of PD is the degeneration of the dopamine-producing cells of the substantia nigra pars compacta (Jenner & Marsden, 1988), which project to the striatum (Agid, 1991). These dopamininergic projections to the caudate nucleus and putamen modulate FSC circuit function in the healthy brain, and the loss of these projections is thought to be the primary substrate of motor and cognitive sequelae in PD (Middleton & Strick, 2000; Owen, 2004; Zgaljardic, Borod, Foldi, & Mattis, 2003). Reduction of dopamine in the putamen and caudate nuclei is as high as 78% to 92% (Fahn, Libsch, & Cutler, 1971; Hornykiewicz, 1973). Early in the disease process, dopamine depletion is greatest in the putamen, which is implicated in the motor deficits associated with PD (Benamer et al., 2003; Kish, Shannak, & Hornykiewicz, 1988; Nurmi et al., 2001). Dopamine depletion in the caudate nucleus, which is thought to mediate the cognitive sequelae of early PD (Marie et al., 1999;

Owen, 2004), is uneven with the greatest loss in the anterodorsal extent of the head

(Kaufman & Madras, 1991; Kish et al., 1988).

PD sequelae may also result from disruption of subcortical connections to brain

regions outside the frontal lobes. For example, cognitive changes associated with the

disease may result in part from disruption of subcortical connections to the temporal

lobes (Cummings & Benson, 1984). In addition, the cerebello-thalamo-cortical loop

may play a role in parkinsonian tremor (Bergman & Deuschl, 2002). Much more work

is needed, however, to elucidate (a) which regions of the brain participate in circuits

with the basal ganglia, (b) which of these circuits are disrupted in PD, and (c) how

disruption to these specific circuits may account for PD symptomatology.

Dopamine changes in the earliest visual processing areas have also been

demonstrated in PD. There is a decrease in dopamine in the retinas of these patients

(Bodis-Wollner, 1990; Harnois & Di Paolo, 1990), which is thought to alter visual

function by changing the receptive field properties of ganglion cells (Jackson &

Owsley, 2003). This is supported by findings of abnormal electroretinograms

following visual stimulation (Langheinrich et al., 2000; Peppe et al., 1995; Sartucci et

al., 2003), and further that levodopa therapy can produce recovery of the

electroretinograms in 'de novo' patients (Peppe et al., 1995). The lateral geniculate

and visual cortex also contain dopaminergic cells (Papadopoulos & Parnavelas, 1990;

Parkinson, 1989; Reader & Quesney, 1986), and this dopamine may be diminished in

PD. Dopamine agonists have been shown to modulate contrast gain in the lateral

geniculate of rats (Albrecht, Quaschling, Zippel, & Davidowa, 1996), suggesting that

a depletion of dopamine in this region may result in altered visual processing. Changes

in visual cortex may play a role in PD visual dysfunction, which is supported by findings of reduced metabolic activity in the occipital cortex of non-demented PD patients (Abe et al., 2003; Bohnen, Minoshima, Giodani, Frey, & Kuhl, 1999; Wang, Kuroiwa, & Kamitami, 1999). Further, strong correlations have been demonstrated between reduced blood flow in occipital regions of non-demented PD patients and performance on the Raven's Coloured Progressive Matrices (Raven, 1965), a test that is used to evaluate visuospatial attention and reasoning (Abe et al., 2003). Differential effects of PD on the magnocellular and parvocellular pathways may also be important for explaining visual impairments in PD (Arakawa, Tobimatsu, Kato, & Kira, 1999). These pathways originate in retinal ganglion cells and maintain their segregation through the lateral geniculate and visual cortex (Livingstone & Hubel, 1988). The parvocellular pathway, which preferentially connects to ventral stream regions of cortex, is thought to be responsible for detecting color and form; the magnocellular pathway, which preferentially connects to dorsal stream regions of cortex, is thought be responsible for detecting depth and movement (Livingstone & Hubel, 1988; Merigan & Maunsell, 1990; Rockland & Pandya, 1979). These pathways are affected independently in PD (Silva et al., 2005). There is some evidence that damage to the magnocellular pathway is correlated with disease progression, and it has been suggested that the magnocellular pathway may be more affected than the parvocellular pathway by the disease (Arakawa et al., 1999; Regan & Maxner, 1987; Tebartz van Elst, Greenlee, Foley, & Lücking, 1997).

Although dopamine is the primary neurotransmitter depleted in PD, other neurotransmitters and modulators are also reduced. These include norepinephrine,

glutamate decarboxylase, serotonin, GABA, methionine-enkephalin, and cholestokinin (Cummings and Benson, 1992). In addition to neuronal loss in the substantia nigra, neuron loss is also seen in other brain stem nuclei, specifically the locus ceruleus, dorsal vagal nucleus, and sympathetic ganglia (McPherson & Cummings, 1996). The presence of Lewy bodies is a hallmark of PD (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Den Hartog Jager & Bethlem, 1960; Gibb, 1989), although these intracytoplasmic inclusions may not be present in some inherited forms of the disease (Sethi, 2002).

III. NEUROCOGNITIVE FEATURES OF PARKINSON'S DISEASE

Parkinson's Disease Dementia

Although many patients with PD have only circumscribed cognitive impairment, many progress to develop Parkinson's Disease with Dementia (PDD). Based on their systematic review of dementia prevalence studies, Aarsland, Zaccai, and Brayne (2005) estimated that 24 to 31 % of PD patients have dementia. Risk factors for PDD include late onset of the disease, duration of the disease, akinetic-rigid subtype, and depression (Emre, 2003; Hely et al., 1995; Mayeux et al., 1992). Although some researchers have identified subtle qualitative differences in the cognitive profiles of PDD and PD (Higginson, Wheelock, Carroll, & Sigvardt, 2005; Zakharov, Akhutina, & Yakhno, 2001), in general the profiles of both groups have executive dysfunction as the core feature, as well as impairments in certain visuospatial functions, memory, and attention (Appollonio et al., 1994; Duke & Kaszniak, 2000; Emre, 2003). Executive dysfunction in PDD has been characterized by difficulties with internally cued behavior, shifting attention, verbal fluency, working memory, and abstract reasoning (Lamar, Swenson, Kaplan, & Libon, 2004; Owen, Roberts, et al., 1993; White, Au, Durso, & Moss, 1992).

In the upcoming sections, the neurocognitive changes observed in nondemented PD patients will be discussed. This discussion will be organized according to the following domains of cognition: executive functions, attention, learning and memory, and language. In later sections of this dissertation, special emphasis will be given to research findings on the constructs of working memory, inhibition of return, and basic visual processing in P

Executive functions

Executive functions, which include numerous higher-level abilities, permit an adaptive balance of maintenance and shifting of responses to environmental demands, allowing longer-term goal-directed behavior rather than reflexive or automated action (Lezak, 1995; Palmer & Heaton, 2000). Executive functions have traditionally been attributed to the frontal lobes (Luria, 1966; Shallice, 1982); however, there is a growing recognition that executive skills may not be fully mediated by the frontal lobes (Palmer & Heaton, 2000). In particular, a role of FSC circuits in executive functioning has been recognized based on observations that behavioral changes associated with frontal dysfunction resemble changes associated with subcortical lesions (Cummings, 1993). Deficits on executive function tasks are frequently observed in nondemented PD (e.g., Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Lees & Smith, 1983; Raskin, Borod, & Tweedy, 1990; Robbins et al., 1994). It has been suggested that these deficits are secondary to dysfunction of FSC circuitry, principally the DLPFC, although the ACC and OFC may also be involved (Lichter, 2001; Zgaljardic et al., 2003).

One of the most commonly used tests of executive functions is the Wisconsin Card Sorting Test (WCST; Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). In this test, examinees are presented with four stimulus cards, which depict designs that vary in color, shape, and number. They are told to match each of 128 response cards to one of the four stimulus cards, and are given feedback after each match as to whether they are right or wrong. Examinees are not told how to match the cards but must determine the rules using feedback, and shift response patterns when

the rules change. This test yields several scores including number of categories completed, number of errors, and number of perseverative responses. Performance of patients with frontal lobe damage is typically characterized by excessive perseverative responding (Milner, 1963). Most studies of the WCST in PD have also identified impairments, although there is disagreement about the nature of their impairment on this test. For example, while some studies have demonstrated increased perseverative responding (Alevriadou, Katsarou, Bostantjopoulou, Kiosseoglou, & Mentenpoulos, 1999; Canavan et al., 1989; Levin, Llabre, & Weiner, 1989), other studies have failed to show this deficit (Bowen, Kamienny, Burns, & Yahr, 1975; Lees & Smith, 1983; Pillon et al., 1986; Taylor et al., 1987). Other indicators of impaired performance that have been identified include number of errors (Bowen et al., 1975), number of trials to learn the initial rule (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991), number of categories achieved (Lees & Smith, 1983; Pillon et al., 1986; Taylor et al., 1987), and failure to maintain set (Alevriadou et al., 1999). Given the variable findings among studies, it is difficult to completely characterize the nature of poor WCST performance in PD.

One possible mechanism of PD patients' deficient performance on the WCST may be an impairment in set-shifting and maintenance, consistent with a number of studies that have identified this impairment in PD patients (e.g., Cools, Van Den Brecken, Horstink, Van Spaendonck, & Berger, 1984; Flowers & Robertson, 1985). Set-shifting and maintenance impairments are more readily observed when an attentional shift to a new stimulus dimension is required (Downes et al., 1989; Gauntlett-Gilbert, Roberts, & Brown, 1999; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Robbins et al.,

1994) and the shift must be directed by internal versus external cues (Brown & Marsden, 1988; Hsieh, Lee & Tai, 1995), which are characteristics also shared by the WCST. This set-shifting and maintenance impairment has been attributed to deficient selective attention (Downes et al., 1989; Gauntlett-Gilbert et al., 1999), and to a depletion of attentional resources (Brown & Marsden, 1991; Woodward, Bub, & Hunter, 2002). The selective attention characterization is consistent with findings from visual attention tasks that suggest PD patients are not impaired in dividing attention between two stimulus dimensions, but are impaired when having to attend selectively to one dimension while ignoring the other dimension (Filoteo & Maddox, 1999; Maddox, Filoteo, Delis, & Salmon, 1996).

PD is also associated with impaired performance on executive function tests of verbal fluency and sequencing. Tests of verbal fluency require time-restricted generation of words according to specific rules. A recent meta-analysis of 68 studies found that PD patients were impaired on tests of semantic fluency and phonemic fluency, with greater impairment in general on tests of semantic fluency (Henry & Crawford, 2004). PD patients are also frequently impaired on tests of sequencing and temporal ordering (Beatty & Monson, 1990; Cooper, Sagar, & Sullivan, 1993; Fama & Sullivan, 2002; Ogden, Growden, & Corkin, 1990; Sullivan, Sagar, Gabrieli, Corkin, & Growdon, 1989; Sullivan & Sagar, 1989; Zalla et al., 1998). Importantly, sequencing deficits are observed within verbal, nonverbal, and motor modalities (i.e., they are not limited to motor sequencing tasks), suggesting that a higher-level sequencing impairment rather than an impairment in simple motor skills underlies poor performance on these tasks in PD.

In contrast to the impairments discussed above, PD patients are often unimpaired on problem solving, concept formation, and abstract reasoning tasks. For example, PD patients generally perform as accurately as controls on the Tower of London Test, which is thought to measure visuomotor problem solving (Alberoni, Della Sala, Pasetti, & Spinnler, 1988; Morris et al., 1988; Owen et al., 1992). Owen and colleagues, for example, demonstrated that only patients with more severe clinical symptoms and impaired spatial working memory performed less accurately. The pattern of performance of PD patients on a verbal problem-solving task in a study by Cronin-Golomb, Corkin, and Growdon (1994) was suggestive of difficulties in set-shifting but intact deductive reasoning. Further, patients in this study performed normally on tests of concept formation and problem solving that did not require set-shifting. The California Card Sorting Test (Delis, Squire, Bihrle, & Massman, 1992) is a useful test for assessing multiple cognitive functions behind the processes of problem solving, abstract thinking, planning, concept formation, and set-shifting. In a study by Dimitrov, Grafman, Soares, & Clark (1999), PD patients without dementia demonstrated normal concept formation and abstract thinking on this test; however, they made a high number of perseverative sorts. The authors argued that their elevated perseverative sorts could not be due to impaired concept formation because the participants were able to adequately verbalize and explain the rule behind each correct sort and were not perseverative in their explanations. Further, the perseverative sorts were not likely the result of impaired abstract thinking because they benefited normally from abstract cues provided by the examiner. The authors argued instead that the elevated number of perseverative sorts could be explained by visuospatial

sequencing and set-shifting difficulties. In sum, patients with PD are generally

unimpaired on executive function tests that require problem-solving, concept

formation, and abstract reasoning, provided that their impairments in other areas,

particularly set-shifting and sequencing as discussed here, do not interfere with their

performance.

<div align="center">Attention</div>

Simple attention, which is usually assessed using span tasks, is generally

unimpaired in nondemented patients with PD (Gilbert, Belleville, Bherer, &

Chouinard, 2005; Goldman, Baty, Buckles, Sahrman, & Morris, 1998; Huber,

Friedenberg, Shuttleworth, Paulson, & Christy, 1989; Pillon et al., 1986; Sullivan

et al., 1993). Many nondemented PD patients also appear to be unimpaired on

tests of sustained attention (Gotham, Brown, & Marsden, 1988; Kraus, 2000). In

contrast, alterations in complex aspects of attention have more consistently been

observed. For example, PD patients are frequently impaired on tests of selective

attention (Filoteo & Maddox, 1999; Filoteo, Maddox, Ing, Zizak, & Song, 2005;

Henik, Singh, Beckley, & Rafal, 1993; Maddox et al., 1996; McDowell & Harris,

1997), shifting attention (Filoteo et al., 1997; Hayes, Davidson, Keele, & Rafal,

1998; Owen, Roberts, et al., 1993; Yamaguchi & Kobayashi, 1998; Wright,

Burns, Geffen, & Geffen, 1990), and negative priming (Filoteo, Rilling, &

Strayer, 2002; Mari-Beffa, Hayes, Machado, & Hindle, 2005; Wylie & Stout,

2002). One partial explanation for these deficits on complex attention tasks is that

they place demands on inhibitory processes, which are frequently impaired in PD

(e.g., Brown & Marsden, 1988; Kensinger et al., 2003; Poliakoff et al., 2003). For

example, in order to attend selectively to task-relevant information in a selective

attention task, one has to suppress interference from task-irrelevant information

(Neill, 1977). The implications of such findings in regard to this proposal will be

discussed in Experiment 2.

<div style="text-align:center">Learning and Memory</div>

<div style="text-align:center">Explicit Learning and Memory</div>

Nondemented patients with PD have been shown to exhibit impairments on tests

of explicit memory (e.g., el-Awar, Becker, Hammond, Nebes, & Boller, 1987;

Faglioni, Saetti, & Botti, 2000; Higginson et al., 2005; Massman, Delis, Butters,

Levin, & Salmon, 1990). In general, their episodic memory profile can be

characterized by difficulties with encoding but preserved retention of novel

information (Massman et al., 1990; Pillon, Deweer, Michon, & Malapani, 1994).

Encoding deficits appear to result in part from impairments in inhibitory processes

(Cooper et al., 1993; Taylor & Saint-Cyr, 1995) and in the spontaneous and self-

directed generation of efficient strategies, such as semantic clustering (Taylor, Saint-

Cyr, & Lang, 1986, 1990; Zizak et al., 2003). These patients have also demonstrated

difficulties with source memory (Hsieh & Lee, 1999; Taylor et al., 1990), proactive

interference (Beatty, Staton, Weir, Monson, & Whitaker, 1989; Helkala, Laulumaa,

Soininen, & Riekkinen, 1989; Rouleau, Imbault, Laframboise, & Bedard, 2001), and

inhibition of distracting information during recall (Cooper et al., 1993). It was once

widely accepted that PD patients display the classic retrieval deficit profile associated

with Huntington's disease (i.e., impaired free recall but near normal or improved

performance at cued recall and recognition testing), but recent research suggests that

most PD patients do not usually show this profile. Instead, PD patients demonstrate similar levels of recall and recognition impairment (Higginson et al., 2005; Whittington, Podd, & Kan, 2000; Zizak et al., 2005). Their recognition memory performance has been characterized by excessive false positive responding, consistent with deficient inhibitory processing (Higginson et al., 2003; Massman et al., 1990; Zizak et al., 2005).

Several authors have suggested that episodic memory deficits in PD are secondary to executive function impairments (Bondi, Kaszniak, Bayles, & Vance, 1993; Gabrieli, 1996; Higginson et al., 2003; Taylor, et al., 1990), which is consistent with the pattern of their memory profile above. For example, Higginson and colleagues (2003) examined nondemented patients with PD on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and several measures of executive functioning. They found that working memory, as measured by the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997), predicted nearly 50% of the variance in CVLT recall measures. Although multiple other aspects of executive function measured in the study correlated with recall, working memory was the best predictor. The relationship between these measures was not mediated by global cognitive impairment. Further, working memory was associated with use of semantic clustering, an efficient encoding strategy that correlates with higher levels of recall. The authors concluded that executive processes, particularly working memory, mediate the relationship between encoding strategy and recall in PD.

Remote Memory

Remote memory has also been examined in non-demented PD, typically using tests of memory for remote events. PD patients in some studies have demonstrated normal remote memory (Fama et al., 2000; Leplow et al., 1997), although in other studies PD patients have demonstrated impairments both in recalling the content and in dating the events (Ivory et al., 1999; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1988; Venneri et al., 1997). Dating capacity in particular appears to be a sensitive measure of remote memory function in PD, and may be independent of dementia (Sagar et al., 1988). A possible mechanism for this deficit may be the impairments in sequencing and temporal ordering that are found in even mild, non-demented PD patients, as discussed above. Remote and anterograde memory performance appear to be dissociable in PD (Fama et al., 2000), suggesting independence of these memory systems.

Implicit Learning

Considerable research has also focused on implicit learning in PD. Tests of implicit learning typically measure improvements in performance after previous exposure to a stimulus, often referred to as priming, or after having performed the task over time, often referred to as procedural learning. Both priming and procedural learning do not require conscious recollection of the previously presented information, and are thought to be neuroanatomically distinct from explicit memory systems (Squire, 1992). There is also evidence that priming may rely on distinct neuroanatomic systems from procedural learning (Heindel, Salmon, Shults, Wallicke, & Butters,

1989; Schwartz & Hashtroudi, 1991; but see Gupta & Cohen, 2002 for an alternative account).

Nondemented patients with PD often perform normally on priming tasks (Appollonio et al., 1994; Bondi & Kaszniak, 1991; Filoteo et al., 2003; Heindel et al., 1989; Hines & Volpe, 1985; Huberman, Moscovitch, & Freedman, 1994; Kuzis et al., 1999). On stem completion priming tasks, participants are presented with words and then later presented with the first few letters of each word, and asked to state the word that immediately comes to mind. PD patients demonstrate normal priming on these tasks; that is, they tend to provide the word that was presented earlier just as often as normal controls (Appollonio et al., 1994; Bondi & Kaszniak, 1991; Heindel et al., 1989; Huberman et al., 1994; Kuzis et al., 1999). On semantic priming tasks, participants are presented with prime and target word pairs, and are asked to determine whether the target is a word or non-word. Normal controls tend to respond faster when the words are semantically related, and this facilitation is thought to reflect the accessing of semantic memory networks (Collins & Loftus, 1975; Neely, 1977, 1991). PD patients have demonstrated hyper priming on some semantic priming tasks (Arnott, Chenery, Murdoch, & Silburn, 2001; Brown, Brown, Christenson, et al., 2002; McDonald, Brown, & Gorrell, 1996; Spicer, Brown, & Gorell, 1994), although they have performed normally on others (Filoteo et al., 2003; Hines & Volpe, 1985). Findings of hyper semantic priming in PD patients have not been attributed to alterations in the structure of semantic knowledge, however, but rather to impairments in decision-making processes (Brown et al., 2002; Filoteo et al., 2003).

Impairments on several different types of procedural learning tasks have been demonstrated in PD (Bondi & Kaszniak, 1991; Butters et al., 1990; Harrington et al., 1990; Koenig et al., 1999; Saint-Cyr et al., 1988; Salmon & Butters, 1995; Sarazin et al., 2002; Yamadori et al., 1996), although these patients have also performed normally on some procedural learning tasks (Bondi & Kaszniak, 1991; Harrington et al., 1990; Heindel et al., 1989). The pursuit rotor task is a commonly used test of procedural motor learning. Nondemented PD patients have exhibited normal learning on this task (Heindel et al., 1989; Sarazin et al., 2002), although not when different rotation speeds are randomly presented (Harrington et al., 1990; Haaland, Harrington, O'Brien, & Hermanowicz, 1997). When different rotation speeds are randomly presented, participants must develop and retrieve different motor programs at the beginning of each trial, and switch between programs on sequential trials. Thus, while patients with PD may be able to successfully learn and execute a single motor procedure, they may have difficulty when required to maintain and switch between multiple motor programs. Some studies have demonstrated deficient performance by PD patients on mirror reading tasks (Koenig et al., 1999; Sarazin et al., 2002), although other studies have demonstrated that they can perform normally (Bondi & Kaszniak, 1991; Harrington et al., 1990; Huberman et al., 1994). These discrepant findings may be explained in part by patient sample differences. For example, Sarazin and colleagues found that the subsample of their nondemented PD patients who demonstrated executive dysfunction on the WCST were impaired on mirror reading, while the patients without executive dysfunction were able to learn the procedure at a rate similar to controls. Similarly, Jackson and colleagues (Jackson, Jackson, Harrison,

& Henderson, 1995) found that only patients with executive dysfunction (also measured by the WCST) demonstrated impaired procedural learning on a serial reaction time task.

<div style="text-align:center">Language</div>

Frank aphasias are not characteristic of PD, and nondemented patients tend to perform normally on tests of vocabulary knowledge, verbal comprehension, and productive syntax (Cooper et al., 1991; Levin et al., 1989; Murray & Lenz, 2001; Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982; Scott, Caird, & Williams, 1984). However, subtle impairments in higher-order linguistic tasks have been reported (Levin & Katzen, 1995). For example, some patients demonstrate impaired comprehension of prosody (Lloyd, 1999) and certain sentence constructions (Kemmerrer, 1999), and deficits in lexical ambiguity resolution (Copland, Chenery, & Murdoch, 2000). Deficient performance on language tasks in nondemented PD patients has nearly always been attributed to concomitant cognitive impairments in other areas including attention, working memory, or the extent of cognitive resources, rather than a language impairment, per se (Bayles, 1990; Copland et al., 2000; Grossman, 1999; Lieberman et al., 1992; but see Skeel et al., 2001 for an alternative account). No study to date that has employed a comprehensive test battery has demonstrated an isolated language disturbance in PD.

Dysarthria is frequently part of the parkinsonian motor symptom complex, particularly in the later stages of the disease. It is characterized by monotony of pitch and loudness, reduced stress, variable rate, imprecise consonants, and a breathy and harsh voice (Pinto et al., 2004).

Summary of Neurocognitive Features

Nondemented PD patients display a complex pattern of spared and impaired abilities that can be observed across multiple domains of cognition. Executive dysfunction in PD is characterized by difficulties with set-shifting and maintenance, verbal fluency, sequencing, and working memory. Impaired inhibitory processing appears to impact performance on tests of complex attention. It has been suggested that explicit learning and memory deficits are mediated by executive dysfunction, particularly impaired working memory. Executive dysfunction may also explain procedural learning difficulties, for example when the procedural learning task requires patients to switch between multiple motor programs. Language appears to be relatively unimpaired in these patients, and when difficulties have been observed, they have generally been attributed to other cognitive difficulties (e.g., involving attention or working memory). In sum, one of the reasons PD patients have demonstrated spared and impaired performances across multiple domains of cognition is because of higher-level impairments involving aspects of executive functioning (e.g., set-shifting and working memory) and inhibitory attention, which are component processes of many tasks.

A selective impairment in visuospatial cognition may also be an important aspect of the neurocognitive profile of PD. Research addressing this possibility, which is the primary focus of the present work, will be reviewed in the later chapters on working memory, inhibition of return, and visual discrimination in PD (Experiments 1-3). In the next chapter, theory and research will be presented on how visual processing systems are organized in the normal brain in order to provide a background for the

present studies. In particular, evidence for neuroanatomical and functional

dissociations of visuospatial and visual object cognition will be presented because of

the relevance of these dissociations to the proposed set of studies.

IV. VISUOSPATIAL AND VISUAL OBJECT COGNITION IN THE NORMAL

BRAIN

Visual information enters the brain through the retina, passing through the axons of ganglion cells that form the optic nerve and optic tract. These ganglion cells separate to form several different pathways, the largest of which is the geniculostriate system. Cells in this system send information through the lateral geniculate of the thalamus and then to striate cortex. The parvocellular pathway of the geniculostriate system connects preferentially to ventral stream regions of cortex and is thought to be responsible for detecting color and form; the magnocellular pathway connects preferentially to dorsal stream regions of cortex and is thought to be responsible for detecting depth and movement (Livingstone & Hubel, 1988; Merigan & Maunsell, 1990; Rockland & Pandya, 1979). Thus, even at this early stage of visual processing, information particularly important to object-based cognition appears to be segregated from information important to spatial-based cogntion. Striate cortex sends axons to other visual cortical areas, which also specialize in processing certain attributes of visual experience. For example, some regions specialize in processing location, motion, orientation, color, or form (Zeki, 1978), or some combination of these attributes based on task demands (Orban et al., 1996).

Segregated pathways for visuospatial and visual object processing are well established within posterior cortical regions in the monkey brain. Dorsal regions, including posterior parietal cortex, are involved preferentially in visuospatial processing, and more ventral regions, including inferior temporal cortex, are involved

in visual object processing (Desimone et al., 1985; Felleman & Van Essen, 1991;

Livingstone & Hubel, 1988; Ungerleider & Mishkin, 1982; Zeki & Shipp, 1988).

Neuroimaging studies with humans have found evidence for a similar dorsal / ventral

dissociation in posterior cortex during visuospatial and visual object working memory

tasks (Belger et al., 1998; Courtney et al., 1996; Postle & D'Esposito, 1999; Smith &

Jonides, 1999). In addition, patients with lesions to posterior parietal cortex tend to

demonstrate impaired processing of spatial but not object information, while patients

with lesions to inferior temporal areas tend to demonstrate impaired processing of

object but not spatial information (Kessels, Postma, Kappelle, & de Haan, 2000;

Newcombe, Ratcliff, & Damasio, 1987; Farah, Hammond, Levine, & Calvanio, 1988;

Levine, Warach, & Farah, 1985).

There is evidence that visuospatial and visual object working memory are also

functionally and anatomically segregated in prefrontal cortex (Courtney, Petit, Haxby,

& Ungerleider, 1998; Levy & Goldman-Rakic, 1999; Smith and Jonides, 1999;

Wilson et al., 1993). For example, using single-cell recording techniques during

delayed-response tasks, Wilson and colleagues (1993) demonstrated that neurons in

monkey prefrontal cortex that code information related to stimulus identity are

dissociable from those that code information related to stimulus location, with the

cortex of the inferior prefrontal convexity functionally specialized for processing

identity-related information, and more dorsal regions specialized for processing

location-related information. In their meta-analysis of functional neuroimaging studies

that compared visuospatial and visual object working memory, Smith and Jonides

(1999) found evidence consistent with this dorsal-ventral functional specialization in

prefrontal cortex. Specifically, visuospatial working memory tasks tended to be associated with greater activation in dorsal regions of prefrontal cortex, while visual object working memory tasks were generally associated with greater activation in more ventral regions.

However, it is not entirely clear if visuospatial and visual object working memory functions are segregated in prefrontal cortex. Several studies suggest that working memory functions in the human prefrontal cortex are neuroanatomically segregated by type of processing required (e.g., manipulation versus maintenance of information) rather than by type of material to be remembered (Owen, 1997; Postle & D'Esposito, 1999; Wager & Smith, 2003). Further, it has been suggested that findings in support of material-specific segregation from electrophysiological studies of monkeys might arise as a by-product of blocked training with one type of stimulus at a time (Bichot, Schall, & Thompson, 1996; Postle & D'Esposito, 1999). Therefore, there is relatively consistent evidence that working memory for spatial information and object information are functionally and neuroanatomically separable in posterior cortex, whereas the extent of anatomical independence in prefrontal cortex is still a subject of debate.

Material-specific functional segregation also appears to occur within the striatum, such that the head of the caudate is preferentially involved in spatial working memory, and more caudal regions may be preferentially involved in object working memory. Levy and colleagues (1997) tested levels of metabolic activity in these regions while monkeys performed visuospatial and visual object working memory tasks. These researchers found topographic segregation by task in the caudate nucleus, with the

spatial task activating the dorsal and central regions of the head of the caudate, and the object task activating the caudal part of the body. Similarly, lesions of the anterodorsal portion of the head of the caudate nucleus (Divac, Rosvold, & Szwarcbart, 1967) and electrical stimulation of this same region (Cohen, 1972) have been shown to impair performance on spatial delayed alternation tasks. Lesions in the tail of the caudate have resulted in impaired visual discrimination learning (Divac et al., 1967; Iverson, 1979). Using fMRI with humans, Postle and D'Esposito (1999) found that the head of the caudate nucleus is involved in the integration of spatial (but not object) mnemonic information with motor responses. Based on their findings, the investigators suggested that spatial working memory plays an important role in the planning and execution of motor action, and that the head of the caudate nucleus is an important mediator of this function. Studies using the autoradiographic technique in monkeys provide additional support for material-specific segregation in the caudate nucleus, because cortical regions that have been implicated in ventral and dorsal visual processing streams demonstrate remarkable segregation in their connections to the caudate. For example, Baizer, Desimone, and Ungerleider (1993) used anterograde and retrograde neuroantaomical path tracing techniques to compare subcortical connections of the posterior parietal and inferior temporal cortex in monkeys. They found that parietal cortex terminates dorsally in the head and body of the caudate, while temporal cortex connects to the genu and tail. Also using the autoradiographic technique in monkeys, Yeterian and Pandya (1991, 1995) found that medial and dorsolateral prefrontal cortex and medial and dorsolateral extrastriate regions connect preferentially to the dorsal and central portions of the head and the body of the caudate nucleus. Further, they

found that the ventral prefrontal, ventral inferotemporal, and ventral extrastriate cortical regions connect preferentially to the ventral section of the body and to the tail of the caudate nucleus. Taken together, these studies suggest that the head of caudate nucleus is anatomically segregated from ventral and caudal regions in these visual processing circuits, such that the head plays a functionally specialized role in visuospatial working memory, and more posterior regions play a specialized role – at least in the monkey brain – in visual object working memory. Given that PD neuropathology is known to preferentially impact the most anterodorsal extent of the head of the caudate as compared more posterior and ventral regions of the head and body (Kaufman & Madras, 1991; Kish et al., 1988; Joyce, 1993), this segregation has potential relevance for explaining visual cognitive impairments in PD. However, previous neuropathological studies of caudate nuclei tissue in PD have not sampled the most posterior regions, so it should be noted that the extent to which PD pathology affects the tail is unknown.

While most research studies on the neuroanatomical dissociations of visuospatial and visual object cognition have employed working memory paradigms, some studies have attempted to delineate the brain regions involved in perceptual versus mnemonic aspects of working memory tasks. Using fMRI with humans, McCarthy and colleagues (1994) reported greater activation of dorsolateral prefrontal cortex during a spatial working memory task than during dot and color detection control tasks. Goldberg, Berman, Randolph, Gold, and Weinberger (1996) found greater activation in dorsolateral prefrontal and superior parietal cortex associated with a spatial working memory task than a control task, which differed from the memory task only in that no

delay was present. The authors interpreted their results to suggest that prefrontal cortex may be involved in mnemonic rehearsal functions, while parietal cortex maintains spatial characteristics of the memoranda. Belger and colleagues (1998) studied both spatial and object working memory and observed that inferior temporal cortex appeared to be involved primarily with perceptual processing of shapes, posterior parietal regions with both perceptual and mnemonic aspects of working memory for locations, and prefrontal regions with primarily the mnemonic aspects of both working memory for shapes and locations. Neurobiological studies in nonhuman primates have found that neurons in dorsolateral prefrontal cortex increase their firing rate beyond the perceptual processing period of delayed response tasks (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1973; Quintana, Yajeya, & Fuster, 1988). In summary, this research generally suggests that prefrontal cortex plays a role in the mneumonic aspects of working memory, parietal cortex plays a role in both the mneumonic and perceptual processing of spatial-based information, and temporal cortex plays a role in the perceptual processing of object-based information.

Behavioral studies in humans have demonstrated double dissociations of visuospatial and visual object working memory using dual task paradigms (Hecker & Mapperson, 1997; Logie & Marchetti, 1991; Tresch, Sinnamon, & Seamon, 1993). For example, Hecker and Mapperson (1997) examined the effects of color changes or achromatic flickering surrounding the central stimulus presentation during working memory for colors, patterns, and locations. Color changes interfered more than the achromatic flicker when the participants were required to remember colors or patterns, but the achromatic flicker interfered more when participants were required to

remember locations. Similarly, Tresh and colleagues (1993) found that performing a movement discrimination task selectively interfered with remembering the location of a dot in a spatial memory test, whereas performing a color discrimination task selectively interfered with remembering the form of an object in an object working memory test. These studies provide additional evidence for a functional dissociation of spatial and object visual systems.

There is also evidence for a distinction between spatial-based attention and object-based attention (Behrmann & Tipper, 1999; Duncan, 1984; Egly, Driver, & Rafal, 1994; Yantis & Serences, 2003). This evidence comes in part from studies of patients with unilateral neglect, who typically have right parietal lesions and ignore stimuli in their left visual field (Rafal, 1998). Historically, this neglect was characterized spatially in that information presented in the left hemifield was ignored. However, it has also been demonstrated that these patients can neglect the left side of objects, even when the object is presented in their right hemifield (Caramazza & Hillis, 1990; Driver, Baylis, Goodrich, & Rafal, 1994; Driver & Halligan, 1991). Studies using spatial precueing paradigms have also demonstrated that attention can be directed at spatial-based or object-based frames of reference, and that this distinction applies to both facilitatory and inhibitory aspects of attention (Egly et al., 1994; Iani, Nicoletti, Rubichi, & Umilta, 2001, Jordan & Tipper, 1998, 1999; Leek, Reppa, & Tipper, 2003; Posner & Cohen, 1984; Soto & Blanco, 2004).

In sum, the distinction between visuospatial and visual object cognition appears to be important for multiple domains of visual cognition, including working memory, attention, and more basic visual processes. Cortical visual areas are broadly separable

into two visual processing streams originating in striate cortex: a dorsal stream specialized for the appreciation of object locations, and a ventral stream specialized for the identification of objects (Underlieder & Mishkin, 1982). Material-specific segregation also appears to occur within the caudate nucleus, with the head of the caudate involved in spatial working memory and more caudal regions involved in object working memory (Levy et al., 1997; Postle & D'Esposito, 1999).

As noted above, PD pathology is associated with uneven dopamine depletion in the caudate nucleus, with the greatest loss in the anterodorsal extent of the head (Kish et al., 1988). Based on this finding and the neuroanatomy of visual cognitive systems discussed above, it follows that PD may be associated with greater impairment in visuospatial than visual object cognition due to altered function in visual circuits involving anterodorsal regions of the caudate. In addition, there is evidence that the magnocellular pathway may be more affected than the parvocellular pathway in PD (Arakawa et al., 1999; Regan & Maxner, 1987; Tebartz van Elst et al., 1997), which provides another possible locus for a selective visuospatial impairment. If the nature of the selective visuospatial impairment is that only higher-level aspects of visuospatial cognition are disrupted in PD, it is likely that FSC circuit dysfunction underlies this impairment, because these circuits have been implicated in executive control processes. The DLPFC may play a particularly important role, considering that dorsolateral prefrontal cortex is segregated in its connections with anterior regions of the caudate, and this region (like the head of the caudate) has been implicated in visuospatial working memory processes. Caudate connections with posterior parietal cortex may also underlie the impairment, given that this region likewise projects to the

dorsal head of the caudate and plays a role in spatial working memory. If visuospatial processing is selectively impaired across multiple domains of cognition including lower level visual discriminations, it is possible that pathological changes in visuospatial perceptual processing regions in posterior cortex may play a role, or that the distinction arises due to differential involvement of the magnocellular and parvocellular pathways. Thus, the present investigation into the nature of a possible selective impairment in visuospatial (versus visual object) cognition may be useful for determining which of these visual pathways is likely to underlie PD visuospatial dysfunction.

In the following sections, the experiments will be introduced and described. The purpose of these experiments is to test the overarching hypothesis that visuospatial cognition is selectively impaired in PD in comparison to visual object cognition, and further to investigate the nature of this possible impairment. The experiments are designed to test this hypothesis by comparing visuospatial and visual object cognition in PD using working memory, inhibition of return, and visual discrimination tasks.

V. EXPERIMENT 1: VISUOSPATIAL AND VISUAL OBJECT WORKING

MEMORY IN PARKINSON'S DISEASE

Experiment 1 Introduction

Working memory is a limited capacity system responsible for transiently

encoding, maintaining, and processing information. This temporary memory system

plays a crucial role in higher-level cognition. For example, performance on working

memory tasks has been shown to correlate highly with measures of controlled

attention (Kane, Bleckley, Conway, & Engle, 2001), logical reasoning (Baddeley &

Hitch, 1974), vocabulary acquisition (Gathercole & Baddeley, 1989), reading

comprehension (Daneman & Carpenter, 1980), abstract reasoning (Kyllonen &

Christal, 1990), and problem solving (Welsh, Satterlee-Cartmell, & Stine, 1999). In

fact, working memory is commonly considered to be an indicator and key component

of one's intellectual capability (Burgess, Braver, & Gray, 2006; Engle, Kane, &

Tuholski, 1999; Kyllonen & Christal, 1990; Miyake, Friedman, Rettinger, Shah, &

Hegarty, 2001; Wechsler, 1981).

Working memory is thought to rely on a dynamic interplay between perceptual

representations and executive control processes. *Perceptual* processes involve the

transmission of sensory information to later systems and the formation of transient

representations that decay rapidly without bottom-up support or further processing

(Potter, 1993; Zeki, 1993). After initial perception of a stimulus, *encoding* processes

are thought to bring perceptual representations 'on-line,' so that they will be available

in the absence of information from the environment (D'Esposito, Postle, & Rypma,

2000; Jolicoeur & Dell'Acqua, 1998; Ranganath, DeGutis, & D'Esposito, 2004;

Rypma & D'Esposito, 1999; Woodman & Vogel, 2005). Once information has been

successfully perceived and encoded, the representations are held on-line via

maintenance processes (Fuster, 1998; Goldman-Rakic, 1987; Woodman & Vogel,

2005). Prefrontal cortex appears to play a critical role in the executive processes

associated with encoding and maintenance, whereas regions in posterior cortex are

associated with perceptual processes and their representations (D'Esposito et al., 2000;

Belger et al., 1998; Funahashi et al., 1989; Fuster, 1973, 1998; Goldberg et al., 1996;

McCarthy et al., 1994; Ranganath et al., 2004; Quintana et al., 1988).

The caudate nucleus is also thought to play a critical role in working memory

(Lewis, Dove, Robbins, Barker, & Owen, 2004; Levy et al., 1997; Niki, Sakai, &

Kubota, 1972; Postle & D'Esposito, 1999). Parkinson's disease is associated with

dramatic alterations in the functioning of this nucleus, due to the degeneration of

midbrain dopaminergic projections (Agid, 1991; Forno, 1996). Dopamine depletion in

the caudate nuclei has been used to explain working memory deficits in PD (Lewis,

Dove, Robbins, Barker, & Owen, 2003; Owen, 2004; Postle, Jonides, et al., 1997),

which have frequently been reported (Bradley, Welch, & Dick, 1989; Bublak, Muller,

Gron, Reuter, & von Cramon, 2002; Cooper et al., 1993; Fournet, Moreaud, Roulin,

Naegele, & Pellat, 2000; Gilbert et al., 2005; Gotham et al., 1988; Kensinger et al.,

2003; Le Bras, Pillon, Damier, & Dubois, 1999; Lewis, Cools, et al., 2003; Morris et

al., 1988; Owen, Beksinska, et al., 1993; Owen, Iddon, Hodges, Summers, & Robbins,

1997; Owen, Roberts, et al., 1993; Pillon et al., 1998; Postle, Jonides, et al., 1997).

However, the nature of these deficits is not entirely clear. For example, there is a

controversy in the literature regarding whether working memory for the locations of stimuli (i.e., spatial working memory) is more impaired than working memory for object features such as shape or color, or for linguistic information such as words or numbers (i.e., object or verbal working memory, respectively). Further, it is unclear if the working memory deficit arises from impairments in perceptual, encoding, or maintenance processes.

Several studies have tested both spatial working memory and non-spatial working memory in nondemented patients with PD, and in general, these studies have demonstrated that spatial working memory is differentially impaired (Bradley et al., 1989; Owen et al., 1997; Owen, Beksinska, et al., 1993; Postle, Jonides, et al., 1997, Postle, Locascio, Corkin, & Growdon, 1997, Swainson et al., 2000, Taylor et al., 1986). For example, Owen and colleagues (1997) administered tests of spatial, verbal, and visual object working memory to patients in various stages of the disease. They found that non-medicated patients with mild symptoms were unimpaired on all three tasks, medicated patients with mild symptoms were impaired on the spatial task only, and medicated patients with severe symptoms were impaired on all three tasks. Based on these findings, these authors suggested that working memory deficits in PD emerge and progress according to a particular sequence by the type of material to be remembered, with spatial working memory deficits emerging earliest. Using a delayed-response paradigm, Taylor et al. (1986) found that PD patients were impaired when required to remember spatial information, but not novel nonsense designs or words. Owen and colleagues (1993) demonstrated that PD patients with severe physical symptoms were impaired on spatial but not pattern recognition. Using similar

tests of spatial and pattern recognition, Swainson and colleagues (2000) demonstrated that *de novo* patients and patients with mild physical symptoms were selectively impaired on the spatial task. Bradley et al. (1989) demonstrated that patients with mild to moderate PD were impaired on a test of spatial working memory, but not on an analogous test of verbal working memory. Postle, Locascio, and colleagues (1997) found that medicated patients with mild PD were impaired on a spatial but not object conditional associative learning task, both of which place considerable demands on working memory. This research group again demonstrated impaired spatial working memory and intact object working memory in early PD using a visual delayed-response task that equated the perceptual difficulty of the tests for each participant (Postle, Jonides, et al., 1997).

In contrast, a few studies have provided evidence that the working memory deficits observed in PD may not be greater for spatial material (Costa et al., 2003; Fournet, et al., 2000; Pillon et al., 1998). Pillon et al. (1998) found that verbal and spatial conditional associative learning were not differentially impaired in nondemented PD patients. Fournet and colleagues (2000) reported that the level of deficits PD patients demonstrated on verbal and spatial span tasks did not differ overall or at varying delays. This result did not change after dopaminergic medication was withdrawn. In a study by Costa and colleagues (2003), patients with PD actually performed better on a visuospatial than a visual object working memory task. The authors considered that this finding was in contradiction to other studies, and argued that the effect was likely due to differences in task difficulty in that the object task was more difficult and probably required greater executive resources than the spatial task.

There is evidence that PD may selectively target brain structures that support spatial working memory as compared to object working memory. Dopamine depletion in the caudate nucleus appears to be greatest in the anterodorsal extent of the head (Kish et al., 1988), and dopamine uptake sites in this structure are reduced more dorsally than ventrally (Joyce, 1993; Kaufman & Madras, 1991; Piggott et al., 1999), although it should be noted that these neuropathological studies sampled the head and body but not the tail of this nucleus. Importantly, as discussed in the earlier section on visuospatial and visual object cognition in the normal brain, dorsal and ventral cortical regions demonstrate remarkable segregation in their connections to the caudate nucleus, such that dorsal regions that are thought to play a critical role in visuospatial processing (e.g., posterior parietal cortex) project preferentially to the dorsal head of the caudate nucleus, and ventral regions that are thought to play a critical role in visual object processing (e.g., inferior temporal cortex) project most strongly to the tail and genu (Baizer et al., 1993; Smith & Jonides, 1999; Ungerleider & Mishkin, 1985; Yeterian & Pandya, 1991, 1995). Further, evidence from studies of nonhuman primates indicates functional segregation within the caudate nucleus, with the dorsal head of the caudate involved in spatial working memory and more caudal or ventral regions involved in object working memory (Cohen, 1972; Divac et al., 1967; Iverson, 1979; Levy et al., 1997). Using fMRI with humans, Postle & D'Esposito (1999) provided evidence that the head of the caudate is involved in the integration of spatial (but not object) mnemonic information with motor responses. Taken together, this body of research suggests that the possible selective deficit in spatial working memory

in early PD could be explained by greater disruption of visuospatial processing circuits that involve anterodorsal regions of the caudate nucleus.

As discussed above, working memory is thought to involve perceptual, encoding, and maintenance processes. Based on this model, a selective deficit in spatial working memory could be due to an impairment in one of these processes (e.g., spatial maintenance), with relative sparing of the analogous non-spatial process (e.g., object maintenance). The integrity of working memory maintenance processes in PD has been examined by varying the length of the delay between presentation and recall of the memoranda with the assumption that if PD patients have deficits in working memory maintenance, their deficits would be greater at the longer delays (Ketcham, Hodgson, Kennard, & Stelmach, 2003; Le Heron, MacAskill, & Anderson, 2005; Lewis et al., 2005; Fournet et al., 2000; Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Marie et al., 1995; Perbal et al., 2005; Sahakian et al., 1988; Sullivan et al., 1993; Owen, Beksinska, et al., 1993). The finding that working memory deficits in PD do not increase as delay intervals lengthen has been demonstrated in several studies examining working memory for verbal information (Fournet et al., 2000; Lewis et al., 2005; Marie et al., 1995; Sullivan et al., 1993; Graceffa et al., 1999), spatial information (Fournet et al., 2000; Ketcham et al., 2003; Le Heron et al., 2005), and visual patterns requiring both object and spatial processing (Owen, Beksinska, et al., 1993; Sahakian et al. 1988). This pattern of working memory performance suggests that when PD patients demonstrate working memory deficits, the underlying impairment does not involve maintenance processes. Instead, it suggests that certain processes required to bring stimuli representations online, such as perceptual or

encoding processes, may be impaired. However, a few studies have demonstrated

greater deficits at longer delays for spatial and verbal stimuli (Perbal et al., 2005;

Sullivan et al., 1993), and object working memory maintenance processes in PD have

not been adequately studied. Thus, it is not clear if working memory maintenance

processes are universally spared in these patients.

Another possibility not adequately addressed by past research is that PD patients'

greater spatial than object working memory deficits may be due to differences in

spatial versus object perception. Consistent with this possibility, PD patients have

demonstrated a normal ability to perceive simple objects (Laatu, Revonsuo, Pihko, &

Rinne, 2004; Tachibana, Aragane, Kawabata, & Sugita, 1997; Russ & Seger, 1995;

DeLancy Horne, 1971), but their ability to make simple spatial judgments, although

inconsistent, has been shown to be impaired (Finton, Lucase, Graff-Radford, & Uitti,

1998; Goldenberg, Wimmer, Auff, & Schnaberth, 1986; Montse, Pere, Carme,

Francesc, Eduardo, 2001; Stelmach, Phillips, & Chau, 1989). However, Postle,

Jonides, and colleagues (1997) found some evidence that the selective spatial deficit is

due to a disruption in working memory rather than perceptual processes. In their study

that demonstrated impaired spatial working memory and spared object working

memory in early PD, they used tasks that equated the perceptual difficulty for each

participant. Because perceptual difficulty was equated for both the spatial and object

working memory tasks, the authors reasoned that PD patients' selective deficit on the

spatial working memory task was due to a specific impairment in spatial working

memory and not due to an impairment in more basic visual processes. However, this

study does not completely rule out the possibility that impairments in spatial perception also play a role in the working memory deficit profile observed in PD.

The purpose of Experiment 1 is to further investigate whether PD is associated with a selective impairment in spatial working memory as compared to object working memory, and also to investigate the nature of this impairment. As noted above, Postle, Jonides, and colleagues (1997) demonstrated that PD patients were impaired on a spatial working memory task, but not on an analogous object working memory task. One limitation of their study, however, was that it only included one delay period, and thus they could not test the integrity of maintenance processes relative to encoding or perceptual processes. If the deficit they observed on the spatial working memory task was in fact due to an impairment in maintaining spatial information in working memory, the accuracy of the PD patients would be expected to decline further with increasing delays relative to controls. In addition, if object working memory is truly intact in PD, normal performance at longer delay periods would be expected.

The present experiment was designed to address these issues. More specifically, it was designed to test the hypothesis that spatial working memory encoding but not maintenance processes are impaired in PD, and further that object working memory encoding and maintenance processes are unimpaired. The task used was adapted from the delayed response task used in the study by Postle, Jonides, et al. (1997), and was likewise composed of analogous spatial working memory and object working memory conditions. Participants in the present study viewed two abstract 'target' shapes for 2 seconds on a computer screen, followed by a variable delay, and then were asked to judge if a third 'probe' shape matched either of the first two shapes in location (spatial

condition) or shape (object condition). The spatial and object conditions differed only in task instructions (i.e., what the participant should attend to, location or shape). In contrast to the task used by Postle, Jonides, and colleagues, the exposure duration of targets were the same for all participants, and the effect of a variable delay period was assessed. A short delay of 1 second was chosen because of previous demonstrations that encoding processes for 1 to 3 visually presented stimuli (letters or symbols) appear to be complete by about 1 second (Jolicoeur & Dell'Acqua, 1998). Performance at this delay is expected to reflect the integrity of perceptual and encoding processes. Longer delays of 5 and 10 seconds were included to additionally engage the patients' ability to maintain the stimuli in working memory over a delay. These manipulations allowed for the evaluation of PD patients' ability to encode and maintain visuospatial and visual object information in working memory, and is the first study to investigate the effect of a variable delay on both spatial and visual object working memory in this patient group. The integrity of visuoperceptual processes and their contribution to working memory performance in PD will be addressed in Experiment 3.

Experiment 1 was also designed to examine the relationship between working memory and motor symptoms in PD, and specifically test the hypothesis that working memory impairments in PD are associated with bradykinesia and rigidity, but not tremor or laterality of symptoms. Motor functioning was assessed using a previously derived factor analysis of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & the UPDRS Development Committee, 1987), with factors corresponding to bradykinesia, tremor, and rigidity (Stebbins & Goetz, 1998). It is

recognized that there are different pathophysiological mechanisms involved in the genesis of these cardinal signs of PD (see Grafton, 2004 for a review). For example, several studies have correlated dopamine loss in the striatum with bradykinesia or rigidity, while no correlation is typically found with tremor (Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). The relationship between working memory deficits in the present study and motor symptoms may provide some suggestion of the underlying pathophysiology of the working memory deficits in PD. For example, if a spatial working memory deficit correlates with bradykinesia or rigidity but not tremor, it would suggest that the pathophysiological changes associated with bradykinesia and rigidity (e.g., dopamine loss in the striatum) are related to the pathophysiology of the spatial working memory deficit. This finding would be supported by studies that have demonstrated an important role for dopamine in the regulation of spatial working memory performance (Chudasama & Robbins, 2006), although it should be noted that studies looking at the effects of dopaminergic medication on spatial and object working memory in PD have not found a consistent relationship (Lange et al., 1992; Fournet et al., 2000; Costa et al., 2003).

In addition, this study will examine whether any observed working memory deficits are associated with unilateral symptoms or the side of symptom onset, which would suggest that the deficit is associated with greater PD symptomatology in the contralateral cerebral hemisphere. Unilateral symptoms were operationalized by scores on the UPDRS and the Finger Tapping Test (Reitan, 1969). Although there is some suggestion in the literature that left-sided motor symptoms or side of symptom onset is differentially associated with spatial cognitive impairments (Beatty, 2002; Blonder,

Gur, Gur, Saykin, & Hurtig, 1989; Cheesman et al., 2005), other studies have found no evidence of functional asymmetry (Postle, Jonides, et al., 1997; Riklan, Stellar, & Reynolds, 1990), or suggest that left-sided motor symptoms are associated with greater cognitive decline in general (Direnfeld et al., 1984; Tomer, Levin, Weiner, 1993).

Experiment 1 Methods

Participants

Eighteen nondemented patients with PD (10 men and 8 women) and 18 normal controls (10 men and 8 women) participated in the study. The patients with PD were recruited from the Parkinson's Disease Research Subject Database of the San Diego VA Health Care System / University of California at San Diego. All patients were diagnosed by a board-certified neurologist who specializes in movement disorders, and based on the presence of at least two of the following symptoms: (1) resting tremor, (2) rigidity, or (3) bradykinesia. The patients had been diagnosed an average of 6.1 years (range = 1 – 20, SD = 4.7) prior to their participation in the study. Motor functioning was assessed by an experienced neurologist using Hoehn and Yahr's (1967) rating scale, and the UPDRS (Fahn et al., 1987). Using Hoehn and Yahr's rating scale, all patients exhibited mild motor impairments (M = 2.0, range = 1 – 2.5, SD = 0.5). Due to an inaccurate UPDRS protocol, there was an error made in scoring the UPDRS for 14 of the 18 participants. On item 25 "rapid alternating movements," participants should have received a score for each hand. Instead, only a score for the worst hand was recorded. Mean scores on the motor examination section were computed twice, once assuming the less symptomatic hand received a score of 0 on

item 25 (representing normal performance), and once assuming this hand received a

score equal to the worst hand. These calculations indicated that if the UPDRS were

scored accurately, the mean score of the PD patients on the motor examination section

would have fallen between 20.78 and 22.11, representing mild motor symptoms.

The patients were treated with their normal regimen of dopaminergic agents at the

time of testing (see Table 1) and were tested at the time of day when they felt

cognitively more alert. No patients were taking anticholinergic or antipsychotic

medication. Normal control participants were recruited from relatives of patients, and

from newspaper advertisements. All participants were screened for a history of

significant neurological disease (other than PD), serious psychiatric illness (major

Table 1. Characteristics of the Parkinsonian patients in Experiment 1

No.	Age	Disease duration[a]	H & Y Stage	Antiparkinsonian medication, daily dose (mg) [b]
1	68	20	2	LeCa 300/75, En 800, Pr 1
2	67	4	2.5	LeCa 600/150, Pr 5, Am 100
3	63	4	2.5	Se 10, Ro 5
4	63	4	1	LeCa 400/100
5	57	4	1	LeCa 200/50, Pr 2, Se 5
6	72	10	2	LeCa 1200/300, Pr 2
7	48	8	1	LeCa 400/100, Ca 100, En 600, Pr 23
8	53	1	2	Pr 3
9	68	4	1.5	LeCa 200/50
10	66	10	2	LeCa 1000/250, Pr 14
11	75	4	2	LeCa 100/25
12	56	7	2.5	LeCa 400/100, Pr 2
13	64	14	2.5	LeCa 100/25, LdCaEn 350, Se 10
14	75	3	2.5	LeCa 400/100, En 200
15	79	4	2	LeCa 800/200, Se 5
16	64	3	2	Se 1
17	79	5	2	LdCaEn 300, Se 10, Ro 15
18	88	3	2.5	LeCa 300/75, Ro 3

[a]Age and disease duration in years.
[b]LeCa, levodopa-carbidopa; En, entacapone; Pr, pramipexole; Am, amantadine; Ro, ropinirole; Se, selegiline; Ca, carbidopa; LdCaEn, levodopa-carbidopa-entacapone.

affective disorder or schizophrenia), and substance abuse. In addition, participants

were excluded if they scored below 132 on the Dementia Rating Scale (DRS; Mattis,

1976) or worse than 20/50 on the Rosenbaum Pocket Vision Screener.

Using an alpha level of .05, the PD patients and the controls did not significantly

differ in age, $t(34) = 0.02$, $p = .98$, years of education, $t(34) = 0.33$, $p = .74$, or DRS

scores, $t(33) = 1.66$, $p = .11$, $d = 0.47$. The range of DRS scores for the controls was

136 to 144, and the range for the PD patients was 133 to 144. The groups did differ in

scores on the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986), $t(32) =$

3.02, $p < .01$, $d = 1.04$. The range of GDS scores for the controls was 0 to 8, and for

the PD patients was 0 to 11.[1] Table 2 shows the mean age, years of education, and

scores on the DRS and GDS for the two groups.

The patients and controls were given a battery of tests in order to characterize

their neuropsychological functioning. In addition to the DRS, Rosenbaum Pocket

Vision Screener, and GDS, participants were administered the Wisconsin Card Sorting

Test (WCST), Judgment of Line Orientation (JOLO; Benton, Varney, & Hamsher,

1978), the American National Adult Reading Test (ANART; Grober & Sliwinski,

1991), the Finger Tapping Test (Reitan, 1969), the California Verbal Learning Test,

Second edition (CVLT-II), and the D-KEFS Verbal Fluency Test (Delis, Kaplan, &

Kramer, 2001). Because of time constraints, some participants did not receive all of

---

[1] Despite the significant difference in GDS scores between the groups, none of the patients exhibited
more than a minimal level of self-reported depression, and on average, the GDS scores of the patients
were not in the depressed range. Further, follow-up analyses to be discussed in the results did not
indicate that differences in depression levels accounted for any of the observed working memory
deficits. Thus, despite the differences between the groups on the GDS, this does not appear to have
contributed to the pattern of results.

these tests, so the range of sample size varied by test from 17 to 18 in the PD group,

and 15 to 18 in the NC group. Table 2 shows the mean scores on selected indices from

these tests for the two groups, and denotes the indices on which the groups

significantly differed based on independent samples t-tests.

Table 2. Demographic characteristics and neuropsychological test scores of
Parkinsonian patients and normal controls

	PD	NC
Age	67.41 (10.12)	67.35 (7.75)
Education	16.69 (2.35)	16.44 (2.18)
DRS	139.39 (3.43)	141.06 (2.38)
Rosenbaum Pocket Vision Screener	20/28.82 (8.20)	20/27.50 (6.58)
Geriatric Depression Scale	5.17 (3.70)	1.88 (2.45)**
WCST categories	4.83 (2.04)	5.13 (1.51)
WCST perseverative responses	15.78 (15.70)	15.87 (14.46)
WCST set losses	0.83 (.86)	0.90 (.23)
JOLO	25.17 (5.24)	25.27 (3.03)
ANART	42.22 (4.88)	40.93 (5.95)
Finger tapping dominant	35.11 (11.74)	44.96 (8.99)*
Finger tapping nondominant	36.57 (10.03)	36.93 (7.64)
CVLT trial 1	6.11 (2.47)	6.27 (2.09)
CVLT trials 1-5	48.72 (12.40)	52.40 (11.75)
CVLT short delay free recall	9.78 (3.02)	11.13 (3.66)
CVLT short delay cued recall	11.00 (2.72)	12.47 (2.77)
CVLT long delay free recall	10.33 (3.41)	12.00 (3.57)
CVLT long delay cued recall	11.50 (2.98)	12.53 (3.09)
CVLT semantic clustering	1.51 (1.95)	1.97 (2.02)
CVLT total repetitions	3.22 (2.82)	5.13 (5.01)
CVLT total intrusions	4.17 (5.22)	3.13 (3.70)
CVLT recognition hits	14.17 (2.28)	15.20 (1.15)
CVLT recognition false positives	2.44 (2.48)	2.67 (4.06)
D-KEFS letter fluency	43.71 (13.38)	43.93 (12.89)
D-KEFS category fluency	38.41 (9.25)	40.07 (7.66)
D-KEFS category switching fluency	14.12 (1.65)	13.80 (4.13)
D-KEFS fluency switching accuracy	13.35 (1.80)	13.00 (4.47)

Values represent mean (s.d.).
*$p<.05$
**$p<.01$

The demographic characteristics of the patients and controls were similar across the three experiments, and are presented in Table 3.

Table 3. Demographic characteristics of Parkinsonian patients and normal controls in the three experiments.

	Age[a]	Education[a]	Proportion Male	DRS
		Experiment 1		
PD	67.41 (10.12)	16.69 (2.35)	.56	139.39 (3.43)
NC	67.35 (7.75)	16.44 (2.18)	.56	141.06 (2.38)
		Experiment 2		
PD	67.04 (8.28)	16.56 (2.18)	.61	139.56 (3.29)
NC	69.44 (8.19)	16.44 (2.23)	.50	140.76 (2.75)
		Experiment 3		
PD	69.49 (9.04)	16.93 (2.25)	.60	139.87 (3.18)
NC	66.73 (8.07)	16.93 (2.40)	.53	141.57 (1.74)

[a]Age and disease duration in years.
Values represent mean (s.d.).

Apparatus and Stimuli

Stimuli were presented on a 50.8 cm. monitor. Randomization and presentation of stimuli, and recording of response accuracy and reaction time, were executed by Eprime software, version 1.1. Participants responded via two keys on a standard computer keyboard, which were designated by colored stickers and labeled with a sign behind the keys. The sign read "match" behind the "z" key, which was colored blue, and "different" behind the "/" key, which was colored red.

The sixty-one shapes used as stimuli were created using a method developed by Attneave and Arnoult (1956). Briefly, this method involves randomly selecting six coordinate pairs on a 10 x 10 matrix. The peripheral points are connected to form a convex polygon, and any remaining interior points are each connected to a side, which is determined randomly. Lines that define sides to which interior points are connected are removed.

A preliminary study was conducted to determine the perceptual similarity of the shapes. Shapes were presented to seven healthy control participants (mean age = 26.0) in a series of pairs that were either non-matched pairs (i.e., 2 different shapes), or matched pairs (i.e., 2 of the same shape). For non-match pairs, each shape was paired with every other shape twice to comprise 3660 non-match trials. The same number of match trials was also presented. All trials were presented randomly. Participants were instructed to press one key with their left hand if the two shapes presented on the screen were the same, and another key with their right hand if they were different. Median reaction times were computed and transformed into z-scores for the non-match trials. Pairs with the longest reaction times were classified as "similar," and were used in the working memory task as "similar" target – probe pairs. Pairs with reaction times clustered around a median reaction time z-score of zero were used as "dissimilar" target-probe pairs. Probes were then matched to shapes with which they had the shortest reaction times to determine the "irrelevant" targets [2]. Adjustments were made to balance the number of times each shape appeared in each category.

The similarities of target-probe pairs also varied in terms of location. Possible stimuli locations were 24 equidistant points around the circumference of an imaginary circle, which centered on the fixation cross and had a radius of 11.3° visual angle. Spatially similar targets were 15 or 30 degrees from their corresponding probe, spatially dissimilar targets were 45 or 60 degrees, and irrelevant targets were 75 to 285 degrees. The height and width of the shapes each subtended approximately 1.1° X 1.1°

---

[2] Although clearly all stimuli are relevant to the task, the term "irrelevant" is used to describe those stimuli that are most distant in terms of location and shape from the probe stimulus.

of visual angle (there is some slight variability in the size of the shapes). The shapes were solid white and presented against a black background.

<p style="text-align:center">Procedure</p>

The working memory tasks used in the present study were modified from those used in two prior studies (Postle, Jonides, et al., 1997; Smith et al, 1995). The spatial and object versions in the present experiment differed only in what the participants were instructed to attend to: stimuli locations or stimuli shapes. Each trial began with the presentation of a white fixation cross for 500 msec, followed by two target stimuli for 2 seconds. The screen was blank during the subsequent variable delay (1, 5, or 10 seconds), which was followed by presentation of the probe stimulus (see Figure 1). Participants were instructed to press the "match" key with their left hand if the probe stimulus matched one of the target stimuli in location or shape (depending on the experimental condition), or the "different" key with their right hand if it did not. The probe remained on the screen until the participant responded. The participants were instructed to strive for accuracy, and no limit was placed on reaction time. Although accuracy was the primary metric of analysis, reaction times were also recorded and analyzed.

Within each trial of the spatial working memory task, the "relevant" target stimulus was more similar to the probe stimulus in terms of location than the "irrelevant" target stimulus. Likewise, within each trial of the object working memory task, the "relevant" target was more similar to the probe in terms of its shape than the "irrelevant" target. Twenty-five percent of relevant target stimuli were classified as
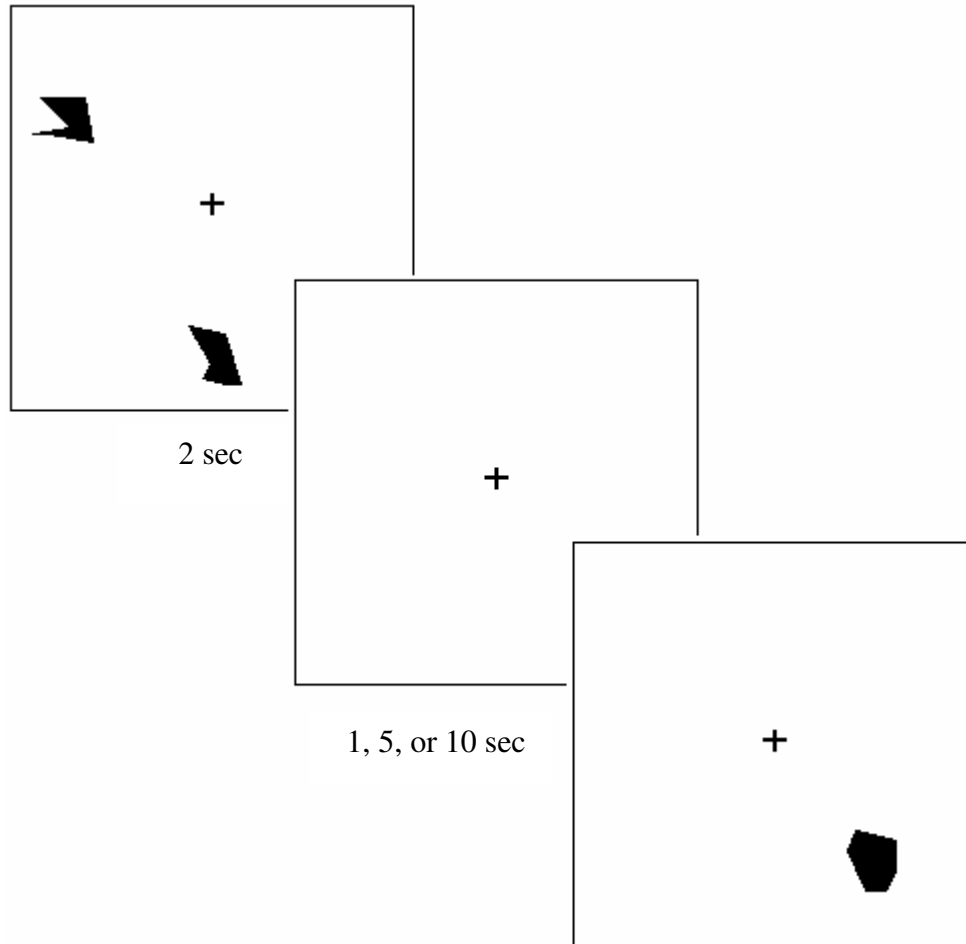
Figure 1. Schematic diagram of a single trial in Experiment 1. Colors have been inverted for this figure.

"similar" to their corresponding probe stimuli, 25 percent as "dissimilar," and 50

percent were an identical match. This classification applied to both spatial and object

similarity within both conditions. Spatial similarity of the relevant target – probe pair

was fully counterbalanced within levels of object similarity so that spatial similarity

did not predict object similarity, and likewise object similarity was counterbalanced

within levels of spatial similarity. Further, spatial and object similarity were

counterbalanced within delay period.

The working memory experiment consisted of 240 randomly presented trials in each task, and breaks were provided after every 40 trials. The order of the tasks was counterbalanced within each group, and the tasks were administered on different days for each participant.

<div align="center">Experiment 1 Results</div>

<div align="center">Validity of Similarity Manipulations</div>

Before testing the predictions based on the primary hypotheses, it was important to test the validity of the spatial and object similarity manipulations within each task. More specifically, the spatially similar trials should be more difficult than the spatially dissimilar trials within the spatial task, and the object similar trials should be more difficult than the object dissimilar trials within the object task. For these analyses and all subsequent analyses, an alpha level of .05 was used for significance testing. These validity checks were supported for the spatial task in controls, $t(17) = 6.54$, $p < .01$, $d = 1.26$, and in patients, $t(17) = 8.57$, $p < .01$, $d = 2.11$; they were also supported for the object task in controls, $t(17) = 7.66$, $p < .01$, $d = 1.39$, and in patients, $t(17) = 9.70$, $p < .01$, $d = 1.79$. In addition, it was important to test whether participants were using object information to determine their responses in the spatial task, or spatial information to determine their responses in the object task. The object similarity manipulation had no significant effect on spatial working memory performance in controls, $t(17) = 0.83$, $p = .42$, or in patients, $t(17) = 0.75$, $p = .46$. Conversely, the spatial similarity manipulation had no significant effect on object working memory performance in controls $t(17) = 0.90$, $p = .38$, or in patients, $t(17) = 0.75$, $p = .46$. These results suggest that participants were using spatial but not object information to

guide their responses in the spatial task, and object but not spatial information in the object task.

<div align="center">Response Bias</div>

The primary dependent measure for the working memory analyses was accuracy on the similar and dissimilar trials. When these non-match trials are analyzed separately from the match trials, however, response bias may have an effect on the proportion correct, because the correct response on these trials is always "no." Because of this possibility, response bias was examined using the response-bias index associated with the two-high threshold model of recognition discriminability (Snodgrass & Corwin, 1988). This index is defined as the probability of responding "yes" (i.e., the target matches the probe) when in the uncertain state. Response bias values represent a "yes" bias as they approach 1, and a "no" bias as they approach 0, with values of .5 indicating a neutral bias. Mean response bias values and standard errors by task, group, and delay are presented in Figure 2.

To examine the effects of group and the task manipulations on response bias, a 2 (group) by 2 (task) by 3 (delay) mixed analysis of variance (ANOVA) was performed. Note that similarity level was not included in this analysis, because the same proportion correct value for match trials is used in the response bias calculations for analogous dissimilar and similar nonmatch trials. This means that the effect of similarity on response-bias is the same as the effect of similarity on the proportion correct. The group by task by delay interaction was significant, $F(2, 68) = 3.19$, $p = .047$. To further examine this interaction, a 2 (group) by 3 (delay) ANOVA was performed for each task. In the spatial task, the group by delay interaction was not

significant, F(2, 68) = 1.29, p = .28, but there was a main effect of delay, F(2, 68) = 13.21, p < .01, such that response bias changed from "yes" to "no" between the 1- and 5-second delays. In the object task, the group by delay interaction was not significant, F(2, 68) = 3.53, p = .07, although there was a trend. Visual inspection of the data suggests that the PD patients tended to demonstrate a more dramatic shift from a "yes" to "no" response bias as the delay increased, relative to controls, although it should be emphasized that this interaction was not significant. As with the spatial task, there was a main effect of delay, F(2, 68) = 39.89, p < .01, such that response bias changed from "yes" to "no" with increasing delays. The groups did not differ in their overall response bias on either the spatial task, F(1, 34) = .47, p = .50, or the object task, F(1, 34) = .06, p = .80.
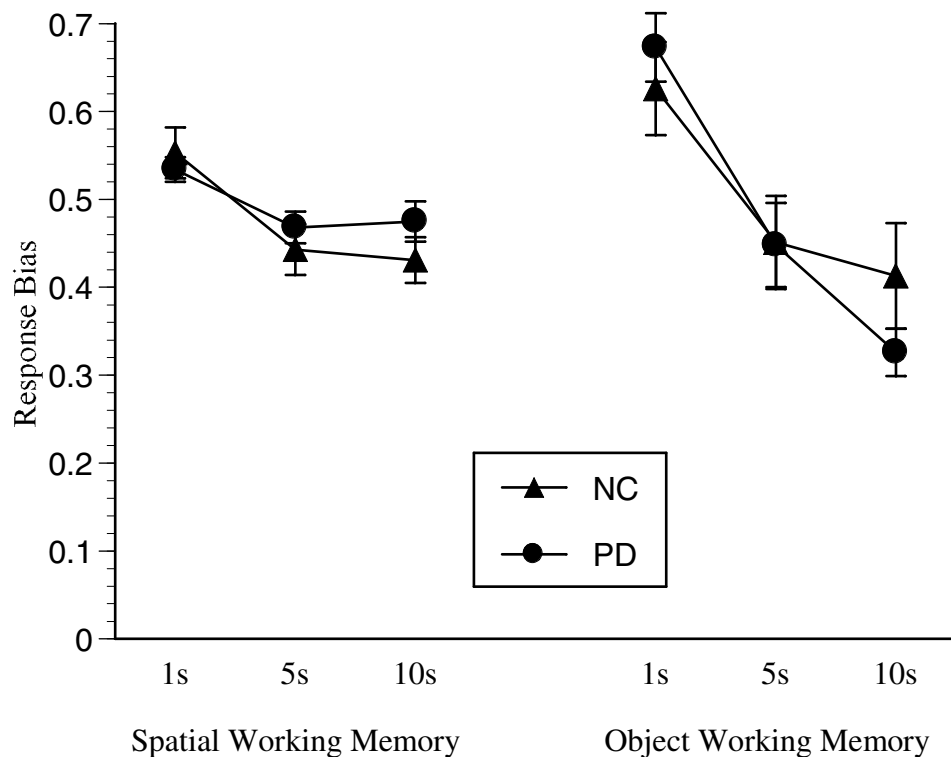

Figure 2. Mean response bias as a function of task, group, and delay

Although the groups did not significantly differ in response-bias as a function of the task manipulations, response bias was nevertheless corrected for in the primary working memory analyses for a few reasons. First, there was a trend for the groups to differ in their response bias in the object-task as a function of the delay. Second, response bias at the individual-subject level may impact the results if it is not accounted for. Third, initial examination of the accuracy data for similar and dissimilar trials indicated that accuracy did not decline over the delay, and in some cases, even improved (see Table 4), thereby giving the impression that the delay did not have any impact on either groups' working memory performances. Based on the response-bias analyses, it was clear that this surprising effect was an artifact of response-bias changes over the delay. The two-high threshold model of recognition memory was used to correct for response bias. This model was chosen because it has been shown to yield a recognition discriminability index that is independent of bias (Snodgrass & Corwin, 1988). Recognition discriminability values approach 1.0 as accuracy increases, and approach 0 as accuracy approaches chance (i.e., 50% correct). Accuracy and recognition discriminability as a function of group and the task manipulations are presented in Table 4.

<u>Working Memory Performance</u>

The recognition discriminability scores were analyzed using a 2 (group) X 2 (task) X 2(similarity) X (3) delay mixed ANOVA.[3] The results of this ANOVA revealed that the group by task by delay by similarity interaction was not significant,

---

[3] The same ANOVA was performed with accuracy as the dependent variable. The same effects were significant, except for the group by task by delay interaction, $F(2, 68) = 0.30$, $p = .74$.

Table 4. Proportion correct and recognition discriminability by task, delay, group, and similarity

	Spatial Working Memory			Object Working Memory		
	1s	5s	10s	1s	5s	10s
Proportion Correct						
PD						
Similar	.51 (.16)	.67 (.14)	.54 (.16)	.60 (.11)	.72 (.14)	.77 (.11)
Dissimilar	.81 (.10)	.80 (.09)	.81 (.09)	.84 (.10)	.88 (.09)	.86 (.12)
Match	.75 (.08)	.72 (.09)	.69 (.10)	.89 (.07)	.75 (.11)	.62 (.11)
NC						
Similar	.67 (.16)	.76 (.13)	.62 (.19)	.69 (.14)	.73 (.16)	.80 (.16)
Dissimilar	.84 (.09)	.83 (.10)	.83 (.10)	.90 (.09)	.89 (.12)	.89 (.10)
Match	.79 (.12)	.76 (.10)	.71 (.11)	.88 (.15)	.77 (.16)	.75 (.18)
Recognition Discriminability						
PD						
Similar	.26 (.21)	.38 (.18)	.23 (.22)	.49 (.11)	.44 (.15)	.38 (.16)
Dissimilar	.53 (.16)	.50 (.16)	.48 (.16)	.71 (.12)	.60 (.12)	.46 (.17)
NC						
Similar	.45 (.24)	.50 (.20)	.37 (.26)	.55 (.16)	.49 (.13)	.53 (.17)
Dissimilar	.61 (.20)	.57 (.18)	.52 (.19)	.75 (.16)	.64 (.16)	.62 (.16)

Values represent mean (s.d.).

$F(2, 68) = 0.59$, $p = .56$. However, the group by task by similarity interaction was significant, $F(1, 34) = 6.28$, $p = .02$, as was the group by task by delay interaction, $F(2, 68) = 5.07$, $p < .01$. These interactions, examined further below, suggested that the patients demonstrated spatial encoding and object maintenance deficits. The group by delay by similarity interaction was not significant, $F(2, 68) = 0.56$, $p = .58$. The group by task interaction was also not significant $F(1, 34) = 0.16$, $p = .69$, but there was a main effect of group, $F(1, 34) = 5.60$, $p = .02$, such that the PDs patients had lower recognition discriminability scores than controls.

To further examine the group by task by similarity interaction, a 2 (group) by 2 (similarity) ANOVA was performed within each task collapsed across delay. For the spatial task, the group by similarity level interaction was significant, $F(1, 34) = 5.49$, $p = .03$. Independent samples t-tests indicated that the PD patients were significantly impaired relative to controls on the similar trials, $t(34) = 2.36$, $p = .02$, $d = 0.79$, but not the dissimilar trials, $t(34) = 1.10$, $p = .28$, $d = 0.37$. For the object task, the group by similarity level interaction was not significant, $F(1, 34) = 0.02$, $p = .89$. Mean recognition discriminability values and standard errors by task, group, and similarity are presented in Figure 3.

Figure 3. Spatial and object recognition discriminability as a function of group and similarity

A 2 (group) by 3 (delay) ANOVA was performed within each task to further examine the group by task by delay interaction. For the spatial task, the group by delay

interaction was not significant, F(2, 68) = 0.65, p = .52. For the object task, the group by delay interaction was significant, F(2, 68) = 5.11, p < .01. Post-hoc independent samples t-tests indicated that the groups did not significantly differ in their recognition discriminability at the 1-second delay, t(34) = 1.24, p = .22, d = 0.42, or at the 5-second delay, t(34) = 1.05, p = .30, d = 0.35. However, PD patients were less accurate than controls at the ten second delay, t(34) = 3.00, p < .01, d = 1.00. Mean recognition discriminability values and standard errors by task, group, and delay are presented in Figure 4.

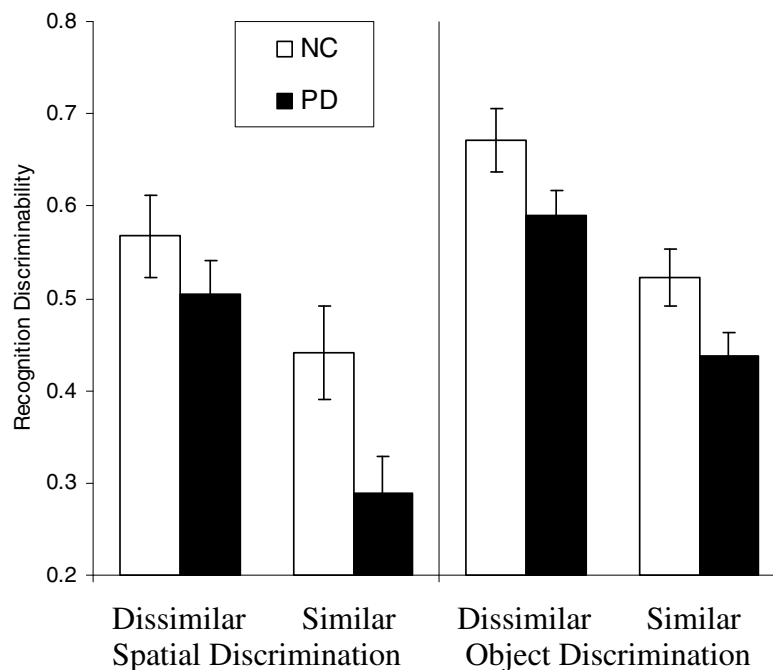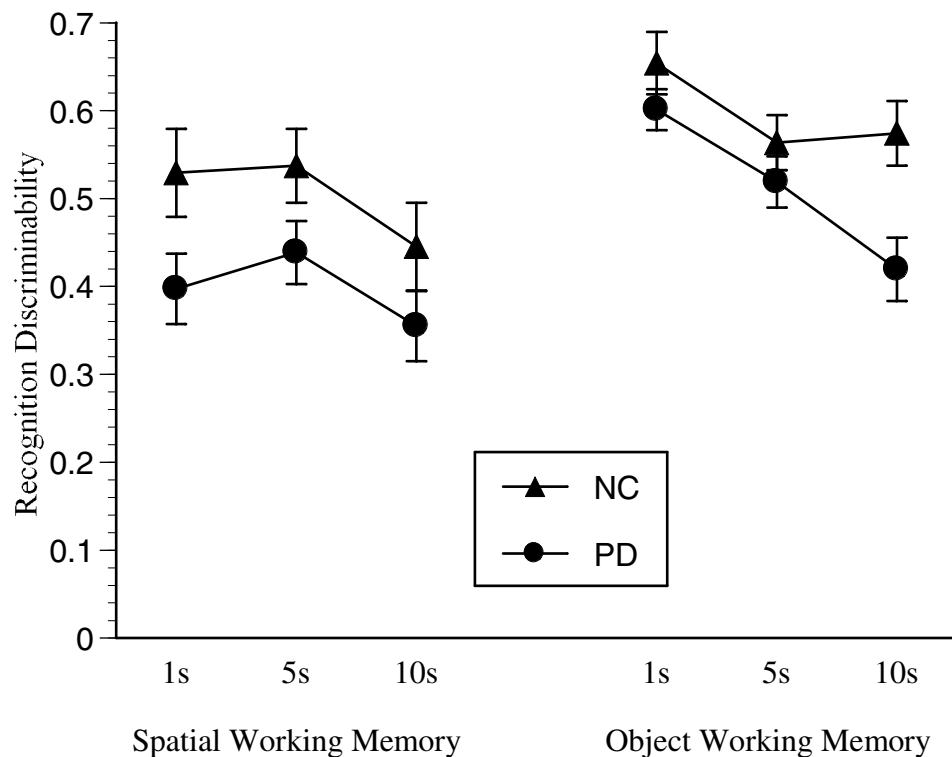Figure 4. Spatial and object recognition discriminability as a function of group and delay

It was important to evaluate whether the patients were demonstrating impairments on only the more difficult aspects of each task. More specifically, if in the control

group the encoding manipulation (i.e., the similarity effect) had a greater effect in the spatial condition, or the maintenance manipulation (i.e., increasing the delay from 5 to 10 seconds) had a greater effect in the object condition, then one possible explanation for the observed deficits in the patients is that they were simply impaired when the task was most difficult. Paired samples t-tests indicated that the effect of the similarity manipulation on recognition discriminability did not differ by task in the controls, $t(17) = 0.94$, $p = .36$, $d = 0.23$, and the effect of increasing the delay from 5 to 10 seconds was actually greater in the spatial task, $t(17) = 3.91$, $p < .01$, $d = 0.94$. In fact, the controls did not exhibit any significant forgetting between the 5- and 10-second delays on the object task, $t(17) = -0.42$, $p = .68$, $d = 0.07$. These analyses indicate that the spatial encoding and object maintenance deficits are not secondary to task difficulty factors.

It was of interest to examine whether the object maintenance and spatial encoding deficits were associated in the patients, which would suggest that they may arise from a shared, underlying impairment. Recognition discriminability on spatially similar trials of the spatial working memory task was chosen to operationalize spatial encoding. All delay periods were included because the groups did not differ in their performance on this task as a function of delay. Recognition discriminability at the 10-second delay on the object working memory task was chosen to operationalize object maintenance. Both similar and dissimilar trials were included in this index because the groups did not differ in their performance as a function of the similarity manipulation. The correlation between the indices of spatial encoding and object maintenance was

not significant in the patients, r = .32, p = .19, suggesting that these deficits may be secondary to different underlying processes.

As mentioned above, the groups significantly differed in their scores on the GDS, indicating that the patients may have been more depressed, on average, than the controls. GDS scores of the patients were correlated with the indices of spatial encoding and object maintenance. Neither the correlation with performance on the spatially similar trials of the spatial working memory task (r = -.30, p = .23), or with performance on 10-second delay trials of the object working memory task (r = .06, p = .81), were significant. These results suggest that the depression scores were not significantly contributing to the working memory deficits observed in the patients.

Relationship between Working Memory Performance and Motor Symptoms

It was predicted that the deficits observed on the working memory tasks would be associated with higher scores on measures of bradykinesia or rigidity, but not with tremor or the side of symptom onset. In addition, it was predicted that if the working memory deficits were significantly associated with unilateral motor symptoms, these associations would not be greater for symptoms on one side of the body than the other. The same working memory indices described above to operationalize spatial encoding and object maintenance were used for these analyses.

The primary measure of motor functioning was the UPDRS. As noted above, item 25 "rapid alternating movements" was not scored correctly: only a score for the worst hand was recorded, instead of a score for each hand. Because of this error, bradykinesia factor scores for the left and right side were summed together rather than

analyzed separately, and item 25 was omitted from unilateral motor symptom analyses (described further below).

In order to operationalize tremor, rigidity, and bradykinesia, factor scores were calculated based on the UPDRS scores of medicated PD patients analyzed by Stebbins and Goetz (1998). Four of the original 6 factors were used to represent the areas of tremor, rigidity, and bradykinesia. Tremor was operationalized by Factor 2 ("rest tremor"), rigidity was operationalized by Factor 3 ("rigidity"), and bradykinesia was operationalized by the total score of Factors 4 and 5 ("bradykinesia – left" and "bradykinesia – right," respectively), with one difference in the factor calculations due to the scoring error on item 25. According to the factor calculation formulas provided by Stebbins and Goetz (1998), item 25 for the left hand loads on Factor 4, and item 25 for the right hand loads on Factor 5. As noted above, item 25 was only scored for the worst hand rather than for each hand individually, so only this single score rather than a score for each hand was included in the bilateral bradykinesia score. The results of these analyses indicated that bradykinesia correlated significantly with spatial encoding, $r = -.48$, $p = .046$, such that patients with more severe bradykinesia had lower scores on the spatial encoding index. The correlation between bradykinesia and object maintenance was not significant, $r = -.37$, $p = .14$. The working memory indices did not significantly correlate with measures of tremor or rigidity. These correlations are presented in Table 5.

T-tests were performed to compare the performance of patients whose symptoms started on the left side of the body ($n = 8$) to patients whose symptoms started on the right side of the body ($n = 10$) on the spatial encoding and object maintenance indices.

The groups did not differ in spatial encoding, $t(16) = 0.73$, $p = .48$, or object

maintenance, $t(16) = 0.37$, $p = .72$.

Unilateral motor symptoms for each side of the body were operationalized by the

sum of UPDRS motor score ratings for the extremities on each side (items 20 through

26 with 25 omitted). These ratings tap symptoms of bradykinesia, rigidity, and tremor

in combination. In addition, unilateral motor symptoms were operationalized by scores

for each hand on the Finger Tapping Test (Reitan, 1969). Poor scores on this test

primarily measure symptoms of bradykinesia and rigidity. The UPDRS motor score

ratings for each side did not significantly correlate with spatial encoding or object

maintenance indices (see Table 5). However, finger tapping on the left significantly

correlated with spatial encoding, $r = .62$, $p < .01$, and there was a trend for finger

tapping on the right to correlate with spatial encoding, $r = .45$, $p = .07$. These

correlations were not significantly different, $t(15) = 0.91$, $p = .38$, suggesting that

spatial encoding may not be more associated with motor symptoms on one side of the

body than the other. However, based on the magnitude of these correlations, the

possibility that spatial encoding impairments are more associated with bradykinetic

symptoms on the left side of the body cannot be ruled out. Finger tapping scores did

not correlate significantly with object maintenance. Correlations between these motor

and working memory indices are presented in Table 5.

<div align="center">Reaction time</div>

Participants were told to strive for accuracy during the working memory tasks,

and no limit was placed on reaction time. However, reaction times were recorded and

analyzed to investigate whether the groups differed in reaction time during either task.

Trials where incorrect or anticipatory responses (< 200 msec) were made were

excluded from these analyses.

Table 5. Correlations between working memory indices and motor symptoms

	Spatial Encoding	Object Maintenance
Tremor	.25	.23
Rigidity	-.36	-.01
Bradykinesia	-.48*	-.37
UPDRS Motor Left	-.25	-.09
UPDRS Motor Right	-.36	-.30
Finger Tapping Left	.62**	.20
Finger Tapping Right	.45	.23

Values represent Pearson product-moment correlations.
*$p<.05$
** $p<.01$

The results of a 2 (group) by 2 (task) mixed ANOVA revealed only a main effect

of task, $F(1, 34) = 20.58$, $p < .01$, $d = 0.36$, with median reaction times on the object

task slower than on the spatial task. The two groups did not differ significantly in

terms of reaction time. Reaction time by group and task are presented in Table 6.

Table 6. Median reaction time by task and group (msec)

	PD	NC
Spatial Working Memory	1,582 (523)	1,489 (876)
Object Working Memory	1,916 (568)	1,640 (709)

Values represent mean (s.d.).

Experiment 1 Discussion

The goal of this study was to investigate whether PD is associated with a selective

impairment in spatial working memory, and also to investigate the nature of this

impairment. Working memory impairments have frequently been reported in PD (e.g.,

Bradley et al., 1989; Lewis, Cools, et al., 2003; Morris et al., 1988). Several studies

have suggested that working memory for spatial information may be more impaired

than working memory for verbal or visual object information in nondemented patients

(e.g., Postle, Jonides, et al., 1997; Owen, Beksinska, et al., 1993; Swainson et al.,

2000), although other studies suggest the working memory impairments are not

greater for spatial material (Costa et al., 2003; Fournet et al., 2000; Pillon et al., 1998).

In addition to investigating whether spatial working memory performance is more

impaired than object working memory in PD, a principal interest of this study was to

investigate whether the working memory impairment is due to deficient encoding or

maintenance processes. It was hypothesized that spatial working memory performance

is differentially impaired in PD as compared to object working memory performance,

and that this selective impairment is due to deficient encoding processes. It was

hypothesized that neither encoding nor maintenance processes of object working

memory are impaired. It should be noted that this experiment was not designed to

independently evaluate perceptual and encoding processes, and so deficits observed at

the encoding stage (i.e., at the 1-second delay) could arise from perceptual

impairments. This possibility will be investigated in Experiment 3.

The PD patients in the present study demonstrated deficits in both spatial and

object working memory. There were some key differences in the quality of their

performance for each type of material, suggesting that these working memory deficits

may be due to impairments in different underlying processes.

The pattern of results on the spatial working memory task suggests that PD

patients are impaired in their ability to encode spatial locations, but their ability to

maintain locations in working memory is intact. Specifically, PD patients were significantly impaired when the targets to be remembered were spatially similar to their probes, but their performance did not differ from that of controls when the target and probe were spatially dissimilar (see Figure 3). Their impaired performance on similar trials relative to intact performance on dissimilar trials indicates that their difficulties with spatial working memory encoding may only arise when a high level of precision is required. The patients did not demonstrate impaired spatial maintenance processes, because both their overall performance and the effect of spatial similarity on their performance did not differ from controls as a function of delay.

The pattern of results on the object working memory task suggests that PD patients did not differ from controls in their ability to encode object information into working memory, but were impaired in their ability to maintain object information over a 10-second delay. This is supported by the finding that PD patients did not differ from controls in their object working memory performance at the 1-second or 5-second delays, but were significantly impaired in their performance, relative to controls, at the 10-second delay (see Figure 4). In addition, the object similarity encoding manipulation did not have a greater impact on performance in the patients, consistent with the interpretation that object encoding is intact.

The PD patients did not demonstrate these single dissociations in encoding and maintenance processes on the more difficult aspects of each task. That is, in the control group, the effect of increasing the similarity level between the target and probe on discriminability was not greater in the spatial versus object task. In addition,

controls were actually able to maintain more information in working memory on the object task than the spatial task between the 5- and 10-second delay periods. In fact, the group difference in object working memory accuracy between the 5- and 10-second delays resulted from stable performance in the controls, and declining performance in the PD patients. This is consistent with other working memory studies that have shown forgetting rates of neurologically healthy individuals can level off as the delays increase (e.g., Sahakian et al., 1988; Sullivan et al., 1993).

The spatial encoding deficit observed in the PD patients was associated with measures of bradykinesia, but not tremor. Thus, the pathophysiology of this spatial working memory deficit is likely related to the pathophysiological changes associated with bradykinesia – that is – dopamine loss in the striatum (Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). Spatial encoding was not significantly associated with greater motor symptoms on either side of the body, or with the side of symptom onset, suggesting that this deficit may not arise from unilateral neuropathology. However, based on the analyses of finger tapping and spatial encoding scores, it could not be ruled out that spatial encoding may be more associated with symptoms of bradykinesia on the left side of the body, and thus right-sided neuropathology. The object maintenance deficit was not significantly associated with any of the motor measures, suggesting that this deficit may not arise from the same pathophysiological changes that result in the motor symptoms of PD.

The spatial working memory findings are consistent with and extend past research on spatial working memory in PD. Spatial working memory impairments have frequently been reported in PD (e.g., Owen et al., 1997; Owen, Beksinska, et al., 1993;

Postle, Jonides, et al., 1997), and past studies have also demonstrated that this impairment is not complicated by lengthening the delay interval (Fournet et al., 2000; Ketcham et al., 2003; LeHeron et al., 2005). Thus, the findings from the present study and from past research suggest that encoding or perceptual but not maintenance processes of spatial working memory are impaired. As mentioned in the introduction to this experiment, encoding processes involve the consolidation of perceptual representations into a temporary store so that they will be available in the absense of stimulation from the environment. Although it is difficult to determine based on the results from this experiment whether spatial perceptual or encoding processes are impaired, the results of Experiment 3 will be able to help address this question.

One apparent inconsistency between the results from this study and the study by Postle, Jonides, and colleagues (1997), is that the spatial similarity manipulation differentially impacted the performance of the PD patients in the present study. One key difference between the two studies that could explain these divergent findings is that Postle and colleagues varied the exposure durations of the targets for each subject based on a preliminary 'perceptual' test (i.e., on a similar task where the delay was held constant at 250 msec). PD patients, on average, were given 1,000 msec to view the stimuli, while NCs, on average, were given only 620 msec. This variation gave PD patients more time to perceive the stimuli than controls, and to encode the stimuli representations into working memory. This advantage for the patients may have allowed them to compensate for their impaired precision in spatial perceptual or encoding processes, which might account for this difference in the similarity effect in the two studies.

Impairments in object working memory have also been reported in PD (Costa et al., 2003; Gotham et al., 1988; Lange et al., 1992; Owen et al., 1997; Owen, Beksinska, et al., 1993; Swainson et al., 2000), consistent with the results of the present study. However, unlike past studies that have observed greater impairments in spatial as compared to object working memory (Owen, Beksinska, et al., 1993; Postle, Jonides, et al., 1997; Postle, Locascio, et al., 1997; Swainson et al., 2000; Taylor et al., 1986), the present study found that the groups were not differentially impaired with regards to overall discriminability for either type of material. However, none of these past studies examined the effect of a long or variable delay period on working memory performance. For example, Postle, Jonides and colleagues held the delay constant at three seconds for both the spatial and object working memory tasks. In contrast, the present study examined the effect of three delay periods, and in fact found that the patients were only impaired in object working memory at the longest (10-second) delay. Thus, the present study is generally consistent with these previous studies, but extends prior work by demonstrating the importance of delay period length on the integrity of object working memory in PD.

The results of this study provide a plausible explanation why Costa and colleagues (2003) found that object working memory was more impaired than spatial working memory in PD, using an n-back design. The spatial working memory task they used did not require a high level of precision in spatial encoding – in fact, only three possible locations were used as stimuli. Both the object and spatial tasks required participants to maintain each stimulus in working memory for 11 seconds, a relatively long time compared to other working memory tasks used with PD patients in past

studies, and long enough to observe an object maintenance deficit in the present study. Thus, the patients may have demonstrated normal spatial working memory because the spatial task did not tap their perceptual and/or encoding impairment, but a deficit in object working memory because the delay was long enough to tap their object maintenance impairment.

Dopamine depletion of the caudate nucleus and the disruption of cortical-striatal circuits is thought to mediate the cognitive sequelae of early PD (Cummings & Benson, 1984; Lewis et al., 2003; Lichter, 2001; Marie et al., 1999; Owen, 2004), and dopamine loss in the caudate nucleus (as well as the putamen) is associated with bradykinesia (Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). Considering the association between bradykinesia and spatial working memory encoding observed in the present study, it is likely that dopamine loss in the striatum affects spatial encoding processes in PD, either directly or through the disruption of cortical-striatal circuits. Spatial encoding relative to object encoding processes may be more disrupted in PD because of disproportionate dopamine depletion in the anterodorsal extent of the caudate head (Kish et al., 1988), an area that has been shown to play an important role in spatial working memory (Cohen et al., 1972; Levy et al., 1997; Postle & D'Esposito, 1999) and is connected to visuospatial processing regions in cortex (Baizer et al., 1993; Yeterian & Pandya, 1991; 1995). The results of the present study suggest the possibility that the anterodorsal head of the caudate plays a particularly important role in the perceptual and / or encoding stages of spatial working memory.

The neuropathological underpinnings of the object maintenance deficit are less clear, although the lack of significant association between object maintenance and

spatial encoding in the patients suggests that the object maintenance deficit may arise from neuropathological changes that differ from those associated with the spatial encoding deficit. It is generally accepted that the caudate tail is part of a different neural circuit than is the head of the caudate, and that this circuit involves inferior temporal and ventral prefrontal cortices (Baizer et al., 1993; Saint-Cyr, Ungerleider, & Desimone, 1990; Yeterian & Pandya, 91, 95). These highly interconnected brain regions play a critical role in visual object processes (Iverson, 1979; Sala, Rama, & Courtney, 2003; Ungerleider & Mishkin, 1985), and also ventral prefrontal cortex in particular is thought to be important for working memory maintenance (D'Esposito et al., 2000; Petrides, 1989, 1994). Based on these understandings, it follows that disruption of this network may underlie the object maintenance impairment. The locus of this disruption is unlikely to be in inferior temporal cortex, because this region appears to be important for perceptual but not mnemonic aspects of object working memory (Belger et al., 1998). Although ventral prefrontal cortex may play a role, dopamine depletion of this region is thought to be relatively preserved in early PD (Cools, 2006; Cools et al., 2003). If the selective object maintenance impairment arises from pathology in the tail of the caudate, it would suggest that the tail of the caudate nucleus, like the anterodorsal head, is particularly affected by PD pathology. However, at this point the extent that PD pathology affects the tail is unknown, because previous neuropathological studies of caudate nuclei tissue in PD have sampled the head and body but not the tail (Kaufman & Madras, 1991; Kish et al., 1988; Joyce, 1993; Piggott et al., 1999). Clearly more work is needed to investigate

the neuropathological underpinnings of the object maintenance deficit observed in this study.

Parts of this chapter are being prepared for the following publication:

Possin, K. L., Filoteo, J. V., Song, D. D., and Salmon, D. P. (2007). Spatial and object working memory deficits in Parkinson's disease are due to impairment in different underlying processes.

VI. EXPERIMENT 2: SPATIAL-BASED AND OBJECT-BASED COMPONENTS

OF INHIBITION OF RETURN IN PARKINSON'S DISEASE

Inhibition of Return in the Normal Brain

When a person's attention is cued to a location in the periphery, stimuli in that location enjoy a processing advantage over stimuli presented in other locations in the visual field for a short period. However, if greater than 300 msec elapses following the cue, stimuli presented in the cued location may be at a processing disadvantage (Maylor, 1985; Posner & Cohen, 1984; Tipper, Driver, & Weaver, 1991). This phenomenon is termed 'inhibition of return' (IOR), and is believed to be an essential component of efficient visual search (Posner & Cohen, 1984). That is, if attention is constantly returned to previously examined locations, the search process would breakdown. It has been argued that this inhibitory mechanism biases attention toward novel locations (Posner & Cohen, 1984).

The original evidence for IOR comes from a simple cueing task developed by Posner and Cohen (1984). A cue (i.e., a brief luminance increase) is presented in one of two squares that are located at equal distances from a central fixation point. Although the cue does not predict the location of the subsequent target and participants are instructed to ignore the cue, attention is automatically drawn there. Following the cue, attention is cued back to fixation by increasing the luminance of the fixation point. Next, a target is presented either in the cued square or the uncued square. Detection of the target is slower when it is in the cued square as compared to the uncued square, which is thought to reflect IOR.

Studies using IOR tasks have demonstrated that attention can be directed at space-based frames of reference (i.e., where the object is in space) or object-based frames of reference (i.e., what dimensions are part of an object; Abrams & Dobkin, 1994; Jordan & Tipper, 1998, 1999; Leek et al., 2003; Tipper et al., 1991; Tipper, Jordan, & Weaver, 1999; Tipper, Weaver, Jerreat, & Burak, 1994; Weaver, Lupianez, & Watson, 1998). For example, Tipper and colleagues (1991) modified the Posner and Cohen (1984) task such that the squares moved around the computer screen after cueing. In one condition, the squares each moved 90° in polar coordinates, so that each square was equidistant from the cued location. If inhibition was based solely on location of the cue, there should be no difference in the reaction times between responses to cued and uncued targets, because the relocated targets were equidistant from the inhibited location. However, reaction times were greater for targets in the cued square, indicating that some of the inhibitory effects of the cue moved with the target, and supported the notion that attention can be directed to the object and not just its location. This finding has been replicated in other IOR studies using dynamic displays (Abrams & Dobkin, 1994; Tipper et al., 1994; Tipper et al., 1999; Weaver et al., 1998).

Jordan and Tipper (1998) provided the first demonstration that inhibition can be directed towards objects in static displays. Participants were presented with cues and targets within a display comprised of "Pac-man" figures that were positioned to form the corners of squares, or scrambled so that no objects were apparent. IOR was greater when the target appeared in regions occupied by an apparent object, compared to no apparent object. Based on these findings, the authors concluded that when a target

appears at the same location as a cued object, both spatial-based and object-based

components of IOR are activated.

Other evidence that attention can be directed toward objects has been provided.

For example, Jordan and Tipper (1999) demonstrated that IOR can spread across an

object's surface to a non-cued location. Specifically, they found that IOR was greater

when the target appeared in the same object but at a different location from the cue,

than when the target appeared in a different object but an equidistant location from the

cue. Leek and colleagues (2003) replicated this finding using a similar paradigm. The

objects used by these authors were two L-shaped figures that each included an internal

boundary, as opposed to rectangles used by Jordan and Tipper. They demonstrated

that IOR was modulated by the object-internal structure, which, according to the

authors, provides additional evidence that object- and location-based IOR are

dissociable.

Several lines of evidence suggest that the superior colliculus (SC) plays an

important role in spatial-based IOR (Berger & Henik, 2000; Dorris, Klein, Everling, &

Munoz, 2002; Fecteau, Bell, & Munoz, 2004; Posner, Rafal, Choate, & Vaughan,

1985; Rafal, Calabresi, Brennan, & Scolto, 1989; Rafal, Posner, Friedman, Inhoff, &

Berstein, 1988; Sapir, Soroker, Berger, & Henik, 1999; Sereno, Briand, Amador, &

Szapiel, 2006). For example, Fecteau and colleagues (2004) monitored visuomotor

neurons in the superior colliculus of monkeys during location-based capture of

attention and inhibition of return tasks, which differed only by the interstimulus

interval. They found strong target-related neural activity during capture of attention,

and weak activity during IOR. There is recent evidence that the attenuated activity

expressed in the SC during spatial-based IOR may reflect inhibition that is generated or modulated by other brain regions, in particular the posterior parietal cortex and the frontal eye fields (Bartolomeo, Chokron, & Sieroff, 1999, 2001; Corbetta & Shulman, 2002; Lepsien & Pollmann, 2002; Sapir, Hayes, Henik, Danzinger, & Rafal, 2004; Vivas, Humphreys, & Fuentes, 2003). These regions of cortex have been implicated in other aspects of spatial-based visual processing, including spatial working memory (Belger et al., 1998; Funahashi et al., 1989; Ungerleider & Mishkin, 1982). In contrast to our understanding of the neural mechanisms of spatial-based IOR, the neural underpinnings of object-based IOR are less well understood, although Tipper and colleagues (1997) provided some evidence for cortical involvement. These authors found that split-brain patients demonstrated object-based IOR toward a cued square when it moved within one visual field, but when it crossed the midline into the opposite visual field, detection was faster in the cued square. According to the authors, object-based IOR requires an intact corpus collosum for interhemispheric transfer, which suggests cortical involvement. One possibility is that object-based IOR recruits more ventral regions of cortex that have been demonstrated to play an important role in other aspects of object-based processing. As described above, PD may differentially impact dorsal stream regions important for aspects of spatial-based processing, while ventral stream regions may be relatively intact. If object-based and spatial-based IOR are subserved in part by ventral stream and dorsal stream regions respectively, it follows that PD may be associated with greater impairments in spatial-based than object-based IOR.

Inhibition of Return in Parkinson's Disease

PD patients have demonstrated impairments in inhibitory attention (Filoteo & Maddox, 1999; Filoteo et al., 2002; Filoteo et al., 1997; Henik et al., 1993; Kensinger et al., 2003; Maddox et al., 1996; Mari-Beffa et al., 2005; McDowell & Harris, 1997). More specifically, there is evidence that PD patients may be impaired in the maintenance of inhibition. For example, PD patients differed from controls on a test that required them to indicate whether they saw a target stimulus that could appear at either a global or local level of a hierarchical stimulus (Filoteo et al., 1994). On consecutive trials, the target could remain at the same level (e.g., be at the local level on both trials) or switch levels (e.g., be at the global level on the first trial and the local level on the next trial). PD patients were slower than controls to respond when the target remained at the same level, but were faster than controls when the target changed levels. These results suggested that the PD patients were impaired in maintaining inhibition at the previous level, which did not allow them to benefit in responding to the target when it appeared at the same level across consecutive trials, but did allow them to switch faster from one level to the other when the target appeared at different levels across consecutive trials.

IOR has been investigated in PD, and there is some evidence from these investigations that these patients are impaired in the maintenance of inhibition, manifesting as reduced IOR. At short stimulus onset asynchronies (SOAs), PD patients typically demonstrate the normal facilitatory effects of covert orienting (Bennett, Waterman, Scarpa, & Castiello, 1995; Filoteo et al., 1997; Sharpe, 1990). However, reduced IOR has been demonstrated at longer SOAs (Filoteo et al., 1997;

Poliakoff et al., 2003; Yamaguchi & Kobayashi, 1998). Filoteo and colleagues, for

example, presented participants with four squares surrounding a central fixation point.

One of the squares was cued by a small change in luminance, and following a variable

SOA of 50, 150, 250, or 1,000 msec, a target appeared in one of the squares. The cue

predicted the location of the target 50% of the time; because there were four possible

target locations, the cue was predictive in terms of the location of the target. PD

patients and controls demonstrated normal facilitatory effects of the cue at intervals of

50, 150, or 250 msec. However, PD patients demonstrated a reduced IOR effect at the

1,000 msec interval. According to the authors, these findings suggest that PD patients

are normal at building up inhibition (because they were not impaired at the shorter

SOAs), but were impaired in maintaining inhibition. In other words, their inhibition

may have decayed more rapidly. Similarly, in an experiment by Yamaguchi and

Kobayashi (1998), participants were required to detect a target that could appear in

one of two locations. A cue predicted the subsequent location 80% of the time. Both

patients and controls demonstrated validity effects (i.e., faster responding to the cued

location as compared to the uncued location) at the shorter SOAs (200 and 500 msec),

but the controls demonstrated a decreased validity effect at the long SOA (800 msec),

which represented the normal IOR effect. PD patients, on the other hand, did not

demonstrate this effect. Thus, in both of these studies, PD patients demonstrated

reduced IOR.

Two distinct mechanisms are thought to cause covert attentional shifts: one is

reflexive and the other is voluntary (Jonides, 1981; Rafal & Henik, 1994). The studies

of IOR in PD discussed above used predictive cues; that is, the targets appeared more

often at the cued than uncued locations. It has been argued that these study designs confound reflexive and voluntary orienting processes (Briand, Hening, Poizner, & Sereno, 2001; Kingstone et al., 2002; Poliakoff et al., 2003). In other words, the cue captures attention reflexively, but also engages voluntary attention processes because it carries information about the upcoming target. For example, in the Filoteo et al. study, although the peripheral cue they used correctly predicted the target location on only 50% of the trials, the target appeared in one of the other 3 locations on 16.7% of the trials. Thus, subjects could have built up some sort of expectancy that the target would appear in the cued location on half the trials, and therefore could have engaged voluntary attentional processes. This issue may be particularly relevant to the study of reflexive orienting in PD because these patients have frequently demonstrated impairments in voluntary orienting (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Crawford, Henderson, & Kennard, 1989; O'Sullivan, Shaunak, Hawkern, Crawford, & Kennard, 1997; Shaunak et al., 1999).

More recent investigations of IOR in PD have used non-predictive cues (Briand et al., 2001; Kingstone et al., 2002). Kingstone and colleagues (2002, Experiment 2) cued one of two possible locations with four dots forming the corners of an imaginary square, and after an SOA of 72 msec or 288 msec, a target circle appeared in one of the two locations with equal probability. Participants pressed a key as soon as they detected the target. PD patients demonstrated normal reflexive orienting at both SOAs, including the same amount of IOR as controls at the 288 msec SOA. Kingstone's findings support the notion that the build-up of IOR in PD is normal. However, because the SOAs used were quite short, whether or not PD is associated with

impairments in the maintenance of inhibition is unclear from this study. Briand and colleagues studied 7 patients with mild to moderate PD off medication, and 8 controls. On a given trial, one of two squares was cued via a brief luminance increment, and following a variable SOA of 67, 133, or 1000 msec, a target was presented with equal probability in one of the squares. Participants responded by making a saccade to the target as quickly as possible. Facilitatory effects at the short SOAs and IOR effects at the long SOA did not differ between patients and controls. One limitation of this study is the small sample size, and the authors acknowledge that their findings must be interpreted with caution. However, these findings of normal IOR in the PD patients may indicate that PD patients are unimpaired on IOR tasks with non-predictive cues.

As reviewed above, there is some evidence for a reduction of IOR in PD, although more research is needed using tasks that do not confound reflexive and volitional orienting by using predictive cues. All tasks used to investigate IOR in PD have been spatial in nature. Although cues and targets usually appeared within squares, it is possible that participants habituated to the presence of these squares because they were irrelevant to the task and not complex, and as a result these objects became easy to ignore. This interpretation is consistent with findings that object-based IOR appears to decline with practice (Jordan & Tipper, 1998; Weaver et al., 1998), suggesting that habituation to the objects does occur, and that IOR effects are strongest when more complex objects are used, which are likely more difficult to ignore (Leek et al., 2003; Jordan & Tipper, 1998). Thus, object-based attention was likely only minimally engaged during these previous studies of IOR in PD. Given recent evidence that suggests IOR can be directed at objects as well as locations, it is unknown how PD

patients would perform on object-based versus spatial-based components of an IOR task. However, numerous studies have identified altered spatial attention in PD (Filoteo et al., 1997; Filoteo et al., 2002; Pollux & Robertson, 2001; Wylie & Stout, 2002; Wright et al., 1990; Yamaguchi & Kobayashi, 1998; but see Hsieh, Lee, Hwang, & Tsai, 1997), whereas in contrast there is evidence that PD patients are unimpaired on some purely object-based attentional tasks (Lee, Wild, Hollnagel, & Grafman, 1999; Possin, Cagigas, Strayer, & Filoteo, 2006). Taken together, these findings suggest that PD patients may display normal attentional processes on object-based, but not spatial-based attention tasks, and thus that PD patients may perform normally on object-based components of an IOR task.

The basal ganglia have frequently been implicated in inhibitory processes (e.g., Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; Filoteo et al., 2002; Graybiel, 2000; Kelly et al., 2004), and dysfunction of these nuclei has been used to explain reduced IOR in PD (Filoteo et al., 1997). If reflexive IOR is impaired in PD (which at this point is not clear), the close anatomical and functional links of the basal ganglia with the superior colliculus (Hikosaka & Wurtz, 1983; Joseph & Boussaoud, 1985; Parent & Hazrati, 1995) may mediate this impairment. Given that the dorsal head of the caudate appears to be preferentially involved in spatial-based working memory as compared to object-based working memory (Levy et al., 1997; Postle & D'Esposito, 1999) and this region is disproportionately affected in PD (Kish et al., 1988; Joyce, 1993), it is possible that PD patients may exhibit greater impairments on spatial components of IOR. This finding, along with the results of Experiment 1,

would suggest that similar brain regions may be involved in spatial working memory encoding and spatial components of IOR.

Experiment 2 investigated IOR in PD using a non-predictive attentional cueing task developed by Leek et al. (2003). This task can be used to assess attentional inhibition for locations as well as for objects. The task has two conditions: in the "object-present" condition objects surround the cues and targets, whereas in the "object-absent" condition surrounding objects are not presented with the cues and targets. The object-present condition is thought to assess both space-based and object-based components of IOR in combination because the subject's attention is cued to both a spatial location and a specific object. In contrast, the object-absent condition is thought to assess only space-based IOR because the subject's attention is cued to only the spatial location. If PD patients are primarily impaired in spatial-based but not object-based IOR attentional processes, it is predicted that they will show decreased IOR in the object-absent condition but normal IOR in the object-present condition.

<div align="center">Experiment 2 Methods</div>

<div align="center">Participants</div>

Eighteen nondemented patients with PD (11 men and 7 women) and 18 normal controls (9 men and 9 women) participated in the study. The same procedures for diagnosing, recruiting, and screening participants were used as in Experiment 1. The patients had been diagnosed an average of 5.4 years (range = 2 - 17, SD = 3.8). Motor functioning was assessed by an experienced neurologist using Hoehn and Yahr's rating scale (1967), and the UPDRS (Fahn, Elton, & the UPDRS Development

Committee, 1987)[4]. According to the Hoehn and Yahr rating scale, all patients

exhibited mild to moderate motor impairments (M = 2.12, range = 1 - 3, SD = 0.57).

There was an error made in scoring the UPDRS for two of the participants.[5] Mean

scores on the motor examination section were calculated twice, using the same

procedure described in Experiment 1 to compensate for this error. These calculations

indicated that the mean score of the PD patients on the motor examination section falls

between 23.82 and 24.06.

Table 7. Characteristics of the Parkinsonian patients in Experiment 2.

No.	Age	Disease duration[a]	H & Y stage	Antiparkinsonian medication, daily dose (mg) [b]
1	67	17	2	LeCa 800/200, Se 5, En 800, Pr 1
2	67	4	2.5	LeCa 600/150, Pr 5, Am 100
3	63	4	2.5	Se 10, Ro 5
4	64	4	1	LeCa 600/150, Pr 2
5	58	5	2	LeCa 200/50, Pr 2, Se 5
6	73	12	2	LeCa 300/75, Pr 2, Am 100, En 400
7	65	5	2.5	Pr 5, LdCaEn 300
8	82	4	3	LeCa 600/150
9	54	2	1	Pr 3
10	68	4	1.5	LeCa 200/50
11	55	7	2.5	LeCa 400/100
12	75	4	2.5	LeCa 800/200, En 800
13	79	4	2	LeCa 800/200, Se 5
14	64	3	2	Se 1
15	79	5	2	Ro 15, LeCaEn 300, Se 10
16	56	2	3	Unmedicated
17	64	9	2	LdCa 900/225, Pr 2, Am 200
18	63	3	2	LeCa 300/75, Am 300

[a]Age and disease duration in years.
[b]LeCa, levodopa-carbidopa; En, entacapone; Pr, pramipexole; Am, amantadine; Ro, ropinirole; Se, selegiline; Ca, carbidopa; LdCaEn, levodopa-carbidopa-entacapone.

---

[4] One patient was not assessed by the neurologist due to time limitations. This patient was diagnosed 3 years prior to testing and appeared to exhibit mild symptoms.
[5] This error is explained in the methods section for Experiment 1. Briefly, due to an inaccurate UPDRS protocol, only the score for the worst hand was recorded for item 25, rather than a score for each hand.

Table 8. Demographic characteristics and neuropsychological test scores of Parkinsonian patients and normal controls.

	PD	NC
Age	67.04 (8.28)	69.44 (8.19)
Education	16.56 (2.18)	16.44 (2.23)
DRS	139.56 (3.29)	140.76 (2.75)
Rosenbaum Pocket Vision Screener	20/27.19 (6.32)	20/24.67 (4.81)
Geriatric Depression Scale	5.91 (4.72)	2.87 (4.16)
WCST categories	5.12 (1.87)	4.92 (1.44)
WCST perseverative responses	14.65 (17.61)	19.08 (17.62)
WCST set losses	0.53 (.80)	0.83 (1.03)
JOLO	25.65 (4.72)	26.17 (3.04)
ANART	41.53 (6.01)	41.43 (5.30)
Finger tapping dominant	36.87 (10.88)	45.38 (10.42)*
Finger tapping nondominant	36.36 (9.11)	36.96 (7.14)
CVLT trial 1	6.11 (2.08)	6.23 (2.55)
CVLT trials 1-5	48.17 (7.68)	48.00 (15.47)
CVLT short delay free recall	9.50 (1.98)	11.31 (3.75)
CVLT short delay cued recall	10.67 (1.85)	12.08 (3.20)
CVLT long delay free recall	9.61 (2.81)	10.92 (4.13)
CVLT long delay cued recall	11.06 (2.21)	11.92 (4.03)
CVLT semantic clustering	0.70 (1.50)	1.99 (2.13)
CVLT total repetitions	4.22 (2.96)	3.46 (3.86)
CVLT total intrusions	4.22 (4.12)	2.38 (3.73)
CVLT recognition hits	14.00 (2.03)	15.23 (1.17)
CVLT recognition false positives	2.44 (1.92)	3.23 (5.39)
D-KEFS letter fluency	45.12 (14.46)	40.92 (12.27)
D-KEFS category fluency	39.24 (9.62)	38.77 (9.10)
D-KEFS category switching fluency	14.12 (1.87)	14.85 (2.79)
D-KEFS fluency switching accuracy	12.82 (1.98)	14.00 (3.19)

Values represent mean (s.d.).
*p<.05

The PD patients were treated with their normal regimen of dopaminergic agents at

the time of testing (see Table 7) and were tested at the time of day when they felt

cognitively more alert. No patients were taking anticholinergic or antipsychotic

medication. Using an alpha level of .05, the PD patients did not differ significantly

from the controls in age, t(34) = 0.88, p = .39, years of education, t(34) = -0.15, p =

.88, GDS scores, t(31) = 1.95, p = .06, or DRS scores, t(33) = -1.18, p = .25 (see Table 8). As in Experiment 1, the patients and controls were given a battery of tests in order to characterize their neuropsychological functioning. Because of time constraints, some participants did not receive all of these tests, so the range of sample size varied by test from 16 to 18 in the PD group, and 12 to 18 in the NC group. Table 8 shows the mean scores on selected indices from these tests for the two groups, and denotes the indices on which the groups significantly differed based on independent samples t-tests. The two groups differed significantly only on Finger Tapping performance with the dominant hand.

<div align="center">Apparatus and Stimuli</div>

Stimuli were presented on a 50.8 cm. monitor. Randomization and presentation of stimuli, and recording of response reaction time and accuracy, were executed by Eprime software, version 1.1.

The stimuli and procedures used in the IOR experiment were modified from those used by Leek and colleagues (2003). The experiment was composed of two conditions: "object-present" and "object-absent." Illustrations of the 6 possible target locations for the object-present condition can be seen in Figure 5. In both conditions, the cue consisted of a white outline square, and the target consisted of a white filled square. The conditions differed only by the presence of L-shaped figures surrounding the cues and targets in the object-present condition. More specifically, segmented, black outline, L-shaped figures were presented in two possible orientations: tilted 45° in either direction from the vertical meridian (figures presented in Figure 5 are in the -

45° orientation). These figures were composed of two rectangles of equal width but differing in length. Following are descriptions of the 6 Cue-Target (CT) Locations used for the object-present condition:

CT Location 1

The target appeared in the exact same location as the cue.

CT Location 2

The target appeared on the same object, same part, but at a different location from the cue.

CT Location 3

The target appeared on the same object, but on a different part from the cue.

CT Location 4

The target appeared on the corresponding part of a different object as the cue, and at the same distance from the cue as in CT Locations 2 and 3.

Filler 1

The target appeared on a different object from the cue, within the larger rectangle segment, at a distance from the cue that is greater than in CT Locations 2-4.

Filler 2

The target appeared on a different object from the cue, within the smaller rectangle segment, at the same distance from the cue as in Filler 1.

The CT Locations used in the object-absent condition were identical, but no surrounding objects were present.
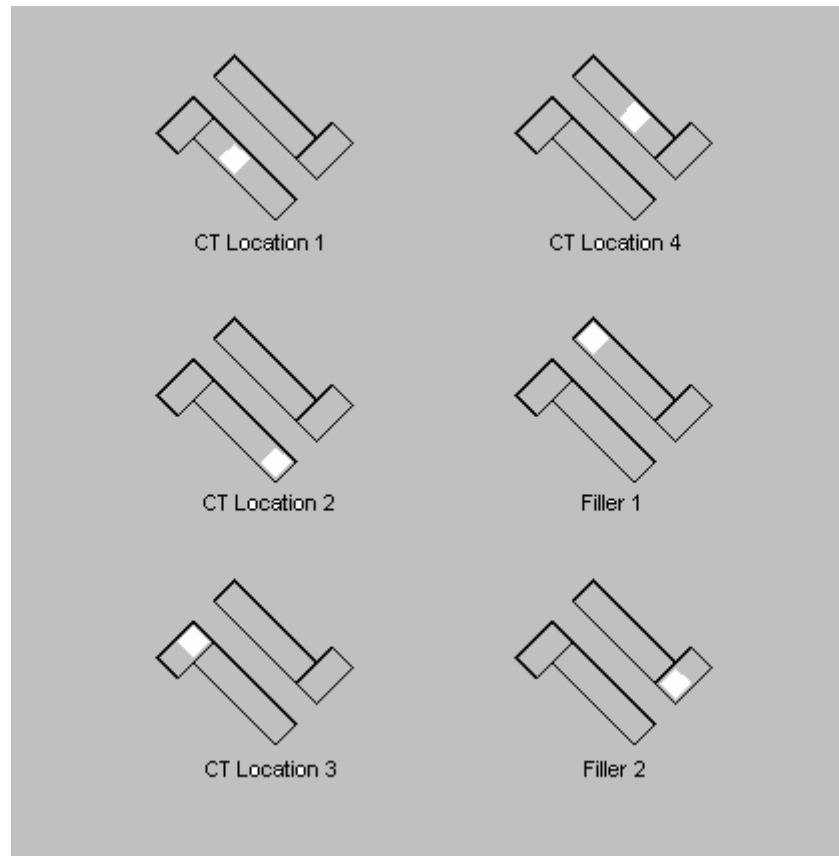
Figure 5. An illustration of the target locations for Experiment 2 based on a cue location at the target position of CT Location 1. The display orientation depicted here is -45° from vertical. Cue and target positions for the object-present and object-absent conditions are identical.

Participants were seated such that their line of sight was perpendicular to the center of the stimulus display, and their viewing distance was 43 cm. The longer rectangles subtended 10.8° X 2.5° and the shorter rectangles 4.6° X 2.5° of visual angle. The cue was a white outline square and the target was a filled white square, and they each subtended 2° X 2° of visual angle. The fixation cross was black and subtended .6° of visual angle. The distance between the center of cues and targets in CT Locations 2, 3, and 4 was always 5.9°. The dimensions of the entire display were

19.2° X 15.9°. In the object-absent condition, the cues, targets, and fixation cross were identical to those in the object-present condition. In both conditions, the stimuli were presented against a gray background.

Procedure

Following is the trial procedure for the object-present condition, which is illustrated in Figure 6. Each trial began with the presentation of the fixation cross. After 1,000 msec, two L-shaped figures appeared on each side of the central black fixation cross. After 1,000 msec, the cue was presented for 90 msec in the middle of one of the L-shaped figures. Following either a short delay (300 msec) or a long delay (500 msec) from cue offset, the fixation cross changed to white for a period of 130 msec, and then reverted back to black. Following another delay of the same length (300 or 500 msec), the target was presented at one of the six possible CT locations. According to this design, SOA had two levels: 820 msec and 1,220 msec. The target remained on the screen until the participant responded by pressing the spacebar or for 1,000 msec. If the participant did not press the spacebar after 1,000 msec, the computer produced a buzz sound. In addition to the trials with targets, there were also "catch" trials, which were composed of an identical procedure but did not have a target. If the participant pressed the spacebar during a catch trial, the buzz sound was produced. These catch trials were included so as to reduce anticipatory responses. The trial procedure for the object-absent condition was identical to the procedure for the object-present condition, except for the absence of the L-shaped figures.
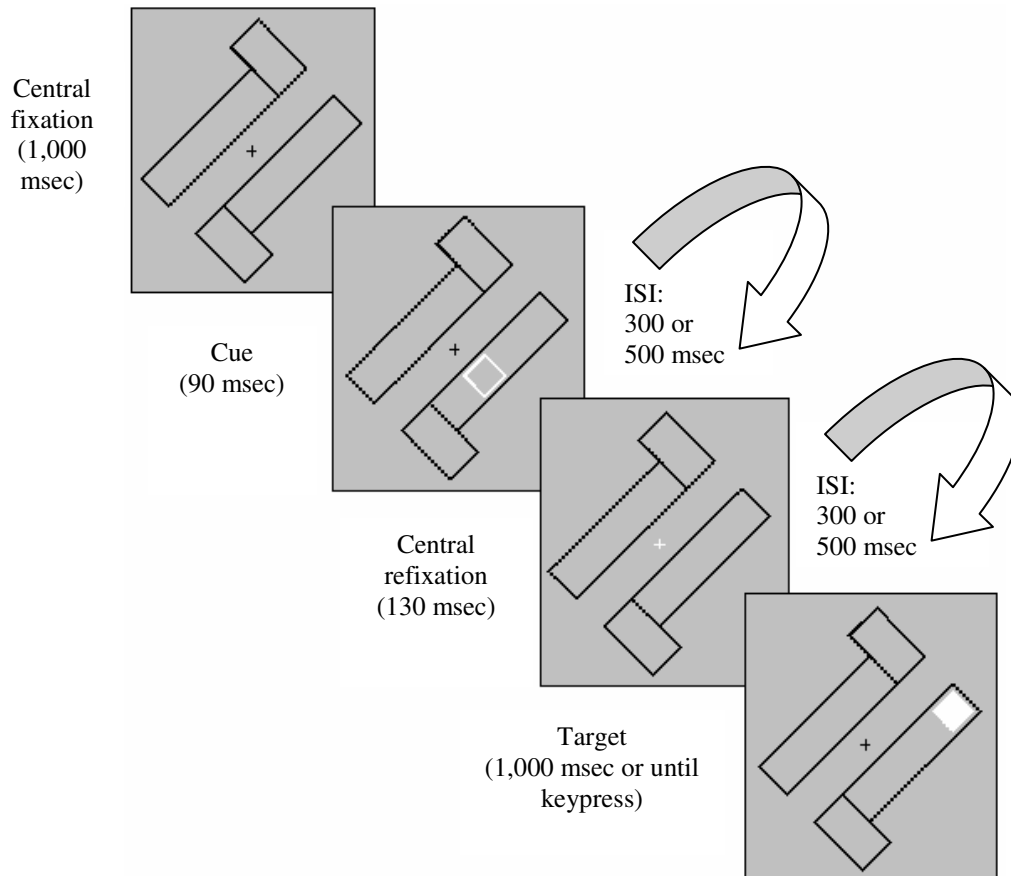
Figure 6. Schematic diagram of a single trial in Experiment 2, object-present condition. During each interstimulus interval (ISI), the display reverted to central fixation.

Participants were informed that the white outline square did not predict the location of the subsequent filled square. They were instructed to press the space bar as quickly as possible after they detected the filled square, and to withhold their response when no filled square appeared. The importance of maintaining their gaze at the fixation cross throughout the experiment was stressed before and after the practice trials.

The object-present and object-absent conditions each consisted of 12 trials for each CT Location within each SOA, with half of these trials presented in each

orientation. In this design, the cues do not provide any predictive validity about the location or object of the subsequent target because the CT Locations are equiprobable and random, and because of the inclusion of "filler" trials. In addition, 48 "catch" trials (i.e., when no target is presented) were included in each condition. The total number of trials within each condition was 192. The order of the conditions was counterbalanced within each group, and administration of the conditions was separated by a minimum of 30 minutes.[6]

Experiment 2 Results

Only trials based on CT Locations 1 through 4 were included in the analyses for Experiment 2. Trials where no responses were made were excluded from the data, which comprised 1.7% of the data for the controls, and 4.0% of the data for the patients. In addition, trials with reaction times greater than 800 msec (slow), or reaction times less than 200 msec (anticipatory), were discarded from the data. These exclusions made up an additional 1.1% of the data for the controls, and 1.7% for the patients. An ANOVA was conducted to evaluate if the total number of trials excluded differed by group or condition. The main effect of group, $F(1, 34) = 2.06$, $p = .16$, main effect of condition, $F(1, 34) = 0.07$, $p = .80$, and the interaction effect, $F(1, 34) = 0.001$, $p = .98$, were all not significant. Mean reaction times by group, condition, CT Location, and SOA are presented in Table 9.

---

[6] An analysis was conducted to determine if the order the conditions were administered had an effect on any of the main findings from this study, discussed below. This was not found to be the case.

Table 9. Reaction time (msec) as a function of group, condition, CT Location, and stimulus onset asynchrony

| | Object-Present Condition | | Object-Absent Condition | |
	820 msec	1220 msec	820 msec	1220 msec
Controls				
CT Location 1	485 (68)	472 (79)	452 (86)	450 (85)
CT Location 2	468 (86)	450 (78)	441 (83)	442 (72)
CT Location 3	470 (72)	461 (80)	432 (90)	430 (82)
CT Location 4	431 (75)	433 (80)	410 (80)	425 (75)
PD Group				
CT Location 1	509 (81)	501 (74)	481 (78)	464 (74)
CT Location 2	482 (88)	469 (75)	459 (83)	463 (74)
CT Location 3	493 (83)	480 (79)	468 (80)	453 (68)
CT Location 4	458 (88)	443 (78)	466 (86)	455 (78)

Values represent mean (s.d.).

Inhibition of Return Effects

IOR effects were calculated within each condition by subtracting the mean reaction time for CT Location 4 from the mean reaction times for CT Locations 1, 2, and 3, which is the same method used in the study by Leek et al. (2003). IOR effects by group, condition, and CT Location are presented in Figure 7. A 2 (group) by 2 (condition) by 3 (CT Location) by 2 (SOA) ANOVA was performed, with IOR effects as the dependent measure. As predicted, the group by condition interaction was significant, $F(1, 34) = 7.76$, $p < .01$. There was also a significant condition by CT Location interaction, $F(2, 68) = 3.31$, $p = .04$. None of the other interaction effects were significant, including group by condition by SOA, $F(1, 34) = 0.002$, $p = .96$, group by condition by CT Location, $F(2, 34) = 0.53$, $p = .59$, or group by condition by CT Location by SOA, $F(2, 68) = 0.28$, $p = .76$. As predicted, IOR was greater in the

object-present condition than the object-absent condition, $F(1, 34) = 32.28$, $p < .01$, d

= 1.02.

To further examine the group by condition interaction, independent samples t-

tests were performed to compare the IOR effects of the groups within each condition,

collapsed across IOR effect type. Within the object-present condition, the groups did

not differ in the magnitude of IOR, $t(34) = -0.38$, $p = .71$, $d = 0.13$. However, as

predicted, the PD patients demonstrated smaller IOR effects than the controls when

the objects were absent from the display, $t(34) = 2.96$, $p < .01$, $d = -0.99$. In fact, while

the controls demonstrated significant IOR on the object-absent condition, $t(17) = 4.35$,

$p < .01$, $d = 1.03$, the IOR effects of the PD patients were not significantly different

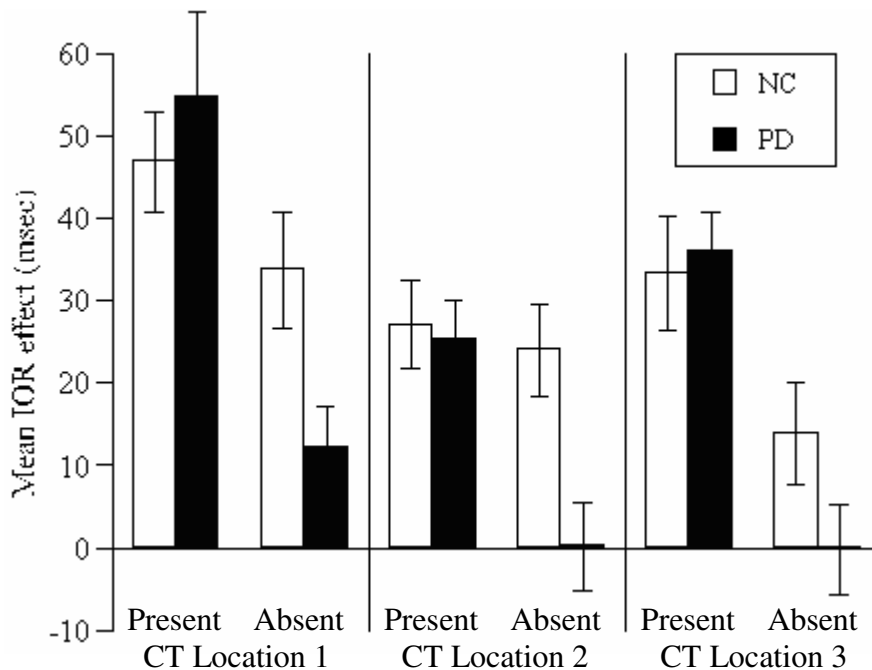from zero, $t(17) = 1.03$, $p = .32$, $d = 0.24$.

Figure 7. Mean inhibition of return (IOR) by group, CT location, and object-present or object-absent condition

The significant condition by CT Location interaction was further examined by performing paired samples t-tests to compare the magnitude of IOR associated with the different CT Locations within each condition, collapsed across the two groups. In the object-present condition, IOR was significantly greater in CT Location 1 than both CT Location 2, $t(35) = 4.65$, $p < .01$, $d = 0.84$, and CT Location 3, $t(35) = 3.28$, $p < .01$, $d = 0.52$. In addition, IOR was significantly greater in CT Location 3 than CT Location 2, $t(35) = 2.51$, $p = .02$, $d = 0.36$. In the object-absent condition, IOR was significantly greater in CT Location 1 than in both CT Location 2, $t(35) = 2.59$, $p = .01$, $d = 0.40$, and CT Location 3, $t(35) = 3.85$, $p < .01$, $d = 0.60$. The magnitude of IOR associated with CT Locations 2 and 3 did not significantly differ, $t(35) = 1.33$, $p = .19$, $d = 0.21$. Although IOR was reduced for CT Locations 2 and 3, significant IOR was observed for these conditions in controls (both $ps < .05$).

<u>Spatial-Based IOR and Motor Symptoms</u>

To determine whether the impairment in spatial-based IOR was associated with the severity of motor symptoms in general or bradykinesia in particular, the IOR effect associated with CT Location 1 in the object-absent condition was correlated with scores on the motor examination section of the UPDRS, and with the sum of previously derived factor scores corresponding to symptoms of bradykinesia (i.e., Factors 4 and 5; Stebbins & Goetz, 1998). The IOR effect associated with CT Location 1 was chosen because this is the best measure of spatial-based IOR, given that the target appears in the exact cued location. As explained above, item 25 on the UPDRS for two participants was only scored for the most symptomatic hand, rather than for each hand individually. As in Experiment 1, only the score for the most

symptomatic hand for this item was included in the UPDRS score calculations.

Neither the correlation between spatial-based IOR and the motor examination, r = -.43, p = .08, or the correlation between spatial-based IOR and bradykinesia, r = -.41, p = .09, were significant. However, there were trends for more severe scores on both of these measures to be associated with a reduction in spatial-based IOR.

Experiment 2 Discussion

The goal of this study was to investigate whether PD is associated with a selective impairment in spatial-based versus object-based reflexive IOR. Impairments in inhibitory attention have frequently been reported in PD (Filoteo & Maddox, 1999; Filoteo et al., 2002; Filoteo et al., 1997; Henik et al., 1993; Kensinger et al., 2003; Maddox et al., 1996; Mari-Beffa et al., 2005; McDowell & Harris, 1997), including a reduction in IOR (Filoteo et al., 1997; Poliakoff et al., 2003; Yamaguchi & Kobayashi, 1998). Previous demonstrations of reduced IOR in PD have used tasks with predictive cues (Filoteo et al., 1997; Yamaguchi & Kobayashi, 1998), and it has been suggested that these study designs have confounded voluntary and reflexive orienting processes (Briand et al., 2001; Kingstone et al., 2002). Thus, it was not clear whether PD patients would demonstrate reduced IOR on a task that tapped purely reflexive orienting processes. Importantly, all visually-based IOR tasks previously used with this population have emphasized spatial components of attention by presenting cues and targets within only simple placeholder boxes or no objects at all, and therefore it is unknown whether PD patients would be impaired on an object-based IOR task. Based on evidence that spatial-based attention is frequently impaired in PD while object-based attention can be unimpaired (Filoteo et al., 1997; Filoteo et al., 2002; Lee et al.,

1999; Pollux & Robertson, 2001; Possin et al., 2006; Wylie & Stout, 2002; Wright et al., 1990), it was predicted that a greater reduction in IOR would be observed on the object-absent condition as compared to the object-present condition.

As predicted, when objects were absent from the display and attention was directed by only spatial-based processes, the PD patients demonstrated a significant reduction in IOR relative to controls. In direct contrast, when attention could be directed by both spatial- and object-based processes (i.e., in the object-present condition), the patients demonstrated virtually identical IOR effects to those of the control subjects. This pattern of results indicates that PD patients are selectively impaired in spatial-based IOR, and are able to bypass this impairment when they can direct their attention at objects. These findings suggest that PD impacts the neural underpinnings of spatial-based IOR, while the neural underpinnings of object-based IOR are spared.

Several lines of converging evidence strongly suggest that midbrain visuomotor pathways, and in particular the superior colliculus (SC), play a key role in spatial-based IOR. For example, single neuron recording studies in the SC of the monkey brain have demonstrated attenuated activity during IOR tasks (Dorris et al., 2002; Fecteau et al., 2004). In human subjects, greater IOR effects have been observed when the cue is presented monocularly in the temporal hemifield, which is represented more strongly in the SC than the nasal hemifield (Berger & Henik, 2000; Rafal et al., 1989). Reduced or no IOR has been demonstrated in patients with SC degeneration due to progressive supranuclear palsy (Rafal et al., 1988), and in patients with vascular lesions to the midbrain (Sapir et al., 1999; Sereno et al., 2006). In contrast, normal

IOR has been observed for the hemianopic field of a patient with a primary visual cortex lesion but not midbrain damage (Danzinger, Fendrich, & Rafal, 1997), and in newborn infants prior to complete cortical development (Clohesy, Posner, Rothbart, & Vecera, 1991; Valenza, Simion, & Umilta, 1994), both suggesting that the geniculostriate visual pathway may not be required for intact spatial-based IOR.

Although a widely held consensus is that the SC is involved in the generation of spatial-based IOR, recent evidence suggests that the SC expresses inhibition that is generated or at least modulated by cortical brain areas (Corbetta & Shulman, 2002; Dorris et al., 2002; Fielding et al., 2006; Klein, 2000; Mayer, Seidenberg, Dorflinger, & Rao, 2004). There is converging evidence from neuropsychological and functional imaging studies indicating that the posterior parietal cortex may play a particularly important role (Bartolomeo et al., 1999, Bartolomeo, Sieroff, Decaix, Chokron, 2001; Lepsien & Pollman, 2002; Rosen et al., 1999; Sapir et al., 2004; Vivas et al., 2003). Sapir and colleagues (2004) studied the performance of patients with parietal lobe lesions on an IOR task that required participants, on some trials, to make a saccade during the interval between the presentation of the cue and target. While controls demonstrated inhibition associated with both the environmental location of the cue and the retinal location of the cue, the patients with parietal lobe lesions demonstrated only retinal-based IOR. It has been suggested that parietal cortex may provide an environmental reference frame that signals the relative salience of locations for attention (Gottlieb, Kusunoki, & Goldberg, 1998; Vivas et al., 2003). There is also evidence that the frontal eye fields play a role in spatial-based IOR. For example, transcranial magnetic stimulation applied over the right frontal eye fields after cue

presentation in a spatial-based IOR task reduced the IOR effect for previously cued targets in the right hemifield (Ro, Farnè, & Chang, 2003), suggesting that the frontal eye fields may be involved in biasing attention and eye movements away from previously attended locations.

As reviewed above, there is evidence that parietal cortex and the frontal eye fields are involved in the generation or modulation of spatial-based IOR. The results from the present study suggest the possibility that the caudate nucleus may also play a key role in spatial-based IOR, because dopamine depletion of this structure is thought to mediate the cognitive sequelae of early PD (Marie et al., 1999; Owen et al., 2004). Consistent with this possibility, there is evidence that the caudate nucleus modulates SC functioning through inhibitory afferent connections via the substantia nigra pars reticulata (Hikosaka, Sakamoto, & Miyashita, 1993; Hikosaka & Wurtz, 1983; Joseph & Boussaoud, 1985). More specifically, it has been suggested that the caudate nucleus sends phasic inhibitory signals to the substantia nigra pars reticulata, which periodically release the superior colliculus from the tonic inhibitory effect of the substantia nigra pars reticulata (Hikosaka, Takikawa, & Kawagoe, 2000). Also consistent, the caudate nucleus is a major input station in the basal ganglia, receiving inputs from association cortices including posterior parietal cortex and the frontal eye fields (Alexander et al., 1986; Baizer et al., 1993; Yeterian & Pandya, 1991, 1995). Thus, the caudate nucleus is ideally positioned to integrate spatial-based information from cortex, and use this information to signal a response through the SC. The caudate nucleus may play a role in the generation of inhibitory signals based on the

environmental reference frame provided by posterior parietal cortex, and further to affect motor responding via connections to midbrain visuomotor pathways.

The generation of inhibitory tags to cued locations in spatial-based inhibition of return tasks must allow for representations of those locations to be encoded and maintained for up to several seconds (Dodd & Pratt, 2006; Samuel & Kat, 2003), and to be flexibly updated based on new information from the environment, for example, during visual search (Peterson, Kramer, Wang, Irwin, & McCarley, 2001; Takeda, 2004). Castel, Pratt, and Craik (2003) demonstrated that performing a secondary spatial working memory task eliminated spatial-based IOR in normal subjects, and based on their findings, suggested that the inhibited location in IOR is encoded and held online in a form of spatial working memory. In support of this view, we have demonstrated that patients with PD can demonstrate both spatial working memory encoding impairments in Experiment 1, and spatial-based IOR impairments in the present Experiment. Further, when SOAs are short (e.g., less than 300 msec) and working memory encoding processes may not be required, patients with PD typically demonstrate the normal facilitatory effects of covert orienting and a normal build-up of inhibitory attention that eventually leads to IOR (Bennett et al., 1995; Filoteo et al., 1997; Kingstone et al., 2002; Sharpe, 1990). If spatial working memory and spatial-based IOR indeed share underlying processes, it is likely, based on the present results, that the caudate nucleus plays a key role in these shared processes.

While the PD patients in this study demonstrated markedly reduced spatial-based IOR relative to controls, they demonstrated normal object-based IOR. This dissociation suggests that the brain areas most affected by mild to moderate PD do not

play a critical role in object-based IOR. The neural underpinnings of object-based IOR are not well understood, although there is evidence that this phenomenon is mediated by cortical structures (Tipper et al., 1997). One possibility is that ventral cortical structures, which are specialized for the identification of objects (Underlieder & Mishkin, 1982), are involved in object-based IOR. As explained in earlier sections of this dissertation, ventral stream and dorsal stream regions of cortex demonstrate remarkable segregation in their connections to the caudate nucleus, such that ventral regions (including inferior temporal cortex) connect preferentially to the tail and genu of the caudate nucleus, and dorsal regions (including posterior parietal cortex) connect preferentially to more anterodorsal regions of the caudate (Baizer et al., 1993). In addition, there is evidence that material-specific functional segregation occurs within the caudate nucleus, such that posterior regions are more involved in object working memory, and the dorsal head of the caudate is more involved in spatial working memory (Cohen, 1972; Divac et al., 1967; Iverson, 1979; Levy et al., 1997; Postle & D'Esposito, 1999). Further, there is evidence that dopamine depletion in the caudate nucleus of PD follows both a rostral / caudal and dorsolateral / ventromedial gradient, such that dopamine depletion is greatest in the anterodorsal extent of the head (Kish et al., 1988), and dopamine uptake sites are most reduced dorsally (Joyce, 1993; Kaufman & Madras, 1991; Piggott et al., 1999). Taken together, one preliminary explanation for the spatial / object IOR dissociation observed in the present study is that spatial processing circuits involving the dorsal head of the caudate nucleus are involved in spatial-based IOR, and object processing circuits involving more ventral and caudal regions are involved in object-based IOR.

The finding from the present study that PD differentially affects spatial-based relative to object-based IOR is the first demonstration that these reference frames of IOR can be dissociated in a patient group, and provides further support for the view that spatial-based and object-based components of attention involve distinct processes. These research findings are in line with studies of patients with unilateral neglect, who typically have right parietal lesions and ignore stimuli in their left visual field (Rafal, 1998). These patients can also neglect the left side of objects, even when the object is presented in their right hemifield (Caramazza & Hillis, 1990; Driver, Baylis, Goodrich, & Rafal, 1994; Driver & Halligan, 1991). Also in support of spatial and object components of attention, studies using spatial precueing paradigms with neurologically healthy individuals have demonstrated that both facilitatory and inhibitory aspects of attention can be directed at spatial-based and object-based frames of reference (Egly et al., 1994; Iani et al., 2001; Jordan & Tipper, 1998, 1999; Leek et al., 2003; Posner & Cohen, 1984; Soto & Blanco, 2004).

Inhibition was reduced for both groups in the object-present and object-absent conditions when the target was not in the same place as the cue. However, IOR did not decay solely as a function of object external features or spatial distance, but was modulated by other factors. When objects were present, greater IOR effects were observed when the cues and targets were separated by an internal boundary of the object (CT Location 3) than when they appeared on the same side of the boundary (CT Location 2), even though the targets in each of these locations were equidistant from the cue (see Figure 7). Leek and colleagues (2003; Reppa & Leek, 2003) also demonstrated this pattern of IOR modulation across an object's internal structure with

younger normal adults. They explained that targets in the same part of the object may be subject to facilitation as well as inhibition effects, while targets in a different part of the same object may only be subject to inhibition (Reppa & Leek, 2003). This pattern of IOR modulation suggests that object-based IOR is not based only on global shape properties, but also internal object structure. As demonstrated in the present study, these aspects of object-based IOR appear to be intact in both older adults and in PD patients.

When objects were absent from the display, it was somewhat surprising to observe slower responses in CT Locations 2 and 3 than in CT Location 4, considering that the targets in all three of these locations are equidistant from the cue. If the spread of spatial inhibition decayed based on spatial distance alone, one would predict that no inhibition would be demonstrated for CT Locations 2 and 3, relative to CT Location 4 (see Figure 7). However, significant IOR was demonstrated by the controls for these conditions in the present study, as well as by the young adult participants in the study by Leek and colleagues (2003). One possible explanation for this effect is that there was a memory trace for the objects from the object-present condition. However, half of the participants were administered the object-absent condition first, and the IOR effects associated with these CT Locations did not vary as a function of the administration order. Another possible explanation for this finding is that, while CT Location 4 was equidistant from the cue, the space between the cue and target was interrupted by the fixation cross. This landmark in the visual field may have divided the field into spatial regions on which attention operated. This may explain these results and suggest that the spread of spatial inhibition is not based on distance alone.

In conclusion, this study demonstrated that patients with PD display reduced IOR when their attention is directed to locations, but not when it is directed to objects. These findings suggest that the caudate nucleus plays a role in spatial-based IOR and that object-based and spatial-based aspects of attention can be dissociated. Considering these results together with the findings from Experiment 1, spatial working memory encoding and spatial-based IOR may share similar underlying processes that are disrupted in PD.

Parts of this chapter are being prepared for the following publication:

Possin, K. L., Filoteo, J. V., Song, D. D., and Salmon, D. P. (2007). Spatial-based but not object-based components of inhibition of return are impaired in Parkinson's disease.

VII. EXPERIMENT 3: VISUOSPATIAL AND VISUAL OBJECT DISCRIMINATION IN PARKINSON'S DISEASE

Experiment 3 Introduction

Patients with PD have frequently demonstrated visuoperceptual deficits. More specifically, impairments have been described on tests of contrast sensitivity (Amick, Cronin-Golomb, & Gilmore, 2003; Bodis-Wollner et al., 1987; Bulens, Meerwaldt, & Van der Wildt, 1988; Tebartz van Elst et al., 1997), color discrimination (Diederich et al., 1998; Pieri, Diederich, Raman, & Goetz, 2000), perceptual speed (Bachmann et al., 1998; Johnson et al., 2004), facial recognition (Levin et al., 1991), oculomotor control (White, Saint-Cyr, Tomlinson, & Sharpe, 1983), pattern perception (Flowers & Robertson, 1995), and figure-ground discrimination (Flowers & Robertson, 1995). Visual acuity is generally at the same level as age-matched controls (Biousse et al., 2004; Regan & Maxner, 1987). Patients with PD regularly report visual and visuospatial symptoms including difficulty estimating spatial relations, double vision, and freezing in narrow spaces (Davidsdottir, Cronin-Golomb, & Lee, 2005). In general, visuoperceptual impairments are more frequently observed in demented patients or patients with more severe clinical symptoms (Flowers & Robertson, 1995; Hirsch et al., 2003; Levin et al., 1991; Locascio, Corkin, & Growdon, 2003; Tagliati, Bodis-Wollner, & Yahr, 1996; Tebartz van Elst et al., 1997), although deficits in visuoperception have been reported on some tasks in nondemented patients in the early stages of the disease (Laatu et al., 2004; Levin et al., 1991).

While it is clear that PD is associated with visuoperceptual impairments, the precise nature of these impairments is not clear. Whether PD is associated with greater

impairments in the visual perception of spatial or object features is of particular relevance to the present set of experiments, because a selective spatial perceptual impairment could explain the deficits observed in Experiments 1 and 2. As defined for the present work, *spatial perception* involves the appreciation of object locations including the distance between two objects, and *object perception* involves the appreciation of shape and color information that may lead to the eventual identification of an object. These definitions were chosen to correspond to the perceptual requirements of most spatial and object working memory and attentional tasks described in investigations of PD.

Most studies that have examined visual perception in PD have used tasks that combine these modalities of processing (e.g., tests of pattern perception, figure-ground discrimination, and mental object rotation involve both modalities). A few studies have employed tasks that isolate object-based from spatial-based visual perceptual processes, and in general, these studies have demonstrated that object-based perceptual processing is unimpaired in PD. Laatu and colleagues (2004), for example, demonstrated that nondemented patients performed normally in terms of both reaction time and error rates on tests of object detection, which involved discriminating between real objects and non-objects. Correct performance on these tests required intact visual object sensory processing as well as access to representations in long-term memory, but spatial perceptual processing was minimized. Bondi and colleagues (1993) demonstrated impaired visual form discrimination in PD, although the authors attributed this deficit to executive dysfunction rather than a more primary visual disturbance. Tachibana, Aragane, Kawabata, and Sugita (1997) administered a shape

discrimination task to nondemented patients with PD while measuring event-related potentials (ERPs). The PD patients did not differ from controls in P3a or P3b components, which the authors interpreted to suggest intact automatic detection and attention-controlled processing of the shapes. Russ and Seger (1995) asked participants to scan two abstract colored patterns comprised of simple shapes, and to indicate as quickly as possible if the patterns were the same, or if one feature differed. The performance of PD patients was slower overall, but their reaction times did not differ from controls as a function of pattern complexity, suggesting intact object perception. PD patients have also shown to be unimpaired on a non-delayed match-to-sample task using Chinese characters (DeLancy Horne, 1971). Boller and colleagues (1984) did demonstrate an impairment in PD on a visual discrimination test, which required participants to match a design to one of four alternatives.

A few studies have employed tasks that isolate spatial perception from object perception, and although results have been mixed, PD patients have generally demonstrated intact spatial perception. Stelmach, Phillips, and Chau (1989) compared the relative contributions of perception, stimulus-response translation, movement preparation, and execution to performance on visual reaction time tasks that were based upon judgments of spatial displacements. These authors found that PD patients were not slower at perceiving spatial displacements or linking perception to action, but demonstrated deficits in the control of movement. Della Sala, Lorenzo, Giodano, & Spinnler (1986) found that PD patients did not differ from controls in their ability to extrapolate and predict where one line would intersect another. In a study by Mosimann and colleagues (2004), nondemented PD patients performed similarly to

controls on tests of space and motion perception, which may indicate intact spatial perception. However, both PD patients and controls made very few errors on these tests, suggesting possible floor effects, so it is possible that PD patients would have displayed a deficit if task difficulty were increased. Although making a judgment about spatial orientation may not tap the exact same processes as making a judgment about object location, it should be noted that PD patients have demonstrated deficits on tests tapping spatial orientation judgments (Boller et al., 1984; Finton et al., 1998; Goldenberg et al., 1986; Montse et al., 2001), suggesting that this aspect of spatial perception is impaired.

As reviewed above, research on visuoperception in nondemented PD does not clearly suggest that either the perception of object or spatial features is differentially impaired, and in fact, these patients are unimpaired on most tasks that isolate these aspects of perception. However, no study to date has directly compared object-based and spatial-based perceptual processing in PD using analogous tasks. Therefore, it is not entirely clear if PD has differential effects on visuospatial and visual object perception.

As discussed in the earlier section on visuospatial and visual object cognition in the normal brain, perceptual components of working memory tasks appear to be subserved primarily by early visual processing areas (e.g., retina, lateral geniculate, and posterior cortex) whereas mneumonic components, including the encoding and maintenance of perceptual representations in posterior cortex, are subserved primarily by prefrontal cortex and FSC circuits (Belger et al., 1998; Constantinidis & Procyk, 2004; Funahashi et al., 1989; Fuster, 1973; Goldberg et al., 1996; Livingstone &

Hubel, 1988; McCarthy et al., 1994; Quintana et al., 1988). If selective deficits on

spatial cognitive tasks (e.g., spatial working memory) are due to changes in early

processing areas, the underlying pathophysiology may be that the magnocellular

pathway is more affected than the parvocellular pathway, which previous research

suggests (Arakawa et al., 1999; Regan & Maxner, 1987; Tebartz van Elst et al., 1997),

or that dorsal regions of posterior cortex are more affected than ventral regions, which

has not been demonstrated. If selective deficits on spatial cognitive tasks are due to

changes in later processing areas, dopamine depletion in the caudate nucleus and its

effects on FSC circuit function may underlie the deficits. This latter possibility is

consistent with research suggesting that these neural changes are the primary

mediators of cognitive deficits in PD (Lichter, 2001; Marie et al., 1999; Owen, 2004;

Zgaljardic et al., 2003, 2006), and that top-down effects such as impairments in

executive skills account for many of the visual cognitive deficits in these patients

(Bondi et al., 1993; Flowers & Roberts, 1995; Ogden et al., 1990).

The purpose of the present study is to examine visuospatial and visual object

discrimination in PD patients to determine if these patients are relatively more

impaired in perceptual processing for either type of material. The design of the tasks

used are analogous to those used in Experiment 1 in terms of the stimuli and similarity

manipulations, but without the working memory component. It was predicted that the

PD patients would not be differentially impaired on the spatial discrimination task,

which would suggest that the spatial encoding deficit observed in Experiment 1, and

the spatial IOR deficit observed in Experiment 2, cannot be attributed to an

impairment in visuospatial perception. However, if the patients were found to be

differentially impaired on the spatial discrimination condition, it would suggest that the spatial encoding and spatial IOR deficits could be attributed, at least in part, to a selective impairment in spatial perception.

<center>Experiment 3 Methods</center>

<center><u>Participants</u></center>

Fifteen nondemented patients with PD (9 men and 6 women) and 15 normal controls (8 men and 7 women) participated in the study. The same procedures for diagnosing, recruiting, and screening participants were used as in the previous experiments. The patients had been diagnosed an average of 6.1 years (range = .2 – 19.9, SD = 4.9). Motor functioning was assessed by an experienced neurologist using Hoehn and Yahr rating scale (1967), and the UPDRS (Fahn et al., 1987). According to the Hoehn and Yahr rating scale, all patients exhibited mild to moderate motor impairments (M = 2.17, range = 1 - 3, SD = 0.52). The mean score on the motor examination section of the UPDRS was 21.73 (range = 9 – 34, SD = 9.68).

The PD patients were treated with their normal regimen of dopaminergic agents at the time of testing (see Table 10) and were tested at the time of day when they felt cognitively more alert. No patients were taking anticholinergic or antipsychotic medication. Using an alpha level of .05, the PD patients did not differ significantly from the controls in age, t(28) = 0.88, p = .38, years of education, t(28) = 0.00, p > .99, or GDS scores, t(24) = 0.73, p = .47. There was a trend for the patients to score lower on the DRS than the controls, t(27) = 1.91, p = .07, d = 0.66. The range of DRS scores for the controls was 139 to 144, and the range for the PD patients was 132 to 144. The

Table 10. Characteristics of the Parkinsonian patients in Experiment 3

No.	Age	Disease duration[a]	H & Y stage	Antiparkinsonian medication, Daily dose (mg) [b]
1	69	20	2	LeCa 300/75, En 800, Pr 1
2	69	6	2.5	LeCa 600/150, Pr 4, Am 100
3	60	7	2	LeCa 450/112, Pr 3, Se 5
4	84	6	3	LeCa 1200/300
5	70	5	1.5	LeCa 400/100
6	57	9	2.5	LeCa 400/100
7	80	5	2	LeCa 800/200, Se 5
8	64	0	2	Se1
9	79	5	2	Se 10, LeCaEn 300, Ro 15
10	76	10	3	LeCa 1100/275, Ro 4
11	88	3	2.5	LeCa 300/75, Ro 4
12	56	2	3	Unmedicated
13	72	8	2.5	LdCa 900/225, Pr 2, Am 200
14	64	9	2	LeCa 500/125, Pr 4
15	63	3	2	LeCa 300/75, Am 300

[a]Age and disease duration in years. Disease duration is rounded to the nearest year.
[b]LeCa, levodopa-carbidopa; En, entacapone; Pr, pramipexole; Am, amantadine; Ro, ropinirole; Se, selegiline; Ca, carbidopa; LdCaEn, levodopa-carbidopa-entacapone.

PD patients had worse scores, compared to controls, on the Rosenbaum Pocket Vision Screener, $t(26) = 2.58$, $p = .02$, $d = 0.92$.[7] The range of Rosenbaum Pocket Vision Screener scores for each group was 20/20 to 20/40. As in Experiments 1 and 2, the participants were given a battery of tests in order to characterize their neuropsychological functioning. Because of time constraints, some participants did not receive all of the tests, so the range of sample size varied by test from 9 to 14 in the control group, and 14 to 15 in the PD group. Table 11 shows the mean scores on

---

[7] Rosenbaum Pocket Vision Screener scores of the patients did not correlate with the primary indices from the visual discrimination task. The correlations with discriminability in the spatial condition, $r = -.17$, $p = .55$, discriminability in the object condition, $r = .04$, $p = .89$, reaction time in the spatial condition, $r = .02$, $p = .93$, and reaction time in the object condition, $r = .15$, $p = .60$, were not significant.

selected indices from these tests for the two groups, and denotes the indices on which

the groups significantly differed based on independent samples t-tests.

Table 11. Demographic characteristics and neuropsychological test scores of
Parkinsonian patients and normal controls

	PD	NC
Age	69.49 (9.04)	66.73 (8.07)
Education	16.93 (2.25)	16.93 (2.40)
DRS	139.87 (3.18)	141.57 (1.74)
Rosenbaum Pocket Vision Screener	20/28.33 (5.88)	20/22.69 (5.63)*
Geriatric Depression Scale	3.93 (2.40)	3.08 (3.45)
WCST categories	5.20 (1.52)	5.70 (.95)
WCST perseverative responses	16.47 (19.22)	8.60 (5.19)
WCST set losses	0.13 (.35)	0.40 (.70)
JOLO	25.80 (4.48)	25.70 (2.83)
ANART	39.40 (9.91)	40.60 (6.02)
Finger tapping dominant	39.46 (9.13)	46.68 (10.10)
Finger tapping nondominant	37.58 (7.53)	39.80 (7.32)
CVLT trial 1	5.73 (2.34)	7.80 (1.87)*
CVLT trials 1-5	46.80 (8.18)	53.90 (12.61)
CVLT short delay free recall	9.47 (2.67)	11.40 (4.48)
CVLT short delay cued recall	10.53 (2.03)	12.90 (3.81)
CVLT long delay free recall	9.27 (3.43)	11.90 (4.53)
CVLT long delay cued recall	11.07 (2.43)	13.00 (4.27)
CVLT semantic clustering	0.93 (1.73)	2.35 (2.54)
CVLT total repetitions	4.53 (3.31)	6.80 (4.78)
CVLT total intrusions	5.47 (4.73)	4.00 (4.27)
CVLT recognition hits	14.33 (1.76)	15.70 (.48)*
CVLT recognition false positives	3.13 (3.46)	2.00 (4.67)
D-KEFS letter fluency	46.47 (13.74)	47.40 (14.74)
D-KEFS category fluency	37.27 (10.98)	44.00 (7.41)
D-KEFS category switching fluency	12.27 (3.01)	14.60 (2.72)
D-KEFS fluency switching accuracy	11.07 (3.58)	14.10 (2.96)*

Values represent mean (s.d.).
*$p<.05$

Apparatus and Stimuli

Stimuli were presented on a 50.8 cm. monitor. Randomization and presentation of stimuli, and recording of response reaction time and accuracy, were executed by Eprime software, version 1.1. Participants responded via two keys on a standard computer keyboard, which were designated by colored stickers and labeled with a sign behind the keys. The sign read "match" behind the "z" key, which was colored blue, and "different" behind the "/" key, which was colored red.

The sixty-one shapes used as stimuli are the same shapes created for Experiment 1. For this experiment, as in the working memory experiment, target-probe pairs varied in terms of shape and location similarity. The same methods were used for classifying target-probe pairs as similar, dissimilar, or match according to shape, based on the pilot study described in Experiment 1. During each trial in the present experiment, two rectangles appeared on the screen, which each subtended 15.6 by 19.3. These rectangles could appear in one of four possible positions: adjacent with the left rectangle 6.5 degrees higher than the right rectangle, adjacent with the left rectangle 6.5 degrees lower than the right rectangle, with one above the other and the one on top shifted 6.5 degrees to the left of the one below, or with one above the other and the one on top shifted 6.5 degrees to the right of the one below. Two target stimuli each appeared in a different rectangle in same, similar, or dissimilar corresponding positions. In the spatial condition, participants compared the positions of the targets relative to their respective rectangles and decided if they matched in location. For non-match location trials, probes varied in location from their corresponding targets by 5.7° in visual angle for the spatial similar condition, and 9.6° in visual angle for the

spatial dissimilar condition. The height and width of the shapes each subtended

approximately 1.1° X 1.1° of visual angle (there was some slight variability in the size

of the shapes). The shapes were solid white and were presented against a black
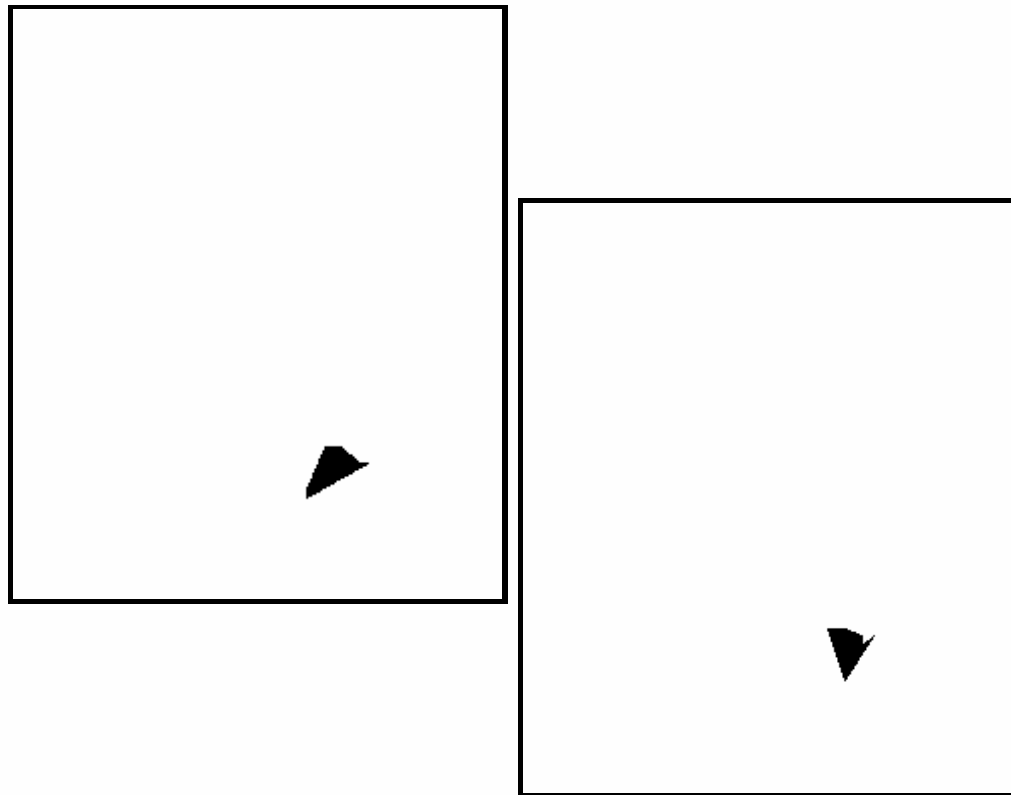
background.

Figure 8. An illustration of stimuli presentation in Experiment 3 for a spatial match,
object similar trial. Colors have been inverted for this figure.

Procedure

The spatial and object conditions of this visual discrimination task differed only in

what the participants were instructed to attend to: stimuli locations or stimuli shapes.

Each trial began with the presentation of a white fixation cross for 500 msec, followed by two target stimuli, each presented in a different rectangle. In the spatial condition, the participant was instructed to press the "match" key with their left hand if the stimuli were in the same position relative to the rectangle frames, or the "different" key with their right hand if they were not in the same position, regardless of stimuli shapes. In the object condition, the participant was instructed to press the "match" key if the stimuli were the same shape, and the "different" key if they were not the same shape, regardless of spatial location. The stimuli remained on the screen until the participant responded. The participants were instructed to respond as quickly as possible while also trying to minimize errors.

Within the spatial condition, 64 trials were classified as spatially similar, 64 as spatially dissimilar, and 128 as spatial match. For each trial, the position of one target was randomly determined from the range of possible coordinates. The other target was moved up, left, right, or down from the corresponding location of the first target for spatial non-match trials (similar or dissimilar), and these directions occurred with equal probability. The four rectangle positions also occurred with equal probability. The following variables were fully counterbalanced: spatial similarity, object similarity, direction, and rectangle position. The object condition appeared identical to the spatial condition, except that participants attended to whether or not the shapes were the same, while ignoring location.

The visual discrimination task consisted of 256 randomly presented trials per condition. Conditions were administered on the same day but separated by at least 30 minutes. The order of the conditions was counterbalanced within each group.

Experiment 3 Results

Response Bias

As in Experiment 1, accuracy on the similar and dissimilar trials was a dependent

measure for the primary analyses. Because the correct response on these non-match

trials is always the same (i.e., the shapes or locations do not match), response bias may

have an effect on accuracy. Response bias was examined using the same index used in

Experiment 1 (Snodgrass & Corwin, 1988). A 2 (group) by 2 (task) mixed ANOVA

was performed. The group by task interaction was not significant, $F(1, 28) = 0.51$, $p =$

.48, nor was the main effect of group, $F (1, 28) = 1.59$, $p = .22$. Although the groups

did not significantly differ in response bias, we decided to correct for response bias

using the two-high threshold model of recognition discriminability (Snodgrass &

Corwin, 1988) in order to keep the visual discrimination analyses on the same metric

as that used in the working memory analyses from Experiment 1, and to account for

response bias differences at the individual level. Mean accuracy and discriminability

values by task, group, and similarity level are presented in Table 12.

Discriminability Analyses

Anticipatory responses (i.e., trials with reaction times less than 200 msec) were

excluded from the analyses. A 2 (group) by 2 (task) by 2 (similarity) mixed ANOVA

was performed, with discriminability as the dependent measure. The group by task by

similarity interaction, $F(1, 28) = 1.06$, $p = .31$, and the group by task interaction, $F(1,$

$28) = 0.02$, $p = .89$, were not significant. The group by similarity interaction, $F(1, 28)$

$= 7.13$, $p = .01$, and the task by similarity interaction, $F(1, 28) = 10.68$, $p < .01$, were

significant. Discriminability scores were lower in the spatial condition, $F(1, 28) =$

6.37, p = .02, d = 0.54, and there was a trend for lower discriminability in the patients

than the controls, F (1, 28) = 3.29, p = .07, d = 0.69.[8]

Table 12. Accuracy and discriminability by task, group, and similarity

	Spatial Discrimination			Object Discrimination		
	Similar	Dissimilar	Match	Similar	Dissimilar	Match
Accuracy						
PD	.92 (.09)	.95 (.06)	.94 (.04)	.89 (.06)	.97 (.02)	.97 (.02)
NC	.95 (.04)	.96 (.04)	.95 (.04)	.95 (.04)	.99 (.02)	.98 (.02)
Recognition Discriminability						
PD	.85 (.11)	.88 (.09)		.86 (.07)	.94 (.03)	
NC	.89 (.06)	.91 (.06)		.92 (.05)	.96 (.03)	

Values represent mean (s.d.).

To follow-up the group by similarity interaction, independent samples t-tests were

performed to compare the groups on similar trials, and on dissimilar trials, collapsed

across tasks. The discriminability scores of the patients were significantly lower than

controls on similar trials, t(28) = 2.23, p = .03, d = 0.82, but not on dissimilar trials,

t(28) = 1.32, p = .20, d = 0.48. The task by similarity interaction was followed-up by

performing within subjects one-way ANOVAs to examine the effect of similarity

within each task. The effect of similarity was significant in both the object task, F(1,

29) = 45.89, p < .01, d = 1.22, and the spatial task, F(1, 29) = 11.50, p <.01, d = 0.26.

[8] The same analysis was performed with mean accuracy as the dependent measure. The same pattern of significant effects was found, except the trend for lower overall discriminability in the patients than the controls was significant when accuracy was the dependent variable, F(1, 28) = 4.83, p = .04.

Based on a comparison of the effect sizes, the similarity effect was greater in the object task. Object and spatial mean discriminability and standard errors by group and similarity level are presented in Figure 9.
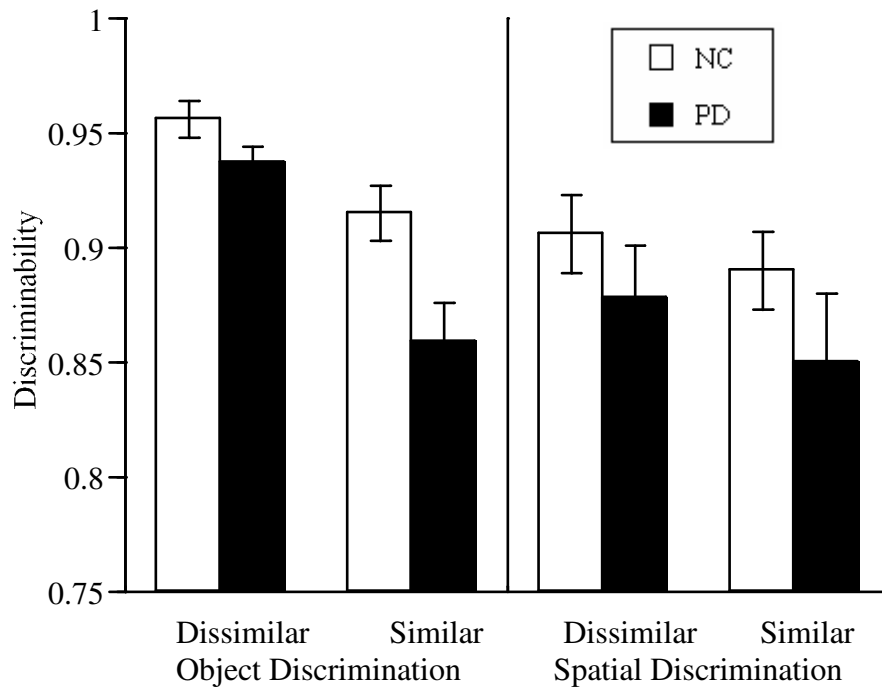

Figure 9. Object and spatial discriminability as a function of group and similarity

Reaction time

The effect of group, task, and similarity on median reaction time was also analyzed, after excluding trials with incorrect or anticipatory responses. The results of this 2 (group) by 2 (task) by 2 (similarity) mixed ANOVA revealed no significant interaction effects, including the group by task by similarity interaction, $F(1, 28) = 2.66$, $p = .11$, the group by task interaction, $F(1, 28) = 1.24$, $p = .28$, and the group by similarity interaction, $F(1, 28) = 0.12$, $p = .74$. There was a trend for the similarity effect to be greater in the object task than the spatial task, $F(1, 28) = 3.55$, $p = .07$.

Participants responded faster during the object task than the spatial task, $F(1, 28) =$ 15.77, $p < .01$, $d = 0.68$, and on dissimilar trials than similar trials, $F(1, 28) = 94.07$, $p < .01$, $d = 0.27$. The group difference in overall reaction time was not significant, $F(1, 28) = 3.24$, $p = .08$, $d = 0.66$, although there was a trend for the patients to respond slower. Group means and standard errors of median reaction time by group and similarity level are presented in Figure 10.
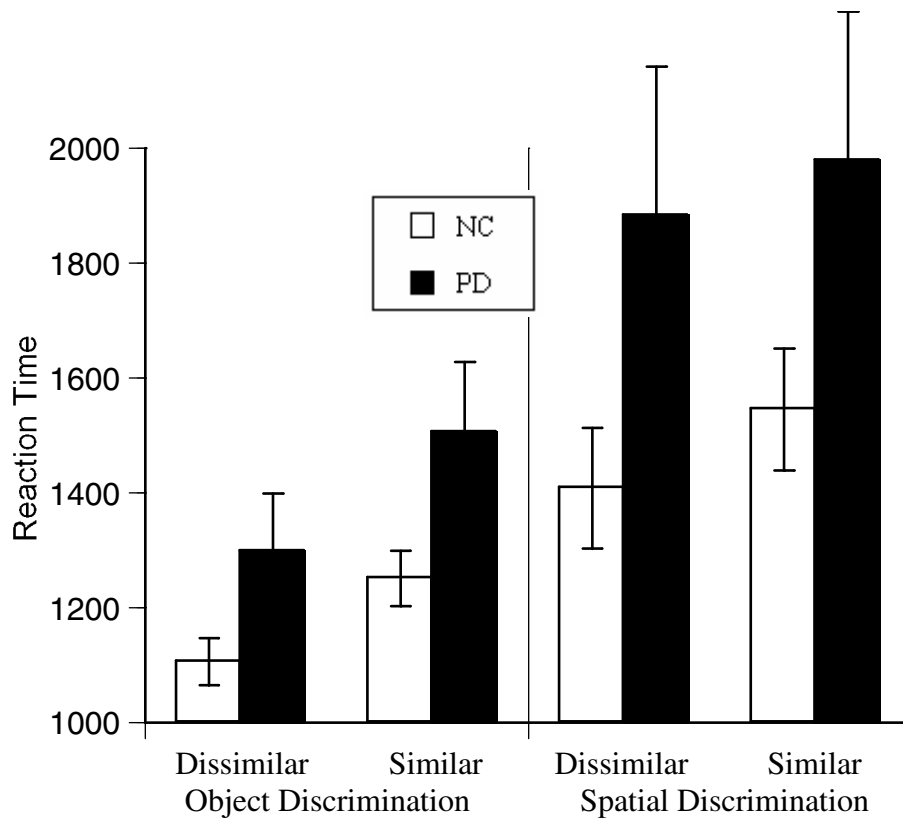

Figure 10. Object and spatial discrimination reaction time as a function of group and similarity

Relationship Between Motor Symptoms and Visual Discrimination Performance

It was predicted that any deficit observed in the PD patients on the spatial discrimination task would not be associated with bradykinesia or the overall severity

of motor symptoms. Discriminability on the spatially similar trials was chosen to operationalize the spatial discrimination deficit, because the patients demonstrated impaired discriminability on similar trials, relative to controls.[9] Bradykinesia was operationalized using the same method as in Experiment 1, based on the UPDRS factor analysis performed by Stebbins and Goetz (1998). In Experiment 1, only the score for the worst hand on item 25 was included in the sum of factors 4 and 5, because of the previously described administration error. Although the UPDRS was scored correctly for this study, this bradykinesia factor score sum was calculated using the same method so that these correlations would be directly comparable. The correlation between discriminability on spatially similar trials and bradykinesia was not significant, $r = -.19$, $p = .50$. The severity of motor symptoms was operationalized by the total score on the UPDRS motor examination section. The correlation between discriminability on the spatially similar trials and motor scores was not significant, $r = -.17$, $p = .54$.

<div align="center">Experiment 3 Discussion</div>

The goal of this study was to examine whether PD patients are differentially impaired in spatial-based versus object-based perceptual processing. Previous research has demonstrated that these patients can show selective spatial deficits on tests of working memory (Experiment 1; Bradley et al., 1989; Owen et al., 1997; Owen, Bedsinska, et al., 1993; Postle, Jonides, et al., 1997, Postle, Locascio, et al., 1997, Swainson et al., 2000, Taylor et al., 1986), and inhibitory attention (Experiment 2;

---

[9] It should be emphasized that the patients were not more impaired on the spatial discrimination task than the object discrimination task. The correlations between the motor measures and object similar discriminability were also performed. Neither the correlation with bradykinesia, $r = -.11$, $p = .71$, or overall severity of motor symptoms, $r = .01$, $p = .98$, were significant.

Filoteo et al., 2002; Possin et al., 2006), relative to similar object-based tests. If PD patients are differentially impaired in spatial versus object perceptual processing, one possible explanation for the spatial working memory and attentional deficits is that they arise from these lower level perceptual impairments. If spatial perceptual processing is not differentially impaired, then it can be inferred that these patients are impaired in a higher-level aspect of spatial cognition.

The results of this study indicate that PD patients do indeed have subtle perceptual processing disturbances, but that spatial perception is not more affected than object perception. In terms of discriminability, the patients were more impaired on similar versus dissimilar discrimination trials relative to controls, but this similarity by group effect did not differ as a function of task. This indicates that the patients were impaired in their ability to discriminate locations and shapes, but were not more impaired in processing either type of information. Although the PD patients were slower in responding than controls, the reaction time differences did not differ as a function of material type or similarity level. Thus, the discriminability results cannot be attributed to a speed / accuracy tradeoff. Taken together, these results suggest that PD patients are not differentially impaired in spatial or object perception.

The perceptual deficits for both locations and shapes were not significantly associated with the severity of motor symptoms, or specifically with the severity of bradykinesia in PD. This suggests that this deficit does not arise from the same pathophysiological changes that result in the motor symptoms of PD, primarily dopamine depletion in the striatum (Brucke et al., 1997; Grafton, 2004; Otsuka et al., 1996). As reviewed above, there is evidence that PD may affect certain brain regions

involved in visual perceptual processing. For one, there is a decrease in dopamine in the retinas of patients with PD (Bodis-Wollner, 1990; Harnois & Di Paolo, 1999). In addition, the lateral geniculate and visual cortex contain dopaminergic cells (Papadopoulos & Parnavelas, 1990; Parkinson, 1989; Reader & Quesney, 1986), and dopamine agonists have been shown to modulate contrast gain in the lateral geniculate of rats (Albrecht et al., 1996). Further, reduced metabolic activity has been observed in the occipital cortex of PD patients (Abe et al., 2003; Bohnen et al., 1999; Wang et al., 1999). Thus, changes in the geniculostriate system may underlie impairments in visual perceptual processing in PD, and based on the results of the present study, these changes do not appear to differentially impact spatial- or object-based processing.

Parts of this chapter are being prepared for the following publication:

Possin, K. L., Filoteo, J. V., Song, D. D., and Salmon, D. P. (2007). Spatial and object working memory deficits in Parkinson's disease are due to impairment in different underlying processes.

VIII. GENERAL DISCUSSION

Previous research suggests that PD may be associated with greater impairment in visuospatial than visual object working memory (e.g., Postle, Jonides, et al., 1997), but the nature and extent of this selective spatial impairment is not clear. For example, the impairment may be limited to either encoding or maintenance processes of working memory. In addition, the selective spatial impairment may extend to aspects of attention or basic visual processes. The goal of the present set of studies was to address these issues.

The purpose of Experiment 1 was to investigate the integrity of encoding and maintenance processes of both visuospatial and visual object working memory in PD. The results of this experiment demonstrated that PD patients can exhibit deficits on tests of both spatial and object working memory, but that these deficits are due to impairments in different underlying processes. More specifically, spatial encoding processes were shown to be impaired in PD and the patients only demonstrated this impairment when a high degree of precision was required during the encoding process. Spatial maintenance processes were not shown to be impaired in that the magnitude of their deficit was the same across the different delay periods. In contrast, the patients were able to normally encode object-based information in that they demonstrated normal performance at the 1-second delay (and the 5-second delay) but were less accurate than controls at the 10-second delay. Importantly, this pattern was the same for similar and dissimilar objects, suggesting that the degree of encoding difficulty did not likely contribute to their object maintenance deficit.

The purpose of Experiment 2 was to investigate the integrity of spatial-based and object-based components of reflexive IOR in PD. When no objects were present in the display and the participants had to rely on spatial-based attentional processes, the patients demonstrated a reduction in IOR. In contrast, when objects were present in the display and the participants could rely on object-based attentional processes, the patients demonstrated normal IOR. These results provide the first demonstration that these reference frames of IOR can be dissociated in a patient group, and further support for the view that spatial-based and object-based components of attention involve distinct processes (e.g., Driver et al., 1994; Leek et al., 2003; Posner & Cohen, 1984; Yantis & Sersences, 2003). In addition, these findings suggest that selective spatial cognitive deficits in PD include this aspect of reflexive, inhibitory attention.

Experiment 3 was designed to investigate the integrity of spatial and object perceptual processes. If PD were associated with a greater impairment in spatial perception than object perception, it might suggest that a deficit in lower-level perceptual processes caused the select deficits on the higher-level visuospatial tasks involving working memory and attention. However, the results of Experiment 3 suggest that this is not the case. Although the patients were impaired on the visual discrimination task in Experiment 3, this impairment did not differ by the type of material to be discriminated.

Taken together, the results of these experiments suggest that the selective visuospatial deficit in PD is not due to a general impairment in spatial cognition, but rather to a specific impairment involving encoding and attentional processes. This

pattern of results suggests that PD pathology selectively disrupts visuospatial cognition at a high level of the visual processing system, rather than at lower perceptual processing areas (i.e., pathways of the geniculostriate system and posterior cortex). As discussed above, dopamine depletion of the caudate nucleus is thought to mediate the cognitive sequelae of early PD (Marie et al., 1999; Owen, 2004), and dopamine depletion of this structure has been shown to be greatest in the anterodorsal extent of the head (Kish et al., 1988). This region of the caudate has been shown to play an important role in spatial working memory (Cohen, 1972; Divac et al., 1967; Levy et al., 1997; Postle & D'Esposito, 1999). In addition, the dorsal head of the caudate receives projections from cortical regions that play a role in spatial working memory and spatial attention, specifically dorsolateral prefrontal cortex, the frontal eye fields, and posterior parietal cortex (Awh & Jonides, 2001; Baizer et al., 1993; Levy & Goldman-Rakic, 1999; Selemon & Godman-Rakic, 1985; Ungerleider & Mishkin, 1982; Yeterian & Pandya, 1991, 1995). High-level visuospatial impairments in PD may arise from pathological changes in the dorsal head of the caudate nucleus and the disruption of associated cortico-subcortical circuits.

One important implication from the results of these experiments is that spatial encoding and spatial-based IOR may involve shared or related underlying processes, which are disrupted by PD. Consistent with this interpretation, several lines of research indicate that attention and working memory are closely intertwined. For example, individual differences in working memory capacity have been shown to predict performance on tests of controlled attention (Kane et al., 2001; Unsworth, Schrock, & Engle, 2004), negative priming (Conway, Tuholski, Shisler, & Engle,

1999), and attentional allocation (Bleckley, Durso, Crutchfield, Engle, & Khanna, 2003). When normal participants must perform a concurrent spatial working memory task, performance on visual search (Oh & Kim, 2004; Woodman & Luck, 2004) and IOR tasks (Castel et al., 2003) is impaired. Visual processing is better at memorized locations than unmemorized locations, suggesting that attention is directed towards locations in working memory (Awh, Jonides, & Reuter-Lorenz, 1998). In addition, the neural substrates of spatial working memory and spatial attention closely overlap, with both involving dorsal regions of cortex (Awh & Jonides, 2001; Funahashi, Chafee, & Goldman-Rakic, 1993). These lines of research support the view that spatial working memory and spatial attention are related both in terms of function and neural substrates, and also that the relationship is complex and multifaceted. The nature of the interaction between working memory and attention depends on the diverse modes of operation within these two systems, including the stage of working memory under consideration (i.e., perception, encoding, or maintenance; Awh, Vogel, & Oh, 2006).

Both spatial working memory encoding and spatial-based IOR may have been disrupted in the patients because of an impairment in biasing the accessibility of relevant over irrelevant information during an encoding process. As explained in the discussion section of Experiment 2, there is evidence that spatial-based IOR relies on working memory processes. Sensory representations of visual stimuli decay within a few hundred milliseconds following physical offset (Coltheart, 1980). However, neurologically healthy individuals demonstrated attentional inhibition associated with cued locations up to 1220 msec after cue presentation in Experiment 2, and up to several seconds in other studies (e.g., Dodd & Pratt, 2006; Samuel & Kat, 2003). This

suggests that inhibitory tags associated with cued locations are transferred from sensory representations into a more durable storage. This relatively durable storage appears to share a number of properties with working memory, including a limited capacity and flexible updating capabilities (Peterson et al., 2001; Snyder & Kingstone, 2000; Takeda, 2004). Interestingly, while the PD patients demonstrated reduced spatial-based IOR in Experiment 2, these patients typically demonstrate the normal facilitatory effects of covert orienting and a normal build-up of IOR when SOAs are shorter (i.e., less than 300 msec; Bennett et al., 1995; Filoteo et al., 1997; Kingstone et al., 2002; Sharpe, 1990) and working memory processes may not be required. Thus, the impairment in spatial-based IOR and spatial working memory both appear to be specific to a disruption in encoding. Spatial encoding may be disrupted because the patients are impaired in their ability to inhibit irrelevant spatial information during encoding, which results in an overload of the limited capacity of working memory and only partial encoding of the relevant information. Consistent with this interpretation, the patients demonstrated an encoding deficit in Experiment 1 only when a high degree of spatial precision was required, indicating that some information was encoded. In sum, attention may serve to increase the salience of relevant information during spatial working memory encoding by inhibiting irrelevant information, and it is at this intersection of attention and working memory that PD patients may be impaired. In contrast, the patients demonstrated an object working maintenance impairment, but object-based IOR was intact. Thus, the object working memory maintenance impairment appears to be independent of this aspect of attention.

In interpreting the results of the present study, it is important to consider that all patients were on dopamine replacement therapy at the time of testing. The relationship between this medication and cognitive function in PD is complex, with the medication associated with improved performance on some tasks (Castiello, Bonfiglioli, and Peppard, 2000; Cools, Barker, Sahakian, & Robbins, 2001, 2003; Costa et al., 2003; Fournet et al., 2000; Gotham et al., 1988; Lange et al., 1992; Lewis et al., 2005; Mollion, Ventre-Dominey, Dominey, & Broussolle, 2003), and either no effect or worse performance on other tasks (Cools et al., 2001, 2003; Fournet et al., 2000; Gotham et al., 1988; Lange et al., 1992; Lewis et al., 2005). It has been suggested that this relationship is secondary to the normalizing effect of dopaminergic medication on the dorsal striatum and dorsolateral prefrontal cortex, brain regions that are severely depleted of dopamine in PD, and the 'overdosing' of the relatively intact ventral striatum and ventral prefrontal cortex (Cools et al., 2003). If this interpretation is correct, one might expect that dopamine replacement therapy would be associated with improved spatial processing and worsened object processing in PD (considering the neuroanatomical underpinnings of these processes, discussed above). However, while studies that have looked at the effects of dopaminergic medications on spatial working memory have demonstrated either improved performance (Costa et al., 2003; Lange et al., 1992) or no effect of the medication (Fournet et al., 2000; Lange, Paul, Naumann, & Gsell, 1995), studies looking at the effect of these medications on object working memory have also demonstrated improvements (Costa et al., 2003; Mollion et al., 2003; but see Gotham et al.,

1988). Much less research has focused on the effects of dopamine replacement therapy on inhibitory attention or visual processing in PD, although there is some evidence that these medications ameliorate inhibitory impairments (Castiello et al., 2000) and have no effect on lower-level visual perceptual or visuoconstructional abilities (Cooper et al., 1992). In sum, while certainly more research is needed to clarify the relationship between dopaminergic medications and the cognitive processes examined in the present experiments, it seems unlikely that the spatial encoding, object maintenance, spatial-based IOR, or visuoperceptual impairments demonstrated by the patients were induced by these medications. Rather, based on the evidence reviewed above that dopaminergic medication typically ameliorates or has no effect on these processes, it is more likely that the observed deficits are due to the effects of PD pathology.

In conclusion, the results of these studies provide new insights into the nature of visuospatial and visual object cognitive deficits in Parkinson's disease. While visuospatial and visual object cognition do not appear to be differentially impacted at lower levels of the visual processing system (i.e., at the level of perception), the disruption of spatial and object cognition at higher levels of cognition appears to involve impairments in different processes. PD patients are impaired in the encoding of spatial information into working memory, as well as the attentional inhibition of cued locations. These impairments may arise from disruption of a shared underlying mechanism involving the inhibition of irrelevant information and specific to the encoding process. Future research will be needed to test this hypothesis and further examine how spatial working memory and

spatial attention interact in PD. Within the realm of higher-level visual object

cognition, both inhibitory attention and working memory encoding processes

appear to be intact, but long-term working memory maintenance is impaired.

REFERENCES

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders, 20*(10), 1255-1263.

Abe, Y., Kachi, T., Kato, T., Arahata, Y., Yamada, T., Washimi, Y., Iwai, K., Ito, K., Yanagisawa, N., & Sobue, G. (2003). Occipital hypoperfusion in Parkinson's disease without dementia: correlation to impaired cortical visual processing. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*(3), 419-422.

Abrams, R. A., & Dobkin, R. S. (1994). Inhibition of return: Effects of attentional cuing on eye movement latencies. *Journal of Experimental Psychology: Human Perception & Performance, 20*(3), 467-477.

Agid, Y. (1991). Parkinson's disease: pathophysiology. *Lancet, 337*(8753), 1321-1324.

Alberoni, M., Della Salla, S., Pasetti, C., & Spinnler, H. (1988). Problem solving ability of parkinsonians. *Italian Journal of Neurological Science, 9*(1), 35-40.

Albrecht, D., Quaschling, U., Zippel, U., & Davidowa, H. (1996). Effects of dopamine on neurons of the lateral geniculate nucleus: an iontophoretic study. *Synapse, 23*(2), 70-78.

Alevriadou, A., Katsarou, Z., Bostantjopoulou, S., Kiosseoglou, G., & Mentenopoulos, G. (1999). Wisconsin Card Sorting Test variables in relation to motor symptoms in Parkinson's disease. *Perceptual and Motor Skills, 89,* 824-830.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research, 85,* 119-146.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Reviews in Neuroscience, 9*, 357-381.

Amick, M. M., Cronin-Golomb, A., & Gilmore, G. C. (2003). Visual processing of rapidly presented stimuli is normalized in parkinson's disease when proximal stimulus strength is enhanced. *Vision research, 43*(26), 2827-2835.

Appollonio, I., Grafman, J., Clark, K., Nichelli, P., Zeffiro, T., & Hallett, M. (1994). Implicit and explicit memory in patients with Parkinson's disease with and

without dementia. *Archives of Neurology, 51*(4), 359-367.

Arakawa K, Tobimatsu S, Kato M, & Kira J. (1999). Parvocellular and magnocellular visual processing in spinocerebellar degeneration and Parkinson's disease: an event-related potential study. *Clinical Neurophysiology, 110*(6),1048-1057.

Arnott, W. L., Chenery, H. J., Murdoch, B. E., & Silburn, P. A. (2001). Semantic priming in Parkinson's disease: evidence for delayed spreading activation. *Journal of Clinical and Experimental Neuropsychology, 23*(4), 502-519.

Attneave, F., & Arnoult, M. D. (1956). The quantitative study of shape and pattern perception. *Psychological Bulletin, 53*(6), 452-471.

Awh, E., Anllo-Vento, L., & Hillyard, S. A. (2000). The role of spatial selective attention in working memory for locations: Evidence from event-related potentials. *Journal of Cognitive Neuroscience, 12*(5), 840-847.

Awh, E., & Jonides, J. (1998). Spatial working memory and spatial selective attention. In R. Parasuraman (Ed.), *The attentive brain* (pp. 353-380). Cambridge, MA: The MIT Press.

Awh, E., & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Science, 5*(3), 119-126.

Awh, E., Jonides, J., & Reuter-Lorenz, P. A. (1998). Rehearsal in spatial working memory. *Journal of Experimental Psychology, 24*(3), 780-790.

Awh, E., Vogel, E. K., & Oh, S.-H. (2006). Interactions between attention and working memory. *Neuroscience, 139,* 201-208.

Bachmann, T., Asser, T., Sarv, M., Taba, P., Lausvee, E., & Põder, E. (1998). Speed of elementary visual recognition operations in parkinson's disease as measured by the mutual masking method. *Journal of Clinical & Experimental Neuropsychology, 20*(1), 118-134.

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. Bower (Ed.), *The psychology of learning and motivation,* (Vol. 8, pp. 47-90). San Diego, CA: Academic Press.

Baizer, J. S., Desimone, R., & Ungerleider, L. G. (1993). Comparison of subcortical connections of inferior temporal and posterior parietal cortex in monkeys. *Visual Neuroscience, 10,* 59-72.

Bartolomeo, P., Chokron, S., & Sieroff, E. (1999). Facilitation instead of inhibition for repeated right-sided events in left neglect. *Neuroreport, 10*(16), 3353-3357.

Bartolomeo, P., Sieroff, E., Decaix, C., & Chokron, S. (2001). Modulating the attentional bias in unilateral neglect: the effects of the strategic set. *Experimental Brain Research, 137*(3-4), 432-444.

Bayles, K. A. (1990). Language and Parkinson disease. *Alzheimer's Disease and Associated Disorders, 4*(3), 171-180.

Beatty, W. W. (2002). Cognition in a patient with very mild right-sided hemiparkinsonism. *Neurocase, 8*(1-2), 28-39.

Beatty, W. W., & Monson, N. (1990). Picture and motor sequencing in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology, 3*(4), 192-197.

Beatty, W. W., Staton, R. D., Weir, W. S., Monson, N., Whitaker, H. A. (1989). Cognitive disturbances in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology, 2*(1), 22-33

Behrmann, M., & Tipper, S. P. (1999). Attention accesses multiple reference frames: evidence from visual neglect. *Journal of Experimental Psychology. Human Perception and Performance, 25*(1), 83-101.

Belger, A., Puce, A., Krystal, J. H., Gore, J. C., Goldman-Rakic, P., & McCarthy, G. (1998). Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. *Human brain mapping, 6*(1), 14-32.

Benamer, H. T., Oertel, W. H., Patterson, J., Hadley, D. M., Pogarell, O., Hoffken, H., Gerstner, A., & Grosset, D. G. (2003). Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. *Movement Disorders, 18*(9), 977-984.

Bennett, K. M., Waterman, C., Scarpa, M., & Castiello U. (1995). Covert visuospatial attentional mechanisms in Parkinson's disease. *Brain, 118* (1), 153-166.

Benton, A. L., Varney, N. R., & Hamsher, K. S. (1978). Visuospatial judgment. *Archives of Neurology*, *35*, 364–367.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *Journal of the International Neuropsychological Society, 2,* 134-140.

Berger, A., & Henik, A. (2000). The endogenous modulation of IOR is nasal-temporal asymmetric. *Journal of Cognitive Neuroscience, 12*(3), 421-428.

Bergman, H., & Deuschl, G. (2002). Pathophysiology of Parkinson's disease: From clinical neurology to basic neuroscience and back. *Movement Disorders, 17,* s28-s40.

Bichot, N. P., Schall, J. D., & Thompson, K. G. (1996). Visual feature selectivity in frontal eye fields induced by experience in mature macaques. *Nature, 381*(6584), 697-699.

Biousse, V., Skibell, B. C., Watts, R. L., Loupe, D. N., Drews-Botsch, C., & Newman, N. J. (2004). Ophthalmologic features of Parkinson's disease. *Neurology, 62*(2), 177-180.

Blanchet, S., Marie, R. M., Dauvillier, F., Landeau, B., Benali, K., Eustache, F., & Chavoix, C. (2000). Cognitive processes involved in delayed non-matching-to-sample performance in Parkinson's disease. *European Journal of Neurology, 7*(5), 473-483.

Bleckley, M. K., Durso, F. T., Crutchfield, J. M., Engle, R. W., & Khanna, M. M. (2003). Individual differences in working memory capacity predict visual attention allocation. *Psychonomic Bulletin Review, 10*(4), 884-889.

Blonder, L. X., Gur, R. E., Gur, R. C., Saykin, A. J., & Hurtig, H. I. (1989). Neuropsychological functioning in hemiparkinsonism. *Brain and Cognition, 9*(2), 244-257.

Bodis-Wollner, I. (1990). Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. *Trends in Neurosciences, 13*(7), 296-302.

Bodis-Wollner, I., Marx, M. S., Mitra, S., Bobak, P., Mylin, L., & Yahr, M. (1987). Visual dysfunction in Parkinson's disease. Loss of spatiotemporal contrast sensitivity. *Brain, 110,* 1675-1698.

Bohnen, N. I., Minoshima, S., Giordani, B., Frey, K. A., Kuhl, D. E. (1999). Motor correlates of occipital glucose hypometabolism in Parkinson's disease without dementia. *Neurology, 52*(3), 541-546.

Boller, F., Passafiume, D., Keefe, N. C., Rogers, K., Morrow, L., & Kim, Y. (1984). Visuospatial impairment in Parkinson's disease. Role of perceptual and motor factors. *Archives of Neurology, 41*(5), 485-490.

Bondi, M. W., & Kaszniak, A. W. (1991). Implicit and explicit memory in Alzheimer's disease and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 13*(2), 339-358.

Bondi, M. W., Kaszniak, A. W., Bayles, K. A., & Vance, K. T. (1993). Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. *Neuropsychology, 7*(1), 89-102.

Bowen, F. P., Kamienny, R. S., Burns, M. M., & Yahr, M. D. (1975). Parkinsonism: effects of levodopa treatment on concept formation. *Neurology, 25,* 701-704.

Bradley, V. A., Welch, J. L., & Dick, D. J. (1989). Visuospatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 1228-1235.

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Research, 318*(1), 121-134.

Briand, K. A., Hening, W., Poizner, H., & Sereno, A. B. (2001). Automatic orienting of visuospatial attention in Parkinson's disease. *Neuropsychologia, 39,* 1240-1249.

Briand, K. A., Strallow, Hening, Poizner, & Sereno (1999). Control of voluntary and reflexive saccades in Parkinson's disease. *Experimental Brain Research, 129,* 38-48.

Brown, G. G., Brown, S. J., Christenson, G., Williams, R. E., Kindermann, S. S., Loftis, C., Olsen, R., Siple, P., Shults, C., & Gorell, J. M. (2002). Effects of task structure on category priming in patients with Parkinson's disease and in healthy individuals. *Journal of Clinical and Experimental Neuropsychology, 24*(3), 356-69.

Brown, R. G., & Marsden, C. D. (1988). Internal versus external cues and the control of attention in Parkinson's disease. *Brain, 111*(2), 323-45

Brown, R. G., & Marsden CD. (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain,114,* 215-31.

Brucke, T., Asenbaum, S., Pirker, W., Djamshidian, S., Wenger, S., Wober, C., Muller, C., & Podreka, I. (1997). Measurement of the dopaminergic degeneration in Parkinson's disease with [123I] beta-CIT and SPECT. Correlation with clinical findings and comparison with multiple system atrophy and progressive supranuclear palsy. *Journal of Neural Transmission, 50,* 9-24.

Bublak, P., Muller, U., Gron, G., Reuter, M., & von Cramon, D. Y. (2002). Manipulation of working memory information is impaired in Parkinson's disease and related to working memory capacity. *Neuropsychology, 16*(4), 577-590.

Bulens, C., Meerwaldt, J. D., & Van der Wildt, G. J. (1988). Effect of stimulus orientation on contrast sensitivity in Parkinson's disease. *Neurology, 38*(1), 76-81.

Burgess, G. C., Braver, T. S., & Gray, J. R. (2006). Exactly how are fluid intelligence, working memory, and executive function related? Cognitive neuroscience approaches to investigating the mechanisms of fluid cognition. *The Behavioral and Brain Sciences, 29*(2), 128-129.

Butters, N., Heindel, W. C., & Salmon, D. P. (1990). Dissociation of implicit memory in dementia: Neurological implications. *Bulletin of the Psychonomic Society, 28*(4), 359-366.

Caramazza, A., & Hillis, A. E. (1990). Spatial representation of words in the brain implied by studies of a unilateral neglect patient. *Nature, 346*(6281), 267-269.

Canavan, A. G., Passingham, R. E., Marsden, C. D., Quinn, N., Wyke, M., & Polkey, C. E. (1989). The performance on learning tasks of patients in the early stages of Parkinson's disease. *Neuropsychologia, 27*(2), 141-56.

Castiello, U., Bonfiglioli, C., & Peppard, R. F. (2000). Dopaminergic effects on the implicit processing of distractor objects in Parkinson's disease. *Experimental Brain Research, 135*(2), 251-258.

Cheesman, A. L., Barker, R. A., Lewis, S. J., Robbins, T. W., Owen, A. M., & Brooks, D. J. (2005). Lateralization of striatal function: evidence from 18F-dopa PET in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*(9), 1204-1210.

Chudasama, Y., & Robbins, T. W. (2006). Functions of frontostriatal systems in cognition: Comparative neuropsychopharamacological studies in rats, monkeys, and humans. *Biological Psychology, 73*(1), 19-38.

Clark, C. R., Geffen, G. M., & Geffen, L. B. (1989). Catecholamines and the covert orientation of attention in humans. *Neuropsychologia, 27*(2), 131-139.

Clohesy, A. B., Posner, M. I., Rothbart, M. K., & Vecera, S. P. (1991). The development of inhibition of return in early infancy. *Journal of Cognitive Neuroscience, 6,* 345-350.

Cohen, S. M. (1972). Electrical stimulation of cortical caudate pairs during delayed successive visual discrimination in monkeys. *Acta Neurobiological Experiments, 32,* 211-233.

Collins, A., & Loftus, E. (1975). A spreading-activation theory of semantic processing. *Psychological Review, 82,* 407-428.

Coltheart, M. (1980). The persistences of vision. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 290*(1038), 57-69.

Constantinidis, C., & Procyk, E. (2004). The primate working memory networks. *Cognitive, Affective, and Behavioral Neuroscience, 4*(4), 444–465.

Conway, A. R., Tuholski, S. W., Shisler, R. J., Engle, R. W. (1999). The effect of memory load on negative priming: an individual differences investigation. *Memory and Cognition, 27*(6), 1042-1050.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex, 11*(12), 1136-1143.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia, 41,* 1431-1441.

Cools, A. R., van den Bercken, J. H., Horstink, M.W., van Spaendonck, K. P., Berger, H. J. (1984). Cognitive and motor shifting aptitude disorder in Parkinson's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 47*(5), 443-453.

Cooper, J. A., Sagar, H. J., Doherty, S. M., Jordan, N., Tidswell, P., & Sullivan, E. V. (1992). Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain, 115,* 1701-1725.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., Sullivan, E. V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain, 114*(5), 2095-2122.

Cooper, J. A., Sagar, H. J., & Sullivan, E. V. (1993). Short-term memory and temporal ordering in early Parkinson's disease: effects of disease chronicity and medication. *Neuropsychologia, 31*(9), 933-49.

Copland, D. A., Chenery, H. J., & Murdoch, B. E. (2000). Understanding ambiguous words in biased sentences: Evidence of transient contextual effects in

individuals with nonthalamic subcortical lesions and Parkinson's disease. *Cortex, 36,* 601-622.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1991). Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. *Journal of Neuroscience, 11*(8), 2383-2402.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201-215.

Costa, A., Peppe, A., Dell'Agnello, G., Carlesimo, G. A., Murri, L., Bonuccelli, U., & Caltagirone, C. (2003). Dopaminergic modulation of visual-spatial working memory in Parkinson's disease. *Dementia and Geriatric Cognitive Disorders, 15,* 55-66.

Courtney, S. M., Petit, L., Haxby, J. V., & Ungerleider, L. G. (1998). The role of prefrontal cortex in working memory: examining the contents of consciousness. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 353*(1377), 1819-1828.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6*(1), 39-49.

Crawford, T., Henderson, L., & Kennard, C. (1989). Abnormalities of nonvisually-guided eye movements in Parkinson's disease. *Brain, 112,* 1537-1586.

Cronin-Golomb, A., Corkin, S., & Growdon, J. H. (1994). Impaired problem solving in Parkinson's disease: impact of a set-shifting deficit. *Neuropsychologia, 32*(5), 579-593.

Crucian, G. P., Barrett, A. M., Burks, D. W., Riestra, A. R., Roth, H. L., & Schwartz, R. L. (2003). Mental object rotation in Parkinson's disease. *Journal of the International Neuropsychological Society, 9*(7), 1078-1087.

Cummings, J. L. (1988). The dementias of Parkinson's disease: prevalence, characteristics, neurobiology, and comparison with dementia of the Alzheimer type. *European Neurology, 28,* 15-23.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology, 50*(8), 873-880.

Cummings J. L., & Benson, D. F. (1984). Subcortical dementia. Review of an emerging concept. *Archives of Neurology, 41*(8), 874-879.

Cummings J. L., & Benson, D. F. (1992). *Dementia: a clinical approach.* Boston: Butterworth-Heinemann.

Dalrymple-Alford, J. C., Kalders, A. S., Jones, R. D., & Watson, R. W. (1994). A central executive deficit in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*(3), 360-367.

Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior, 19,* 450-466.

Danzinger, S., Fendrich, R., & Rafal, R. D. (1997). Inhibitory tagging of locations in the blind field of hemianopic patients. *Consciousness and Cognition, 6,* 291-307.

Davidsdottir, S., Cronin-Golomb, A., & Lee, A. (2005). Visual and spatial symptoms in Parkinson's disease. *Vision research, 45*(10), 1285-1296.

DeLancy Horne, D. J. (1971). Performance on delayed response tasks by patients with Parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry, 34*, 192-194.

Delis, D., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function System manual.* San Antonio, Texas: The Psychological Corporation.

Delis, D., Kaplan, E., Kramer, J., & Ober, B. (2000). *California Verbal Learning Test-II.* San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *California Verbal Learning Test: Adult version manual*. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Squire, L. R., Bihrle, A., & Massman, P. (1992). Componential analysis of problem-solving ability: performance of patients with frontal lobe damage and amnesic patients on a new sorting test. *Neuropsychologia, 30*(8), 683-697.

Della Sala, S., Di Lorenzo, G., Giordano, A., & Spinnler, H. Is there a specific visuo-spatial impairment in Parkinsonians? *Journal of Neurology, Neurosurgery, and Psychiatry, 49*(11), 1258-1265.

Den Hartog Jager, W. A., & Bethlem, J. (1960). The distribution of Lewy bodies in the central and autonomic nervous systems in idiopathic paralysis agitans. *Journal of Neurology, Neurosurgery, and Psychiatry, 23,* 283-290.

Desimone, R., Schein, S. J., Moran, J., & Ungerleider, L. G. (1985). Contour, color and shape analysis beyond the striate cortex. *Vision Research, 25*(3), 441-452.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research, 133*(1), 3-11.

Diederich, N. J., Goetz, C. G., Raman, R., Pappert, E. J., Leurgans, S., & Piery, V. (1998). Poor visual discrimination and visual hallucinations in Parkinson's disease. *Clinical Neuropharmacology, 21*(5), 289-95.

Dimitrov, M., Grafman, J., Soares, A. H., & Clark, K. (1999). Concept formation and concept shifting in frontal lesion and Parkinson's disease patients assessed with the California Card Sorting Test. *Neuropsychology, 13*(1), 135-143.

Direnfeld, L. K., Albert, M. L., Volicer, L., Langlais, P. J., Marquis, J., & Kaplan, E. (1984). Parkinson's disease. The possible relationship of laterality to dementia and neurochemical findings. *Archives or Neurology, 41*(9), 935-941.

Divac, I., Rosvold, H. E., & Szwarcbart, M. K. (1967). Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative Physiology and Psychology, 63,* 184-190.

Dodd, M. D., & Pratt, J. (in press). Rapid onset and long-term inhibition of return in the multiple cuing paradigm. *Psychological Research.*

Dorris, M. C., Klein, R. M., Everling, S., & Munoz, D. P. (2002). Contribution of the primate superior colliculus to inhibition of return. *Journal of Cognitive Neuroscience, 14*(8), 1256-1263.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins T. W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia, 27*(11-12), 1329-43.

Driver, J., Baylis, G. C., Goodrich, S. J., & Rafal, R. D. (1994). Axis-based neglect of visual shapes. *Neuropsychologia, 32*(11), 1353-1365.

Driver, J., & Halligan, P. W. (1991). Can visual neglect operate in object-centered coordinates? An affirmative single-case study. *Cognitive Neuropsychology, 8,* 475-496.

Duke, L. M., & Kaszniak, A. W. (2000). Executive control functions in degenerative dementias: a comparative review. *Neuropsychological Review, 10*(2), 75-99.

Duncan, J. (1984). Selective attention and the organization of visual information. *Journal of Experimental Psychology, General, 113*(4), 501-517.

Egly, R., Driver, J., & Rafal, R. D. (1994). Shifting visual attention between objects and locations: Evidence from normal and parietal lesion subjects. *Journal of Experimental Psychology, General, 123*(2), 161-177.

Ehmann, T. S., Beninger, R. J., Gawal, M. J., & Riopelle, R. J. (1990). Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects. *Journal of Geriatric Psychiatry and Neurology, 3*(1), 3-9.

el-Awar, M., Becker, J. T., Hammond, K. M., Nebes, R. D., Boller, F. (1987). Learning deficit in Parkinson's disease. Comparison with Alzheimer's disease and normal aging. *Archives of Neurology, 44*(2),180-184.

Elbaz, A., Bower, J.H., Maraganore, D.M., McDonnell, S.K., Peterson, B.J., Ahlskog, J.E., Schaid, D.J., & Rocca, W.A. (2002). Risk tables for parkinsonism and Parkinson's disease. *Journal of Clinical Epidemiology, 55*(1), 25-31.

Emre, M. (2003). Dementia associated with Parkinson's disease. *Lancet Neurology, 2*(4), 229-237.

Engle, R. W. (1996). Working memory and retrieval: An inhibition – resource approach. In J. T. E. Richardson, R. W. Engle, L. Hasher, R. H. Logie, E. R. Stolzfus, & R. T. Zacks (Eds.), *Working memory and human cognition* (pp. 89-110). New York: Oxford University Press.

Engle, R. W., Kane, M. J., Tuholski, S. W. (1999). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 102-134). New York: Cambridge University Press.

Factor, S. A., Molho, E. S., Podskalny, G. D., Brown, D. (1995). Parkinson's disease: drug-induced psychiatric states. *Advances in Neurology, 65,* 115-138.

Faglioni, P., Saetti, M. C., & Botti, C. (2000). Verbal learning strategies in Parkinson's disease. *Neuropsychology, 14*(3), 456-470.

Fahn, S. (2003). Descripton of Parkinson's disease as a clinical syndrome. *Annals of the New York Academy of Sciences, 991,* 1-14.

Fahn, S., Elton, R. L., & the UPDRS Development Committee (1987). Unified Parkinson's Disease Rating Scale. In S. Fahn, C. D. Marsden, D. Calne, & M.

Goldstein (Eds.), *Recent developments in Parkinson's disease,* (Vol. 2, pp.153-163). Florham Park, N.J.: Macmillan Healthcare Information.

Fahn, S., Libsch, L. R., & Cutler, R. W. (1971). Monoamines in the human neostriatum: Topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea, and tremor. *Journal of Neurological Sciences, 14*(4), 427-455.

Fama, R., & Sullivan, E. V. (2002). Motor sequencing in Parkinson's disease: relationship to executive function and motor rigidity. *Cortex, 38*(5), 753-67

Fama, R., Sullivan, E. V., Shear, P. K., Stein, M., Yesavage, J. A., Tinklenberg, J. R., & Pfefferbaum, A. (2000). Extent, pattern, and correlates of remote memory impairment in Alzheimer's disease and Parkinson's disease. *Neuropsychology, 14*(2), 265-276.

Farah, M. J., Hammond, K. M., Levine, D. N., & Calvanio, R. (1988). Visual and spatial mental imagery: dissociable systems of representation. *Cognitive Psychology, 20*(4), 439-462.

Faust, M. E., & Balota, D. A. (1997). Inhibition of return and visuospatial attention in healthy older adults and individuals with dementia of the alzheimer type. *Neuropsychology, 11*(1), 13-29.

Fecteau, J. H., Bell, A. H., & Munoz, D. P. (2004). Neural correlates of the automatic and goal-driven biases in orienting spatial attention. *Journal of Neurophysiology, 92*(3), 1728-1737.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex, 1*(1), 1-47.

Fielding, J., Georgiou-Karistianis, N., Bradshaw, J., Millist, L., Churchyard, A., & White, O. (2006). Accelerated time-course of inhibition of return in Huntington's disease. *Behavioural Brain Research, 166,* 211-219.

Filoteo, J. V., Delis, D. C., Demadura, T. L., & Salmon, D. P. (1994). Abnormally rapid disengagement of covert attention to global and local stimulus levels may underlie the visuoperceptual impairment in parkinson's patients. *Neuropsychology, 8*(2), 210-217.

Filoteo, J. V., Delis, D. C., Salmon, D. P., Demadura, T. L., Roman, M. J., & Shults, C. W. (1997). An examination of the nature of attentional deficits in patients with Parkinson's disease: Evidence from a spatial orienting task. *Journal of the International Neuropsychological Society, 3*, 337-347.

Filoteo, J. V., Friedrich, F. J., Rilling, L. M., Davis, J. D., Stricker, J. L., & Prenovitz, M. (2003). Semantic and cross-case identity priming in patients with Parkinson' disease. *Journal of Clinical and Experimental Neuropsychology, 25*(4), 441-456.

Filoteo, J. V. & Maddox, T. W. (1999). Quantitative modeling of visual attention processes in patients with Parkinson's disease: Effects of stimulus integrality on selective attention and dimensional integration. *Neuropsychology, 13*, 206-222.

Filoteo, J. V., Maddox, W. T., Ing, A. D., Zizak, V., & Song, D. D. (2005). The impact of irrelevant dimensional variation on rule-based category learning in patients with Parkinson's disease. *Journal of the International Neuropsycholgoical Society, 11*(5), 503-513.

Filoteo, J.V., Rilling, L.M., & Strayer, D.L. (2002). Negative priming in patients with Parkinson's disease: Evidence for a role of the striatum in inhibitory attentional processes. *Neuropsychology, 16*(2), 230-241.

Fimm, B., Zahn, R., Mull, M., Kemeny, S., Buchwald, F., Block, F., & Schwarz, M. (2001). Asymmetries of visual attention after circumscribed subcortical vascular lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 71*(5), 652-657.

Finton, M. J., Lucas, J. A., Graff-Radford, N. R., & Uitti, R. J. (1998). Analysis of visuospatial errors in patients with Alzheimer's disease or Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 20*(2), 186-193.

Flowers, K. A. & Robertson, C. (1985). The effect of Parkinson's disease on the ability to maintain a mental set. *Journal of Neurology, Neurosurgery, and Psychiatry, 48*(6), 517-529.

Flowers, K. A., & Robertson, C. (1995). Perceptual abnormalities in Parkinson's disease: top-down or bottom-up processes? *Perception, 24,* 1201-1221.

Forno, L. S. (1996). Neuropathology of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology, 55*(3), 259-272.

Fournet N, Moreaud O, Roulin JL, Naegele B, & Pellat J. (2000). Working memory functioning in medicated Parkinson's disease patients and the effect of withdrawal of dopaminergic medication. *Neuropsychology, 14*(2), 247-253.

Freedman, M., & Oscar-Berman, M. (1986). Selective delayed response deficits in Parkinson's and Alzheimer's disease. *Archives of Neurology, 43*(9), 886-890.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology, 61*(2), 331-349.

Funahashi, S., Chafee, M. V., & Goldman-Rakic, P. S. (1993). Prefronal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature, 365,* 753-756.

Fuster, J. M. (1973). Unit activity in prefrontal cortex during delayed-response performance: Neuronal correlates of transient memory. *Journal of Neurophysiology, 36*(1), 61-78.

Fuster, J. M. (1998). Distributed memory for both short and long term. *Neurobiology of Learning and Memory*, *70*(1-2), 268-274.

Gabrieli, J. D. (1996). Memory systems analyses of mnemonic disorders in aging and age-related diseases. *Proceedings of the Natlional Academy of Science, 93*(24), 13534-13540.

Gathercole, S. E., & Baddeley, A. D. (1989). Evaluation of the role of phonological STM in the development of vocabulary in children: a longitudinal study. *Journal of Memory and Language, 28,* 200-213.

Gauntlett-Gilbert, J., Roberts, R. C., & Brown, V. J. (1999). Mechanisms underlying attentional set-shifting in Parkinson's disease. *Neuropsychologia, 37,* 605-616.

Gibb, W. R. G. (1989). Dementia and Parkinson's disease. *British Journal of Psychiatry, 154,* 596-614.

Gilbert, B., Belleville, S., Bherer, L., & Chouinard, S. (2005). Study of verbal working memory in patients with Parkinson's disease. *Neuropsychology, 19*(1), 106-114.

Goldberg, T. E., Berman, K. F., Randolph, C., Gold, J. M., & Weinberger, D. R. (1996). Isolating the mnemonic component in spatial delayed response: A controlled PET [15]o-labeled water regional cerebral blood flow study in normal humans. *Neuroimage, 3,* 69-78.

Goldenberg, G., Wimmer, A., Auff, E., & Schnaberth, G. (1986). Impairment of motor planning in patients with Parkinson's disease: Evidence from ideomotor apraxia testing. *Journal of Neurology, Neurosurgery, and Psychiatry, 49*(11), 1266-1272.

Goldman, W. P., Baty, J. D., Buckles, V. D., Sahrmann, S., & Morris, J. C. (1998). Cognitive and motor functioning in Parkinson disease: subjects with and without questionable dementia. *Archives Neurology, 55*(5), 674-680.

Goldman-Rakic, P. S. (1987). Circuitry of the prefrontal cortex and the regulation of behavior by representational memory. In F. Plum & V. Mountcastle (Eds.), *Handbook of Physiology, Sec. 1. The Nervous System,* (Vol. 5), 373-417.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). 'Frontal cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain, 111*, 299-321.

Gottlieb, J. P., Kusunoki, M., & Goldberg, M. E. (1998). The representation of visual salience in monkey parietal cortex. *Nature, 391*(6666), 481-484.

Graceffa, A. M., Carlesimo, G. A., Peppe, A., & Caltagirone, C. (1999). Verbal working memory deficit in Parkinson's disease subjects. *European Journal of Neurology, 42*(2), 90-94.

Grafton, S. T. (2004). Contributions of functional imaging to understanding parkinsonian symptoms. *Current Opinions in Neurobiology, 14*(6), 715-719.

Graybiel, A. M. (2000). The basal ganglia. *Current Biology, 10*(14), R509-11.

Grober, E., & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology, 13*(6), 933-949.

Grossman, M. (1999). Sentence processing in Parkinson's disease. *Brain and Cognition, 40*(2), 387-413.

Gupta, P., & Cohen, N. J. (2002). Theoretical and computational analysis of skill learning, repetition priming, and procedural memory. *Psychological Review, 109*(2), 401-448.

Haaland, K. Y., Harrington, D. L., O'Brien, S., & Hermanowicz, N. (1997). Cognitive-motor learning in Parkinson's disease. *Neuropsychology, 11*(2), 180-186.

Harnois, C., & Di Paolo, T. (1990). Decreased dopamine in the retinas of patients with Parkinson's disease. *Investigative Ophthalmology and Vision Science, 31*(11), 2473-2475.

Hayes, A. E., Davidson, M. C., Keele, S. W., Rafal, R. D. (1998). Toward a functional analysis of the basal ganglia. *Journal of Cognitive Neuroscience, 10*(2), 178-198.

Harrington, D. L., Haaland, K. Y., Yeo, R. A., & Marder, E. (1990). Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology, 12*(2), 323-339.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtis, G. (1993). *Wisconsin Card Sorting Test (WCST) Manual Revised and Expanded.* Odessa, FL: Psychological Assessment Resources.

Hecker, R., & Mapperson, B. (1997). Dissociation of visual and spatial processing in working memory. *Neuropsychologia, 35*(5), 599-603.

Heindel, W. C., Salmon, D. P., Shults, C. W., Walicke, P. A., & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *Journal of Neuroscience, 9*(2), 582-587.

Helkala, E. L., Laulumaa, V., Soininen, H., & Riekkinen, P. J. (1989). Different error pattern of episodic and semantic memory in Alzheimer's disease and Parkinson's disease with dementia. *Neuropsychologia, 27*(10), 1241-1248.

Hely, M. A., Morris, J. G., Reid, W. G., O'Sullivan, D. J., Williamson, P. M., Broe, G.A, & Adena, M. A. (1995). Age at onset: the major determinant of outcome in Parkinson's disease. *Acta Neurology Scandinavia, 92*(6), 455-463.

Henik, A., Rafal, R. D., & Rhodes, D. (1994). Endogenously generated and visually guided saccades after lesions of the human frontal eye fields. *Journal of Cognitive Neuroscience, 6*(4), 400-412.

Henik, A., Singh, J., Beckley, D. J., & Rafal, R. D. (1993). Disinhibition of automatic word reading in Parkinson's disease. *Cortex, 29*(4), 589-599.

Henry, J. D., & Crawford, J. R. (2004). Verbal fluency deficits in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society, 10*(4), 608-622.

Higginson, C. I., King, D. S., Levine, D., Wheelock, V. L., Khamphay, N. O., & Sigvardt, K. A. (2003). The relationship between executive function and verbal memory in Parkinson's disease. *Brain and Cognition, 52*(3), 343-352

Higginson, C. I., Wheelock, V. L., Carroll, K. E., Sigvardt, K. A. (2005). Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis. *Journal of Clinical and Experimental Neuropsychology, 27*(4), 516-528.

Hikosaka, O., Sakamoto, M., & Miyashita, N. (1993). Effects of caudate nucleus stimulation on substantia nigra cell activity in monkey. *Experimental Brain Research, 95,* 457-472.

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews, 80*(3), 953-978.

Hikosaka, O., & Wurtz, R. H. (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulate, IV. Relation of substantia nigra to superior colliculus. *Journal of Neurophysiology, 49*(5), 1285-1301.

Hines, T. M., & Volpe, B. T. (1985). Semantic activation in patients with Parkinson's disease. *Cortex, 29,* 589-599.

Hirsch, O., Lehmann, W., Corth, M., Röhrle, B., Schmidt, S., & Schipper, H. I. (2003). Mental imagery, motor imagery and mental rotation in patients with Parkinson's disease/Visuelle vorstellungsfähigkeit, bewegungsvorstellung und mentales rotieren bei morbus Parkinson. *Zeitschrift für Neuropsychologie, 14*(2), 67-80.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology, 17*, 427-442.

Hornykiewicz, O. (1973). Dopamine in the basal ganglia. Its role and therapeutic implications (including the clinical use of L-DOPA). *Brain Medicine Bulletin, 29*(2), 172-178.

Hsieh, S., & Lee, C. Y. (1999). Source memory in Parkinson's disease. *Perceptual and Motor Skills, 89*(2), 355-367.

Hsieh, S., Lee, C. Y., Hwang, W. J., & Tsai, J. J. (1997). Object-based and location-based shifting of attention in Parkinson's disease. *Perceptual and Motor Skills, 85,* 1315-1325.

Hsieh, S., Lee, C. Y., & Tai, C. T. (1995). Set-shifting aptitude in Parkinson's disease: external versus internal cues. *Psychological Reports, 77*(1), 339-49

Huber, S. J., Freidenberg, D. L., Shuttleworth, E. C., Paulson, G. W., Christy, J. A. (1989). Neuropsychological impairments associated with severity of Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience, 1*(2), 154-8

Huberman, M., Moscovitch, M., & Freedman, M. (1994). Comparison of patients with Alzheimer's and Parkinson's disease on different explicit and implicit tests of memory. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 7*(3), 185-193.

Iani, C., Nicoletti, R., Rubichi, S., & Umilta, C. (2001). Shifting attention between objects. *Cognitive Brain Research, 11,* 157-164.

Iverson, S. D. (1979). Behavior after neostriatal lesions in animals. In I. Divac & R. G. E. Oberg (Eds.), *The Neostriatum* (pp. 192-210). Oxford: Pergamon.

Ivory, S. J., Knight, R. G., Longmore, B. E., & Caradoc-Davies, T. (1999). Verbal memory in non-demented patients with idiopathic Parkinson's disease. *Neuropsychologia, 37*(7), 817-28

Jackson, G. M., Jackson, S. R., Harrison, J., & Henderson, L. (1995). Serial reaction time learning and Parkinson's disease: Evidence for a procedural learning deficit. *Neuropsychologia, 33*(5), 577-593.

Jackson, G. R., & Owsley, C. (2003). Visual dysfunction, neurodegenerative diseases, and aging. *Neurology Clinics, 21*(3), 709-28.

Jankovic, J. & Kapadia, A. S. (2001). Functional decline in parkinson disease. *Archives of Neurology, 58*(10), 1611-1615.

Jellinger, K. A. (1999). Post mortem studies in Parkinson's disease – is it possible to detect areas for specific symptoms? *Journal of Neural Transmission Supplement, 56*, 1-29.

Jenner, P. & Marsden, C. D. (1988). Adaptive changes in brain dopamine function as a result of neuroleptic treatment. *Advances in Neurology, 49*, 417-431.

Johnson, A. M., Almeida, Q. J., Stough, C., Thompson, J. C., Singarayer, R., & Jog, M. S. (2004). Visual inspection time in Parkinson's disease: deficits in the early stages of cognitive processing. *Neuropsychologia, 42,* 577-583.

Jolicoeur, P., & Dell'Acqua, R. (1998). The demonstration of short-term consolidation. *Cognitive Psychology, 36*(2), 138-202.

Jonides, J. (1981). Voluntary versus automatic control over the mind's eye's movement. In J. B. Long & A. D. Baddeley (Eds.), *Attention and performance* (Vol. 9, pp. 187-203).

Jordan, H., & Tipper, S. P. (1998). Object-based inhibition of return in static displays. *Psychonomic Bulletin and Review, 5,* 504-509.

Jordan, H., & Tipper, S. P. (1999). Spread of inhibition across an object's surface. *British Journal of Psychology, 90,* 495-507.

Joseph, J. P., & Boussaoud, D. (1985). Role of the cat substantia nigra pars reticulata in eye and head movements. I. Neural activity. *Experimental Brain Research, 57*(2), 286-296.

Joyce, J. N. (1993). Differential response of striatal dopamine and muscarinic cholinergic receptor subtypes to the loss of dopamine. III. Results in Parkinson's disease cases. *Brain Research, 600*(1), 156-160.

Kane, M. J., Bleckley, M. K., Conway, A. R., & Engle, R. W. (2001). A controlled-attention view of working memory capacity. *Journal of Experimental Psychology, 130*(2), 169-183.

Karnath, H. O., Himmelbach, M., & Rorden, C. (2002). The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar. *Brain, 125*(2), 350-360.

Kaufman, M. J., & Madras, B. K. (1991). Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's-diseased striatum. *Synapse, 9*(1), 43-49.

Kelly, A. M., Hester, R., Murphy, K., Javitt, D. C., Foxe, J. J., & Garavan, H. (2004). Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. *European Journal of Neuroscience, 19*(11), 3105-1312.

Kemmerer, D. (1999). Impaired comprehension of raising-to-subject constructions in Parkinson's disease. *Brain and Language, 66,* 311-328.

Kensinger, E. A., Shearer, D. K., Locascio, J. J., Growdon, J. H., & Corkin, S. (2003). Working memory in mild Alzheimer's disease and early Parkinson's disease. *Neuropsychology, 17*(2), 230-239.

Kessels R. P., Postma, A., Kappelle, L. J., & de Haan, E. H. (2000). Spatial memory impairment in patients after tumour resection: evidence for a double dissociation. *Journal of Neurology, Neurosurgery, & Psychiatry, 69*(3), 389-391.

Ketcham, C. J., Hodgson, T. L., Kennard, C., & Stelmach, G. E. (2003). Memory-motor transformations are impaired in Parkinson's disease. *Experimental Brain Research, 149*(1), 30-39.

Kingstone, A., Klein, R., Morein-Zamir, S., Hunt, A., Fisk, J., & Maxner, C. (2002). Orienting attention in aging and Parkinson's disease: Distinguishing modes of control. *Journal of Clinical and Experimental Neuropsychology, 24*(7), 951-967.

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *New England Journal of Medicine, 318*(14), 876-880.

Klein, R. M. (2000). Inhibition of return. *Trends in Cognitive Sciences, 4*(4), 138-147.

Koenig, O., Thomas-Anterion, C., & Laurent, B. (1999). Procedural learning in Parkinson's disease: intact and impaired cognitive components. *Neuropsychologia, 37*(10), 103-109.

Kraus, C. D. (2000). Attentional processing in parkinson's disease: Hyperkinetic and akinetic type. *Dissertation Abstracts International: Section B: The Sciences & Engineering, 61* (3-B), 1664.

Kuzis, G., Sabe, L., Tiberti, C., Merello, M., Leiguarda, R., Starkstein, S. E. (1999). Explicit and implicit learning in patients with Alzheimer disease and Parkinson's disease with dementia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 12*(4), 265-269.

Kyllonen, P. C., & Christal, R. E. (1990). Reasoning ability is (little more than) working memory capacity. *Intelligence, 14,* 389-433.

Laatu, S., Revonsuo, A., Pihko, L., Portin, R., & Rinne, J. O. (2004). Visual object recognition deficits in early Parkinson's disease. *Parkinsonism and Related Disorders, 10,* 227-233.

Lamar, M., Swenson, R., Kaplan, E., & Libon, D. J. (2004). Characterizing alterations in executive functioning across distinct subtypes of cortical and subcortical dementia. *The Clinical Neuropsychologist, 18*(1), 22-31.

Lange, K. W., Paul, G. M., Naumann, M., Gsell, W. (1995). Dopaminergic effects on cognitive performance in patients with Parkinson's disease. *Journal of Neural Transmission, 46,* 423-432.

Lange K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., & Paul, G. M. (1992). L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology, 107*(2-3), 294-404.

Langheinrich, T., Tebartz van Elst, L., Lagreze, W. A., Bach, M., Lucking, C. H., & Greenlee, M. W. (2000). Visual contrast response functions in Parkinson's disease: evidence from electroretinograms, visually evoked potentials and psychophysics. *Clinical Neurophysiology, 111*(1), 66-74.

Le Bras, C., Pillon, B., Damier, P., & Dubois B (1999). At which steps of spatial working memory processing do striatofrontal circuits intervene in humans? *Neuropsychologia, 37*(1), 83-90.

Lee, A. C., Harris, J. P., & Calvert, J. E. (1998). Impairments of mental rotation in parkinson's disease. *Neuropsychologia, 36*(1), 109-114.

Lee, S. S., Wild, K., Hollnagel, C., & Grafman, J. (1999). Selective visual attention in patients with frontal lobe lesions or Parkinson's disease. *Neuropsychologia, 37,* 595-604.

Leek, E. C., Reppa, I., & Tipper, S. P. (2003). Inhibition of return for objects and locations in static displays. *Perception and Psychophysics, 65*(3), 388-395.

Lees, A. J., & Smith, E. (1983). Cognitive deficits in the early stages of parkinson's disease. *Brain, 106,* 257-270.

Le Heron, C. J., MacAskill, M. R., & Anderson, T. J. (2005). Memory-guided saccades in Parkinson's disease: long delays can improve performance. *Experimental Brain Research, 161*(3), 293-298.

Leplow, B., Dierks, C., Herrmann, P., Pieper, N., Annecke, R., & Ulm, G. (1997). Remote memory in Parkinson's disease and senile dementia. *Neuropsychologia, 35*(4), 547-57.

Lepsien, J., & Pollmann, S. (2002). Covert reorienting and inhibition of return: an event-related fMRI study. *Journal of Cognitive Neuroscience, 14*(2), 127-144.

Levin, B. E., & Katzen, H. L. (1995). Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. *Advances in Neurology, 65,* 85-95.

Levin, B. E., Llabre, M. M., Reisman, S., Weiner, W. J., Sanchez-Ramos, J., Singer, C., & Brown, M. C. (1991). Visuospatial impairment in Parkinson's disease. *Neurology, 41,* 365-369.

Levin, B. E., Llabre, M. M., & Weiner, W. J. (1989). Cognitive impairments associated with early Parkinson's disease. *Neurology, 39,* 557-561.

Levine, D. N., Warach, J., & Farah, M. (1985). Two visual systems in mental imagery: dissociation of "what" and "where" in imagery disorders due to bilateral posterior cerebral lesions. *Neurology, 35*(7), 1010-1018.

Levy, R., Friedman, H.R., Davachi, L., & Goldman-Rakic, P.S. (1997). Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. *Journal of Neuroscience, 17,* 3870-3882.

Levy, R., & Goldman-Rakic, P. S. (1999). Association of storage and processing functions in the dorsolateral prefrontal cortex of the nonhuman primate. *Journal of Neuroscience, 19*(12), 5149-5158.

Lewis, S. J., Cools, R., Robbins, T. W., Dove, A., Barker, R. A., & Owen, A. M. (2003). Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. *Neuropsychologia, 41,* 645-654.

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontalstriatal neural circuitry. *Journal of Neuroscience, 23,* 6351-6356.

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2004). Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. *The European Journal of Neuroscience, 19*(3), 755-760.

Lewis, S. J., Slabosz, A., Robbins, T. W., Barker, R. A, & Owen, A. M. (2005). Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia, 43*(6), 823-32.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Lichter, D. G. (2001). Movement disorders and frontal-subcortical circuits. In D. G. Lichter & J. L. Cummings (Eds.), *Frontal-subcortical circuits in psychiatric and neurological disorders* (pp. 260-313). New York, NY: The Guilford Press.

Lichter, D. G., & Cummings, J. L. (2001). Introduction and Overview. In D. G. Lichter & J. L. Cummings (Eds.), *Frontal-subcortical circuits in psychiatric and neurological disorders* (pp. 1-43). New York, NY: The Guilford Press.

Lieberman, P., Kako, E., Friedman, J., Tajchman, G., Feldman, L. S., & Jiminez, E. B. (1992). Speech production, syntax comprehension, and cognitive deficits in Parkinson's disease. *Brain and Language, 43,* 169-189.

Livingstone, M., & Hubel, D. (1988). Segregation of form, color, movement, and depth: Anatomy, physiology, and perception. *Science, 240*(4853), 740-749.

Lloyd, A. J. (1999). Comprehension of prosody in Parkinson's disease. *Cortex, 35,* 389-402.

Locascio, J. J., Corkin, S., & Growdon, J. H. (2003). Relation between clinical characteristics of Parkinson's disease and cognitive decline. *Journal of Clinical & Experimental Neuropsychology, 25*(1), 94-109.

Logie, R. H., & Marchetti, C. (1991). Visuo-spatial working memory: Visual, spatial, or central executive? In R. Logie and M. Denis (Eds.), *Mental images in human cognition* (pp. 105-115). North Holland: Amsterdam.

Louis, E. D., Tang, M. X., Cote, L., Alfaro, B., Mejia, H., & Marder, K. (1999). Progression of parkinsonian signs in Parkinson's disease. *Archives of Neurology, 56*(3), 334-337.

Luria, A. R. (1966). *Higher cortical functions in man.* New York: Basic Books.

Maddox, W. T., Filoteo, J. V., Delis, D. C., & Salmon, D. P. (1996). Visual selective attention deficits in patients with Parkinson's disease: A quantitative model-based approach. *Neuropsychology, 10*(2), 197-218.

Mari-Beffa, P., Hayes, A. E., Machado, L., & Hindle, J. V. (2005). Lack of inhibition in Parkinson's disease: evidence from a lexical decision task. *Neuropsychologia, 43*(4), 638-646.

Marie, R. M., Barre, L., Dupuy, B., Viader, F., Defer, G., & Baron, J. C. (1999). Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neuroscience Letters, 260*(2), 77-80.

Martin, W. R., & Wieler, M. (2003).Treatment of Parkinson's disease. *Canadian Journal of Neurological Science, 30,* S27-33.

Massman, P. J., Delis, D. C., Butters, N., Levin, B. E, & Salmon, D. P. (1990). Are all subcortical dementias alike? verbal learning and memory in Parkinson's and Huntington's disease patients. *Journal of Clinical & Experimental Neuropsychology, 12*(5), 729-744.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellak & T. B. Karasu, (eds.) *Geriatric Psychiatry* (pp. 77-101). New York: Grune and Stratton.

Mayer, A. R., Seidenberg, M., Dorflinger, J. M., & Rao, S. M. (2004). An event-related fMRI study of exogenous orienting: supporting evidence for the cortical basis of inhibition of return? *Journal of Cognitive Neuroscience, 16*(7), 1262-1271.

Mayeux, R., Denaro, J., Hemenegildo, N., Marder, K., Tang, M. X., Cote, L. J., & Stern, Y. (1992). A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. *Archives of Neurology, 49*(5), 492-497.

Maylor, E. A. (1985). Facilitatory and inhibitory components of orienting in visual space. In M. I. Posner & O. S. M. Marin (Eds.), *Attention and performance* (Vol. 11, pp 189-204). Hillsdale, NJ: Erlbaum.

McAuliffe, J., Pratt, J., & O'Donnell, C. (2001). Examining location-based and object-based components of inhibition of return in static displays. *Perception and Psychophysics, 63*(6), 1072-1082.

McCarthy, G, Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G, Hyder, F, Goldman-Rakic, P, & Shulman RG. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Science, 91*(18), 8690-8694.

McDonald, C., Brown, G. G., & Gorell, J. M. (1996). Impaired set-shifting in Parkinson's disease: new evidence from a lexical decision task. *Journal of Clinical and Experimental Neuropsychology, 18*, 793-809.

McDonald, W. M., Richard, I. H., & DeLong, M. R. (2003). Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biological Psychiatry, 54*(3), 363-375.

McDowell, S. A., & Harris, J. (1997). Irrelevant peripheral visual stimuli impair manual reaction times in Parkinson's disease. *Vision Research, 37*(24), 3549-3558.

McPherson, S., & Cummings, J. L. (1996). Neuropsychological aspects of Parkinson's disease and parkinsonism. In I. Grant & K. Adams (Eds.), *Neuropsychological assessment of neuropsychiatric disorders, second edition* (pp. 288-311). Oxford: Oxford University Press.

Menza, M. A., & Mark, M. H. (1994). Parkinson's disease and depression: the relationship to disability and personality. *Journal of Neuropsychiatry Clinics and Neuroscience, 6*(2), 165-169.

Merrigan, W. H., & Maunsell, J. H. R. (1990). Macaque vision after magnocellular lateral geniculate lesions. *Visual Neuroscience, 5,* 347-352.

Middleton, F. A., & Strick, P. L. (2000). Basal ganglia output and cognition: Evidence from anatomical, behavioral, and clinical studies. *Brain and Cognition, 42,* 183-200.

Milner, B. (1963). Effects of different brain lesions on card sorting: the role of the frontal lobes. *Archives of Neurology, 9,* 90-100.

Miyake, A., Friedman, N. P., Rettinger, D. A., Shah, P., & Hegarty, M. (2001). How are visuospatial working memory, executive functioning, and spatial abilities related? A latent-variable analysis. *Journal of Experimental Psychology, 130*(4), 621-640.

Mollion, H., Ventre-Dominey, J., Dominey, P. F., & Broussolle, E. (2003). Dissociable effects of dopaminergic therapy on spatial versus non-spatial working memory in Parkinson's disease. *Neuropsychologia, 41,* 1442-1451.

Montse, A., Pere, V., Carme, J., Francesc, V., & Eduardo, T. (2001). Visuospatial deficits in Parkinson's disease assessed by judgment of line orientation test: error analyses and practice effects. *Journal of Clinical and Experimental Neuropsychology, 23*(5), 592-598.

Morris, R. G., Downes, J. J., Sahakian, B. J., Evenden, J. L., Heald, A., & Robbins, T. W. (1988). Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 51*(6), 757-66.

Mosimann, U. P., Mather, G., Wesnes, K. A., O'Brien, J. T., Burn, D. J., McKeith, I. G. (2004). Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology, 63*(11), 2091-2096.

Murray, L. L., & Lenz, L. P. (2001). Productive syntax abilities in Huntington's and Parkinson's disease. *Brain and Cognition, 46,* 213-219.

Neely, J. H. (1977). Semantic Priming and retrieval from lexical memory: Roles of inhibitionless spreading activation and limited-capacity attention. *Journal of Experimental Psychology: General, 106,* 226-254.

Neely, J. H. (1991). Semantic Priming effects in visual word recognition: A selective review of current findings and theories. In D. Besner & G. W. Humphreys (Eds.), *Basic processing in reading: Visual word recognition* (pp. 264-336). Hillsdale, NY: Erlbaum.

Neill, W. T. (1977). Inhibitory and facilitatory processes in selective attention. *Journal of Experimental Psychology: Human Perception & Performance, 3*(3), 444-450.

Newcombe, F., Ratcliff, G., & Damasio, H. (1987). Dissociable visual and spatial impairments following right posterior cerebral lesions: clinical, neuropsychological and anatomical evidence. *Neuropsychologia, 25*(1B), 149-161.

Niki, H., Sakai, M., & Kubota, K. (1972). Delayed alternation performance and unit activity of the caudate head and medial orbitofrontal gyrus in the monkey. *Brain Research, 38*(2), 343-353.

Nurmi, E., Ruottinen, H. M., Bergman, J., Haaparanta, M., Solin, O., Sonninen, P., & Rinne, J. O. (2001). Rate of progression in Parkinson's disease: a 6-[18F]fluoro-L-dopa PET study. *Movement Disorders*, *6*(4), 608-615.

Ogden, J. A., Growdon, J. H., & Corkin, S. (1990). Deficits on visuospatial tests involving forward planning in high-functioning parkinsonians. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 3*(2), 125-139.

Oh, S. H., & Kim, M. S. (2004). The role of spatial working memory in visual search efficiency. *Psychonomic Bulletin & Review, 11*(2), 275-281.

Orban, G. A., Dupont, P., Vogels, R., & De Bruyn, B. (1996). Task dependency of visual processing in the human visual system. *Behavioural Brain Research, 76*(1-2), 215-223.

O'Sullivan, E. P., Shaunak, L. H., Hawken, M., Crawford, T. J., Kennard, C. (1997). Abnormalities of predictive saccades in Parkinson's disease. *Neuroreport, 8,* 1209-1213.

Otsuka, M., Ichiya, Y., Kuwabara, Y., Hosokawa, S., Sasaki, M., Yoshida, T., Fukumura, T., Masuda, K., & Kato, M. (1996). Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms. *Journal of Neurological Science, 136*(1-2),169-73.

Owen, A. M. (1997). The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *European Journal of Neuroscience, 9*(7), 1329-1339.

Owen, A. M. (2004). Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist, 10*(6), 525-537.

Owen, A. M., Beksinska, M., James, M., Leigh, P. M., Summers, B. A., Marsden, C. D., Quinn, N. P., Sahakian, B. J., & Robbins, T. W. (1993). Visuo-spatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia, 31,* 627-644.

Owen, A. M., Downes, J. D., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28,* 1021-1034.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia, 35,* 519-532.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Lange, K.W., & Robbins TW. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 115*(6), 727-751.

Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1996). Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions, or amygdalo-hippocampectomy in man. *Brain, 119,* 1597-1615.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain, 116*(5), 1159-1175.

Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short term recognition memory and learning after temporal lobe excisions, frontal lobe excisions, or amygdalo-hippocampectomy in man. *Neuropsychologia, 33,* 1-24.

Palmer, B. W. & Heaton, R. K. (2000). Executive dysfunction in schizophrenia. In T. Sharma & P. D. Harvey (Eds.), *Cognition in schizophrenia.* Oxford: Oxford University Press.

Papadopoulos, G. C., & Parnavelas, J. G. (1990). Distribution and synaptic organization of dopaminergic axons in the lateral geniculate nucleus of the rat. *Journal of Comparative Neurology, 294*(3), 356-61.

Parent, A. & Hazrati, L. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortico loop. *Brain Research, Brain Research Reviews, 20,* 91-127.

Parkinson, D. (1989). Evidence for a dopaminergic innervation of cat primary visual cortex. *Neuroscience, 30*(1), 171-9.

Paulus, W., & Jellinger, K. (1991). The neuropathologic basis of different clinical subgroups of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology, 50*(6), 743-755.

Peppe, A., Stanzione, P., Pierelli, F., De Angelis, D., Pierantozzi, M., & Bernardi, G. (1995). Visual alterations in de novo Parkinson's disease: pattern electroretinogram latencies are more delayed and more reversible by levodopa than are visual evoked potentials. *Neurology, 45*(6), 1144-1148.

Perbal, S., Deweer, B., Pillon, B., Vidailhet, M., Dubois, B., & Pouthas, V. (2005). Effects of internal clock and memory disorders on duration reproductions and duration productions in patients with Parkinson's disease. *Brain and Cognition, 58*(1), 35-48.

Peterson, M. S., Kramer, A. F., Wang, R. F., Irwin, D. E., McCarley, J. S. (2001). Visual search has memory. *Psychological Science, 12*(4), 287-292.

Petrides, M. (1989). Frontal lobes and memory. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (pp. 601-614). Amsterdam, New York: Elsevier.

Petrides, M. (1994). Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (pp. 59-84). Amsterdam: Elsevier.

Pieri, V., Diederich, N. J., Raman, R., & Goetz, C. G. (2000). Decreased color discrimination and contrast sensitivity in Parkinson's disease. *Journal of Neurological Science, 172*(1), 7-11.

Piggott, M. A., Marshall, E. F., Thomas, N., Lloyd, S., Court, J. A., Jaros, E., Burn, D., Johnson, M., Perry, R. H., McKeith, I. G., Ballard, C., & Perry, E. K. (1999). Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. *Brain, 122*(8), 1449-1468.

Pillon, B., Deweer, B., Michon, A., & Malapani, C. (1994). Are explicit memory disorders of progressive supranuclear palsy related to damage to striatofrontal circuits? comparison with Alzheimer's, Parkinson's, and Huntington's diseases. *Neurology, 44*(7), 1264-1270.

Pillon, B., Deweer, B., Vidailhet, M., Bonnet, A. M., Hahn-Barma, V., & Dubois, B. (1998). Is impaired memory for spatial location in Parkinson's disease domain-specific or dependent on 'strategic' processes? *Neuropsychologia, 36*(1), 1-9.

Pillon, B., Dubois, B., Lhermitte, F., & Agid, Y. (1986). Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. *Neurology, 36,* 1179-1185.

Pinto, S., Ozsancak, C., Tripoliti, E., Thobois, S., Limousin-Dowsey, P., Auzou, P. (2004). Treatments for dysarthria in Parkinson's disease. *Lancet Neurology, 3*(9), 547-556.

Pirozzolo, F. J., Hansch, E. C., Mortimer, J. A., Webster, D. D., & Kuskowski, M. A. (1982). Dementia in Parkinson disease: a neuropsychological analysis. *Brain and Cognition, 1*(1), 71-83.

Pluck, G. C., & Brown, R. G. (2002). Apathy in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 73*(6), 636-642.

Poliakoff, E., O'Boyle, D. J., Moore, A. P., McGlone, F. P., Cody, F. W., & Spence, C. (2003). Orienting of attention and Parkinson's disease: tactile inhibition of return and response inhibition. *Brain, 126*(9), 2081-92.

Pollux, P. M., & Robertson, C. (2001). Voluntary and automatic visual spatial shifts of attention in Parkinson's disease: an analysis of costs and benefits. *Journal of Clinical and Experimental Neuropsychology, 23*(5), 662-670.

Posner, M. I., & Cohen, Y. (1984). Components of visual orienting. In H. Bouma & D. G. Bouwhuis (Eds.), *Attention and performance X* (pp. 531-556). Hillsdale, NJ: Erlbaum.

Posner, M. I., Rafal, R. D., Choate, L. S., & Vaughan, J. (1985). Inhibition of return: Neural basis and function. *Cognitive Neuropsychology, 2*(3), 211-228.

Possin, K. L., Cagigas, X. E., Strayer, D. L., & Filoteo, J. V. (2006). Lack of impairment in patients with Parkinson's disease on an object-based negative priming task. *Perceptual and Motor Skills, 102*(1), 219-230.

Postle, B. R., Awh, E., Jonides, J., Smith, E. E., & D'Esposito, M. (2004). The where and how of attention-based rehearsal in spatial working memory. *Cognitive Brain Research, 20*(2), 194-205.

Postle, B. R., & D'Esposito, M. D. (1999). Dissociation of human caudate nucleus activity in spatial and nonspatial working memory: an event related fMRI study. *Cognitive Brain Research, 8,* 107-115.

Postle, B.R., Jonides, J., Smith, E.E., Corkin, S., & Growdon, J.H. (1997). Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology, 11*(2), 171-179.

Postle, B.R., Locascio,, J. J., Corkin, S., & Growdon, J.H. (1997). The time course of spatial and object learning in Parkinson's disease. *Neuropsychologia, 35,* 1413-1422.

Potter, M. C. (1993). Very short-term conceptual memory. *Memory & Cognition, 21,* 156-161.

Quintana, J., Yajeya, J., & Fuster, J. M. (1988). Prefrontal representation of stimulus attributes during delay tasks: I. unit activity in cross-temporal integration of sensory and sensory-motor information. *Brain research, 474*(2), 211-221.

Rafal, R. D. (1998). Neglect. In R. Parasuraman (Ed.), *The attentive brain* (pp.489-525). Cambridge, MA: MIT Press.

Rafal, R. D., Calabresi, P. A., Brennan, C. W., & Sciolto, T. K. (1989). Saccade preparation inhibits reorienting to recently attended locations. *Journal of Experimental Psychology: Human Perception & Performance, 15*(4), 673-685.

Rafal, R. D., & Henik, A. (1994). The neurology of inhibition: Integrated controlled and automatic processes. In T. Carr & D. Dagenbach (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 1-51). New York: Academic Press.

Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., & Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain, 111*(2), 267-280.

Rafal, R. D., Posner, M. I., Walker, J. A., & Friedrich, F. J. (1984). Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. *Brain, 107*(4), 1083-1094.

Ranganath, C., DeGutis, J., & D'Esposito, M. (2004). Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Cognitive Brain Research, 20*(1), 37-45.

Raskin, S. A., Borod, J. C., & Tweedy, J. (1990). Neuropsychological aspects of Parkinson's disease. *Neuropsychological Review, 1*(3), 185-221.

Raven, J. (1965). *Guide to using the Raven's coloured progressive matrices.* London: Lewis.

Reader, T. A., & Quesney, L. F. (1986). Dopamine in the visual cortex of the cat. *Experientia, 42*(11-12), 1242-4.

Regan, D., & Maxner, C. (1987). Orientation-selective visual loss in patients with Parkinson's disease. *Brain, 110*(2), 415-432.

Reitan, R.M. (1969). *Manual for Administration of Neuropsychological Test Batteries for Adults and Children.* Bloomington, IN: Indiana University Press.

Reppa, I., & Leek, E. C. (2003). The modulation of inhibition of return by object-internal structure: implications for theories of object-based attentional selection. *Psychonomic Bulletin & Review, 10*(2), 493-502.

Richards, M., Cote, L. J., & Stern, Y. (1993). The relationship between visuospatial ability and perceptual motor function in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 56*(4), 400-406.

Ridenour, T. A., & Dean, R. S. (1999). Parkinson's disease and neuropsychological assessment. *International Journal of Neuroscience, 99*, 1-18.

Riklan, M., Stellar, S., & Reynolds, C. (1990). The relationship of memory and cognition in Parkinson's disease to lateralisation of motor symptoms. *Journal of Neurology, Neurosurgery, and Psychiatry, 53*(4), 359-360.

Ro, T., Farnè, A., & Chang, E. (2003). Inhibition of return and the human frontal eye fields. *Experimental Brain Research, 150,* 290-296.

Robbins, T. W., James, M., Owen, A. M., Lange, K. W., Lees, A. J., Leigh, P. N., Marsden, C. D., Quinn, N. P., & Summers, B. A. (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *Journal of Neurology, Neurosurgery, and Psychiatry, 57,* 79-88.

Rockland, K. S., & Pandya, D. N. (1979). Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Research, 179*(1),3-20.

Rouleau, I., Imbault, H., Laframboise, M., & Bedard, M. A. (2001). Pattern of intrusions in verbal recall: comparison of Alzheimer's disease, Parkinson's disease, and frontal lobe dementia. *Brain and Cognition, 46*(1-2), 244-249.

Russ, M. O., & Seger, L. (1995). The effect of task complexity on reaction times in memory scanning and visual discrimination in Parkinson's disease. *Neuropsychologia, 33*(5), 561-75.

Rypma, B., & D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: effects of memory load and individual differences. *Proceedings of the National Academy of Science, 96*(11), 6558-6563.

Sagar, H. J., Cohen, N. J., Sullivan, E. V., Corkin, S., & Growdon, J. H. (1988).Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain,111*(1), 185-206.

Sahakian, B. J., Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M., & Robbins, T. W. (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain, 111*(3), 695-718.

Saint-Cyr, J. A., Taylor, A. E., & Lang, A. E. (1988). Procedural learning and neostriatal dysfunction in man. *Brain, 111*(4), 941-59.

Saint-Cyr, J. A., Ungerleider, L. G., & Desimone, R. (1990). Organization of visual cortical inputs to the striatum and subsequent outputs to the pallido-nigral complex in the monkey. *Journal of Computational Neurology, 298*(2), 129-56.

Sala, J. B., Rama, P., & Courtney, S. M. (2003). Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia, 41*(3), 341-56.

Salmon, D. P., & Butters, N. (1995). Neurobiology of skill and habit learning. *Current Opinions in Neurobiology, 5*(2), 184-90.

Samuel, A. G., & Kat, D. (2003). Inhibition of return: a graphical meta-analysis of its time course and an empirical test of its temporal and spatial properties. *Psychonomic Bulletin & Review, 10*(4), 897-906.

Sapir, A., Hayes, A., Henik, A., Danziger, S., & Rafal, R. (2004). Parietal lobe lesions disrupt saccadic remapping of inhibitory location tagging. *Journal of Cognitive Neuroscience, 16*(4), 503-509.

Sapir, A., Rafal, R., & Henik, A. (2002). Attending to the thalamus: inhibition of return and nasal-temporal asymmetry in the pulvinar. *Neuroreport, 13*(5), 693-7.

Sapir A., Soroker, N., Berger, A., & Henik, A. (1999). Inhibition of return in spatial attention: direct evidence for collicular generation. *Nature Neuroscience, 2*(12), 1053-1054.

Sarazin, M., Deweer, B., Merkl, A., Von Poser, N., Pillon, B., & Dubois, B. (2002). Procedural learning and striatofrontal dysfunction in Parkinson's disease. *Movement Disorders, 17*(2), 265-73

Sartucci, F., Orlandi, G., Lucetti, C., Bonuccelli, U., Murri, L., Orsini, C., & Porciatti V. (2003). Changes in pattern electroretinograms to equiluminant red-green and blue-yellow gratings in patients with early Parkinson's disease. *Journal of Clinical Neurophysiology, 20*(5), 375-81.

Scholl, B. J. (2001). Objects and attention: the state of the art. *Cognition, 80*(1-2), 1-46.

Schwartz, B. L., & Hashtroudi, S. (1991). Priming is independent of skill learning. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 17*(6), 1177-1187.

Scott, S., Caird, F. I., & Williams, B. O. (1984). Evidence for an apparent sensory speech disorder in Parkinson's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 47*(8), 840-3.

Selemon, L. D., & Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of cortico-striatal projections in the rhesus monkey. *Journal of Neurosciences, 5,* 776-794.

Sereno, A. B., Briand, K. A., Amador, S. C., & Szapiel, S. V. (2006). Disruption of reflexive attention and eye movements in an individual with a collicular lesion. *Journal of Clinical and Experimental Neuropsychology, 28,* 145-166.

Sethi, K. D. (2002). Clinical aspects of Parkinson's disease. *Current Opinion in Neurology, 15,* 457-460.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, 298,* 199-209.

Sharpe, M. H. (1990). Patients with early parkinson's disease are not impaired on spatial orientating of attention. *Cortex, 26*(4), 515-524.

Shaunak, S., O'Sullivan, E., Blunt, S., Lawden, M., Crawford, T., Henderson, L., & Kennard, C. (1999). Remembered saccades with variable delay in Parkinson's disease. *Movement Disorders, 14*(1), 80-86.

Sheikh J. I., & Yesavage, J. A. (1986). Geriatric depression scale (GDS): Recent evidence and development of a shorter version. In *Clinical Gerontology : A Guide to Assessment and Intervention*, (pp.165-173), NY: The Haworth Press.

Silva, M. F., Faria, P., Ragateiro, F. S., Forjaz, V., Januario, C., Freire, A., & Castelo-Branco, M. (2005). Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease. *Brain, 128*(10), 2260-2271.

Skeel, R. L., Crosson, B., Nadeau, S. E., Algina, J., Bauer, R. M., & Fennell, E. B. (2001). Basal ganglia dysfunction, working memory, and sentence comprehension in patients with Parkinson disease. *Neuropsychologia, 39,* 962-971.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*(5408), 1657-1661.

Smith, E. E., Jonides, J., Koeppe, R. A., Awh, E., Schumacher, E. H., & Minoshima, S. (1995). Spatial versus object working memory: PET investigations. *Journal of Cognitive Neurosciences, 7,* 337-356.

Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: applications to dementia and amnesia. *Journal of Experimental Psychology, 117*(1), 34-50.

Snyder, J. J., & Kingstone, A. (2000). Inhibition of return and visual search: how many separate loci are inhibited? *Perception and Psychophysics, 62*(3), 452-458.

Sohn, M., Ursu, S., Anderson, J. R., Stenger, V. A., & Carter, C. S. (2000). The role of prefrontal cortex and posterior parietal cortex in task switching. *Proceedings of the National Academy of Sciences, 97,* 13448-13453.

Soto, D., & Blanco, M. J. (2004). Spatial attention and object-based attention: a comparison within a single task. *Vision Research, 44*(1), 69-81.

Spicer, K. B., Brown, G. G., & Gorell, J. M. (1994). Lexical decision in Parkinson's disease: Lack of evidence fro generalized bradyphrenia. *Journal of Clinical and Experimental Neuropsychology, 16,* 457-471.

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*(2), 195-231.

Stebbins, G. T., & Goetz, C. G. (1998). Factor structure of the Unified Parkinson's Disease Rating Scale: Motor examination section. *Movement Disorders, 13,* 633-636.

Stebbins, G. T., Goetz, C. G., Lang, A. E. & Cubo, E. (1999). Factor analysis of the motor section of the Unified Parkinson's Disease Rating Scale during the off-state. *Movement Disorders, 14*(4), 585-589.

Stelmach, G. E., Phillips, J. G., & Chau, A. W. (1989). Visuo-spatial processing in parkinsonians. *Neuropsychologia, 27*(4), 485-493.

Sullivan, E. V., & Sagar, H. J. (1989). Nonverbal recognition and recency discrimination deficits in Parkinson's disease and Alzheimer's disease. *Brain, 112*(6), 1503-1517.

Sullivan, E. V., Sagar, H. J., Cooper, J. A., & Jordan, N. (1993). Verbal and nonverbal short-term memory impairment in untreated Parkinson's disease. *Neuropsychology, 7*(3), 396-405.

Sullivan, E. V., Sagar, H. J., Gabrieli, J. D., Corkin, S., & Growdon, J. H.(1989). Different cognitive profiles on standard behavioral tests in Parkinson's disease and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 11*(6), 799-820

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia, 38*(5), 596-612.

Tachibana, H., Aragane, K., Kawabata, K., & Sugita, M. (1997). P3 latency change in aging and Parkinson disease. *Archives of Neurology, 54*(3), 296-302.

Tagliati, M., Bodis-Wollner, I., & Yahr, M. D. (1996). The pattern electroretinogram in Parkinson's disease reveals lack of retinal spatial tuning. *Clinical Neurophysiology, 100,* 1-11.

Takeda, Y. (2004). Search for multiple targets: evidence for memory-based control of attention. *Psychonomic Bulletin & Review, 11*(1), 71-76.

Tanner, C. M., Ottman, R., Goldman, S. M., Ellenberg, J., Chan, P., Mayeux, R., & Langston, J. W. (1999). Parkinson disease in twins: an etiologic study. *Journal of the American Medical Association, 281*(4), 341-346.

Taylor, A. E., & Saint-Cyr, J. A. (1995). The neuropsychology of Parkinson's disease. *Brain and Cognition, 28*(3), 281-296.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain, 109*(5), 845-83.

Taylor, A. E., Saint-Cyr, J. A., Lang, A. E. (1987). Parkinson's disease. Cognitive changes in relation to treatment response. *Brain, 110*(1), 35-51.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1990). Memory and learning in early parkinson's disease: Evidence for a "frontal lobe syndrome." *Brain and Cognition, 13*(2), 211-232.

Tebartz van Elst, L. T., Greenlee, M. W., Foley, J. M., & Lücking, C. H. (1997). Contrast detection, discrimination and adaptation in patients with parkinson's disease and multiple system atrophy. *Brain, 120*(12), 2219-2228.

Tipper, S. P., Driver, J., & Weaver, B. (1991). Short report: Object-cenetered inhibition of return of visual attention. *Quarterly Journal of Experimental Psychology, 43A,* 289-298.

Tipper, S. P., Jordan, H., & Weaver, B. (1999). Scene-based and object-centered inhibition of return of visual attention. *Quarterly Journal of Experimental Psychology, 43A,* 289-298.

Tipper, S. P., Rafal, R., Reuter-Lorenz, P. A., Starrveldt, Y., Ro, T., Egly, R., Danzinger, S., & Weaver, B. (1997). Object-based facilitation and inhibition from visual orienting in the human split-brain. *Journal of Experimental Psychology, 23*(5), 1522-1532.

Tipper, S. P., Weaver, B., Jerreat, L. M., & Burak, A. L. (1994). Object-based and environment-based inhibition of return of visual attention. *Journal of Experimental Psychology, Human Perception and Performance, 20,* 478-499.

Tomer, R., Levin, B. E., & Weiner, W. J. (1993). Side of onset of motor symptoms influences cognition in Parkinson's disease. *Annals of Neurology, 34*(4), 579-584.

Tresch, M. C., Sinnamon, H. M., & Seamon, J. G. (1993). Double dissociation of spatial and object visual memory: evidence from selective interference in intact human subjects. *Neuropsychologia, 31*(3), 211-219.

Umilta, C. (1988). Orienting of attention. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 1). Amsterdam: Elsevier.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In M. A. Goodale, D. J. Ingle, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549-585). Cambridge, MA: MIT Press.

Unsworth, N., Schrock, J. C., & Engle, R. W. (2004). Working memory capacity and the antisaccade task: individual differences in voluntary saccade control. *Journal of Experimental Psychology, Learning, Memory, and Cognition, 30*(6), 1302-1321.

Valenza, E., Simion, F., Umilta, C. (1994). Inhibition of return in newborn infants. *Infant Behavior and Development, 17,* 293-302.

Venneri, A., Nichelli, P., Modonesi, G., Molinari, M. A., Russo, R., & Sardini, C. (1997). Impairment in dating and retrieving remote events in patients with early Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 62*(4), 410-3.

Vivas, A. B., Humphreys, G. W., & Fuentes, L. J. (2003). Inhibitory processing following damage to the parietal lobe. *Neuropsychologia, 41*(11), 1531-1540.

Vriezen, E. R., & Moscovitch, M. (1990). Memory for temporal order and conditional associative-learning in patients with Parkinson's disease. *Neuropsychologia, 28*(12), 1283-1293.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. *Cognitive, Affective, and Behavioral Neuroscience, 3*(4), 255-274.

Wang, L., Kuroiwa, Y., & Kamitani, T. (1999). Visual event-related potential changes at two different tasks in nondemented Parkinson's disease. *Journal of Neurological Science, 164*(2), 139-47.

Weaver, B., Lupianez, J., & Watson, F. L. (1998). The effects of practice on object-based, location-based, and static-display inhibition of return. *Perception and Psychophysics, 60*(6), 993-1003.

Wechsler, D. (1981). *WAIS-R manual: Wechsler Adult Intelligence Scale-Revised.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale – Third edition.* San Antonio, TX: The Psychological Corporation.

Welsh, M. C., Satterlee-Cartmell, T., & Stine, M. (1999). Towers of Hanoi and London: Contribution of working memory and inhibition to performance. *Brain & Cognition, 41*(2), 231-242.

White, O. B., Saint-Cyr, J. A., Tomlinson, R. D., Sharpe, J. A. (1983). Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain, 106*(3), 571-87.

Whittington, C. J., Podd, J., & Kan, M. M. (2000). Recognition memory impairment in Parkinson's disease: power and meta-analyses. *Neuropsychology, 14*(2), 233-246.

Wilson, F. A., O'Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260*(5116), 1955-1958.

Woodman, G. F., & Luck, S. J. (2004). Visual search is slowed when visuospatial working memory is occupied. *Psychonomic Bulletin & Review, 11*(2), 269-274.

Woodman, G. F. & Vogel, E. K. (2005). Fractionating working memory: consolidation and maintenance are independent processes. *Psychological Science, 16*(2), 106-113.

Woodward, T. S., Bub, D. N., & Hunter, M. A. (2002). Task switching deficits associated with Parkinson's disease reflect depleted attentional resources. *Neuropsychologia, 40*(12), 1948-1955.

Wright, M. J., Burns, R. J., Geffen, G. M., & Geffen, L. B. (1990). Covert orientation of visual attention in Parkinson's disease: An impairment in the maintenance of attention. *Neuropsychologia, 28*, 151-159.

Wylie, S. A., & Stout, J. C. (2002). Enhanced negative priming in Parkinson's disease. *Neuropsychology, 16(2),* 242-250.

Yamadori, A., Yoshida, T., Mori, E., & Yamashita, H. (1996). Neurological basis of skill learning. *Cognitive Brain Research, 5*(1-2), 49-54.

Yamaguchi, S., & Kobayashi, S. (1998). Contributions of the dopaminergic system to voluntary and automatic orienting of visuospatial attention. *Journal of Neuroscience, 18*(5), 1869-1878.

Yantis, S., & Serences, J. T. (2003). Cortical mechanisms of space-based and object-based attentional control. *Current Opinions in Neurobiology, 13*(2), 187-193.

Yeterian, E. H., & Pandya, D. N. (1991). Prefrontal connections in relation to cortical architectonic organization in rhesus monkeys. *The Journal of Comparative Neurology, 312,* 43-67.

Yeterian, E. H., & Pandya, D. N. (1995). Corticostriatal connections of extrastriate visual areas in rhesus monkeys. *The Journal of Comparative Neurology, 352,* 436-457.

Zakharov, V. V., Akhutina, T. V, & Yakhno, N. N. (2001). Memory impairment in Parkinson's disease. *Neuroscience and Behavioral Physiology, 31*(2), 157-163.

Zalla, T., Sirigu, A., Pillon, B., Dubois, B., Grafman, J., & Agid, Y. (1998). Deficit in evaluating pre-determined sequences of script events in patients with Parkinson's disease. *Cortex, 34*(4), 621-627.

Zeki, S. M. (1978). Functional specialisation in the visual cortex of the rhesus monkey. *Nature, 274*(5670), 423-428.

Zeki, S. M. (1993). *A vision of the brain.* Oxford, England: Blackwell Scientific Publications.

Zeki, S., & Shipp, S. (1988). The functional logic of cortical connections. *Nature, 335*(6188), 311-317.

Zizak, V. S., Filoteo, J. V., Possin, K. L., Lucas, J. A., Rilling, L. M., Davis, J. D., Peavy, G., Wong, A., & Salmon, D. P. (2005). The ubiquity of memory retrieval deficits in patients with frontal-striatal dysfunction. *Cognitive and Behavioral Neurology, 18*(4), 198-205.

Zizak, V., Possin, K.L., Delis, D.C., Jacobson, M., Jerkins, S., & Filoteo, J.V (2003). *Performance of Parkinson's disease patients on the CVLT-II.* Poster session presented at the annual meeting of the International Neuropsychological Society, Waikiki, Hawaii.

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., & Mattis, P. (2003). A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. *Cognitive and Behavioral Neurology, 16*(4), 193-210.

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Mattis, P., Gordon, M. F., Feigin, A., & Eidelberg, D. (2006). An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 28*(7), 1127-1144.