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Deficits in Visual Cognition in Lewy Body Disorders

A Dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Neurosciences

by

Kelly Marie Landy

Committee in charge:

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2014

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Chair

University of California, San Diego

2014

DEDICATION

For Mom and Dad – thank you for always encouraging me and believing in me. Thank you for working hard to ensure that I had the opportunity to get an excellent education; I appreciate that more than I can ever express. For my fiancé, Ravi – thank you for all the love and encouragement throughout the past ten years; it always felt like you were right by my side, even when you were 3810.4 kilometers away.

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ABSTRACTS

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ABSTRACT OF THE DISSERTATION

Deficits in Visual Cognition in Lewy Body Disorders

by

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Doctor of Philosophy in Neurosciences

University of California, San Diego, 2014

Professor David P. Salmon, Chair

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder characterized pathologically by cell loss and the deposition of α-synuclein-positive, eosinophilic inclusions (i.e., Lewy bodies) in brainstem, limbic, and neocortical regions. Clinical features of DLB include progressive dementia, spontaneous Parkinsonism, well-formed and recurrent visual hallucinations, and fluctuations in consciousness and cognition. The symptoms of DLB overlap considerably with those of Alzheimer's disease (AD), and it is often difficult to clinically distinguish between the two disorders. However, retrospective studies of autopsy-confirmed cases indicate

that DLB patients may have early and disproportionately severe deficits in visual cognition compared to equally demented patients with AD.

The studies in this dissertation aimed to further characterize the nature and extent of deficits in visual cognition in DLB and related disorders. Study 1 examined the ability of DLB patients to discriminate simple horizontal motion. Patients with DLB were markedly impaired with greater deficits than patients with AD. The effect was sustained in a small subset of the AD and DLB patients with autopsy-confirmed diagnoses. Study 2 assessed the integrity of single-feature and dual-feature visual search in patients with DLB or AD. Patients with DLB were generally slow in performing search, but showed a normal pattern of performance in both tasks. Patients with AD, in contrast, were impaired in performing dual-feature search, perhaps due to a breakdown in cortico-cortical connectivity that attenuates the ability to integrate visual features.

To better understand the role of Lewy body pathology *per se* in disruption of visual cognition, Study 3 examined higher order visual cognition in non-demented patients with Parkinson's disease (PD). Patients with PD have Lewy body pathology in brainstem nuclei (e.g., substantia nigra) and a disruption of basal ganglia and certain cortical functions due to the loss of dopaminergic projections from these nuclei. They do not have significant cortical Lewy bodies or concomitant AD pathology that often occurs in DLB. The results of Study 3 showed that PD patients had no deficits in either search efficiency for subtle differences in shape or speed of motion stimuli, or visual search that required the integration of color and motion information. However,

patients with PD were impaired on a task that required integration of motion and luminance information. Because both luminance and motion are processed through the dorsal visual processing stream, this task may have taxed the dorsal visual processing stream, allowing subtle impairment to be revealed. Thus, Lewy body pathology may be associated with specific impairments in information processing carried out in the dorsal visual processing stream.

Chapter 1

Introduction

Dementia with Lewy Bodies (DLB) is a common cause of neurodegenerative dementia (Kosaka & Iseki, 1996; Perry, Irving, Blessed, Fairbairn, & Perry, 1990), second only to Alzheimer's disease (AD) in prevalence (Heyman et al., 1999; Mirra et al., 1991; Perry et al., 1990). The disease overlaps pathologically and clinically with AD and Parkinson's disease (PD) (Salmon, Galasko, & Hansen, 2001). Because of the significant symptom overlap with AD, DLB is often misdiagnosed (McKeith et al., 1996; Merdes et al., 2003); currently post-mortem examination of neural tissue is the only way to definitively diagnose DLB and distinguish it from AD. One of the clinical features that serves to differentiate the two disorders is a marked impairment in visuospatial ability in DLB patients when compared to AD patients at the same level of overall dementia (Salmon et al., 2001). Therefore, the work described in this dissertation will examine visual cognition in DLB in detail. In addition, because DLB shares overlapping symptoms and Lewy body pathology with PD, an examination of higher order visual cognitive ability in PD will be carried out to inform our understanding of deficits in visual cognition conferred as a result of the burden of Lewy body pathology. With few treatments and no cure currently available for DLB, much remains to be learned with regard to the nature and extent of the disease process. Examining the neuropsychological profile of patients with DLB in comparison to patients with other neurodegenerative diseases can provide insight into which areas of the brain are impacted most severely. With more knowledge about the effects of the

disease on cognition, researchers can eventually take a more targeted approach in the search for effective treatments and cures. This dissertation will examine visual cognition across various Lewy body disorders to further elucidate the nature of the neuropsychological deficits associated with this pathology.

Clinical Characterization of DLB

DLB is a clinical and pathological condition that is characterized by progressive dementia associated with neurodegenerative changes (McKeith et al., 1996). The diagnostic criteria for DLB include the presence of progressive dementia along with at least two of the following cardinal signs: well-formed and recurrent visual hallucinations, fluctuations in consciousness and cognition, and spontaneous parkinsonism (McKeith et al., 2005). There is significant symptom overlap between DLB and AD. Therefore, differential diagnosis of DLB is difficult and clinicians often assign a diagnosis of AD instead of DLB. Accurate diagnosis is confounded by the fact that approximately 30% of neuropathologically-confirmed DLB cases do not show any of the core features during life other than dementia (Merdes et al., 2003). It is also confounded by significant pathological overlap in many cases. Thus, diagnosing antemortem DLB clinically has been consistently described as problematic and difficult (Lopez et al., 2000; Merdes et al., 2003). In spite of the diagnostic difficulties, DLB is recognized as the second most common cause of dementia after AD (McKeith et al., 2005).

Visual hallucinations are common in the clinical course of DLB, and these can sometimes be confusing and frightening to patients with DLB and their loved ones.

Persons with DLB report seeing well-formed images: children, small animals, and insects are frequently described (Manford & Andermann, 1998). Auditory hallucinations can occur, but visual ones are more common (McKeith et al., 1996). Some studies point to an association between the frequency of visual hallucinations and deficits on neuropsychological tasks of object identification such that DLB patients with a higher rate of hallucinations tended to be more impaired on tasks of visual perception (Mori et al., 2000; Simard, van Reekum, & Myran, 2003). A study that retrospectively examined cases of autopsy-confirmed DLB and AD found that DLB patients with severe visual impairment on a block design test early in the course of the disease were more likely to go on to develop hallucinations; importantly, this effect did not hold in the AD cohort (Hamilton et al., 2012). The mechanism by which the brain generates these well-formed visual hallucinations is still unknown, but some (Calderon et al., 2001) have speculated that the hallucinations common to DLB are the result of fluctuations in attention combined with degraded visual input and/or neurochemical abnormalities.

Fluctuations in consciousness and cognition are also considered to be a cardinal symptom of DLB. A patient with DLB who is experiencing fluctuations in alertness might be observed to stare off into space for long periods of time, seem drowsy and lethargic, or sleep for several hours during the day despite getting sufficient night-time sleep (Ferman et al., 2004); in addition, the person's flow of ideas might seem disorganized or illogical, and they can have "good days" and "bad days" (Ferman et al., 2004; Gibb, Esiri, & Lees, 1987). Higher rates of syncope and

transient loss of consciousness are found in DLB compared to AD (McKeith, Perry, Fairbairn, Jabeen, & Perry, 1992). Previous research demonstrates that DLB patients show more neuropsychiatric features and more attentional fluctuations than patients with AD (Ballard et al., 1999; Walker et al., 2000), and one study claims that fluctuations occur in up to 90% of DLB patients (Byrne, Lennox, Lowe, & Godwin-Austen, 1989). Fluctuations are hard to assess quantitatively in a clinical setting, but some groups (Gibb et al., 1987) have attempted to operationalize the definition of fluctuations. Mayo Clinic investigators developed a scale to assess fluctuations (Ferman et al., 2004) and found that disorganized speech and disturbed arousal patterns were specific aspects of fluctuations that could help differentiate DLB from AD (Ferman et al., 2004).

The third cardinal sign of DLB is spontaneous parkinsonism. In order to meet diagnostic criteria for DLB, the parkinsonism cannot be provoked by neuroleptic medications. Spontaneous parkinsonism encompasses symptoms common in PD such as slowness of movement (bradykinesia), rigidity, tremor, and cogwheeling (McKeith et al., 1996). The parkinsonism can be mild at first, and symptoms can include a change in gait, problems with balance and falls, hypomimia, and hypophonia. Although these symptoms can also occur in AD, they occur more frequently and at earlier stages of disease in DLB (McKeith et al., 1996). One study estimates that 75% of DLB patients present with spontaneous parkinsonism, with the caveat that, although action tremor can occur, parkinsonism occurs more often in the phenotype of DLB characterized by postural instability and gait disorders (PIGD) (Burn et al., 2003).

Movement problems are also common during sleep, as the rate of REM sleep behavior disorder (RBD) is higher in DLB than in AD; this is also true of the rate of falls, with falls occurring more often in DLB (McKeith et al., 1992; Rojo, Aguilar, Navas, & Quintana, 2002). Although there is significant overlap between clinical symptoms of DLB and those of PD, there is a diagnostic distinction between DLB and Parkinson's disease dementia (PDD). A diagnosis of DLB is given if cognitive symptoms appear first, and motor symptoms appear concurrently or within 1 year of the cognitive symptoms. A diagnosis of PDD is given when motor symptoms appear first, and cognitive problems appear at least 1 year after the onset of motor symptoms. It is important to note that at later stages in the disease course, PDD and DLB have a very similar presentation and progression (Morra & Donovick, 2013).

Despite the many clinical similarities between DLB and AD, accurate diagnosis of DLB is extremely important. While some research shows that DLB and AD progress equally (Helmes, Bowler, Merskey, Munoz, & Hachinski, 2003; Heyman et al., 1999; Johnson, Shafi, Parker, & Parker, 2005; Stern et al., 2001), several studies comparing autopsy-confirmed cases suggest that DLB patients have a more rapid rate of decline in their disease course than AD patients (Galasko, Katzman, Salmon, & Hansen, 1996; Kraybill et al., 2005; Olichney et al., 1998). Understanding the typical course of disease progression is extremely important for caregivers and family members as they care for the person with DLB. Another salient aspect of DLB that underscores the importance of accurate diagnosis is the fact that patients with DLB can show extreme sensitivity to the neuroleptic drugs that are often used to treat the

psychiatric symptoms of AD, such as hallucinations (Levy, 1994; McKeith et al., 1996; McKeith et al., 1992). Neuroleptic sensitivity can cause very severe reactions to these medications in DLB patients, even leading to death in some cases (Levy, 1994; McKeith et al., 1996). There are very few approved treatments for DLB; sometimes levodopa is prescribed to treat the motor symptoms, but improvement can be minimal and the efficacy of levodopa treatment in DLB is unclear (Bonelli et al., 2004).

Cognitive impairment in DLB

Similar to AD, the cognitive deficits in DLB are global with impairment present in the cognitive domains of memory, attention, executive function, and language. The significant overlap in cognitive symptoms between AD and DLB can make it difficult for clinicians to differentiate between the two disorders, but research has pointed to a somewhat distinct pattern of impairment in DLB that can help distinguish it from AD. For example, previous work has demonstrated that the pattern of memory impairment in DLB and AD is different. When examining DLB and AD patients with equivalent scores on a measure of global cognition such as the Dementia Rating Scale (DRS; (Mattis, 1988)), DLB patients tended to score higher on the memory subscales, thus demonstrating less memory impairment than their AD counterparts (Connor et al., 1998; Hamilton et al., 2004). Not only may the memory impairment in DLB be less severe than in AD patients (Connor et al., 1998; Heyman et al., 1999) (but see (Galasko et al., 1996; L. Hansen et al., 1990)), but the two disorders may have a differential impact on learning, retention, and recognition (Salmon et al., 1996). One study examined the performance of 24 autopsy-confirmed

DLB cases and 24 autopsy-confirmed AD cases on the California Verbal Learning Test (CVLT) and the Wechsler Memory Scale-Revised Logical Memory subtest, two frequently used measures of memory ability. When comparing the total number of words learned across 5 test trials, DLB and AD groups showed a similar performance; they also remembered a similar number of words in a free recall test after a delay. However, on a test of recognition, the DLB group showed more improvement (relative to free recall performance) than the AD group; the AD group's scores were not improved when recognition cues were presented (Hamilton et al., 2004). These results showed that, even at the same level of overall dementia, the nature of the episodic memory deficit in DLB is different than in AD.

Other cognitive domains also show distinct patterns of deficits in DLB and AD. Many studies have demonstrated that DLB patients are impaired in both attention (L. Hansen et al., 1990) and executive function (Connor et al., 1998; Galasko et al., 1996; L. Hansen et al., 1990; Salmon et al., 1996), and some studies show that these deficits are more pronounced in DLB patients than AD patients at an equivalent level of global cognitive function. For example, DLB patients outperform AD patients on the memory subscale of the DRS, but DLB patients show a greater deficit on the initiation and perseveration subscales (Connor et al., 1998). This deficit in initiation and perseveration was confirmed in another retrospective study of DLB patients (Aarsland, Litvan, et al., 2003). In general, these attentional and executive function deficits are more consistent with a pattern of subcortical dysfunction, since deficits in these cognitive domains also occur in patients with PD and patients with Huntington's

disease who primarily have basal ganglia dysfunction and other subcortical damage. An interruption of circuits linking frontal cortex and subcortical structures could be responsible for this pattern of deficits (Salmon & Filoteo, 2007).

Visuospatial ability is particularly susceptible to impairment in DLB. DLB patients have consistently demonstrated impairment in visual perception and visuospatial ability across a broad range of studies. When examining DLB and AD patients at the same level of global cognitive impairment or with similar levels of memory dysfunction, DLB patients demonstrate a disproportionately severe deficit in visual cognition (Connor et al., 1998; Salmon et al., 1996; Walker et al., 2000). Neuropsychologically, various aspects of visuospatial ability and visual perception have been assessed in order to better characterize the visual cognition impairment in DLB. This research has shown that DLB patients' disproportionate impairment encompasses visuospatial ability, visuoperceptual ability, and constructional ability (Aarsland, Litvan, et al., 2003; Ala, Hughes, Kyrouac, Ghobrial, & Elble, 2001; Galasko et al., 1996; Hamilton et al., 2004; L. Hansen et al., 1990; Johnson et al., 2005; Mori et al., 2000; Salmon et al., 1996). For example, patients with DLB had significant deficits in tasks that required drawing complex two-dimensional figures (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Connor et al., 1998; Galasko et al., 1996; Gnanalingham, Byrne, Thornton, Sambrook, & Bannister, 1997; L. Hansen et al., 1990; Noe et al., 2004; Salmon et al., 1996) or the construction of three-dimensional objects (Hamilton et al., 2004; L. Hansen et al., 1990; Salmon, Galasko, Hamilton, Thal, & Hansen, 2002; Shimomura et al., 1998). Tiraboschi and

colleagues reported that visuospatial deficits may be a particularly salient marker for DLB. They noted that marked impairment in the visuospatial domain was often evident early in the disease course in DLB patients, and this was a strong negative predictor of DLB pathology – i.e., its absence predicted the absence of Lewy body pathology (Tiraboschi et al., 2006). Importantly, retrospective studies of DLB patients with (Connor et al., 1998; Forstl, Burns, Luthert, Cairns, & Levy, 1993; Galasko et al., 1996; L. Hansen et al., 1990; Heyman et al., 1999) and without (Galasko et al., 1996; Salmon et al., 1996) a significant degree of AD pathology showed similar profiles of deficits in visual cognition. In daily life, deficits in visual perception and visuospatial ability could manifest as difficulties judging distances, difficulty with depth perception, misidentifying objects, or getting lost in familiar places, even within one's own home.

Further examination of visuospatial deficits in DLB can be considered in the context of the organization of the human visual system. Very broadly, the human visual system is organized in two anatomically distinct processing streams that process different aspects of a visual scene (Ungerleider & Haxby, 1994). These two functionally specialized visual processing streams originate in the primary visual cortex (V1) and project to distinct higher cortical regions. Visual information processing becomes increasingly more complex in a hierarchical fashion as information flows from V1. The ventral stream emerges from V1 via V2 to encompass the ventromedial surface of the temporal and occipital cortices in the lingual and posterior fusiform gyri (Haxby et al., 1991; Haxby et al., 1994; Kohler, Kapur,

Moscovitch, Winocur, & Houle, 1995). In humans, studies have shown that this stream processes information about color (Beauchamp, Haxby, Jennings, & DeYoe, 1999; Chao & Martin, 1999; Clarke, Walsh, Schoppig, Assal, & Cowey, 1998; Cowey & Heywood, 1995; Zeki & Marini, 1998), form (Larsson et al., 2002), and facial features (Haxby et al., 1994; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Puce, Allison, Gore, & McCarthy, 1995). The dorsal stream projects from V1 to the junction of the parietal, occipital, and temporal cortices. Recent fMRI research in humans demonstrates that the posterior parietal regions that are part of this stream play a pivotal role in attention to motion (Friston & Buchel, 2000). In addition, the lateral occipitotemporoparietal junction of this stream is selectively activated by motion perception (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; J. D. Watson et al., 1993; Zeki & Marini, 1998) and spatial localization (Haxby et al., 1991; Haxby et al., 1994; Kohler et al., 1995), and also processes luminance information (Ungerleider & Haxby, 1994). Conceptually, then, the ventral stream is thought to process "what" an object is, and the dorsal stream to process "where" that object is in space (Ungerleider & Haxby, 1994). More specifically, in humans, certain "blobs" in V1, thin stripes of V2, the V4 complex, and regions just anterior to V4 process color. Motion is primarily processed in layer 4B of V1, thick strips of V2, and in the V5/MT complex and other regions just beyond this (Bartels & Zeki, 2000; Brewer, Liu, Wade, & Wandell, 2005). Therefore, performance on tests of color discrimination assesses

the integrity of the ventral visual stream, whereas tests of motion discrimination assess the integrity of the dorsal visual stream.

Previous studies of visual cognition in patients with DLB have shown that they are impaired on tasks mediated by both the ventral and dorsal processing streams. On the one hand, DLB patients were impaired on tasks of object discrimination, form discrimination, and identification of fragmented letters that are mediated by ventral stream processes (Calderon et al., 2001). Deficits were also seen in ventral stream-dependent tasks such as discriminating real objects from non-objects (Calderon et al., 2001) and size discrimination (Mori et al., 2000; Mosimann et al., 2004). On the other hand, DLB patients were impaired on dorsal stream processing tasks such as these that required the segregation of overlapping figures (Calderon et al., 2001), identification of the spatial location of dots (Mosimann et al., 2004), and motion perception (Mosimann et al., 2004).

An aspect of visual cognition that combines elements of visuospatial ability and visual attention is visual search. Previous work showed that DLB patients were impaired on tasks of visual search. On a hidden search task, DLB patients showed a deficit in the ability to use efficient search strategies to complete the task (Sahgal et al., 1992). In the only study to date to compare visual search ability in DLB and AD patients, Cormack and colleagues found that DLB patients, but not those with AD, were impaired in single-feature search where the target is thought to “pop out” from the distractors (Cormack, Gray, Ballard, & Tovee, 2004). Although cautioning that the results need to be replicated in a larger study, Cormack et al. speculated that DLB

patients were impaired in single-feature search due to dysfunction in occipital cortices that are integral to visual processing.

Hamilton and colleagues investigated the relationship between deficits in visual cognition and the strength of the prototypical DLB clinical phenotype (Hamilton et al., 2008). This study showed that poor baseline performance in tests of visuospatial ability correlated with a rapid rate of decline in DLB, but not in AD. This study suggests that identifying the severity of deficits in visual cognition in DLB early in the disease course may be particularly important in helping to identify cases that may show a particularly rapid or malignant disease course (Hamilton et al., 2008).

Neuropathology of DLB

The distinct cognitive profile that emerges in a prototypical DLB syndrome is consistent with the neuropathology of the disease. Currently, the only way to diagnose DLB with certainty is upon confirmation of relevant neuropathology via autopsy. DLB is characterized histopathologically by Lewy bodies which are round, eosinophilic inclusions within the cytoplasm of neurons that were first characterized by F.H. Lewy (Schiller, 2000; Spillantini, Crowther, Jakes, Hasegawa, & Goedert, 1998). The inclusions are composed of a protein known as alpha-synuclein. Pathologically, DLB is characterized by Lewy body deposition and neuron loss in areas of the brain that are typically affected by PD (e.g., midbrain and brainstem nuclei) (Galasko et al., 1996). Because of similarities in the type and distribution of pathology in PD and DLB, a pathologist cannot necessarily discern whether a person had PD for a long period of time followed by dementia, or whether the person suffered

from dementia prior to developing parkinsonism (i.e., DLB) (Kosaka, 1993). However, patients with DLB tend to have fewer Lewy bodies and less cell loss in the substantia nigra than patients with PD (L. Hansen et al., 1990; Ince, Perry, & Morris, 1998; Perry et al., 1990). The quantity of Lewy body pathology has been related to the severity of dementia in DLB (Haroutunian et al., 2000); however, neuropathological markers of both AD and DLB were correlated with the severity of dementia (Sabbagh et al., 1999; Samuel, Alford, Hofstetter, & Hansen, 1997; Samuel, Galasko, Masliah, & Hansen, 1996). Thus, the exact role of Lewy bodies *per se* in generating the DLB syndrome is not yet known. In general, there is more severe fronto-striatal dysfunction in DLB than in AD (Galasko et al., 1996) which may explain the greater loss of executive function commonly observed in DLB.

In most cases of DLB, there is some level of concomitant AD pathology found upon neuropathological examination (Armstrong, Cairns, & Lantos, 1998; Galasko et al., 1996; L. A. Hansen & Terry, 1997). DLB cases often have neurofibrillary tangles and neuritic plaques in the same limbic and neocortical distribution as in AD (Armstrong et al., 1998; L. Hansen et al., 1990; Lieb et al., 1999). However, the AD pathology usually does not occur to the same extent as in "pure" AD, and the clinical phenotype of DLB appears "weaker" in patients with extensive AD pathology (Merdes et al., 2003). In the same vein, the clinical syndrome that is strongly prototypical of DLB is usually associated with greater Lewy body burden (Cormack et al., 2004; Harding, Broe, & Halliday, 2002). The common occurrence of concomitant AD

pathology with DLB pathology contributes to the difficulty in making a differential clinical diagnosis.

The distribution of pathology in DLB compared to AD is consistent with the observed differences in neuropsychological profiles. For example, the somewhat milder episodic memory deficit in DLB than in AD is consistent with less severe medial temporal lobe pathology in these patients than in patients with AD (Barber et al., 2000; Barber, McKeith, Ballard, Gholkar, & O'Brien, 2001; Hashimoto et al., 1998; Lippa, Johnson, & Smith, 1998; Lippa, Smith, & Swearer, 1994). Because the clinical picture of DLB suggests a marked impairment in visual cognition, several studies have examined the neuroanatomical basis of visual impairment in the brains of DLB patients, to investigate whether areas integral to visuospatial cognition may be selectively vulnerable to DLB pathology and show a pattern of damage in DLB distinct from AD. Somewhat surprisingly, these studies have shown that Lewy body density is less severe in the occipital cortex than in other cortical regions (Gomez-Tortosa et al., 1999; Harding et al., 2002; Kosaka, 1993; Rezaie, Cairns, Chadwick, & Lantos, 1996). However, other abnormalities exist in this region including white matter spongiform changes with gliosis. These neuropathological features are not typically seen in patients with AD. Thus, there is a greater degree of pathology in this visual processing region in DLB compared to AD (Higuchi et al., 2000; Kosaka & Iseki, 1996; Pellise, Roig, Barraquer-Bordas, & Ferrer, 1996; Rezaie et al., 1996).

Additionally, imaging studies of DLB have found hypometabolism and decreased blood flow compared to AD in primary and visual association cortices

(Albin et al., 1996; Higuchi et al., 2000; Imamura et al., 1999; Imamura et al., 2001; Ishii et al., 1998; Lobotesis et al., 2001). Imaging studies that examined the integrity of white matter tracts with diffusion tensor imaging found areas of reduced white matter integrity in DLB patients, primarily in parieto-occipital white matter tracts. In contrast, white matter damage in AD patients showed a more diffuse pattern (R. Watson et al., 2012).

Taken together, the neuropathological findings and evidence from neuropsychological studies suggest that further examination of the nature and extent of visual cognitive deficits in DLB is warranted. Furthermore, pronounced deficits in visual cognition may be a quantifiable marker that will help identify and accurately diagnose patients with DLB.

Parkinson's Disease: A Disorder on the Lewy Body Spectrum

The studies in this dissertation seek to discover whether there are unique impairments in visual cognition associated with Lewy body pathology. Because Lewy bodies are the primary pathological hallmark of both DLB and PD, an examination of higher order visual cognition deficits in PD is warranted. A better understanding of visual cognition in non-demented patients with PD can inform our understanding of the deficits in visual cognition that are associated strongly with the presence of Lewy bodies in the brains of patients with PD with dementia (PDD) and DLB. Since cases of DLB usually have some degree of concomitant AD pathology but also have subcortical impairment, an understanding of visual cognition in PD could also help to determine whether higher order visual cognitive deficits extend into the non-motor and

pre-dementia stages of Lewy body disease. If deficits in visual cognition in non-demented PD are similar to the deficits found in DLB, we could infer that the parkinsonian component of the DLB syndrome is probably contributing strongly to the deficit in visual cognition.

Clinical Characterization and Cognitive Impairment in PD

Parkinson's disease (PD) is a progressive neurological disorder characterized by the cardinal motor signs of resting tremor, rigidity, postural abnormality, and bradykinesia (Emre, 2003; Gelb, Oliver, & Gilman, 1999). It is one of the most common movement disorders, and is currently thought to affect approximately 650,000 persons in the United States (Emre, 2003). Currently there is no single test that serves as a gold standard for the diagnosis of PD. Neuropathologically, PD is characterized by loss of dopaminergic neurons in the substantia nigra. Dopamine-replacement therapy is available and effective for the treatment of the motor symptoms associated with the disease, and these treatments are usually taken multiple times per day. Dyskinesias can result from unnecessarily high doses of dopamine-replacement (Zesiewicz, Sullivan, & Hauser, 2007). Major depression and depressive symptoms are common in PD, and apathy is often concurrent with depressive symptoms. Depression and apathy have both been correlated with the postural instability phenotype of PD (Hassan et al., 2014), with apathy more strongly correlated with postural instability than depression. The postural instability and gait disorder (PIGD) phenotype of PD is often associated with a more severe disease course in comparison to the tremor dominant phenotype (Stebbins et al., 2013). REM sleep

behavior disorder (RBD) occurs often in patients with PD and is associated with a decrease in quality of life (Rolinski et al., 2014).

Although PD is most often associated with prominent motor impairment, the disease also impacts cognition (Caviness et al., 2007). Recent research suggests that subtle but detectable cognitive impairment in PD begins earlier than previously realized (Litvan et al., 2011; Litvan et al., 2012). The concept of Mild Cognitive Impairment (MCI) in PD is gaining traction with the development of consensus diagnostic criteria (Litvan et al., 2012). Studies suggest that MCI in PD patients is associated with increased age, increased disease duration, and disease severity (Litvan et al., 2011; Litvan et al., 2012). Some studies suggest that approximately one-quarter of non-demented PD patients would meet criteria for PD-MCI (Aarsland & Kurz, 2010). The most common type of mild cognitive impairment in PD is non-amnestic, single-domain impairment (Litvan et al., 2011; Litvan et al., 2012) usually involving executive function and attention. However, there is significant individual variation in the pattern of MCI observed among PD patients. In PD-MCI, subtle deficits can exist in multiple cognitive domains despite a high level of overall functioning where the deficits are not yet serious enough to warrant a diagnosis of dementia (Litvan et al., 2011).

Dementia is not uncommon in PD (Aarsland, Litvan, et al., 2003). By definition, dementia does not occur at the time of the motor symptom onset in PD, but research suggests that approximately 60-80% of patients with PD may develop dementia ten to fifteen years after the onset of motor symptoms (Aarsland, Andersen,

et al., 2003; Aarsland & Kurz, 2010). When dementia does occur in the course of PD, it appears extremely similar to the presentation of DLB. Patients with PD and dementia (PDD) are often indistinguishable from DLB patients with regard to the results of standard neuropsychological testing (Mosimann et al., 2004; Noe et al., 2004).

Studies of cognition in PD suggest that the cognitive abilities that are disproportionately impaired in DLB are also mildly impaired in populations of non-demented patients with PD (Jacobs et al., 1995; Stern, Marder, Tang, & Mayeux, 1993). Deficits in the domains of attention and frontal-executive functions are very common in PD (G. S. Watson & Leverenz, 2010). Deficits in visual cognition are also apparent in PD, perhaps due to damage to the basal ganglia and its afferent and efferent projections to posterior cortical brain regions (Clower, Dum, & Strick, 2005). Studies of visual cognition in PD have shown deficits on visuospatial orienting and attention tasks and tasks that involve mental rotation. There is also evidence of deficits in size perception, motion detection, and motion discrimination (Cronin-Golomb & Braun, 1997; Ezzati, Khadjevand, Zandvakili, & Abbassian, 2010; Trick, Kaskie, & Steinman, 1994). Additionally, there is evidence for impairment on certain types of visual search tasks that combine elements of visual cognition with visual attention. Some studies show decreased performance by PD patients on single-feature search tasks (Lieb et al., 1999; Tales et al., 2002; Troscianko & Calvert, 1993; Weinstein, Troscianko, & Calvert, 1997), although others do not (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999). Weinstein, Troscianko, and Calvert suggested that

PD patients' impairment on single-feature search was due to the fact that they were employing a dual-feature search strategy on a single-feature search task (Weinstein et al., 1997). A study that did not find a single-feature search deficit in patients with PD (Cormack et al., 2004) used a task designed for patients with dementia that may have been too simplistic to be sensitive to subtle deficits in non-demented PD patients. Taken together, this conflicting evidence impels further investigation of visual cognition in PD to clarify the extent and nature of their deficits.

Neuropathology of PD

Parkinson's disease is characterized by the loss of dopaminergic neurons and the presence of alpha-synuclein positive intraneuronal protein aggregates (i.e. Lewy bodies) in the substantia nigra (Hurelbrink & Lewis, 2011). Lewy bodies and neuron loss are present in additional brainstem nuclei such as the locus coeruleus, dorsal vagal nucleus, and nucleus basalis of Meynert. Lewy bodies are also seen in the hypothalamus and the ganglia in the sympathetic nervous system (Fearnley, Revesz, Brooks, Frackowiak, & Lees, 1991; Jellinger, 2009). Pathology in the substantia nigra and other brainstem nuclei results in the loss of dopaminergic projections from the midbrain to cortex (Hurelbrink & Lewis, 2011). Loss of dopaminergic projections throughout the brain can help explain the motor impairments in PD. Dopamine replacement therapy is able to improve the motor symptoms (Poewe, 2009).

Some cortical Lewy bodies have been found in PD patients (Kovari et al., 2003), but not to the extent seen in DLB. Despite the difference in distribution of Lewy bodies in PD and DLB, there are very few differences in the composition of the

Lewy bodies themselves, regardless of their location in the brain. Brainstem Lewy bodies are remarkably similar to cortical Lewy bodies (Kosaka, Oyanagi, Matsushita, & Hori, 1976; Okazaki, Lipkin, & Aronson, 1961). Some research has shown a correlation between higher quantities of Lewy body pathology and faster cognitive decline in PD (Aarsland et al., 2005). However, there is not convincing evidence for the same correlation in DLB patients (Samuel et al., 1997; Samuel et al., 1996).

Many studies show evidence of deficits in visual cognition in PD that may be related to damage in brain areas important to visual processing. Previous research has shown that contrast sensitivity is impacted in PD, with a decreased ability to see sinusoidal gratings equally well in all directions (Bulens, Meerwaldt, & Van der Wildt, 1988; Lieb et al., 1999; Regan & Maxner, 1987; Trick et al., 1994). Loss of dopaminergic input to the primary visual cortex could be the reason behind this impairment since orientation selective neurons are not found until V1 (Carandini, Movshon, & Ferster, 1998). There is also evidence for reduced metabolic activity (Garnett, Nahmias, & Firnau, 1984) in the visual cortex of non-demented patients with PD. The retina may also be impacted by the systemic loss of dopamine in PD, and this could impact visual ability. However, this deficit is thought to be mediated by dopamine replacement therapy which normalizes retinal dopamine (I. Bodis-Wollner, 1990; I. G. Bodis-Wollner & Paulus, 1999; Wink & Harris, 2000). All patients with PD in the present set of studies were tested “on” medication to avoid these potential deficits in visual processing. Furthermore, all visual tasks were designed at a contrast level well above the threshold where PD patients begin to exhibit difficulty.

Imaging data supports the possibility that there are visual cognition deficits in PD. A recent study using diffusion tensor imaging found that there was extensive and widespread damage to the microstructure of white matter in both the frontal and parietal lobes in patients with PD (Gattellaro et al., 2009). This damage was present in the early stages of PD prior to any dementia. Other imaging studies found correlations between cognitive status and white matter alteration in PD. One study showed that PD-MCI patients had reductions in bilateral parietal white matter tracts that correlated with MMSE scores, as well as posterior parietal hypoperfusion compared with controls. This suggests that white matter damage may contribute to the cognitive impairment in PD. Alterations in function (hypometabolism) may occur first, followed by changes in white matter, and finally gray matter atrophy (Hattori et al., 2012).

Summary

Although a distinct profile of deficits in visual cognition has emerged in DLB, many aspects of visual cognition across the Lewy body spectrum of PD, PDD and DLB need to be addressed. While it is clear that there is a significant degree of visuospatial impairment in DLB, few studies have examined basic visuoperceptual processes like motion discrimination and visual search. The studies in this dissertation will examine the ability of DLB patients to discriminate the direction of simple horizontal motion, and will investigate whether visual search abilities are affected in DLB patients. Additionally, studies of higher order visual cognition will be extended to a population of non-demented patients with PD in order to inform our

understanding of the nature of visual cognition in patients across the spectrum of Lewy body disorders.

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Chapter 2

Motion Discrimination in Dementia with Lewy Bodies and Alzheimer's Disease

ABSTRACT

Objective: Greater occipitoparietal dysfunction in Dementia with Lewy bodies (DLB) than in Alzheimer's disease (AD) suggests that visual processing abilities mediated by the dorsal visual processing stream may be more severely affected in DLB than in AD and effectively differentiate between the two disorders. This was assessed psychophysically using a simple horizontal motion discrimination task that engages the dorsal visual processing stream.

Methods: Participants included mildly-demented patients with DLB, AD or Parkinson's disease with dementia (PDD), non-demented patients with Parkinson's disease (PD), and normal controls (NC). Participants indicated the left or right direction of coherently moving dots that were embedded within dynamic visual noise provided by randomly moving dots. The proportion of coherently moving dots was increased or decreased across trials to determine a threshold at which participants could correctly indicate their direction with greater than 80% accuracy.

Results: Motion discrimination thresholds of DLB and PDD patients were comparable and significantly higher (i.e., worse) than those of patients with AD. The thresholds of AD and PD patients were normal. These results were confirmed in subgroups of DLB/PDD and AD patients with autopsy-confirmed disease. A motion discrimination threshold greater than .23 distinguished between DLB/PDD and AD patients with 67% sensitivity and 85% specificity.

Conclusions: Differential deficits in detecting direction of simple horizontal motion suggest that dorsal processing stream dysfunction is greater in DLB and PDD than in AD. Therefore, performance on simple visual motion discrimination tasks that specifically engage occipitoparietal brain regions may help clinically differentiate DLB from AD.

Structural and functional abnormalities in the occipitoparietal brain region in patients with dementia with Lewy bodies (DLB) suggest that visual processes mediated by the dorsal visual processing stream may be vulnerable to the disease (Albin et al., 1996; Beyer, Larsen, & Aarsland, 2007; Gilman et al., 2005; Higuchi et al., 2000; Ishii et al., 2007; Kasama, Tachibana, Kawabata, & Yoshikawa, 2005; Kasanuki et al., 2012; Minoshima et al., 2001; Mito et al., 2005; Mosconi et al., 2008; R. Watson et al., 2012). Numerous studies in humans and non-human primates indicate that an important function of the dorsal stream is to process stimuli related to motion and location of an object in space (for review, see Ungerleider & Haxby, 1994). Thus, processing features of motion, such as its direction or speed, should be difficult for patients with DLB. Consistent with this possibility, a recent study showed that perception of motion produces lower than normal fMRI activation in the dorsal processing stream (i.e., cortical area V5/MT) of patients with DLB (Taylor et al., 2012). Unfortunately, behavioral measures of motion perception were not obtained, so it is not known if this reduced activity was associated with a perceptual deficit.

Because occipitoparietal dysfunction is greater in DLB than in AD (Higuchi et al., 2000; Kasanuki et al., 2012; Minoshima et al., 2001; Mosconi et al., 2008), differences in the ability to discriminate aspects of motion might distinguish between the two disorders. Two studies that addressed this possibility provide equivocal support. The first showed worse performance in DLB patients than in those with AD on a task that required determining which of two side-by-side displays of moving dots had faster motion (Mosimann et al., 2004). It is possible, however, that the

groups differed in attention processes needed to simultaneously monitor two displays rather than in the ability to judge speed of motion. The second, an fMRI study of complex biological motion processing, showed lower activation in cortical area V5 in DLB than in AD, but only a trend towards slower reaction times in deciding direction of motion (Sauer, ffytche, Ballard, Brown, & Howard, 2006). Difficulty in behaviorally distinguishing between DLB and AD patients with this biological motion discrimination task may be because it engages both motion processing and occipitotemporal-dependent object identity processing that can be affected in both disorders. Previous studies show that patients with AD are impaired on complex motion discrimination tasks that require perceiving shapes from motion (Kim, 2012; Rizzo & Nawrot, 1998).

A better test of the possibility that DLB has a greater effect than AD on dorsal visual processing abilities might be to compare the groups on discrimination of simple horizontal motion. A number of studies show that simple horizontal motion discrimination is preserved in patients with AD (Festa et al., 2005; Rizzo, Anderson, Dawson, & Nawrot, 2000; Rizzo & Nawrot, 1998; Velarde, Perelstein, Ressmann, & Duffy, 2012) (but see Yamasaki et al., 2012), even though they are impaired in discriminating simple motion in an outward or inward radial flow (Rizzo et al., 2000; Rizzo & Nawrot, 1998; Taylor et al., 2012; Tetewsky & Duffy, 1999; Velarde et al., 2012) or simple horizontal motion when radial and horizontal flow trials are mixed throughout the discrimination task (Kavcic, Vaughn, & Duffy, 2011). Simple horizontal motion discrimination has not been examined in patients

with DLB, but their disproportionately severe occipitoparietal dysfunction suggests that it may be worse than in those with AD and effectively distinguish between the two disorders.

Therefore, we compared the ability of patients with DLB or AD to identify the left or right direction of global motion (i.e., coherently moving dots) embedded within dynamic visual noise (i.e., randomly moving dots) in a global coherence paradigm (Festa et al., 2005). We predicted that patients with DLB would require a higher than normal proportion of coherently moving dots to accurately identify the direction of motion (i.e., have a higher perceptual threshold) and would be more impaired than patients with AD. We also examined the performance of cognitively normal patients with Parkinson's disease (PD) and patients with PD and dementia (PDD) to determine if motion processing is affected across the spectrum of Lewy body disorders or only in those with prominent cortical involvement due to Lewy body or combined Lewy body and AD pathology (i.e., PDD or DLB).

METHODS

Participants

One-hundred-eight individuals participated in the study: 21 patients with DLB, 14 patients with PDD, 19 non-demented patients with PD, 29 patients with AD, and 25 cognitively normal controls (NC). The patient groups consisted of clinically diagnosed individuals and those who died subsequent to testing and received a definite diagnosis of disease at autopsy. Neuropathological confirmation at autopsy was obtained in 5 DLB, 1 PD, 3 PDD and 8 AD. The DLB, AD and NC

participants were recruited from the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). The PDD and PD patients were recruited from the ADRC, UCSD Movement Disorders Clinics, or from community neurologists. Clinical diagnoses were based on published criteria and made by board-certified neurologists with expertise in dementia and movement disorders. Neuropathologic diagnoses were made by a board certified neuropathologist with expertise in AD, DLB and PD. Detailed neuropathologic methods and diagnostic procedures are described in supplementary materials (Appendix 1).

Probable DLB was diagnosed clinically using established criteria (McKeith et al., 2005; McKeith et al., 1996) based on the presence of dementia and at least two of three additional core features: mild parkinsonism, well-formed visual hallucinations, and fluctuations in consciousness or attention. In all cases, cognitive decline was the presenting symptom and preceded parkinsonism by more than one year. Idiopathic PD was clinically diagnosed by the presence of at least two of the cardinal motor signs of resting tremor, rigidity, and bradykinesia in accordance with established criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992).

Patients with atypical findings or secondary causes of PD were excluded. PD patients did not have sufficient cognitive or functional decline to warrant a diagnosis of dementia. In accordance with established criteria (Emre et al., 2007), the clinical diagnosis of PDD was based on the presence of at least two of the cardinal motor signs of PD, as well as objective cognitive deficits on neuropsychological tests and functional decline due to cognitive problems. In all cases, motor signs preceded

cognitive decline by more than one year. Probable AD was diagnosed according to NINCDS-ADRDA criteria (McKhann et al., 1984). Elderly NC participants were judged to be cognitively normal following extensive assessment through the ADRC.

Procedure

Participants were tested individually in a quiet, well-lit room. Motor functioning was assessed with procedures outlined in Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) by a board-certified neurologist. The Mini-Mental State Examination (MMSE) and the apparent motion discrimination task were administered by a trained examiner.

The research protocol was reviewed and approved by the human subjects review board at UCSD. Written informed consent to participate in the study was obtained prior to testing from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

Motion Discrimination Task. This psychophysical task was presented on a 12-inch Macintosh iBook. Detailed methods are presented in supplementary materials (Appendix 2). Briefly, the stimulus consisted of a dynamic array of 200 dots of 0.18° diameter presented within a circular aperture of 12° diameter. The apparent motion stimulus was a percept of a subset of dots streaming across the circular aperture (at ~8.24º/sec) amidst randomly moving "noise" dots. Each motion stimulus lasted 1.01 seconds. On any given trial, the signal and noise dots were identical in cue value (i.e., all black or all white presented on a gray background) and

could be distinguished only on the basis of motion information. The luminance value of the dots was randomly assigned across trials. The participant was seated at a viewing distance of approximately 75 cm in front of the computer. The angle of the screen was adjusted to eliminate glare and otherwise provide maximal visibility of the stimuli. The task was described while the participant viewed sample displays. The participant was told that the dots would be in motion and that a portion of the dots would be moving in a consistent direction, either left or right. Their task was to identify the motion direction, guessing if necessary. When the participant indicated a direction verbally or nonverbally (by pointing), their response was recorded by the examiner. They were told that across trials the number of dots moving in a consistent direction would be adjusted according to their performance. Practice trials were administered until the participant was comfortable with the task. Signal strength thresholds were obtained using a QUEST staircase procedure (A. B. Watson & Pelli, 1983) in which the number of signal dots necessary to accurately discriminate direction of motion was adjusted across trials to an estimated threshold value that would yield 82% correct performance.

Forty-three test trials were administered to obtain a threshold value. Signal strength remained constant in the first three trials (to allow subjects to get into set) and then adjusted according to the staircase procedure in the remaining forty trials. The starting value of the staircase for the first threshold determination was 0.25 signal strength (i.e., 50 signal dots, 150 noise dots). Subsequent threshold determinations started at the participant's previous threshold. Threshold was

determined two times. If the two threshold values differed by more than 0.10 signal strength, a third threshold was determined. The two best thresholds were averaged for the measure of motion discrimination ability.

Data Analysis

Statistical analyses were completed using SPSSv20. Group differences in demographic characteristics, clinical test scores and motion discrimination thresholds were tested using one-way analysis of variance (ANOVA). Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. Post-hoc pair-wise group comparisons were made with Tukey's Least Significant Difference (LSD) test (alpha for significance set at $p<.05$). Correlations between MMSE scores and motion discrimination thresholds were examined with Pearson product-moment (r) tests. Comparisons of motion discrimination thresholds between groups of patients with or without visual hallucinations were made with student's t-tests. The effectiveness of the motion discrimination threshold in differentiating between DLB and AD patients was examined using receiver-operating characteristic (ROC) analyses to determine the area under the curve (for overall effectiveness) and the sensitivity and specificity for differentiating between the two patient groups at an optimal cut-off threshold score.

RESULTS

Participant Characteristics

Of the 108 participants who attempted the motion discrimination task, 17 (DLB=6, PDD=4, PD=3, AD=3 and NC=1) could not attain a reliable threshold

(i.e., 2 of 3 thresholds were greater than .40, a point above which the QUEST procedure may be unreliable with 40 trials) and were dropped from further analyses. The final sample included 24 NC participants and 15 DLB, 10 PDD, 16 PD, and 26 AD patients. The final groups did not differ significantly in age ($F(4,86) = 1.60$; $p>0.1$; ${}_p\eta^2=0.07$) or years of education ($F(4,86) = 0.50$; $p>0.7$; ${}_p\eta^2=0.02$) (See Table 2.1). The DLB, PDD, and PD groups, but not the AD or NC groups, included significantly more men than women ($X^2(4) = 9.64$; $p<.05$). As expected, groups differed in MMSE scores ($F(4, 85)=17.24$; $\underline{p} < 0.001$; ${}_p\eta^2 =0.45$). The MMSE scores of DLB, PDD and AD patients did not differ, but were significantly lower than those of the PD and NC groups. The MMSE scores of the PD and NC groups did not differ. Patients with DLB, PDD, or PD scored higher than AD patients or NC participants (the latter two did not differ) on the UPDRS ($F(4, 89)=34.2$; $\underline{p}<0.001$; ${}_p\eta^2 =0.62$). PDD, DLB and PD patients did not differ from each other.

Motion Discrimination Thresholds

The mean motion discrimination thresholds achieved by the DLB, PDD, PD, AD and NC groups are shown in Figure 2.1. There were significant differences in motion discrimination thresholds among the groups ($F(4, 86)=5.98$; $\underline{p}<0.001$; ${}_p\eta^2=0.22$). Post-hoc pair-wise comparisons showed that DLB and PDD patients had significantly higher thresholds than AD patients, PD patients or NC participants. There was no significant difference in the thresholds of DLB and PDD patients. Motion discrimination

thresholds of AD patients, PD patients, and NC participants were not significantly different.

Analyses of motion discrimination thresholds were repeated with only autopsy-confirmed cases. The 5 patients with definite DLB and the 3 with definite PDD were combined into a single group (i.e., a Lewy Body Dementia group) and compared to the 8 patients with autopsy-confirmed AD (Figure 2.2). Patients with Lewy Body Dementia had significantly higher motion discrimination thresholds than patients with AD ($t(14)=2.40$; $p<0.05$). There were no significant correlations between motion discrimination thresholds and MMSE scores for a combined DLB/PDD group ($r=-.07$; $p=0.73$) or for the AD group ($r=-.10$; $p=0.63$). DLB/PDD patients with visual hallucinations had marginally higher motion discrimination thresholds (mean = .30, standard deviation = .08) than those without hallucinations (mean = .23, standard deviation =.09) ($t(23) = 2.08$; $p=0.05$); however, DLB/PDD patients with ($t(36)=4.97$; $p<.001$) or without ($t(37)=2.12$; $p=0.04$) visual hallucinations had higher motion discrimination thresholds than AD patients.

A receiver-operating-characteristic (ROC) curve was plotted to compare how effectively motion discrimination threshold differentiated patients with DLB from those with AD (Figure 2.3). The area under the curve was .78. Because it was decided *a priori* that sensitivity and specificity were of equal importance, the optimal cut-off was chosen to be where the sum of sensitivity and specificity reached a maximum value. An optimal cut-off threshold score of .23 provided 67%

sensitivity for having DLB and 85% specificity for not having DLB (i.e., for having AD).

Values were similar when the combined DLB/PDD group was compared to AD. The area under the curve was .79, sensitivity was 68%, and specificity was 85% for an optimal cut-off threshold score of .23.

DISCUSSION

Mildly-demented patients with DLB or PDD were impaired in the ability to discriminate direction of simple horizontal motion. Equally-demented patients with AD, in contrast, performed at a level that was indistinguishable from normal controls. These results are consistent with numerous studies which show that structural and metabolic abnormalities in areas of the brain related to visual processing are more pronounced in patients with DLB than in those with AD. Functional neuroimaging studies using SPECT, PET or arterial spin labeling MRI consistently show a pattern of posterior cortical hypometabolism in patients with DLB that is not apparent in patients with AD (Albin et al., 1996; Gilman et al., 2005; Higuchi et al., 2000; Ishii et al., 2007; Kasama et al., 2005; Minoshima et al., 2001; Mito et al., 2005; Mosconi et al., 2008). A study using diffusion tensor imaging found decreased integrity of occipitoparietal white matter tracts in patients with DLB compared to more diffuse white matter damage in patients with AD (R. Watson et al., 2012). In addition, neuropathologic studies show that white

matter spongiform change (Higuchi et al., 2000), gliosis (Higuchi et al., 2000) and α-synuclein immunoreactivity (but not number of Lewy bodies) in visual areas (i.e., Brodmann's areas 17 and 18) are greater in DLB than in AD (Kasanuki et al., 2012).

Patients with DLB and patients with PDD displayed comparable motion discrimination deficits. This finding is consistent with the similarity in the neuropathology of the two disorders. Although brainstem pathology may be more pronounced in PDD than DLB and contribute to earlier and more prominent movement disorder, both groups have extensive cortical pathology that includes Lewy bodies, Lewy neurites, and in many cases, neuritic plaques and neurofibrillary tangles of AD (Tsuboi & Dickson, 2005). Aspects of this neocortical pathology extend into posterior cortical areas (Higuchi et al., 2000; Kasanuki et al., 2012) and likely contribute to the motion discrimination deficits observed in the present study. The finding that basic horizontal motion discrimination was normal in non-demented patients with PD is consistent with previous results (Amick, Cronin-Golomb, & Gilmore, 2003) and suggests that the deficit observed in the DLB and PDD patients is not related to subcortical dysfunction common to the three conditions.

Replicating previous studies (Festa et al., 2005), simple horizontal motion discrimination was normal in patients with AD. This finding is consistent with the relative preservation of primary visual and occipitoparietal visual association cortices in AD (O'Brien et al., 2001). Although patients with AD are often impaired on tests of visuospatial or visuoperceptual ability (for review, see Salmon & Hamilton, 2006), these deficits may be largely related to dysfunction in the ventral

visual processing stream and primarily affect performance on tasks that require object recognition (for review, see Possin, 2010) or the integration of information across visual streams (e.g., Festa et al., 2005; Rizzo & Nawrot, 1998). Even when these visuospatial and visuoperceptual processing deficits are apparent, they are generally milder in patients with AD than in those with DLB who are at a similar level of global cognitive impairment (for reviews, see Metzler-Baddeley, 2007; Troster, 2008).

From a clinical perspective, the motion discrimination task was moderately effective at distinguishing between mildly-demented patients with DLB or AD. The most effective cut-off threshold score had 67% sensitivity and 85% specificity for differentiating patients with DLB from those with AD. The high specificity and moderate sensitivity indicates that good performance on the test was more strongly associated with the absence of DLB (and the presence of AD) than poor performance was associated with the presence of DLB (and the absence of AD). Better ability to identify those demented patients who do not have DLB than those with DLB is consistent with a previous study which showed that the absence of marked visuospatial impairment early in the disease predicts the likely absence of Lewy body pathology in demented patients who have AD pathology at autopsy (i.e., visuospatial impairment is a negative predictor of DLB (Tiraboschi et al., 2006)). Clinical identification of visuoperceptual deficits in patients with DLB using the simple motion discrimination task may also provide important prognostic information. Previous research shows that the early occurrence of marked

visuoperceptual or visuospatial deficits in patients with DLB is predictive of a more malignant disease course (Hamilton et al., 2008) and correlated with a higher prevalence and incidence of visual hallucinations (Hamilton et al., 2012). Visual hallucinations were associated with worse motion discrimination in the present study, but even DLB patients without visual hallucinations had worse motion discrimination than patients with AD. The relationship between these features of DLB and simple motion discrimination deficits warrants further research.

Additional research is also needed to identify the neural basis of the motion discrimination deficits of patients with DLB and PDD. In the present study, autopsy confirmation of disease was available in only 8 DLB/PDD cases and 8 AD cases. It is noteworthy that the overall results were replicated in this relatively small autopsy-confirmed sample. Larger autopsy-confirmed samples would allow examination of the differential contributions of various types of pathology (e.g., Lewy bodies or neurites, neuron or synapse loss, concomitant AD pathology), and their location, to the motion discrimination deficit of patients with DLB or PDD. Autopsy-confirmed samples would also allow examination of any contribution simple motion discrimination performance might make to the accurate clinical diagnosis of DLB beyond that of the clinical features that are currently used (i.e., mild parkinsonism, visual hallucinations, fluctuations in consciousness or attention). Finally, functional imaging studies that compare occipitoparietal activation during the simple horizontal motion discrimination task in patients with DLB and AD might identify group differences in both neural activation patterns

and behavioral performance. Past functional imaging studies have been suggestive but inconclusive in this regard (e.g., Mosimann et al., 2004; Sauer et al., 2006), perhaps because they have focused on complex motion processing that engages brain areas affected in both disorders.

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Chapter 2, in full, was submitted for publication in 2013 with the following co-authors: Landy, Kelly M.; Salmon, David P.; Galasko, Douglas; Filoteo, J. Vincent; Festa, Elena K.; Heindel, William C.; Hansen, Lawrence A.; Hamilton, Joanne M. The dissertation author was the primary investigator and author of this paper.

Table 2.1: Mean (Standard Deviation; SD) Age, Education, Mini-Mental State Exam (MMSE) and Uniform Parkinson's Disease Rating Scale (UPDRS) scores for the final sample of Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD). The percentage of males in each group, and the percentage of DLB, PDD and AD patients with past or current visual hallucinations is also shown.

	NC	PD	DLB	PDD	AD
	n = 24	n = 16	n = 15	n = 10	n = 26
Age	73.7 (6.8)	71.0 (8.0)	75.1 (8.2)	77.3 (8.2)	75.0 (4.3)
Sex (% men)	50%	75%	87%	90%	58%
Education	16.2 (2.4)	16.0 (3.0)	15.9 (2.2)	15.6 (1.8)	15.2 (3.1)
MMSE	29.4 (0.9)	28.3 (1.9)[1]	24.1 (3.8)	24.4 (4.4)	23.5 (3.4)
UPDRS	1.5 (4.1)	19.5 (7.3)	21.3 (13.8)	19.0 (5.6)	2.0 (4.4)
Hallucinations	------	------	60%	30%	15%

[1] The Mattis Dementia Rating Scale instead of the MMSE was administered to two non-demented PD patients. In both cases the patients' scores were within the normal range (142/144 and 143/144).

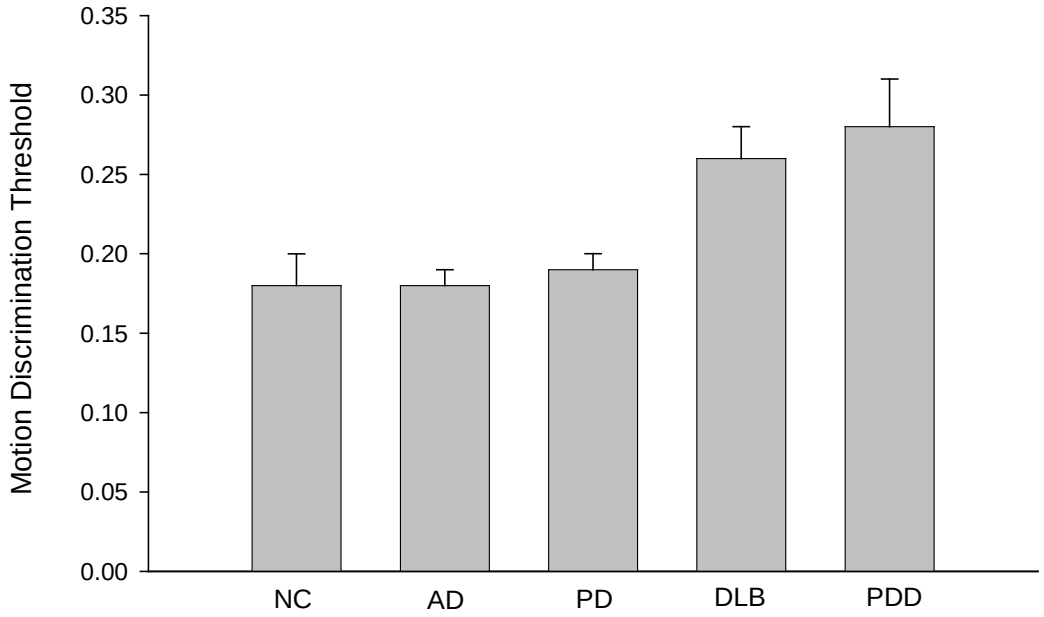

Figure 2.1: The mean motion discrimination thresholds achieved by patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Alzheimer's Disease (AD) or Parkinson's Disease (PD), and normal control (NC) participants. Error bars are the standard error of the mean. The DLB and PDD groups had significantly higher thresholds than other groups, but did not differ from each other. Thresholds for the AD, PD and NC groups did not significantly differ from each other.

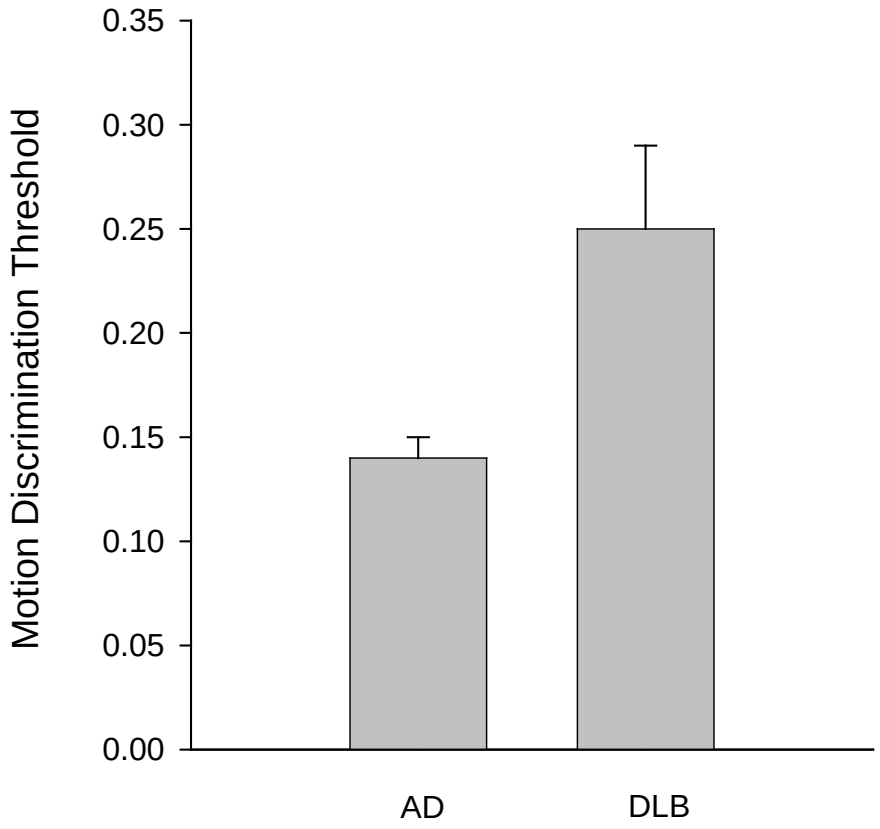

Figure 2.2: The mean motion discrimination thresholds achieved by patients with autopsy- confirmed Lewy Body Dementia (LBD) (i.e. Dementia with Lewy Bodies or Parkinson's Disease with Dementia) or Alzheimer's Disease (AD). Error bars are the standard error of the mean. The LBD group had a significantly higher threshold than the AD group.

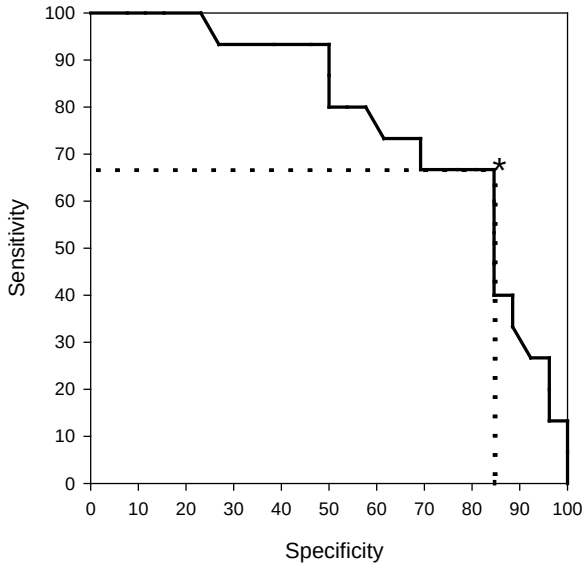

Figure 2.3: Receiver Operating Characteristic (ROC) curve comparing patients with Dementia with Lewy Bodies and patients with Alzheimer's disease on the motion discrimination task. The sensitivity and specificity of the most effective cut-off threshold score (.23*) is indicated with broken lines.

Appendix 1: Neuropathologic Methods and Diagnosis

Autopsy was performed within 12 hours of death using a protocol described by Terry, Peck, DeTeresa, Schechter and Horoupian (Terry, Peck, Deteresa, Schechter, & Horoupian, 1981). Briefly, the left hemibrain was fixed by immersion in 10% formalin for 5–7 days. Paraffin-embedded blocks from midfrontal, rostral superior temporal and inferior parietal neocortex, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons were cut at 7-μm thickness for hematoxylineosin (H & E) and thioflavin-S counts. Total plaques, neuritic plaques, and neurofibrillary tangle (NFT) counts, and the presence or absence of Lewy bodies in the locus coeruleus, substantia nigra, nucleus basalis and neocortex, were determined by the same examiner (LAH) using the same criteria. A modified Braak stage was obtained for each case using methods described by Hansen and Terry (Hansen & Terry, 1997). Briefly, the modified Braak stage for AD pathology involves counting the number of NFT in at least five neuron clusters in layer two of the entorhinal cortex and then averaging the results. Cases with modified Braak Stage I to IV have fewer than 18 tangles, on average, in layer two of the entorhinal cortex and sparse neocortical tangles. Modified Braak Stage V cases have moderate numbers of tangles in at least two neocortical sections. In modified Braak Stage VI, all neocortical areas assessed have at least moderate numbers of tangles. Lewy bodies were absent in cases of "pure" AD.

The DLB cases met consensus criteria for the pathologic diagnosis of DLB based on H & E staining, antiubiquitin immunostaining, and anti-α-synuclein immunostaining. Cases were only construed as DLB if Lewy bodies were found in the locus coeruleus, substantia nigra, and/or nucleus basalis of Meynert, as well as in the neocortex. Since all cases categorized as DLB had at least some Lewy bodies in multiple brainstem nuclei and the superior temporal gyrus neocortex, all Lewy body cases in the study qualified for either limbic (transitional) or diffuse neocortical categories proposed in consensus guidelines for the pathologic diagnosis of DLB (McKeith et al., 1996). Furthermore, all DLB cases were neocortical Stage V or VI according to the proposed Lewy body–based staging of brain pathology related to sporadic Parkinson disease (Braak et al., 2003). Cases were not classified as DLB if Lewy bodies were only found in the amygdala.

The PDD cases meet neuropathologic criteria for DLB, either limbic or diffuse neocortical type based on Lewy bodies in the locus coeruleus, substantia nigra, substantia innominate, and limbic neocortex. PDD cases were segregated from DLB cases based on clinical presentation. If the patients had been diagnosed with Parkinson's disease at least a year before receiving diagnoses of dementia, they were classified as PDD. If dementia was the presenting clinical manifestation of Lewy body disease, or if dementia and Parkinsonism were initial and concurrent at presentation, the brains were classified as DLB.

Of the 8 DLB/PDD cases, 2 achieved a high AD-Braak stage of V or VI, indicative of notable cortical neurofibrillary tangle formation, and 6 achieved a

low Braak stage (i.e., I-IV). All 8 of the AD cases achieved a high AD-Braak stage of V or VI.

Appendix II: Motion Discrimination Task Methods

Visual stimuli for the apparent motion discrimination task were created using the Psychophysics Toolbox extensions for MATLAB (Brainard, 1997; Pelli, 1997). The task was presented on a 12-inch Macintosh iBook LCD screen with 1024 x 768 pixel resolution at a viewing distance of approximately 75 cm. The stimulus consisted of a dynamic array of 200 dots of 0.18° diameter presented within a circular aperture of 12° diameter. The apparent motion stimulus was produced by presenting fifteen successive frames of static dots with an inter-frame interval of 67ms. Across the successive frames, the signal dots were systematically offset 0.55° horizontally while the noise dots were given new randomly-selected x-y positions. The resulting percept was that of a subset of dots streaming across the circular aperture (at ~8.24°/sec) amidst flickering noise. Signal dots had a five-frame limited lifetime after which new signal dots were selected from noise dots. These new signal dots continued the same horizontal trajectory relative to their positions on the previous frame. On the first frame of each trial, random positions within the circular aperture were chosen for the dots. The initial positions of the signal dots were limited to only those positions for which the motion trajectory would not extend beyond the aperture edge across the five-frame dot-life. The noise dots were given new x-y positions on each frame of the motion stimulus. The direction of motion was randomized (left or right) from trial to trial. Each motion stimulus lasted for a total duration of 1.01 seconds.

A PR-650 Spectra colorimeter was used to measure the luminance (Y) and Commission Internationale de l'Êclairage (CIE) coordinates (x,y) of the stimuli. Black (Y= 0.41 cd/m^2; x=0.259, y= 0.268) or white (Y= 90.67 cd/m^2; x= 0.321, y= 0.335) dots were presented on a gray (Y= 6.34 cd/m^2; x= 0.269, y= 0.276) background (giving a Michelson contrast of 88% or 87% for the black or white dots from the background, respectively). On any given trial, the signal and noise dots were identical in cue value (i.e., all black or all white) and could be distinguished only on the basis of motion information. The luminance value of the dots was randomly assigned across trials.

Signal strength thresholds were obtained using a QUEST staircase procedure (A. B. Watson & Pelli, 1983). This procedure samples a range of values across trials, based on the subject's responses in conjunction with a Bayesian estimator, to converge on a value that would yield 82% correct performance on the task. Unlike other threshold procedures, this method allows a stable threshold to be obtained with a relatively low number of trials. Forty-three test trials were administered to obtain a threshold value. The signal strength remained constant in the first three trials (to allow subjects to get into set) and then was adjusted according to the staircase procedure in the remaining forty trials. The starting signal strength value of the staircase was 0.25 (i.e., 50 signal dots and 150 noise dots).

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Chapter 3

Visual Search is Differentially Impaired in Dementia with Lewy Bodies, Parkinson's Disease with Dementia, and Alzheimer's Disease

Navigating a complex visual environment is a task that most people complete easily and with relatively little conscious effort. However, patients with neurodegenerative diseases often have marked impairment in the ability to pick out a target among distractors while processing a visual scene. Visual search processes by which we recognize and detect objects in a complex scene have historically been divided into two components (Treisman & Gelade, 1980). One component, single-feature (or parallel) search is generally considered to involve pre-attentive identification of a salient feature in a scene. Often called "pop-out" search, the target seems to literally "pop out" from the background. This process is thought to be relatively automatic in nature with multiple features of a visual scene processed in parallel (Treisman & Gelade, 1980). In single-feature search, the amount of time needed to identify the target is generally constant no matter how many distractors accompany a target in the visual scene; additional distractors in the scene do not come with any time cost (Treisman & Gelade, 1980).

The second component of visual search is feature conjunction. In contrast to single-feature search, this element of visual search is more complex and requires higher order visual processing as multiple features of the target item (i.e., shape and color) must be conjoined before the target item can be correctly identified (Treisman & Gelade, 1980). Dual-feature search is an effortful process in which the environment

is searched sequentially. Thus, as the number of distractors in the visual scene increases, so does the reaction time to find the target (i.e., there is an increased time cost in serial search) (Treisman & Gelade, 1980).

Neural correlates of serial and parallel search have been localized to specific regions in the brain. Evidence suggests that single-feature search is mediated by primary and secondary visual cortex (Lamme, 1995; Lee, Yang, Romero, & Mumford, 2002), whereas search requiring feature conjunction is mediated by parietal and temporal cortex (Corbetta, Shulman, Miezin, & Petersen, 1995; Stemmler, Usher, & Niebur, 1995; Wachsmuth, Oram, & Perrett, 1994). This dissociation is supported by a study that showed that patients with lesions in the occipito-temporal cortex were impaired on parallel search tasks but not serial search tasks (Humphreys, Freeman, & Muller, 1992). In another study, patients with lesions in the occipital-parietal cortex were impaired in serial search but not in parallel search (Atkinson & Braddick, 1989). When parietal cortex was inactivated by transcranial magnetic stimulation, serial search was impaired but parallel search was not (Ashbridge, Walsh, & Cowey, 1997; Walsh, Ellison, Battelli, & Cowey, 1998).

In older adults, neurodegenerative disease can impact visual attention and performance on visual search tasks. Alzheimer's disease (AD) is an age-related degenerative brain disorder that is the leading cause of memory impairment and global cognitive decline in the elderly. Previous work by Foster et al. showed that AD patients were disproportionately impaired on a conjunction search task; their reaction time increased disproportionately with increasing array size in a conjunction task,

even more than would be expected with global cognitive slowing (Foster, Behrmann, & Stuss, 1999). Tales et al. tested patients with AD on single-feature and dual-feature conjunction search tasks while keeping attentional load similar in the two tasks. Tales et al. found that AD patients were impaired in the conjunction task, but not in the single-feature task, compared to healthy older adults (Tales et al., 2002). This result suggests that AD patients may have difficulty when tasks require integration of more than one type of feature, and these impairments are not solely attention-related in AD (Tales et al., 2002). Tales and colleagues hypothesized that AD patients' deficits in conjoining multiple features of a stimulus may result from damage to cortico-cortical circuits which connect various distinct visual processing brain regions. Consistent with this possibility, when AD patients do exhibit notable visual symptoms, pathology tends to occur disproportionately within visual association pathways (Morrison, Hof, & Bouras, 1991).

Although visual perception is usually relatively spared in AD, DLB affects visual perception and visuospatial abilities relatively early in the course of disease (Ala, Hughes, Kyrouac, Ghobrial, & Elble, 2001; Galasko, Katzman, Salmon, & Hansen, 1996; Mori et al., 2000; Salmon et al., 1996). Dementia with Lewy bodies overlaps clinically and pathologically with AD, but there are important distinctions between the two neurodegenerative diseases. DLB is characterized pathologically by Lewy bodies and neuron loss in areas of the brain that are affected by Parkinson's disease (Galasko et al., 1996) and has Lewy bodies diffusely distributed in the

neocortex. DLB also commonly occurs with concomitant Alzheimer's disease pathology such as neocortical plaques and tangles (Galasko et al., 1996).

Although a number of neuropsychological studies have shown that DLB patients display a pattern of cognitive deficits that is similar to patients with AD, DLB patients show disproportionately severe deficits in visuospatial ability compared to AD patients (Ala et al., 2001; Galasko et al., 1996; Mori et al., 2000; Salmon et al., 1996). Marked impairment in the visuospatial cognitive domain is often evident early in the course of DLB and is a strong negative predictor of DLB pathology – i.e., its absence predicts absence of Lewy body pathology (Tiraboschi et al., 2006). Severity of visuospatial deficits also appears to be a strong indicator of the DLB phenotype, such that DLB patients with severe deficits have a more malignant disease course (Hamilton et al., 2008) and greater occurrence of visual hallucinations (Hamilton et al., 2012). In addition, DLB patients display deficits in executive function and attention, and they may have less of a memory impairment than AD patients (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; Hamilton et al., 2004; Salmon et al., 1996).

Neuroimaging studies have found structural and metabolic abnormalities in the areas of the brain related to visual processing in DLB patients, including primary visual cortex (Albin et al., 1996; Higuchi et al., 2000; Minoshima et al., 2001) Functional imaging studies using SPECT and PET imaging have shown patterns of posterior hypometabolism in DLB patients, particularly in the occipital cortex, which is involved in visual processing (Ishii et al., 2007; Kasama, Tachibana, Kawabata, &

Yoshikawa, 2005; Mito et al., 2005). Structural imaging studies have also noted atrophy in temporal, parietal, and occipital regions consistent with these functional imaging abnormalities (Beyer, Larsen, & Aarsland, 2007). This evidence suggests there are important anatomical abnormalities in the brains of DLB patients which may relate to their visuospatial deficits.

Given the disproportionately severe visuospatial deficits and attentional difficulties seen clinically in patients with DLB, visual search tasks should serve as a good means of identifying these patients since both of these elements are involved in visual search task performance. However, few studies have directly examined the performance of DLB patients on visual search tasks.

Only one set of studies to date has examined visual search mechanisms in DLB using both single-feature and dual-feature search tasks (Cormack, Gray, Ballard, & Tovee, 2004). On each trial, subjects were instructed to state whether a target stimulus (red circle) was present or absent. In the single-feature parallel search task, the target red circle was placed in a field of 2, 8, or 16 green circles, which served as distractors. In the dual-feature serial search task, subjects were instructed to state whether the target red circle was present among 2, 8, or 16 distractors; this time, the distractors were green circles and red squares. With the rationale that motor difficulties in this patient population could impair the validity of reaction time measures, only the accuracy of verbal responses was measured; no reaction time data was collected. In order to measure the speed of subjects' visual search performance, the experimenters varied the length of time the stimuli were displayed. The stimulus screens could be

displayed for either 800 ms, 400 ms, or 200 ms. After each stimulus was shown, a written prompt was displayed on the screen, which asked the subjects whether the target was present or absent. The results demonstrated that DLB patients performed worse than PD, AD, and control subjects on both the single-feature search task and the dual-feature search search task (Cormack et al., 2004). Fluctuations in attention were cited as one reason for DLB patients' impairment in single-feature parallel search tasks relative to other patient groups. Cormack et al. maintained that their results were consistent with the hypothesis that DLB patients are impaired on a parallel search task due to occipital hypometabolism and related pathology.

Several methodological features of the study by Cormack et al. make interpretation of their results difficult. These methodological concerns were addressed in the present study. First, the studies described in Cormack et al. (Cormack et al., 2004) displayed the visual scene to DLB patients for less than one full second, and asked the patients to verbally respond to indicate whether or not they had seen the target stimulus. With motor and cognitive slowing in mind, the visual scene stimuli in the present study remained on the screen for three seconds, in order to give patients an adequate amount of time to process the visual scene. Second, the studies presented in Cormack et al. did not include a reaction time component (Cormack et al., 2004); the present studies did include a reaction time measure in order to quantify performance differences across patient groups. Third, the present study included several patient groups for direct comparison with regard to visual search performance. We recruited non-demented PD patients to serve as a control for the motor deficits that occur in

DLB patients. To determine if disproportionate visual search deficits are specific to DLB, we included patients with Parkinson's disease and dementia (PDD) as another Lewy body disease group. In PDD, a diagnosis of Parkinson's disease had been made at least one year prior to notable symptoms of cognitive impairment that led to a diagnosis of dementia. We also included AD patients as a control for dementia, to ensure that any differences in visual search patterns in DLB and PDD patients were not due simply to the presence of dementia. These patient groups allow us to draw conclusions about which, if any, aspect of visual search performance may be driven by the presence of Lewy bodies or the presence of AD pathology.

Because DLB patients have a high rate of concomitant AD pathology upon autopsy (Armstrong, Cairns, & Lantos, 1998), the predicted pattern of DLB patients' performance on visual search tasks was not completely clear. It is plausible that basic visual processing deficits in DLB patients will lead them to perform in an unexpected pattern on visual search tasks; however, given the high rate of concomitant AD pathology in DLB patients, it is also possible that DLB patients will perform visual search tasks in a pattern that is very similar to that of AD patients. DLB pathology could merely exacerbate the impairment that AD patients display when visual search tasks require the conjunction of multiple features. However, a different pattern of impairment may arise in DLB patients as a result of their posterior cortical abnormalities and the combination of Lewy body and AD pathology in the brain. We hypothesize that AD patients will show intact performance in single-feature search and impairment on conjunction search, consistent with results from previously published

studies. In PD patients, we hypothesize that motor impairment might slow performance on both visual search tasks, and that the combination of dementia and motor impairment in PDD patients could lead to deficits on both types of visual search tasks.

METHODS

Participants

Ninety-five individuals participated in the study: 20 patients with DLB, 13 patients with PDD, 18 non-demented patients with PD, 31 patients with AD, and 13 cognitively normal controls (NC). The DLB, PDD, AD and NC participants were recruited from the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC). The PD patients were recruited from the UCSD Movement Disorders Clinic or from community neurologists.

The patient groups consisted of clinically diagnosed individuals and those who died subsequent to testing and received a definite diagnosis of disease at autopsy. Neuropathologic confirmation at autopsy was obtained in 7 patients with DLB and 6 with AD. Neuropathologic diagnoses were made by a board-certified neuropathologist with expertise in AD, DLB and PD. Detailed neuropathologic methods and diagnostic procedures are described in supplementary materials (Appendix 1 of Chapter 2).

Clinical diagnoses were based on published criteria and made by board-certified neurologists with expertise in dementia and movement disorders. Probable DLB was diagnosed clinically using established criteria (McKeith et al., 2005;

McKeith et al., 1996) based on the presence of dementia and at least two of three additional core features of mild parkinsonism, well-formed visual hallucinations, and fluctuations in consciousness or attention. In all cases, cognitive decline was the presenting symptom and preceded parkinsonism by more than one year. Idiopathic PD was clinically diagnosed by the presence of at least two of the cardinal motor signs of resting tremor, rigidity, and bradykinesia in accordance with established criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992). Patients with atypical findings or secondary causes of PD were excluded. PD patients did not have sufficient cognitive or functional decline to warrant a diagnosis of dementia. In accordance with established criteria (Emre et al., 2007), the clinical diagnosis of PDD was based on the presence of at least two of the cardinal motor signs of PD, as well as objective cognitive deficits on neuropsychological tests and functional decline due to cognitive problems. In all PDD cases, motor signs preceded cognitive decline by more than one year. Probable AD was diagnosed according to criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984). Elderly NC participants were judged to be cognitively normal following extensive neurological, medical, psychiatric and neuropsychological assessment through the UCSD ADRC.

Procedure

Participants were tested individually in a quiet room with ambient lighting. Motor functioning was assessed with Part III of the Unified Parkinson’s Disease

Rating Scale (UPDRS) by a board-certified neurologist. The Mini-Mental State Examination (MMSE), Dementia Rating Scale (DRS; (Mattis, 1988)) and three visual attention tasks were administered by a trained examiner. The research protocol was reviewed and approved by the human subjects review board at UCSD. Informed consent to participate in the study was obtained prior to testing from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

The three visual attention tasks were a simple visual detection task, a single-feature visual search task, and a dual-feature visual search task. The three tasks were presented on a laptop computer with a 17" Dell Flat Panel LCD monitor. Participants viewed the screen from a distance of approximately 75 cm. Stimulus control, timing and response recording were controlled using E-Prime software. Responses consisted of a button press on a Psychology Software Tools 200a Serial Response box. In all cases, participants were instructed to use their dominant hand to press a 1 cm x 1 cm button on the response box. The response box was modified so that only one button (the far left) was accessible, to reduce the likelihood of erroneous responses due to problems with fine motor control. Prior to beginning the test session, participants were familiarized with the response box.

Stimuli were a solid black circular dot (0.9˚ in diameter) for the simple visual detection task, solid black and solid white dots (each 0.9˚ in diameter) for the single-feature visual search task, and solid black and solid white dots (each 0.9˚ in diameter), as well as solid black squares (0.9˚ diagonal), for the dual-feature visual search task.

All stimuli were presented against a gray background. Stimuli were created with Adobe Photoshop.

The simple visual detection task was presented first, followed by the single-feature visual search task and the dual-feature visual search task. The order of the latter two tasks was counterbalanced across participants. A short rest period was provided between tasks.

Simple Visual Detection Task. In this task, participants were instructed to respond with a button press as soon as they saw a single target stimulus (i.e., a black dot) appear on the screen. The position of the target was determined pseudo-randomly, with the stipulation that the target could appear with equal likelihood in all quadrants of the display. The target remained on the screen until a response was made. Reaction time was measured in milliseconds (ms) on each of 20 trials. Five practice trials were initially presented to orient the participant to the task and ensure that they used the response box accurately.

Single-Feature Visual Search Task. In this task participants had to determine whether or not a target stimulus (i.e., a black dot) was present among 3, 6, or 12 distractor stimuli (i.e., white dots). The target and distractors were presented against a gray background. The position of the target was determined pseudo-randomly, with the stipulation that it could appear with equal likelihood in all quadrants of the display. The distractor stimuli appeared at random locations throughout the display. There were a total of 120 trials: 60 target-present trials with 20 each having 3, 6 or 12 distractors, and 60 target-absent trials with 20 each having 4, 7, or 13 distractors.

Thus, an equal number of stimuli appeared on target-present and target-absent trials. Trials were presented in four blocks of 30. Each block contained an equal number of the 6 trial types. The various trial types were presented randomly within blocks. The blocks were separated by a short rest period to reduce eye strain and visual fatigue.

At the start of the task, participants were familiarized with the target and distractor stimuli and instructed to press the response button as quickly as possible if the target dot was in the display. They were told not to respond if the target was absent. On each trial a fixation cross appeared for 500 ms in the center of the screen, followed immediately by the stimulus display. The stimulus display remained on-screen until the participant responded, or for a maximum of 3 seconds (well within the average response time reported for PD patients and AD patients). Immediately after a response or after 3 seconds with no response, the fixation cross for the start of the next trial appeared. Accuracy was recorded for each trial. Reaction time was recorded for trials with a response. The primary measure of interest was reaction time on target-present trials. Therefore, if a target-present trial ended after three seconds without a response, the trial was re-administered (with the same display) at the end of the 30 trial block. Similarly, if an anticipatory response occurred less than 100 ms after stimulus presentation on a target-present trial, the trial was rejected and re-administered (with the same display) at the end of the 30 trial block. This was repeated until all 15 target-present trials in a block had a response. In this way, we could examine performance 1) based only on the first 30 trials in each block with any of the 15 target-present trials without a response considered missing, or 2) based on the 15

target-present trials with a response that included those re-administered at the end of the 30-trial block. A third option was to examine performance based on only the first 30 trials in each block, assigning a maximum reaction time of 3000 ms to any of the 15 target-present trials without a response.

Dual-Feature Visual Search Task. This task was designed exactly as the single-feature visual search task with the exception that there were two types of distractors on each trial, those that differed from the target (a black dot) only in luminance (i.e., white dots) and those that differed only in shape (i.e., black squares). Thus, participants had to determine whether or not a target stimulus (i.e., a black circle) was present among 3, 6, or 12 distractor stimuli (i.e., white dots and black squares). An equal number of white dot and black square distractors were presented on each trial, with the exception that two white dots and one black square appeared on target-present trials with three distractors (equal numbers of trials with 2 white dots and 1 black square, or 1 white dot and 2 black squares, as distractors occurred throughout the block). The target and distractors were presented against a gray background. The position of the target was determined pseudo-randomly, with the stipulation that it appear with equal likelihood in all quadrants of the display. The distractor stimuli appeared at random locations throughout the display. There were a total of 120 trials: 60 target-present trials with 20 each with 3, 6 or 12 distractors, and 60 target-absent trials with 20 each with 4, 7, or 13 distractors. Trials were presented in four blocks of 30. Each block contained an equal number of the 6 trial types with the various trial types presented randomly within blocks. The blocks were separated

by a short rest period to reduce eye strain and visual fatigue. All task procedures, trial methodology and parameters, and scoring were exactly as in the single-feature visual search task.

Data Analysis

Statistical analyses were completed using SPSSv20. Group differences in demographic characteristics and clinical test scores were tested using one-way analysis of variance (ANOVA). Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. Post-hoc pair-wise group comparisons were made with Tukey's Least Significant Difference (LSD) test (alpha for significance set at $p<.05$). Pair-wise group comparisons of gender distribution and prevalence of hallucinations were made with X^2 tests.

Simple Visual Detection Task. Median reaction time was calculated for each subject after anticipatory responses that had occurred less than 100 ms after stimulus presentation were dropped. Group differences in median reaction times were tested using one-way analysis of variance (ANOVA). Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. Post-hoc pair-wise group comparisons were made with Tukey's Least Significant Difference (LSD) test (alpha for significance set at $p<.05$).

Single-Feature and Dual-Feature Visual Search Tasks. Data from the single-feature and dual feature tasks were analyzed separately. Median reaction times on the 3 types of target-present trials (i.e., with 3, 6 or 12 distractors) were calculated for each subject after anticipatory responses that had occurred less than 100 ms after stimulus presentation were dropped. The initial analyses focused only on the first 15

target-present trials in each block (a total of 60 target-present trials) with trials with no response considered missing. The median reaction time data were subjected to repeated measures ANOVA with Group (between subjects) and Distractor Set Size (within subjects repeated measure) as factors. Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. If the Group X Distractor Set Size interaction effect was significant, the interaction was explored by comparing groups on a difference score between reaction times with 3 versus 12 distractors (i.e., reaction time for 12 distractors minus reaction time for 3 distractors) using one-way analysis of variance (ANOVA). Post-hoc pair-wise group comparisons were made with Tukey's Least Significant Difference (LSD) test (alpha for significance set at $p<.05$). To examine the impact of slowing on the single-feature and dual-feature visual search tasks, the analyses were repeated with repeated measures analyses of covariance (ANCOVA) that included reaction time on the Simple Visual Detection Task as a covariate.

Group differences in the numbers of false negative (not responding on a target-present trial) errors made in the first 30 trials of each block of the Single-Feature and Dual-Feature Visual Search tasks were examined with repeated measures ANOVAs with Group (between subjects) and Distractor Set Size (within subjects repeated measure) as factors. Partial eta-squared ($_p\eta^2$) was used to measure effect sizes. The numbers of false-positive errors (responding on a target-absent trial) were too few to analyze.

RESULTS

Seven of the participants were unable to complete all components of the three visual attention tasks and were dropped from the analyses. Of these, one patient with AD and one patient with DLB had reaction times on the simple visual detection task that were more than 3 standard deviations slower than their group mean, and 2 DLB and 3 PDD patients made errors on 40% of the 60 initial trials of either the single-feature or dual-feature visual search task (more than 2 standard deviations beyond their group mean). The final groups used in the analyses consisted of 17 patients with DLB, 10 patients with PDD, 18 non-demented patients with PD, 30 patients with AD, and 13 NC.

Demographic information, cognitive test scores and motor function scores for the five subject groups are presented in Table 3.1. The groups did not differ significantly in age ($F_{(4,83)}$=1.52; $\underline{p}$= .20) or education ($F_{(4,83)}$=1.31; $\underline{p}$= 0.27). The DLB, PDD and PD groups had a greater proportion of men than the AD and NC groups (X^2=9.84; p=0.04), but did not differ from each other in this regard. The AD and NC groups had similar proportions of men. As expected, PDD, DLB, and AD groups performed worse than PD and NC groups on measures of global cognitive functioning, the MMSE ($F_{(4, 80)}$ = 13.24; $\underline{p}$<0.001) and the DRS ($F_{(4,81)}$ = 21.48; $\underline{p}$<0.001). The three demented groups did not differ significantly from each other on these tests, nor did PD differ from NC subjects. The Unified Parkinson's Disease Rating Scale (UPDRS) scores were significantly different across groups ($F_{(4,80)}$= 28.18; $\underline{p}$<0.001). Patients with PD, PDD, or DLB had more Parkinsonian symptoms

(i.e., higher UPDRS scores) than AD patients or NC participants, but did not differ from each other. The AD patients and NC participants did not differ on UPDRS scores. The proportion of individuals with visual hallucinations differed across groups (X^2=30.61; p<0.001). A greater proportion of patients had visual hallucinations in the DLB group than in any other group.

Simple Visual Detection Task

The average median reaction times produced by each group on the simple visual detection task are presented in Table 3.2. The groups differed significantly ($F_{(4, 83)}$ = 7.66; p<0.001; ${}_p\eta^2$=0.27) with DLB patients slower than all other groups, and AD patients slower than PD patients and NC participants. The PD, PDD and NC groups had similar reaction times.

Single-Feature Visual Search Task

The average median reaction times produced by each group on only the first 15 target-present trials in each block of the Single-Feature Visual Search task are presented as a function of distractor set size in Figure 3.1a. A Group X Distractor Set Size (3, 6, or 12 distractors) repeated measures ANOVA revealed a significant main effect of group ($F_{(4,83)}$=7.71; p<0.001; ${}_p\eta^2$=0.96), but no significant effect of distractor set size ($F_{(2,82)}$=2.08,p=0.13; ${}_p\eta^2$=0.05) or Group X Distractor Set Size interaction effect ($F_{(8,164)}$=0.54; p=0.83; ${}_p\eta^2$=0.03). Post-hoc analyses revealed that the DLB group performed the single-feature visual search task significantly slower than all other patient groups (p's<0.001), while the other groups did not differ from each other. A repeated measures ANCOVA with median reaction time on the simple visual

detection task as a covariate (to control for simple search speed) revealed no significant Group ($F_{(4,82)}$=1.42; $\underline{p}$=0.24; $_{p}\eta^{2}$=0.07), Distractor Set Size ($F_{(2,81)}$=0.71; $\underline{p}$=0.49; $_{p}\eta^{2}$=0.02) or Group X Distractor Set Size interaction ($F_{(8,162)}$=0.29; $\underline{p}$=0.97; $_{p}\eta^{2}$=0.01) effects. The same pattern of results was obtained if median reaction times were based on only the first 30 trials in each block with a maximum reaction time of 3000 ms assigned to target-present trials without a response, or based on the 15 target-present trials with a response that included those re-administered at the end of the 30-trial block (data not shown).

The mean numbers of false negative (not responding on a target-present trial) and false-positive (responding on a target-absent trial) errors made in the first 30 trials of each block of the Single-Feature Visual Search task are shown as a function of Distractor Set size in Table 3.3. A Group X Distractor Set Size repeated measures ANOVA of false-negative errors revealed a significant main effect of Group ($F_{(4,83)}$=2.93; $\underline{p}$<0.05; $_{p}\eta^{2}$=0.12), but no effect of Distractor Set Size ($F_{(1,83)}$=0.87; $\underline{p}$=0.35; $_{p}\eta^{2}$=0.01) or interaction effect ($F_{(4,83)}$=0.77; $\underline{p}$=0.55; $_{p}\eta^{2}$=0.04). Post-hoc analyses showed that the DLB group made more false-negative errors than all other groups, but the mean number of false-negative errors in all participant groups (including DLBs) was less than 1 error in each distinct distractor set size, so the overall error rate was minimal. The numbers of false-positive errors were too few to analyze.

Dual-Feature Visual Search Task

The average median reaction times produced by each group on only the first 15 target-present trials in each block of the Dual-Feature Visual Search task are presented as a function of distractor set size in Figure 3.1b. A Group X Distractor Set Size repeated measures ANOVA revealed significant main effects of Group ($F_{(4,83)}$=10.41; p<0.001; $_p\eta^2$=0.94) and Distractor Set Size ($F_{(2,82)}$=166.46,p<0.001; $_p\eta^2$=0.80), and a significant Group X Distractor Set Size interaction effect ($F_{(8,164)}$=2.44; p=0.02; $_p\eta^2$=0.11). A repeated measures ANCOVA with median reaction time on the simple visual detection task as a covariate (to control for simple search speed) revealed the same pattern of results. The interaction effect was explored by comparing groups on a difference score between reaction times with 3 versus 12 distractors (i.e., reaction time for 12 distractors minus reaction time for 3 distractors). The difference scores for all groups, shown in Figure 3.2b, were significantly greater than zero (all p's<.001) indicating that time to detect the target increased for each group with increasing numbers of distractors. A one-way ANOVA comparing difference scores across groups was significant ($F_{(4,83)}$=3.70,p=0.008; $_p\eta^2$=0.15), and post-hoc pairwise comparisons showed that patients with AD had a significantly larger difference score than patients with PD or NC participants (p's<0.05). No other pair-wise group comparisons were significant.

The same pattern of results was obtained on the repeated measures ANOVA when median reaction times were based on only the first 30 trials in each block with a maximum reaction time of 3000 ms assigned to target-present trials without a

response. However, the Group X Distractor Set Size interaction effect in the ANCOVA was not significant ($F_{(8,162)}$=1.50,$\underline{p}$=0.16; $_p\eta^2$=0.07) when median reaction time on the simple visual detection task was used as a covariate to control for simple search speed. The interaction effect in the ANOVA was explored by comparing difference scores between reaction times with 3 versus 12 distractors. All group difference scores were significantly greater than zero (all $\underline{p}$'s<.001). A one-way ANOVA comparing difference scores across groups was significant ($F_{(4,83)}$=3.81,$\underline{p}$=0.007; $_p\eta^2$=0.15), and post-hoc pairwise comparisons showed that patients with AD and DLB patients had similar difference scores that were greater than those of patients with PD or NC participants ($\underline{p}$'s<0.05). PDD patients' difference scores did not differ significantly from those of any other group.

The same pattern of results was also obtained on the repeated measures ANOVA when median reaction times were based on the 15 target-present trials with a response that included those re-administered at the end of the 30-trial block. However, the Group X Distractor Set Size interaction effect in the ANCOVA only approached significance ($F_{(8,162)}$=1.89,$\underline{p}$=0.06; $_p\eta^2$=0.09) when median reaction time on the simple visual detection task was used as a covariate to control for simple search speed. Exploration of the interaction effect with difference scores between reaction times with 3 versus 12 distractors showed that all group difference scores were significantly greater than zero (all $\underline{p}$'s<.001). A one-way ANOVA comparing difference scores across groups was significant ($F_{(4,83)}$=3.93,$\underline{p}$=0.006; $_p\eta^2$=0.15). Post-hoc pairwise comparisons showed that difference scores for AD patients were

significantly greater than those of PD patients and NC participants, and that those of DLB patients were significantly greater than those of PD patients. No other pair-wise group comparisons were significant.

The mean numbers of false negative (not responding on a target-present trial) and false-positive (responding on a target-absent trial) errors made in the first 30 trials of each block of the Dual-Feature Visual Search task are shown as a function of Distractor Set size in Table 3.3. A Group X Distractor Set Size repeated measures ANOVA of false-negative errors revealed a significant main effect of Group ($F_{(4,83)}$ = 5.42; $\underline{p}$=0.001; ${}_p\eta^2$=0.21) and Distractor Set Size ($F_{(1,83)}$ = 15.95, $\underline{p}$<0.001; ${}_p\eta^2$=0.16), but no interaction effect ($F_{(4,83)}$=2.40; $\underline{p}$=0.06; ${}_p\eta^2$=0.10). These analyses indicate that the number of errors increased with an increase in set size. Post-hoc analyses revealed that DLB and AD patients made similar numbers of errors, and these 2 groups made more false-negative errors than any other participant group (PD, NC, PDD). The numbers of false-positive errors were too few to analyze.

DISCUSSION

The results of this study demonstrate that DLB patients show some degree of impairment on both single-feature and dual-feature visual search tasks, but the pattern of performance is not markedly different from other neurologically-impaired participant groups. Furthermore, DLB participants produced the expected pattern of performance on the single-feature and dual-feature search tasks. In single-feature search, no additional time cost was incurred as the number of distractors increased; in dual-feature search, additional time costs occurred as the number of distractors

increased. In light of the posterior cortical abnormalities that exist in DLB, we had hypothesized that DLB patients would show deficits in single-feature visual search tasks. This was not the case, as DLB patients showed a pattern of performance that was similar to all other patient and control groups (AD, PDD, PD, and NC).

Impairment in the DLB group was evident in overall reaction times; the DLB group completed the single-feature search task with significantly slower reaction times than all other participant groups. The slowness of DLB patients compared to all other patient groups in both the simple visual detection task and the single-feature search task is consistent with research noting psychomotor slowing and bradykinesia in DLB patients (McKeith et al., 2005). Despite the additional time required for DLB patients to complete these search tasks, the pattern of performance in the DLB group was not different from the pattern of performance in other patient groups.

Patients with AD displayed a marked degree of impairment in the dual-feature search task that required integration of luminance (black or white) and shape (circle or square) information in order to correctly identify the target. Previous research has shown that information related to luminance is processed in the dorsal visual processing stream, while information necessary to identify the shape of objects is processed in the ventral visual processing stream (Ungerleider & Haxby, 1994). In the dual-feature task used in the present study, both of these cortically distinct processing streams must work in concert to correctly identify the target. The AD group displayed a significantly increased time cost (relative to the PD and NC groups) to identify a black dot among white dots and black squares as the number of distractors increased.

Previous research on visual search tasks in AD populations showed impairment in dual-feature search tasks (Foster et al., 1999), with the impairment hypothesized to be due to problems in shifting attention. However, when attentional demands were controlled across single-feature and dual-feature tasks, Tales et al. (Tales et al., 2002) still found that AD patients were impaired in dual-feature search tasks. These investigators suggested that this deficit could result from a problem in feature binding due to a breakdown in cortico-cortical connections. Other studies support the idea that cortico-cortical impairment may be responsible for the deficit in dual-feature search performance observed by Tales et al. and in the present study. When AD patients were asked to perform a motion integration task that placed demands solely on one visual processing stream, they performed at the level of healthy older adults; however, when the task required integration of color and motion information (carried in two distinct cortical processing streams), AD patients showed marked impairment compared to healthy adults (Festa et al., 2005).

A breakdown in cortico-cortical connectivity could also help to explain the similarity in performance between DLB and AD patients on this dual-feature search task. Since many DLB patients display some degree of concomitant Alzheimer's pathology (Galasko et al., 1996), the marked impairment in dual-feature search ability associated with advancing Alzheimer's pathology could also be impacting patients with DLB (although to a somewhat lesser degree). It does not appear that the additional burden of Lewy body pathology in the DLB group is associated with a unique pattern of impairment in dual-feature search. Interpretation of these results

would be aided by neuropathological studies which could help determine if the relative quantities of AD and DLB pathology in these cases might be associated with distinct patterns of performance on visual search tasks. Patients with DLB also displayed a pattern similar to patients with AD in the single-feature search task, despite the fact that DLB patients performed the task more slowly. Again, the fact that many DLB cases occur with concomitant AD pathology (Galasko et al., 1996) could explain the similar pattern of performance in the two groups. If Lewy body pathology does not contribute its own unique signature of impairment in single-feature search tasks, then DLB patients and AD patients' performance would look very similar.

The results of the present study failed to replicate the results from an earlier study (Cormack et al., 2004) that found a particularly severe impairment in single-feature search tasks in DLB patients. Cormack and colleagues hypothesized that this impairment in the ability to complete single-feature search tasks with the expected pattern of performance was consistent with occipital hypometabolism and occipital pathology that has been found in DLB patients (Albin et al., 1996; Ishii et al., 2007). There are several possible reasons why our cohort of DLB patients did not display the same pattern of impairment in single-feature tasks observed by Cormack and colleagues (Cormack et al., 2004). First, in the Cormack single-feature search task, reaction time was not assessed under the rationale that motor impairment may have confounded the results. Therefore, the Cormack et al. study varied the length of time that they displayed the stimuli to participants (200 ms, 400 ms, or 800 ms) (Cormack et al., 2004). Participants were then asked to provide a verbal response to indicate

whether or not they had seen the target. This method of presenting stimuli may have been problematic for a DLB cohort. In the present study, 7 participants were removed from the analysis because they could not reliably complete the task; this was mostly due to the fact that the 3-second stimulus display time was not a long enough period of time for the participant to give a response. In our single-feature search task, the mean of the median reaction time was approximately 600 ms. Two of the three stimulus display times (200 ms and 400 ms) in the Cormack study were *less* than the mean reaction time in the present study. The fact that 3000 ms was not enough time for some of our DLB subjects to process the visual stimuli in our tasks suggests that stimulus display times in the Cormack et al. paper (all less than 1 second) did not allow sufficient time for the DLB group to process the visual stimuli with a reliable degree of accuracy. The measures of reaction time used in the present study provide a more quantitative look at the degree of impairment in the DLB group and showed that the pattern of performance they produced (i.e., no increasing cost in reaction time as the number of distractors increased) was similar to all other participant groups.

Second, it is possible that different patterns of performance would arise when comparing patients with "pure" DLB syndrome vs. patients with a mix of AD and DLB pathology. Since neuropathological confirmation was unavailable in both the present study and the Cormack et al. study, we cannot directly compare the extent of DLB pathology in both cohorts.

Third, the group of DLB participants in the present study was younger (mean age of 73.4 years) than the DLB group in the Cormack et al. study (79.7 years). The

advanced age of the Cormack et al. DLB cohort may have contributed in some way to the reported pattern of impairment.

In the Cormack et al. study, errors increased as distractor set size increased (Cormack et al., 2004). In the present study, overall error rates in both single-feature and dual-feature search tasks were extremely low; the mean number of errors across all distractor set size conditions was less than one per distractor set size in the single-feature search task, and less than four per distractor set size in the dual-feature search task. Thus, it is unlikely that commission or omission error rates significantly impacted the performance of any group on either the single-feature or dual-feature search task.

The present study does have important limitations. Group membership was based on autopsy-confirmed diagnoses when available, but clinical diagnoses were predominantly used. Accurate clinical diagnosis of DLB is difficult, and some cases misidentified as AD during life may have DLB pathology (Hohl, Tiraboschi, Hansen, Thal, & Corey-Bloom, 2000). This would mean that the DLB group might increase in numbers after autopsy confirmation revealed the presence of Lewy bodies in some cases currently presumed to be AD. A more distinct pattern of impairment in DLB participants might be evident once the DLB cases were determined with certainty. In addition, neuropathological information would allow analyses that could correlate performance on visual search tasks with the quantity of DLB and AD pathology in order to elucidate any disease-specific patterns of impairment in visual search.

In summary, although one previous study showed that DLB patients had a marked impairment in single-feature search performance (Cormack et al., 2004), the present study did not replicate those findings. Patients with DLB were slower than all other participant groups in simple visual detection tasks and single-feature search tasks, but they did not display a unique pattern of performance on single-feature tasks. On dual-feature tasks, they showed a pattern of deficits similar to AD patients who have difficulty integrating information processed in two distinct cortical areas. Although DLB pathology is associated with impairment in many tasks of visuospatial ability, Lewy body pathology alone does not appear to be associated with a distinct pattern of impairment in visual search. Future studies with neuropathological information would be helpful in determining the varying contributions of AD and DLB pathology to the ability to perform visual search tasks.

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M. The dissertation author was the primary investigator and will be the primary author of this manuscript.

Table 3.1: Mean (Standard Deviation; SD) Age, Education, Mini-Mental State Exam (MMSE) and Uniform Parkinson's Disease Rating Scale (UPDRS) scores for the final sample of Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD). The percentage of males in each group, and the percentage of DLB, PDD and AD patients with past or current visual hallucinations and fluctuations in consciousness or cognition are also shown.

	NC	PD	DLB	PDD	AD
	n = 13	n = 18	n = 17	n = 10	n = 30
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	72.0 (7.0)	71.2 (7.0)	73.4 (8.1)	76.1 (8.4)	75.5 (6.0)
Sex (% men)	62%	72%	94%	90%	57%
Education	17.2 (2.3)	16.0 (3.1)	15.5 (2.7)	15.5 (1.7)	15.3 (2.6)
MMSE	29.2 (1.0)	28.4 (1.8)	23.2 (5.0)	26.1 (1.8)	22.1 (4.7)
Mattis DRS	140.7 (1.8)	139.7 (2.8)	116.1 (14.2)	126.7 (6.2)	117.6 (14.1)
UPDRS	2.2 (5.3)	19.7 (6.9)	22.3 (12.8)	24.6 (10.9)	3.2 (5.7)
Hallucinations	-----	33%	75%	30%	7%

Table 3.2: Mean (Standard Deviation; SD) of the median simple Reaction Time (RT) to the presentation of a single visual target stimulus for the Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD).

	NC	PD	DLB	PDD	AD
	n = 13	n = 18	n = 17	n = 10	n = 30
Reaction Time (ms)					
Mean	344.3	340.1	519.5	382.7	419.6
SD	54.6	51.2	194.7	63.7	92.0

Table 3.3: Mean (Standard Deviation; SD) number of errors in Single-Feature and Dual-Feature Visual Search Tasks for the final sample of Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD). Errors of commission (C; responding when the target was not present) and errors of omission (O; not responding when the target was present) are noted.

	NC N=13		PD N=18		DLB N=17		PDD N=10		AD N=30	
	C	O	C	O	C	O	C	O	C	O
<u>Single Feature</u>										
3 Distractors	0.0 (0.0)	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)	0.2 (0.6)	0.1 (0.5)	0.0 (0.0)	0.1 (0.3)	0.1 (0.3)	0.2 (0.5)
6 Distractors	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.2)	0.3 (0.5)	0.5 (1.5)	0.0 (0.0)	0.0 (0.0)	0.1 (0.3)	0.1 (0.4)
12 Distractors	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.0 (0.0)	0.2 (0.8)	0.4 (0.5)	0.2 (0.4)	0.0 (0.0)	0.0 (0.2)	0.2 (0.5)
<u>Dual Feature</u>										
3 Distractors	0.2 (0.4)	0.0 (0.0)	0.3 (0.5)	0.2 (0.7)	0.4 (0.6)	1.5 (1.5)	0.7 (1.1)	0.8 (1.7)	0.5 (0.8)	0.8 (1.3)
6 Distractors	0.2 (0.6)	0.1 (0.8)	0.3 (0.6)	0.2 (0.5)	0.4 (0.8)	1.9 (2.0)	0.9 (0.9)	0.7 (1.3)	0.4 (0.7)	1.1 (1.6)
12 Distractors	0.2 (0.6)	0.0 (0.0)	0.1 (0.2)	0.6 (1.0)	0.4 (0.6)	3.7 (3.8)	0.5 (1.1)	1.9 (2.4)	0.5 (0.9)	2.5 (3.6)

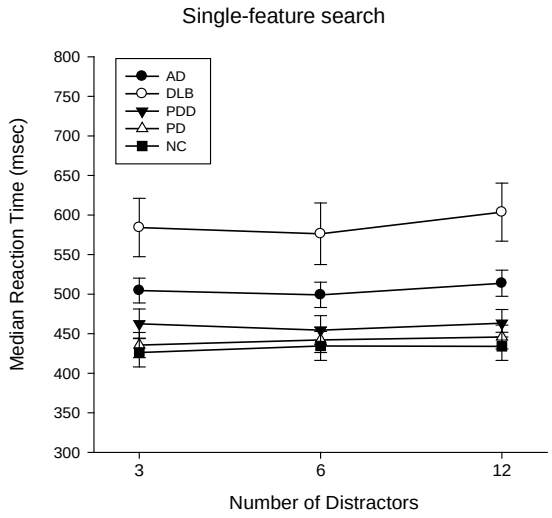

Figure 3.1a: Mean (with standard error bars) of median reaction times to the presentation of a single-feature visual search task as a function of distractor set size for Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD).

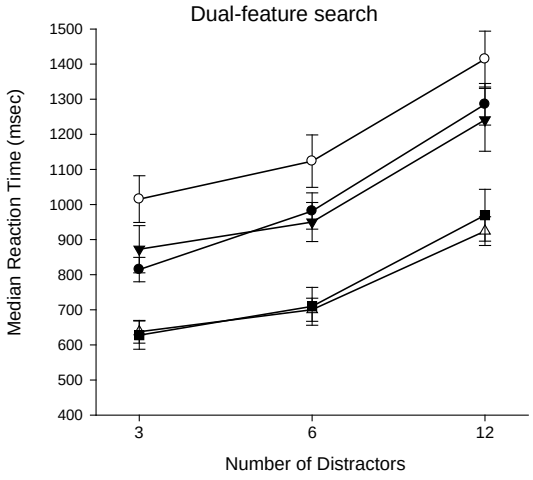

Figure 3.1b: Mean (with standard error bars) of median reaction times to the presentation of a dual-feature visual search task as a function of distractor set size for Normal Control (NC) Participants and Patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD).

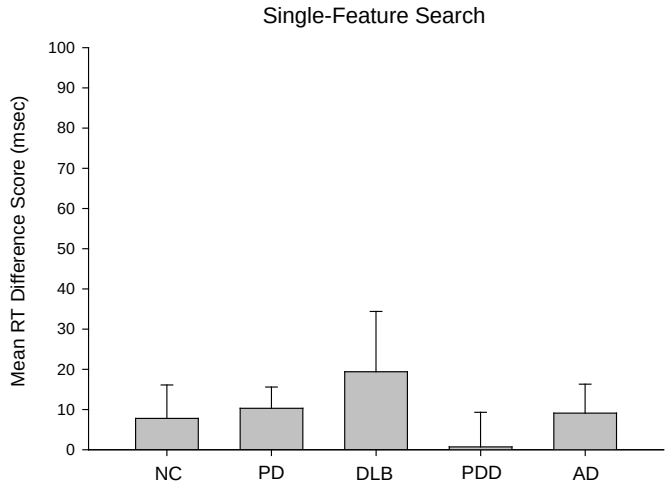

Figure 3.2a: Mean (with standard error bars) of RT difference scores (difference between reaction time at a set size of 3 and a set size of 12) from a single-feature visual search task presented to Normal Control (NC) participants, patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease (AD).

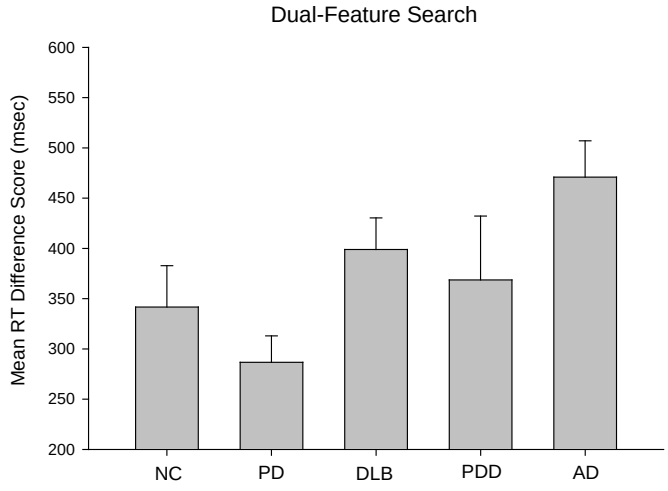

Figure 3.2b: Mean (with standard error bars) of RT difference scores (difference between reaction time at a set size of 3 and a set size of 12) from a dual-feature visual search task presented to Normal Control (NC) participants, patients with Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), or Alzheimer's Disease.

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Chapter 4

An Examination of Higher Order Visual Cognition in Parkinson's Disease

In the following experiments, we examine visual cognition in non-demented patients with Parkinson's disease (PD). The studies described in Chapters 2 and 3 included non-demented PD patients, but the tasks used to assess visual cognition were designed so that a person with dementia could complete them. When tasks are designed with increased difficulty to pose a challenge to non-demented PD patients, deficits in visual cognition may become evident. Knowledge of the status of visual cognition in patients with PD can inform our understanding of such deficits in patients with Dementia with Lewy bodies (DLB) since the two disorders share a number of pathological features.

Parkinson's disease is characterized by the loss of dopaminergic neurons and the presence of alpha-synuclein positive intraneuronal protein aggregates (i.e. Lewy bodies) in the substantia nigra (Hurelbrink & Lewis, 2011). Lewy bodies and neuron loss are present in additional brainstem nuclei such as the locus coeruleus, dorsal vagal nucleus, and nucleus basalis of Meynert. Lewy bodies are also seen in the hypothalamus and the ganglia in the sympathetic nervous system (Fearnley, Revesz, Brooks, Frackowiak, & Lees, 1991; Jellinger, 2009). Pathology in the substantia nigra and other brainstem nuclei results in the loss of dopaminergic projections from the midbrain to basal ganglia and cortex (Hurelbrink & Lewis, 2011). The loss of these dopaminergic projections underlies the motor symptoms of PD (Poewe, 2009) which include gait and posture abnormalities, tremor, and bradykinesia.

Although most often conceptualized as a disease of motor impairment (Kempster, Gibb, Stern, & Lees, 1989), studies show that cognitive deficits are evident even in the early stages of PD. A study of newly diagnosed PD patients (with a disease duration of 2 years) showed cognitive impairment on a wide range of neuropsychological tests (Reid, 1992). Another study found that more than 50% of non-demented PD patients displayed some type of cognitive impairment (Janvin, Aarsland, Larsen, & Hugdahl, 2003). Dementia is thought to eventually occur in approximately 78% of PD patients (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). Because of these and similar findings, the concept of mild cognitive impairment (originally applied in relation to Alzheimer's disease (AD) (Petersen et al., 2001)) has now been defined with diagnostic criteria specific to PD. These criteria embrace the notion that non-motor symptoms are widespread in PD and may warrant the attention of clinicians even though cognitive deficits may not rise to the level of dementia (Litvan et al., 2011; Litvan et al., 2012).

Patients with PD share some of the cognitive deficits that have been observed in patients with DLB. For example, deficits in attention and frontal-executive functions that occur in DLB are common in PD (G. S. Watson & Leverenz, 2010). Deficits are also evident in the visuospatial domain and have been noted on tasks that involve size perception, visuospatial orienting and attention, mental rotation, motion detection, and discrimination of motion direction (Cronin-Golomb & Braun, 1997; Ezzati, Khadjevand, Zandvakili, & Abbassian, 2010; Trick, Kaskie, & Steinman, 1994). Unfortunately, many of these studies do not distinguish between demented and

non-demented patients with PD, and have not examined multiple aspects of visual cognition in the same patients.

Visual search is an aspect of visual cognition that has received some research attention in patients with PD. This is because tasks that require visual search may be particularly sensitive to PD, since they combine elements of visual perception and visual attention. Visual search is generally considered to be the process by which we detect and recognize visual objects in a complex scene. It is often thought to encompass two components: parallel or single-feature search that is thought to involve relatively automatic pre-attentive identification of a salient feature in a scene, and serial or dual-feature search that requires effortful higher order visual processing since multiple features of the target item (i.e., shape and color) must be conjoined before the target item can be correctly identified (Treisman & Gelade, 1980).

Findings regarding the impact of PD on single-feature visual search are inconsistent. While some studies showed that PD patients performed as well as normal control subjects on single-feature search tasks (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Cormack, Gray, Ballard, & Tovee, 2004), others found that PD patients were impaired on these tasks (Lieb et al., 1999; Troscianko & Calvert, 1993; Weinstein, Troscianko, & Calvert, 1997). In cases where PD patients were impaired, it sometimes appeared that they were using dual-feature search strategies to perform the single-feature task (Weinstein et al., 1997). It is possible that deficits in single-feature search in patients with PD are due to abnormalities within primary visual cortex (Calvert, 2001). In some cases where PD patients were not impaired, the

single-feature search task was designed to be used with demented patients and may have been too simple to detect subtle deficits in visual cognition in non-demented PD patients (Cormack et al., 2004). The inconsistency in the existing literature regarding the existence and nature of visual search deficits in patients with PD suggests the need for systematic study of visual search with manipulation of task difficulty (i.e., degree of similarity between the target and distractors) and the type of visual stimuli to be detected (e.g., those that preferentially engage the dorsal or ventral visual processing stream).

Another aspect of visual cognition that has been studied to a small extent in patients with PD is their performance on various tasks that engage the dorsal visual processing stream such as motion detection, luminance discrimination, and the localization of objects in space (Ungerleider & Haxby, 1994). Studies that included demented and non-demented patients found that motion perception is globally impaired in PD (Trick et al., 1994). This is consistent with event-related potential studies which describe an electrophysiological abnormality in patients with PD in the dorsal (or magnocellular) visual processing stream that is important for processing motion information (Arakawa, Tobimatsu, Kato, & Kira, 1999). Studies related to spatial localization in patients with PD have conflicting results. One study showed that male patients with PD, but not female patients, were impaired on a mental rotation task (Crucian et al., 2003). In contrast, another study of mental rotation found that patients with PD performed as well as normal control participants (Cronin-Golomb & Braun, 1997).

The presence of deficits in visual cognition in non-demented patients with PD is supported by findings from imaging studies. A recent study of non-demented PD patients using volumetric measures from structural MRI scans (Filoteo, Reed, Litvan, & Harrington, 2013) found that poorer scores on measures of visuospatial cognition correlated with decreased volumes in structures in the so-called object-based system (which would approximate the structures involved in the ventral processing stream). Alterations in white matter in patients with PD were correlated with visual attention deficits (Hattori et al., 2012). Finally, blood flow studies showed a correlation between hypoperfusion in the occipital cortex and impaired cortical visual processing in non-demented patients with PD (Abe et al., 2003).

Because PD shares Lewy body pathology with DLB but has far fewer cortical Lewy bodies and is not likely to have concomitant AD pathology, characterizing visual cognition deficits in these patients should shed light on the neurological bases of the visuospatial impairment in DLB. If non-demented PD patients display visuospatial deficits similar to those of patients with DLB, it would suggest that those particular deficits in visual cognition could be related to subcortical Lewy body pathology (and the various striato-cortical connections it disrupts) common to the two disorders rather than to the extensive neocortical Lewy body deposition or concomitant AD that only occurs in DLB. On the other hand, if a particular aspect of visual cognition is normal in non-demented patients with PD but markedly impaired in DLB, it is likely that the deficit is due to cortical Lewy body pathology, cortical AD pathology, or the interaction between the two.

In the following experiments, a cohort of non-demented patients with PD completed a battery of visual cognition tests that included: 1) tests of visual search ability and visual search efficiency that focused on either the dorsal or ventral visual processing stream, 2) a sensory integration task using luminance or color motion segmentation cues to assess integration within the dorsal visual stream (luminance cues) and across the dorsal and ventral visual processing streams (color cues), and 3) a visual search task that required the conjunction of color and motion information processed in the ventral and dorsal visual processing streams, respectively. This detailed examination of higher order visual cognition in PD may elucidate the nature of visual cognitive deficits in Lewy body disorders, and inform our understanding of cognitive deficits in DLB that may stem from the neurodegenerative processes common to both DLB and PD.

General Methods

Subjects: Forty individuals participated in all three experiments: 20 patients with PD and 20 healthy, cognitively normal older adults who served as a control group (NC). All PD patients were non-demented; 1 of the PD patients had undergone deep-brain stimulation (DBS) surgery. All of the NC participants and 6 of the PD patients were recruited from the longitudinal study at the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). The remaining 14 patients were referred from a comprehensive PD research program in the laboratory of Dr. Vincent Filoteo at the San Diego VA Health System and UCSD Department of Psychiatry. Clinical diagnoses of PD were based on published criteria (Gelb, Oliver, & Gilman, 1999;

Hughes, Ben-Shlomo, Daniel, & Lees, 1992) and were made by board-certified neurologists with expertise in movement disorders. Participants in the NC group were judged to be cognitively normal after extensive assessment that included comprehensive neuropsychological testing and neurological examination. All cases of PD were idiopathic and diagnosed based on the presence of at least 2 of the following cardinal signs: resting tremor, rigidity, and bradykinesia. In addition, a positive response to treatment with L-dopa or an equivalent medication was required for diagnostic confirmation. Cases with secondary causes of PD or atypical findings were not included in this study. None of the PD patients had sufficient cognitive decline to warrant a diagnosis of dementia; however, 9 of the 20 fit the most recent criteria for diagnosis of mild cognitive impairment in PD (PD-MCI) (Litvan et al., 2012).

Only PD patients and NC participants above the age of 55 were considered for participation in the present study. Patients with PD were required to be testable and generally have Hoehn and Yahr staging of between 1 and 3 (Hoehn & Yahr, 1998). Only one PD patient was Hoehn and Yahr stage 4 and his physical limitations prevented him from performing the one cognitive task in the current study that required the use of both hands. Individuals were also excluded for dementia, the presence of a neurological condition other than PD, or the presence of another disease with Parkinsonian features (i.e. supranuclear palsy, multisystem atrophy, etc.). Individuals with any significant medical illness other than PD (e.g., active cancer, recent heart attack, history of stroke) or psychiatric illnesses (e.g., substance dependence, major depression, schizophrenia) were also excluded.

Because most of the tasks used in the present study were visual in nature, patients with severe uncorrected vision loss were excluded. All participants' visual acuity was at least 20/100. Individuals with red-green color-blindness, macular degeneration, severe cataracts, or glaucoma were excluded. The effect of PD pathology on the retina cannot be ignored in a study of visual cognition. In particular, retinal damage in PD affects visual processing (I. G. Bodis-Wollner & Paulus, 1999; Wink & Harris, 2000) and studies consistently show that PD patients perform worse than controls on tests of color discrimination and contrast sensitivity (Pieri, Diederich, Raman, & Goetz, 2000). In studies that used sinusoidal gratings as visual stimuli, contrast sensitivity was decreased in PD patients when the gratings lay in the horizontal direction but not the vertical direction (Bulens, Meerwaldt, & Van der Wildt, 1988; Lieb et al., 1999; D. Regan & Maxner, 1987; Trick et al., 1994). PD patients often remark that their vision is blurred, and some experience double vision (Pieri et al., 2000). However, it is important to note that contrast sensitivity was found to increase with age in both the controls and patients with PD in a recent study (Pieri et al., 2000). With contrast sensitivity issues in mind, the tasks used in the present study were created with high Michelson contrast values, far above the level where PD patients would normally demonstrate impairment (Tebartz van Elst, Greenlee, Foley, & Lucking, 1997). Although many studies report that color discrimination is impaired in PD (Birch, Kolle, Kunkel, Paulus, & Upadhyay, 1998; Buttner, Kuhn, Muller, Patzold, & Przuntek, 1995; Haug, Kolle, Trenkwalder, Oertel, & Paulus, 1995; Muller, Kuhn, Buttner, & Przuntek, 1997; Pieri et al., 2000; Price, Feldman, Adelberg, &

Kayne, 1992), some studies find no impairment when fine motor control is not required to complete the task (B. C. Regan, Freudenthaler, Kolle, Mollon, & Paulus, 1998). Problems with color discrimination in patients with PD are usually related to blue hues (Haug et al., 1995; Muller et al., 1998; Pieri et al., 2000) and are thought to be related to loss of dopamine in the retina (Birch et al., 1998; Pieri et al., 2000). Dopamine-replacement therapy is thought to normalize retinal functioning in PD patients (I. Bodis-Wollner, 1990).

All PD participants in the present study used L-dopa or an equivalent medication to mediate the motor deficits of PD. Patients were tested "on" L-dopa or an equivalent medication. Participants were told not to alter their medication routine in any way for this testing; every effort was made to schedule participants at a time when they felt their best, which was typically one hour after the most recent dose of L-dopa. Testing participants while "on" dopamine-replacement medication should have minimized the effect of retinal damage on visual cognition. The single PD participant with a deep brain stimulator was also tested with stimulation "on".

Demographic information, clinical test scores, and motor function scores for the PD and NC groups are presented in Table 4.1. One of the NC participants refused to complete the full sensory integration task and was not included in the analyses for that task. One of the PD patients had limited use of the non-dominant hand and was therefore dropped from search efficiency data analyses. The groups did not differ significantly in age ($t(38) = 1.23$, $p = .22$), or education ($t(38) = 0.00$, $p = 1.00$). The PD group (containing some persons with mild cognitive impairment) performed worse

than the NC group on measures of global cognitive functioning, including the MMSE ($t(36) = 2.13$, $p<.05$) and the DRS ($t(38) = 2.16$, $p<0.05$). As expected, the UPDRS scores of PD patients were significantly higher than those of NC participants ($t(38) = -5.42$, $p<.001$). A higher proportion of individuals in the PD group than in the NC group had visual hallucinations ($X^2(1) = 10.00$, $p<.01$). REM sleep behavior disorder (RBD) was more common in the PD group than the NC group ($X^2(1) = 13.79$, $p<.001$). Fluctuations were reported at a low rate in the PD group, but occurred more frequently in the PD group than in the NC group ($X^2(1) = 8.64$, $p<.01$) . The groups were composed of similar proportions of men and women ($X^2(1) = 2.849$; $p=0.09$).

General Procedure: Participants were tested individually in a quiet, well-lit room. In order to avoid the effects of visual fatigue, the neuropsychological tests were completed on 2 separate testing days. Motor functioning was assessed by a board-certified neurologist using procedures outlined in Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003). UPDRS scores were obtained within one year of neuropsychological testing. The MMSE and the Dementia Rating Scale (DRS) (Lopez, Charter, Mostafavi, Nibut, & Smith, 2005; Mattis, 1988) were administered by a trained examiner within 6 months of the date of the visual cognition testing. Mood was assessed using the Geriatric Depression Scale (Yesavage, 1988). The presence of visual hallucinations was assessed with the Mosimann Semi-Structured Interview to Assess Visual Hallucinations in Older People (Mosimann et al., 2008).

The Mayo Sleep Questionnaire was administered (Boeve et al., 2013) to assess the frequency of REM sleep behavior disorder (RBD). A selection of questions was chosen from the Mayo Fluctuations Questionnaire (Ferman et al., 2004) to assess the relative frequency of fluctuations in attention, consciousness, and alertness. Hoehn and Yahr stage was obtained from neurological records or was derived from UPDRS Part III scores (Scanlon, Katzen, Levin, Singer, & Papapetropoulos, 2008). Participants provided a comprehensive list of all medications and supplements being taken. Visual acuity was assessed with a Jaeger near vision card.

The research protocol was reviewed and approved by the Human Subjects board at UCSD. Written informed consent to participate in the study was obtained from all participants prior to testing; capacity to consent was also assessed with a standard interactive questionnaire in use at the ADRC. All participants demonstrated intact ability to consent to participation, and written informed consent was obtained with procedures in accordance with California State law.

Prior to testing in the three main experiments described below, all participants were tested on a simple visual detection task.

Simple Visual Detection Task: A simple visual detection test was administered on a 15.4" Dell laptop computer. Participants were instructed to press a response key as quickly as possible after they detected that a single black circle (diameter of 1 cm) had appeared on the screen. Reaction time was recorded in milliseconds. The average median reaction times produced by the PD patient and NC

groups are displayed in Figure 4.1. The groups did not differ in reaction time to respond to a single visual target ($t(38) = 0.13$, $p = 0.90$).

Experiment 3A: Shape-Based Search Efficiency

This experiment examined the impact of PD without dementia on single-feature visual search for a stimulus that is primarily processed in the ventral visual processing stream. The target stimulus was a solid black circle that appeared among solid black ovals that served as distractors. Difficulty of the search task was systematically manipulated by employing three levels of similarity between the target stimulus and the distractors. The level of similarity was varied randomly from trial to trial.

Procedure: The task was administered on a 15.4" Dell laptop computer. Each trial started with a small fixation cross shown in the center of the screen. A display was then presented that contained 80 distractor stimuli in a 9 x 9 grid with a small degree of offset to make the task more challenging, and on half of the trials, a target stimulus. The target stimulus was a solid black circle or dot that was 1 cm in diameter. The distractors were solid black ovals that differed from the target at one of three levels of similarity. Distractors were created by distorting the target circle so that the area remained constant but the diameter changed, making an oval or oblong shape. Distractors were 65% similar to the target in the easiest level, 70% similar in the medium level, and 75% similar in the hardest level. All distractors on a given trial were identical oval shapes. On target present trials, the target circle occurred at a

random position in the distractor array. Participants were told to look for a solid black circle (the target) and to press a response key marked “yes” as soon as they saw the target, or a response key marked “no” if a target was not present in the display. Participants were told that the target would not appear on every trial. The response keys assigned to “yes” and “no” were on separate sides of the keyboard; to account for motor impairments in PD that may impair precision in striking a single key, the keys surrounding each response key were also activated. Thus, it was not necessary to strike the response key precisely in each trial. There was no overlap in the keys activated for “yes” and “no” responses. The stimulus display remained present until a response was made or for 3000 ms. Accuracy and reaction time were recorded. Immediately after a response was made, or immediately after the interval timed-out, the display disappeared and the fixation cross appeared to begin the next trial.

A total of 144 trials were run. Half of the trials were target present trials. Target present and target absent trials occurred randomly. Trials of each level of difficulty appeared pseudo-randomly to prevent more than 3 consecutive trials of the same difficulty level. The task was divided into 3 blocks, with a short rest break in between blocks to prevent eye strain or fatigue. Each block consisted of 48 trials (24 target-present, 24 target-absent). In each block, 8 trials at each of 3 difficulty levels were evenly distributed among target-present and target-absent trials. Thus, in the 24 target-present trials in a block, the participant would see 8 trials each with a target present and distractors that were either 65%, 70% or 75% similar to the target. The 24

target-absent trials in each block were also evenly divided among 8 target-absent trials with distractors that were 65%, 70% or 75% similar to the target.

A short practice version of the task was administered prior to the test trials to familiarize patients with the task, the appearance of the target, and the appropriate response keys.

Data Analysis: Responses that occurred less than 250 ms after stimulus presentation were considered invalid (i.e., anticipatory responses) and eliminated from analyses. Since each stimulus was only displayed for 3 seconds, there were no outliers in reaction time. Only correct responses from target-present trials were used in reaction time analyses. A 2 x 3 (Group by Reaction Time (RT) at each of 3 levels of difficulty) ANOVA was used to assess group differences in reaction time at each of the 3 levels of difficulty in the shaped-based search efficiency task.

Accuracy was assessed using d′ (discriminability index). This index is indicative of a participant's ability to discriminate signal from noise and can be conceptualized in terms of hits and false alarms as: Z(hit rate) – Z(false alarm rate), where Z-scores are calculated based on the sample population's mean hit rate and mean false alarm rate. A 2 x 3 repeated measures ANOVA was used to assess group differences in d′ in the PD and NC groups at each of 3 levels of difficulty in the search efficiency task. Student's t-tests (alpha for significance set at $p<.05$) were used to assess group differences in overall rates of hits, misses, correct rejections, and false alarms across all 3 levels of difficulty.

Results and Discussion: The average median reaction times produced by each group on the shaped-based visual search efficiency task are presented as a function of difficulty level in Figure 4.2. A Group X Difficulty Level (65% similar, 70% similar, or 75% similar) repeated measures ANOVA revealed a significant effect of difficulty level ($F(1,37) = 23.37$, $p<.001$, $\eta_p^2 = 0.39$), but no main effect of group ($F(1, 37) = 0.40$, $p = 0.53$, $\eta_p^2 = 0.01$) or Group X Difficulty Level interaction effect ($F(1,37) = 0.02$, $p = 0.90$, $\eta_p^2 = 0.00$). Overall rates of hits, misses, correct rejections, and false alarms for each group across all 3 difficulty levels are presented in Figure 4.3. The PD and NC groups performed comparably in overall rates of hits ($t(37) = 1.53$, $p = 0.14$), misses ($t(37) = -1.52$, $p = 0.14$), correct rejections ($t(37) = -0.03$, $p = 0.97$), and false alarms ($t(37) = -0.03$, $p = 0.98$) collapsed across all levels of difficulty in the shape search efficiency task.

Mean d′ (discriminability index) scores produced by each group in the shape-based visual search efficiency task are presented as a function of difficulty level in Figure 4.4. Mean d′ scores were subjected to a repeated measures ANOVA which revealed a significant effect of Difficulty Level ($F(1,37) = 127.85$, $p<.001$, $\eta_p^2 = 0.78$), but no significant Group effect ($F(1.37) = 1.41$, $p=0.24$, $\eta_p^2=0.04$) or Group X Difficulty Level interaction ($F(1,37) = 0.06$, $p=0.81$, $\eta_p^2=0.00$).

These results suggest that single-feature search for stimuli that should engage ventral visual stream processing are intact in patients with PD. Patients with PD appear to retain the ability to accurately discriminate subtle differences in shape. Even as the degree of difficulty of the visual search task increased, patients with PD

performed comparably to NC participants. These findings are consistent with previous studies that showed that PD patients performed as well as normal control subjects on single-feature search tasks (Berry et al., 1999; Cormack et al., 2004).

Experiment 3B: Motion-Based Search Efficiency

This experiment examined the impact of PD without dementia on single-feature visual search for a stimulus that is primarily processed in the dorsal visual processing stream. Difficulty of the search task was systematically manipulated by employing three levels of similarity between the target stimulus and distractors. The target stimulus was a solid black circle that moved horizontally across a display of identical solid black circles that moved in the same direction but at a slower speed. That is, the participant had to detect the target stimulus based only on its speed of motion. Difficulty of the search task was systematically manipulated by employing three levels of similarity between the speed of the target stimulus and the speed of the distractors. The level of similarity varied randomly from trial to trial.

Procedure: The task was administered on a 15.4" Dell laptop computer. Each trial started with a small fixation cross shown in the center of the screen. A display was then presented that contained 15 distractor stimuli, and on half of the trials, a target stimulus. The target stimulus was a solid black circle or dot, .8 cm in diameter, that moved horizontally across the display at a speed of 3.5 cm/sec. The distractors were solid black circles identical to the target stimulus that also moved horizontally across the display, but at one of three speeds that were all slower than the target.

Distractors moved at 75% of target speed in the easiest level, 80% of target speed in the medium level, and 85% of target speed in the hardest level. On target present trials, the target circle (the circle moving faster than all the other circles) appeared at a random position on the screen among the 14 distractor circles. On each trial, the direction of motion (left to right or right to left) was chosen randomly. Items on every trial appeared in a 15-row grid, with one circle appearing per row at a randomly assigned horizontal position in the row. The target appeared in one random row out of the 15 rows.

Participants were told to look for a circle that was moving faster than the others and to press a response key marked “yes” as soon as they saw the target (i.e., one circle moving faster than the other circles), or a response key marked “no” if a target was not present in the display (i.e., all circles are moving at the same speed). Participants were told that the target would not appear on every trial. The response keys assigned to “yes” and “no” were on separate sides of the keyboard; to account for motor impairments in PD that may impair precision in striking a single key, the keys surrounding each response key were also activated. Thus, it was not necessary to strike the response key precisely in each trial. There was no overlap in the keys activated for “yes” and “no” responses. The stimulus display remained present until a response was made or for 3000 ms. Accuracy and reaction time were recorded. Immediately after a response was made, or immediately after the interval timed-out, the display disappeared and the fixation cross appeared beginning the next trial.

A total of 144 trials were run. Half of the trials were target present trials. Target present and target absent trials occurred randomly. Trials of each level of difficulty appeared pseudo-randomly to prevent more than 3 consecutive trials of the same difficulty level. The task was divided into 3 blocks, with a short rest break in between blocks to prevent eye strain or fatigue. Each block consisted of 48 trials (24 target-present, 24 target-absent). In each block, 8 trials at each of 3 difficulty levels were evenly distributed among target-present and target-absent trials. Thus, in the 24 target-present trials in a block, the participant would see 8 trials each with a target present and distractors that were either 75%, 80%, or 85% similar to the target. The 24 target-absent trials in each block were also evenly divided among 8 target-absent trials with distractors that were 75%, 80% or 85% similar to the target.

A short practice version of the task was administered prior to the test trials to familiarize patients with the task, the appearance of the target, and the appropriate response keys.

Data Analyses: The statistical analyses for the motion-based search efficiency task were identical to those of the shape-based task described above (Experiment 3A).

Results and Discussion: The average median reaction times produced by each group in the motion search efficiency task are presented as a function of difficulty level in Figure 4.5. A Group X Difficulty Level (75%, 80%, 85%) repeated measures ANOVA revealed a significant effect of difficulty level ($F(1,37) = 89.58$, $p < .001$, $\eta_p^2 = 0.71$), but no significant main effect of Group ($F(1.37) = 0.19$, $p = 0.67$, $\eta_p^2 = 0.01$) or Group X Difficulty Level interaction ($F(1,37) = 0.33$, $p = 0.57$, $\eta_p^2 = 0.01$).

Overall rates of hits, misses, correct rejections, and false alarms across all 3 difficulty levels are presented in Figure 4.6. The PD and NC groups did not differ significantly in hits ($t(37) = 0.89$, $p = 0.44$), misses ($t(37) = -0.80$, $p=0.43$), correct rejections ($t(37)=0.99$, $p=0.33$), or false alarms ($t(37) = -1.15$, $p=0.26$) collapsed across all difficulty levels.

Mean d′ (discriminability index) scores produced by each group in the motion search efficiency task are presented as a function of difficulty level in Figure 4.7. Repeated measure ANOVA revealed a significant effect of Difficulty Level ($F(1.37) = 55.30$, $p<.001$, $\eta_p^2=0.60$), but no significant Group ($F(1,37) = 1.18$, $p=0.29$, $\eta_p^2=0.03$) or Group X Difficulty Level interaction effect ($F(1.37) = 0.52$, $p=0.48$, $\eta_p^2=0.01$).

These results suggest that patients with PD are able to perform visual search for a motion-based stimulus at a level comparable to NC participants. This remains true as the difficulty of the search task becomes more difficult. Thus, single-feature search for stimuli that should engage dorsal visual stream processing appear to be relatively intact in patients with PD.

Experiment 3C: Sensory Integration

A previous study of sensory integration using motion and color cues showed that the ability to integrate information across two distinct cortical processing streams was impaired in AD (Festa et al., 2005). Although it is unlikely that PD patients suffer from the same degradation in cortico-cortical connectivity as AD patients, an investigation of the ability to integrate motion and luminance (which would rely on the dorsal processing stream) or color (which would rely on the ventral processing stream)

information will further assess the integrity of the dorsal visual processing stream in patients with PD.

Procedure: Patients with PD and NC participants were tested with an apparent motion paradigm previously used by Festa and colleagues to assess sensory integration in patients with AD (Festa et al., 2005). The task included separate conditions that examined integration of motion and luminance information or motion and color information. In the former condition, both types of information are predominantly processed by the dorsal visual stream. In the latter condition, the types of information are processed in the dorsal (i.e., motion) and ventral (i.e., color) streams. Thus, information must be integrated within a single stream in the luminance cue condition, and across relatively independent visual streams in the color cue condition. Prior to the task, participants were screened for red-green color-blindness and all participants passed a simple red-green color discrimination task with 100% accuracy. One member of the NC group refused to complete the task.

Stimuli. The visual stimuli for the apparent motion sensory integration tasks were created using the Psychophysics Toolbox extensions for MATLAB (Brainard, 1997). The task was presented on a 12-inch Macintosh iBook LCD screen with a pixel resolution of 1024 x 768, at a viewing distance of approximately 75 cm. Across both cue types, the stimulus consisted of a dynamic array of 200 dots of 0.18° diameter presented within a circular aperture of 12° diameter. The apparent motion stimulus was produced by presenting fifteen successive frames of static dots with an inter-frame interval of 67 ms. Across the successive frames, the signal dots were

systematically offset 0.55° horizontally while the noise dots were given new randomly selected x-y positions. The resulting percept was that a subset of dots were streaming across the circular aperture (at ~8.24°/sec) amid flickering noise. Signal dots had a five-frame limited lifetime; after that, new signal dots were selected from noise dots. These new signal dots continued the same horizontal trajectory relative to their positions on the previous frame. On the first frame of each trial, random positions within the circular aperture were chosen for the dots. The initial positions of the signal dots were limited to only those positions for which the motion trajectory would not extend beyond the aperture edge across the five-frame dot-life. The noise dots were given new x-y positions on each frame of the motion stimulus. The direction of motion was randomized (left or right) from trial to trial. Each motion stimulus lasted for a total duration of 1.01 seconds.

Subjects used two distinct types of cues to segment the signal from the noise: luminance cues (black vs. white dots) and color cues (isoluminant red vs. green dots). A PR-650 Spectra colorimeter was used to measure the luminance (Y) and Commission Internationale de l'Êclairage (CIE) coordinates (x,y) of the stimuli. Different background colors were used in the two cue conditions to maximize the luminance contrast between the isoluminant color dots and the backgrounds. The motion information in both the color and luminance cues was believed to be processed by the dorsal processing stream. In the luminance cue type, black (Y=0.41 cd/m^2; x = 0.259, y = 0.268) and white (Y=90.67 cd/m^2; x = 0.321, y = 0.335) dots appeared on a gray (Y=6.34 cd/m^2; x = 0.269; y=0.276) background. This resulted in a Michelson

contrast of 88% and 87% for the black and white dots (respectively) from the background. In the color cue type, the red and green dots were isoluminant and differed only in chromaticity. Red (Y=22.00 cd/m^2; x=0.566, y = 0.335) and green (Y=21.97 cd/m^2; x=0.297; y=0.505) dots appeared on a black (Y=0.41 cd/m^2; x=0.259; y=0.268) background. This resulted in a Michelson contrast of about 96% for both red and green dots from the background black color.

Test Conditions. For each of three test conditions (baseline, coupled, and uncoupled), thresholds were determined for detecting the direction of movement with luminance or color cues. In the baseline condition, the signal and noise dots were identical in cue (for example, all black dots or all white dots in the luminance condition; all red dots or all green dots in the color condition). In the baseline condition, the signal and noise dots could be differentiated on the basis of motion information alone; no cue helped to differentiate direction of motion. The cue value (red or green; white or black) was randomly assigned across trials.

In the coupled condition, the signal and noise dots could be distinguished on the basis of motion and cue information. The signal dots were shown in one color (or luminance) and the noise dots were shown in the other color (or luminance). The cue value ratio (black to white or red to green) was equal to the signal to noise ratio. The cue value polarity (white signal among black noise vs. black signal among white noise, or red signal among green noise vs. green signal among red noise) was randomly assigned across trials.

In the uncoupled condition, motion and cue information was identical to that which was presented in the coupled condition. However, in the uncoupled condition, the cue information was not coupled with the motion information. The signal-to-noise dot ratio and the cue value ratio were equal to that in the coupled condition, but the color (or luminance) was randomly assigned to the dots on each frame. In the uncoupled condition, color (or luminance) could no longer serve as a cue to aid the participant in segmenting the signal from the noise and differentiating the motion direction. In the uncoupled condition, the signal and noise dots could only be distinguished on the basis of motion information alone. The cue (luminance or color) was actually a source of potential interference in this condition of the task. Also, the polarity of the cue value (white signal vs. black noise or black signal vs. white noise; red signal vs. green noise or green signal vs. red noise) was randomly assigned across trials.

Test Procedure. Subjects were seated approximately 75 cm in front of the laptop computer. The screen was adjusted to eliminate glare and provide the best viewing of the stimuli. To ensure that all subjects could discriminate red and green colors, 10 static images of dot stimuli were shown. The dots were all red or all green, and subjects verbally identified the color of the display. Sample displays allowed the subjects to familiarize themselves with the motion discrimination task while the experimenter described the task. Subjects were told that they would see moving dots, and a portion of the dots would be moving in a consistent direction (left or right). Subjects were told that the task was to identify the direction of motion (left or right)

and to guess if needed. Subjects could indicate a direction verbally or nonverbally (by pointing), and the response was recorded by the experimenter. Participants were told that the proportion of dots moving in a consistent direction would be adjusted as a result of their performance. Practice trials were administered before each condition before the threshold was determined. During practice trials, the task was clarified and feedback on performance was provided. None of the participants needed to be reminded of the task objectives or procedures during the test trials. During test trials, no feedback was provided; the experimenter provided non-specific words of encouragement to the participant on an as-needed basis. The task was difficult, and nonspecific words of encouragement provided reassurance that the subject was completing the task correctly. Subjects were encouraged to guess if they were unsure of the motion direction on any given trial.

The luminance and color cue types were administered in 2 separate test sessions (on different days) with the order counterbalanced among subjects. Within each test session, the motion discrimination threshold was determined twice for each of the 3 conditions (baseline, coupled, uncoupled). The order of the conditions (baseline, coupled, uncoupled) was randomized for the first set of thresholds. The second set of thresholds reversed the order of the conditions. If the two threshold values for any condition differed by more than 0.10 signal strength, a threshold was determined with a third run of the condition, with the condition(s) presented in a new randomized order. For each subject, the two best motion discrimination thresholds in each condition were averaged.

A QUEST staircase procedure (A. B. Watson & Pelli, 1983) was used such that the number of signal dots needed to accurately discriminate the direction of motion was adjusted across the trials to converge on an estimated threshold value that would yield correct performance 82% of the time. The QUEST procedure uses a Bayesian estimator to sample a range of values, which were based on the subjects' responses in conjunction with the Bayesian estimator, and this converges on a value that yields 82% correct performance on the task. The QUEST method was chosen because it allows a relatively stable threshold to be obtained with a relatively low number of trials.

In each condition, 43 test trials were administered in order to obtain a threshold value. The signal strength was constant in the first 3 trials in each condition to allow the subjects to get into set; then the signal strength was adjusted according to the QUEST staircase procedure over the remaining 40 trials. The starting value for the staircase for the first set of thresholds was 0.25 signal strength (i.e., 50 signal dots and 150 noise dots). To obtain subsequent thresholds for a particular condition, we used the subjects' previous threshold for that condition as a starting value. Rest periods were given as needed after each block of 43 trials.

Data Analysis: SPSS v21 was used to carry out statistical analyses for the sensory integration task. Group differences in baseline motion threshold scores in the luminance condition were analyzed using student's t-tests (alpha level for significance set at $p<.05$). In the baseline condition, the motion threshold scores were subjected to repeated measures ANOVA with Group (between subjects) and Cue Type (within-

subjects repeated measure) as factors. Partial eta-squared (η_p^2) was used to measure effect sizes. An alpha for significance was set at $p<.05$ to examine whether the Group X Cue Type interaction was significant in the baseline condition.

In a subsequent analysis, mean motion discrimination thresholds were subjected to repeated measures ANOVA with Group (between subjects), Cue Type (within-subjects repeated measure), and Condition (within-subject repeated measure) as factors. Partial eta-squared (η_p^2) was used to measure effect sizes. An alpha for significance was set at $p<.05$ to examine significant main effects of group, cue type, condition, and any resultant interactions between factors.

To further examine group differences in performance, separate two-way mixed model ANOVAs were conducted for each cue type. For the luminance cue type, motion threshold scores were subjected to repeated measures ANOVA with Group (between subjects) and Condition (coupled and uncoupled) as factors. Partial eta-squared (η_p^2) was used to measure effect sizes. An alpha for significance was set at $p<.05$ to examine whether the Group X Condition interaction was significant in the luminance cue type.

For the color cue type, motion threshold scores were subjected to repeated measures ANOVA with Group (between subjects) and Condition (coupled and uncoupled) as factors. Partial eta-squared (η_p^2) was used to measure effect sizes. An alpha for significance was set at $p<.05$ to examine whether the Group X Condition interaction was significant in the color cue type.

Results and Discussion: Baseline Condition. Mean motion discrimination threshold scores for the PD and NC groups in the baseline condition of both the luminance and color cues are shown in Figures 4.8 and 4.9, respectively. A two-way mixed model analysis of variance (ANOVA) showed a significant main effect of Cue Type ($F(1, 37) = 19.341$, $p < .001$, $\eta_p^2 = .34$), indicating lower thresholds for luminance than for color cues. There was no significant main effect of Group ($F(1, 37) = 3.03$, $p = .09$, $\eta_p^2 < .1$) or Group × Cue Type interaction, ($F(1, 37) = 0.31$, $p = .584$, $\eta_p^2 < .01$). T-tests showed that baseline thresholds for the PD and NC groups did not differ with either luminance ($t(37) = -1.56$, $p = .13$) or color cues ($t(37) = -1.69$, $p = .10$). With similar mean baseline thresholds in both cue types, this indicates that the PD and NC groups were well-matched in their basic ability to detect the direction of simple horizontal motion in both the luminance and color stimulus displays.

Analysis of Cue Type, Condition, and Group main effects. Mean motion discrimination threshold scores for the PD and NC groups in the coupled and uncoupled conditions for the luminance cue are shown in Figure 4.8; threshold scores for the coupled and uncoupled conditions for the color cue are shown in Figure 4.9. A three-way mixed model ANOVA revealed a significant main effect of Cue Type, $F(1, 37) = 38.83$, $p < .001$, $\eta_p^2 = .51$, Condition, $F(1, 37) = 228.79$, $p < .001$, $\eta_p^2 = .86$, a significant Condition × Group interaction, $F(1, 37) = 6.29$, $p < .05$, $\eta_p^2 = .15$, and a significant Cue Type × Condition interaction, $F(1, 37) = 106.24$, $p < .001$, $\eta_p^2 = .74$. A main effect of Group approached significance, $F(1, 37) = 3.96$, $p = .054$, $\eta_p^2 = .10$, but

there was no Group × Cue Type × Condition interaction, $F(1, 37) = 1.14$, $p = .29$, $\eta_p^2 = .03$.

Luminance Cue. To further examine performance across cue types by group, we conducted separate two-way mixed model ANOVAs for each cue type. For the luminance cue type, a significant main effect of Condition, $F(1, 37) = 251.34$, $p < .001$, $\eta_p^2 = .87$, and a significant Group × Condition interaction, $F(1, 37) = 4.82$, $p < .05$, $\eta_p^2 = .12$ were found, while a main effect of Group approached significance $F(1, 37) = 3.70$, $p = 0.05$, $\eta_p^2 = .09$. This indicates that the difference between the coupled and uncoupled conditions was larger for the NC group than the PD group in the luminance cue type.

Color Cue. A similar analysis for the color cue type showed a significant main effect of Condition, $F(1, 37) = 6.38$, $p < .05$, $\eta_p^2 = .15$, but no significant Group effect ($F(1,37) = 3.114$, $p=0.09$, $\eta_p^2=0.08$) or Group X Condition interaction ($F(1,37) = 0.96$, $p=0.33$, $\eta_p^2 = 0.03$). This indicates that the PD and NC groups did not perform differently from each other in either the coupled or the uncoupled condition; the uncoupled condition was more difficult for both groups in the color cue type. Thus, despite a fairly equivalent baseline performance with both cue types, the PD and NC participants displayed different patterns of results in the coupled and uncoupled conditions across the luminance and color cue types.

The present results indicate that patients with PD are impaired relative to controls when attempting to use luminance as a cue to aid in segmenting the signal from the noise and detecting the correct direction of motion. That is, PD patients do

not show the same degree of improvement (reflected in a lower value of signal strength threshold) as their NC counterparts in the “coupled” condition, when luminance information validly cues the direction of motion. It could be argued that the lack of improvement in the coupled condition in the luminance cue condition in PD patients represents a generalized deficit in the ability to detect motion (i.e., no matter how much aid is provided, their performance in every condition in the luminance task represents the best performance possible for a PD patient with poor motion discrimination). However, the ability of PD patients to detect the direction of motion in the baseline condition of the luminance cue as well as normal controls does not support this contention. In addition, if PD patients have a generalized deficit in the ability to detect motion, then they should have been impaired on the motion speed visual search task from Experiment 3B that they were able to perform normally.

It may be the case that PD patients’ deficit in motion detection arises when the dorsal processing stream is taxed or when extra demands are placed upon it. When one must use luminance information to segment the direction of a motion signal from noise, PD patients are not able to use this cue to the same extent as controls because both types of information must be processed in the dorsal visual stream.

In the sensory integration task, a particularly striking increase in motion threshold scores is apparent when comparing the baseline and coupled threshold scores to the uncoupled threshold scores in the luminance cue condition. In both patient groups (PD and NC), a large increase in motion discrimination threshold is evident in the uncoupled condition. The uncoupled condition is the most complex and

challenging condition in either of the cue types, because no cue exists to aid participants in segmenting the signal from the noise. It is possible that performance suffers in this condition because the stimuli are competing with one another, and there is no way to find a reliable cue to assist in segmenting the signal from the noise in this condition. Thus, it is possible that there is such a striking increase in the thresholds in the uncoupled condition of the luminance cue condition because this condition is difficult for all participants, not just those with a neurodegenerative disease.

We might expect that the known impairment in contrast sensitivity in patients with PD contributes to an impairment in the luminance cue condition. While we cannot ignore that contrast sensitivity is impaired in PD as a result of dopamine depletion in the retina, dopamine-replacing agents are thought to normalize this retinal abnormality. All of our PD participants completed the visual cognitive battery while "on" their dopamine replacement therapies. Additionally, with contrast sensitivity issues in mind, these sensory integration tasks were designed at very high levels of Michelson contrast that should be well beyond the levels at which PD patients demonstrate impairments in ability to detect contrast (Tebartz van Elst et al., 1997). Also, if impairment in contrast sensitivity was the only driving force behind the decreased ability of PD patients to use luminance to segregate motion in this task, then this impairment in the ability to tell the difference between black and white dots would have been consistent across all task conditions, and the baseline task performance should have closely mirrored signal strength thresholds obtained across all 3 conditions in the luminance cue condition. Instead, it is important to note that the

performance of the PD group in the baseline condition of the luminance cue condition was not significantly different from the performance of the NC group. Also, both the PD and NC groups showed a similar jump in signal strength threshold needed to differentiate motion in the uncoupled condition. Thus, it does not appear likely that the performance of PD patients was driven by any impairment in contrast sensitivity.

The results from the color cue condition are difficult to interpret with any degree of certainty. In earlier work using this sensory integration task (Festa et al., 2005), a cohort of normal controls performed differently from present controls in the color cue condition. The normal cohort in the earlier work did show an improvement in ability to segment motion in the coupled condition in the color cue condition. This suggests that the normal controls in the earlier work effectively used color as a cue to segment motion direction. In the present study, there is no statistically significant difference between the baseline, coupled, and uncoupled conditions of the color cue condition for either the NC participants or PD patients. Without a clear enhancement from coupled color cues in the NC group, it is difficult to make a statement about the ability of patients with PD to integrate color and motion information in the color cue condition. We can only say that the PD and NC groups performed equally on the color condition, and cannot reliably claim that either group was able to use color to segment motion in this particular portion of the motion integration task. It is unclear why the present normal control cohort did not show the same pattern of results in the color cue as those in Festa et al. (Festa et al., 2005).

Regardless of the fact that there are no group differences between PD and NC participants in the color cue condition, it is important to note that the performance of the PD group in both the color and luminance cues conditions represents an important departure from the performance of AD patients on this task. Whereas AD patients were not different from normal controls in any of the conditions in the luminance cue condition (baseline, coupled, uncoupled) (Festa et al., 2005), they were not able to use color as a cue to segment motion in the color condition, presumably because of the cortico-cortical degeneration that may be relatively specific to AD. Patients with AD showed a deficit in the ability to integrate information across visual processing streams, but their ability to integrate information within a single processing stream was intact. Patients with PD also perform differently than AD patients in the luminance condition. Their motion detection ability is not helped by the presence of luminance motion segmentation cues, while AD patients are helped. This result suggests that PD patients may have an integration deficit, but it may be limited to information processed in the dorsal processing stream.

Experiment 3D: Color-Motion Visual Search

Part of the difficulty in interpreting the results from the color cue condition of the sensory integration task may arise from the overall difficulty of the task. Therefore, the next experiment examined the ability of PD patients to integrate information processed in distinct visual processing streams using a simpler task. The supporting task was a dual-feature visual search task that required the integration of

color information (processed primarily in the ventral visual stream) and motion information (processed primarily in the dorsal visual stream).

Procedure: This task was programmed using E-Prime software and presented on a Dell 15" laptop computer. Each trial of this task began with a fixation cross presented in the center of a blank screen. On each trial a number of dots appeared in a circular pattern around the fixation cross. All dots were either red or green and all were moving either up and down or left to right at presentation. The number of dots changed from trial to trial between 1, 3, and 5 dots. There were 54 target-present trials with an equal number (18 each) of each set size of 1, 3, or 5. There were also 54 target-absent trials with an equal number (18 each) of each set size of 1, 3, or 5. Targets could appear with equal frequency in any quadrant of the screen. Participants were instructed to press a response key (the space bar) as soon as they saw a red dot moving up and down (the target). They were encouraged to respond as quickly as possible without sacrificing accuracy. No feedback was given after the response. Subjects were told that they would not see the target on every trial, and were told to make no response on target-absent trials. Each stimulus display remained on the screen until the subject responded, or for a maximum of 3500 ms. Accuracy and reaction time in milliseconds was measured for each trial.

A 12-trial practice test was administered prior to the test trials. After each practice trial, feedback was given to the participant to let them know whether their response was correct or incorrect (whether they missed a target, or whether they hit "yes" when there was no target and had a false alarm). The practice trials included 6

that were target-present and 6 that were target-absent. Two target-absent and two target-present trials were presented for each of 3 set sizes (1,3, or 5) during the practice trials.

Data Analysis: SPSS v21 and Excel were used to carry out statistical analyses. Average median reaction times were computed on target-present trials as a function of set size (1, 3, 5). Slopes (difference in reaction times as set size increased) were calculated for both participant groups using Excel functions. The median reaction time data were subjected to repeated measures ANOVA with Group (between subjects) and Set Size (within subjects repeated measure) as factors. Partial eta-squared (η_p^2) was used to measure effect sizes. An alpha for significance was set at $p<.05$ to examine whether the Group X Set Size interaction was significant. Independent t-tests were used to examine group differences in median reaction times at each set size (alpha for significance set at $p<.05$). Independent samples t-tests were also used to examine group differences in slope of reaction time as the set size increased (alpha for significance set at $p<.05$). Difference scores were calculated for each participant group by taking the difference between the median reaction time at set size of 5 and the median reaction time at a set size of 1. Independent samples t-tests were used to examine group differences in difference scores (alpha for significant set at $p<.05$). Accuracy on target-present and target-absent trials, and the distribution of hits, misses, false alarms, and correct rejections across the two participant groups was analyzed using a nonparametric independent samples Mann-Whitney U test (alpha for significance set at $p<.05$).

Results and Discussion: Average median reaction times for each group as a function of set size are displayed in Figure 4.10 and Tables 4.2-4.4. A Group X Set size repeated measures ANOVA on reaction times showed no significant effect of Group ($F(1,38) = 0.21$, $p = 0.65$, , $\eta_p^2 = 0.01$), but did show a significant main effect of Set Size ($F(1,38) = 281.35$, $p < .001$, $\eta_p^2 = 0.88$), and a significant Group X Set size interaction ($F(1,38) = 6.91$, $p < .05$, $\eta_p^2 = 0.15$). The interaction appears to be driven by the fact that patients with PD had reaction times that were longer than those of NC participants at set size 1, and faster reaction times at set size 5. Follow-up independent samples t-tests demonstrated no group differences in the median reaction times at a set size of 1 ($t(38) = -0.72$, $p=0.48$), a set size of 3 ($t(38)= 0.16$, $p=0.87$), or at a set size of 5 ($t(38) = 1.39$, $p=0.17$). Slopes were computed to examine the increasing time cost as set size increased. A t-test showed that the slope of the normal control group was significantly steeper than the slope of the PD group ($t(1,38) = 2.63$, $p<.05$), indicating that the PD group had a smaller than normal time cost to identify the target as the set size increased. Nonparametric Mann-Whitney U-tests revealed no significant differences in the distribution of hits ($p=0.93$), misses ($p=0.93$), false alarms ($p=0.15$), or correct rejections ($p=0.16$) across groups, nor a group difference in the distribution of accuracy rates across groups on target-present ($p=0.93$) or target-absent trials ($p=0.16$).

Although the results of the color condition in the sensory integration task of the previous experiment were ambiguous because the NC group did not show the expected increase in the ability to segment motion using the color cue, the present

results from the color-motion visual search task support the claim that patients with PD are able to bind color and motion information (processed in two distinct cortical areas) at a level comparable to (or even better than) NC participants. Overall accuracy on both target-present and target-absent trials was comparable in the two groups, and the PD patients and NC participants did not differ significantly in rates of hits, misses, correct rejections, or false alarms (although false alarms occurred marginally more often in the PD group than in the NC group). An examination of group differences in reaction time at each set size showed that reaction time increased as set size increased to a greater degree in NC participants than in patients with PD. This may mean that PD confers a benefit on the ability to perform search tasks that require dual-stream integration of color and motion. This unexpected result needs to be confirmed in future studies. However, even a cautious interpretation of the results suggests that there is no deficit in the ability of PD patients to combine information from the dorsal and ventral processing streams to accurately complete a dual-feature visual search task.

General Discussion

Taken together, the results from the three experiments in this study indicate that patients with PD do not have a selective deficit in visual attention or a general deficit in sensory binding. This appears to be true even when an integration task puts demands on two distinct cortical processing streams. The relative lack of deficits in visual cognition in non-demented patients with PD suggests that the severe visual cognition deficits exhibited by patients with DLB are not due to the pathology that the

two disorders have in common. Thus, the visual cognition deficits in patients with DLB most likely arise from cortical Lewy body pathology unique to DLB, or to an interaction between cortical Lewy body pathology and concomitant AD pathology. It should be noted, however, that even though PD patients did not display generalized deficits in visual cognition, further investigation is warranted along the spectrum of Lewy body disorders. Specific patterns of deficits may emerge as the disease evolves from non-demented PD to PD-MCI to PD with dementia.

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Table 4.1: Mean (Standard Deviation; SD) Age, Education, Mini-Mental State Exam (MMSE), Dementia Rating Scale (DRS), and Uniform Parkinson's Disease Rating Scale (UPDRS), and Geriatric Depression Scale (GDS) scores for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD. The ratio of men to women in each group, and the percentage of NC and PD participants with past or current visual hallucinations, REM sleep behavior disorder (RBD), and fluctuations in consciousness or cognition are also shown.

	NC n = 20 Mean (SD)	PD n = 20 Mean (SD)
Age	71.4 (5.7)	69.1 (5.8)
Sex (m:w)	11:9	16:4
Education	16.6 (1.9)	16.6 (2.8)
MMSE	29.3 (1.0)	28.3 (1.7)
DRS	141.8 (1.5)	140.0 (3.5)
UPDRS	0.2 (0.9)	18.7 (15.2)
GDS	0.3 (0.6)	5.4 (5.6)
Hallucinations	---	40 %
Fluctuations	15%	60%
RBD	5%	60%

Table 4.2: Mean (Standard Deviation; SD) overall accuracy rates and raw number of hits, misses, correct rejections, and false alarms (out of 108 total trials) in a color motion visual search task for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

	NC n = 20 Mean (SD)	PD n = 20 Mean (SD)
Target-absent accuracy rate	0.99 (0.01)	0.98 (0.05)
Target-present accuracy rate	0.99 (0.02)	0.99 (0.02)
Hits	53.40 (0.75)	53.25 (1.12)
Correct Rejections	53.70 (0.47)	52.70 (2.74)
Misses	0.60 (0.75)	0.75 (1.12)
False Alarms	0.30 (0.47)	1.30 (2.74)

Table 4.3: Mean (Standard Deviation; SD) of median reaction time in milliseconds for simple visual detection task; mean (SD) slope; mean (SD) difference score; and mean (SD) median reaction time in milliseconds as a function of set size in a color motion visual search task for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

	NC n = 20 Mean (SD)	PD n = 20 Mean (SD)
Simple Visual Detection: Median Reaction Time	380.5 (52.5)	369.3 (70.0)
Median Reaction Time (ms): Set Size of 1	810.3 (144.6)	854.2 (231.6)
Median Reaction Time (ms): Set Size of 3	1182.5 (141.3)	1171.2 (276.0)
Median Reaction Time (ms): Set Size of 5	1431.7 (257.4)	1307.2 (305.8)
Difference Score (RT at Set Size 5 – RT at Set Size 1)	621.4 (251.1)	453.1 (137.9)
Slope	155.4 (62.8)	113.3 (34.5)

Table 4.4: Mean (Standard Deviation; SD) accuracy rates and raw numbers of hits, misses, correct rejections, and false alarms (out of 108 total trials) in a color-motion visual search task as a function of set size for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

	NC n = 20 Mean (SD)			PD n = 20 Mean (SD)		
	Set Size 1	Set Size 3	Set Size 5	Set Size 1	Set Size 3	Set Size 5
Target-Absent Accuracy	0.99 (0.02)	0.99 (0.02)	1.00 (0.01)	0.98 (0.05)	0.98 (0.04)	0.96 (0.07)
Target-Present Accuracy	1.00 (0.01)	0.99 (0.02)	0.98 (0.04)	0.98 (0.03)	0.99 (0.03)	0.99 (0.03)
Correct Rejections	17.90 (0.31)	17.85 (0.37)	17.95 (0.22)	17.70 (0.80)	17.65 (0.75)	17.35 (1.35)
Hits	17.95 (0.22)	17.85 (0.37)	17.60 (0.68)	17.65 (0.59)	17.80 (0.52)	17.80 (0.62)
False Alarms	0.10 (0.31)	0.15 (0.37)	0.05 (0.22)	0.30 (0.80)	0.35 (0.75)	0.65 (1.35)
Misses	0.05 (0.22)	0.15 (0.37)	0.40 (0.68)	0.35 (0.59)	0.20 (0.52)	0.20 (0.62)

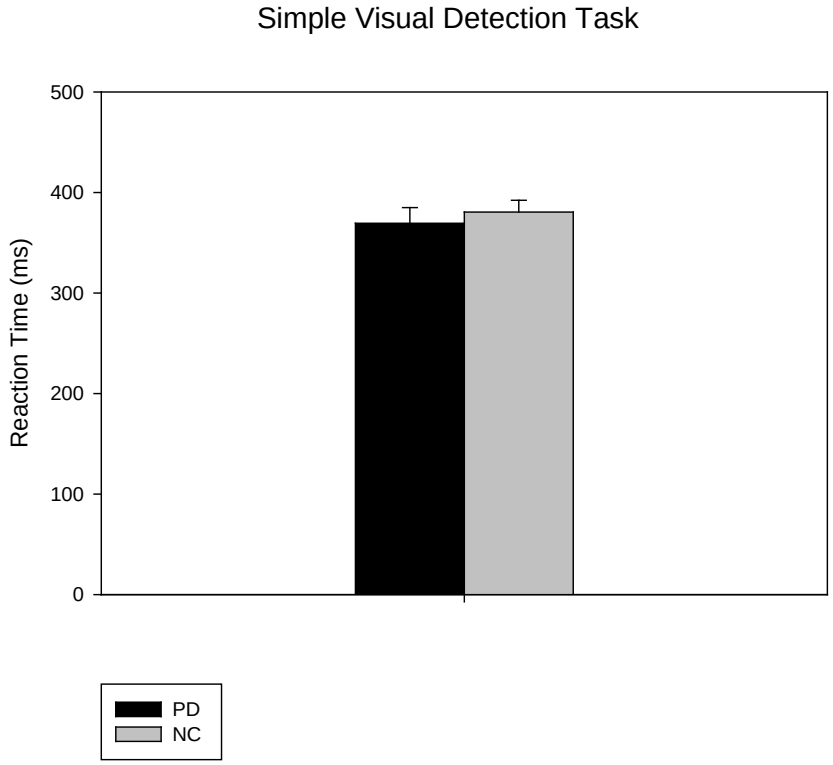

Figure 4.1: Mean (with standard error bars) of median reaction time to the presentation of a single visual stimulus for Normal Control Participants (NC) and Patients with Parkinson's Disease (PD).

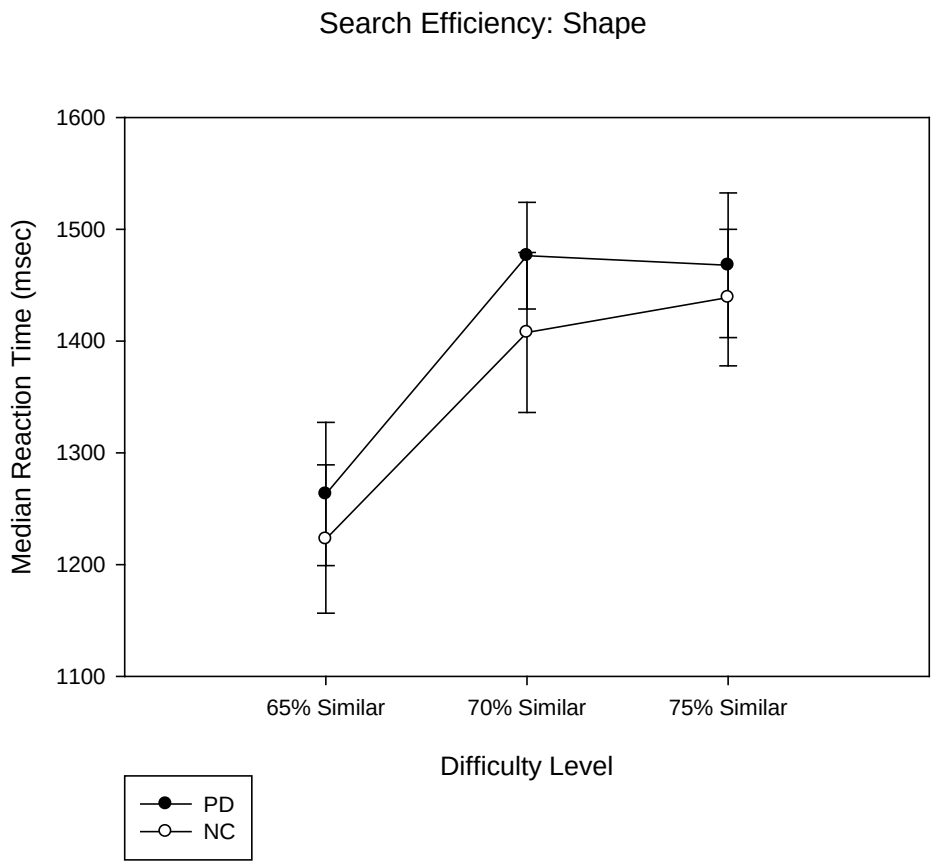

Figure 4.2: Mean (with standard error bars) of median reaction times to the presentation of a shape-based search efficiency task as a function of difficulty level for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

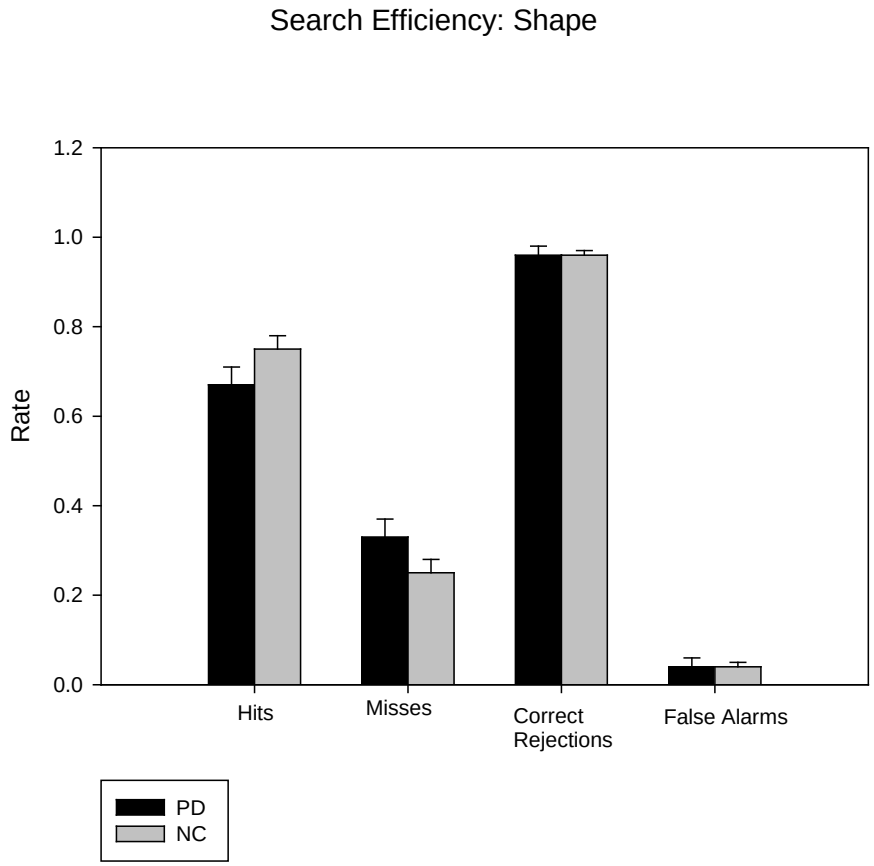

Figure 4.3: Mean (with standard error bars) rate of hits, misses, correct rejections, and false alarms across all conditions of a shape-based search efficiency task for Normal Control Participants (NC) and Patients with Parkinson's Disease (PD).

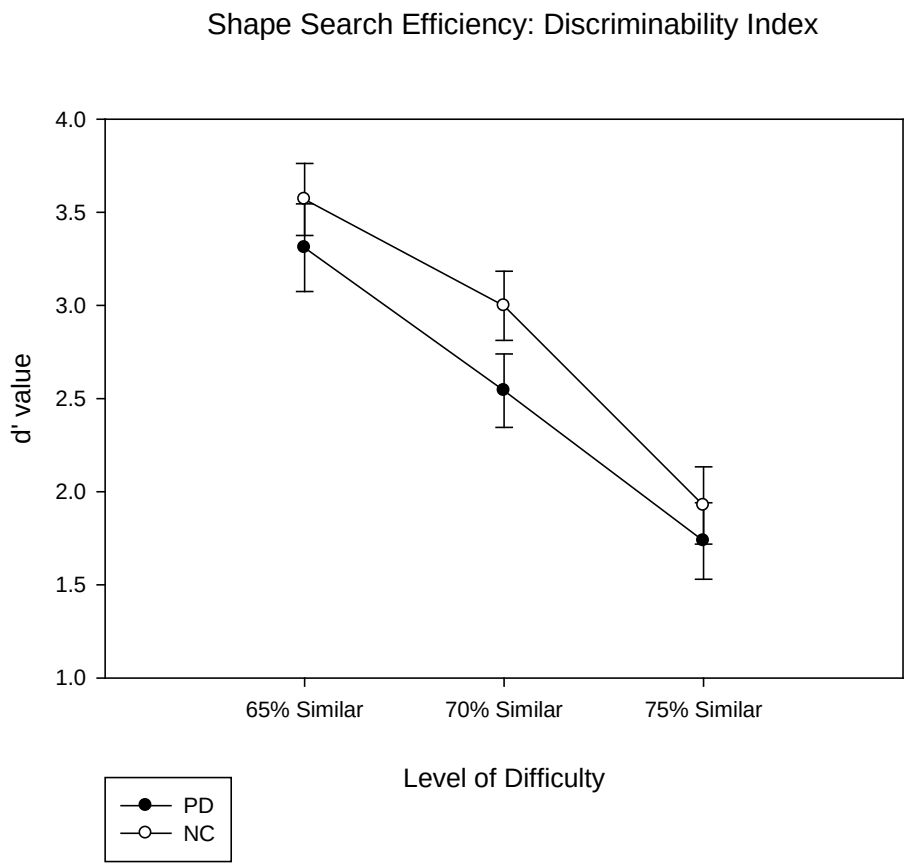

Figure 4.4: Mean (with standard error bars) of d′ (discriminability index) values produced in a shape-based search efficiency task as a function of difficulty level for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

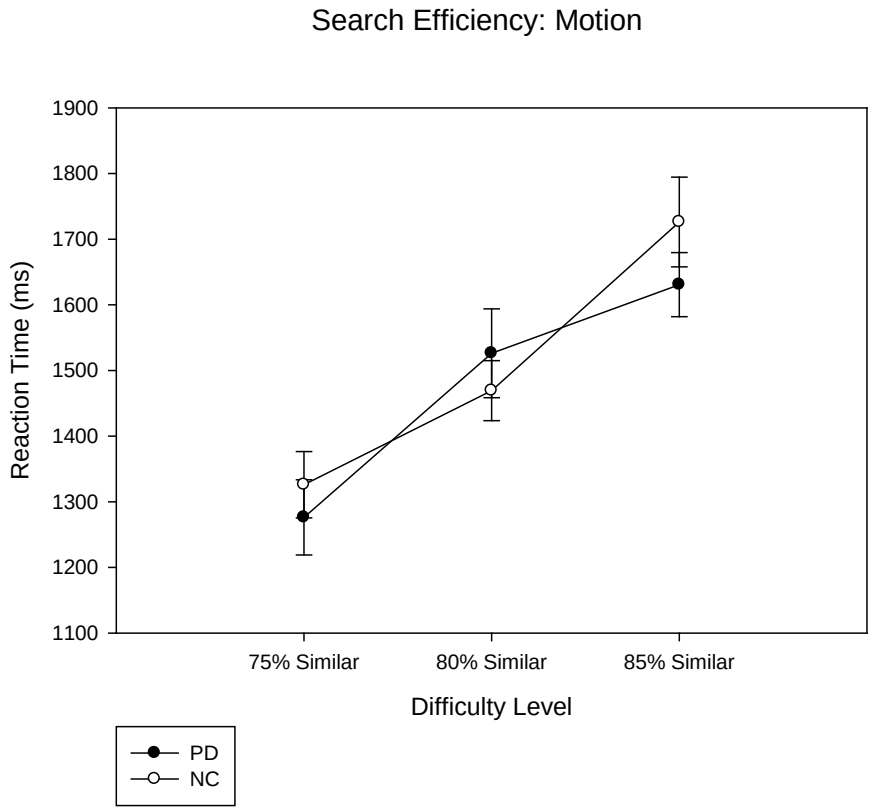

Figure 4.5: Mean (with standard error bars) of median reaction times to the presentation of a motion-based search efficiency task as a function of difficulty level for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

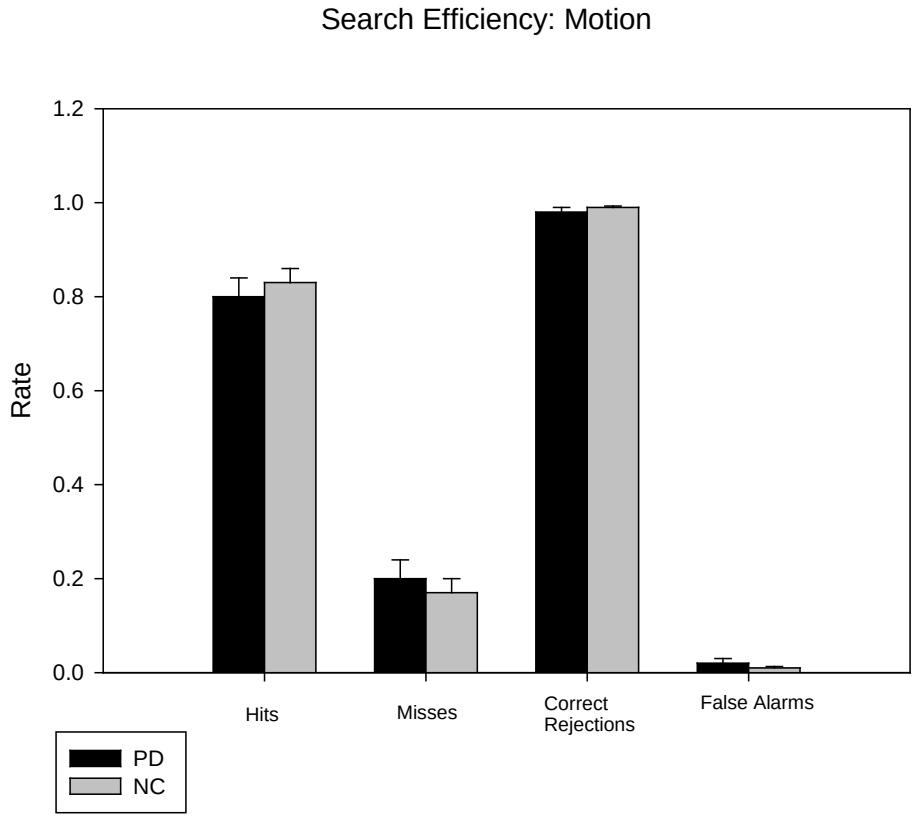

Figure 4.6: Mean (with standard error bars) rate of hits, misses, correct rejections, and false alarms across all conditions of a motion-based search efficiency task for Normal Control Participants (NC) and Patients with Parkinson's Disease (PD).

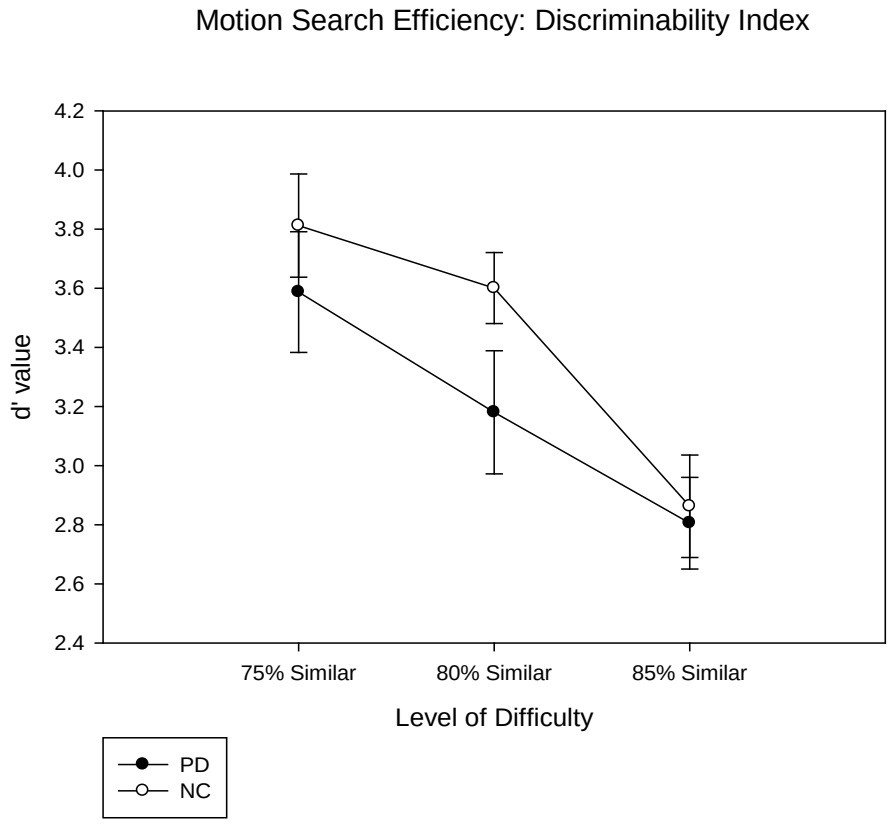

Figure 4.7: Mean (with standard error bars) of d′ (discriminability index) values produced in a motion-based search efficiency task as a function of difficulty level for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

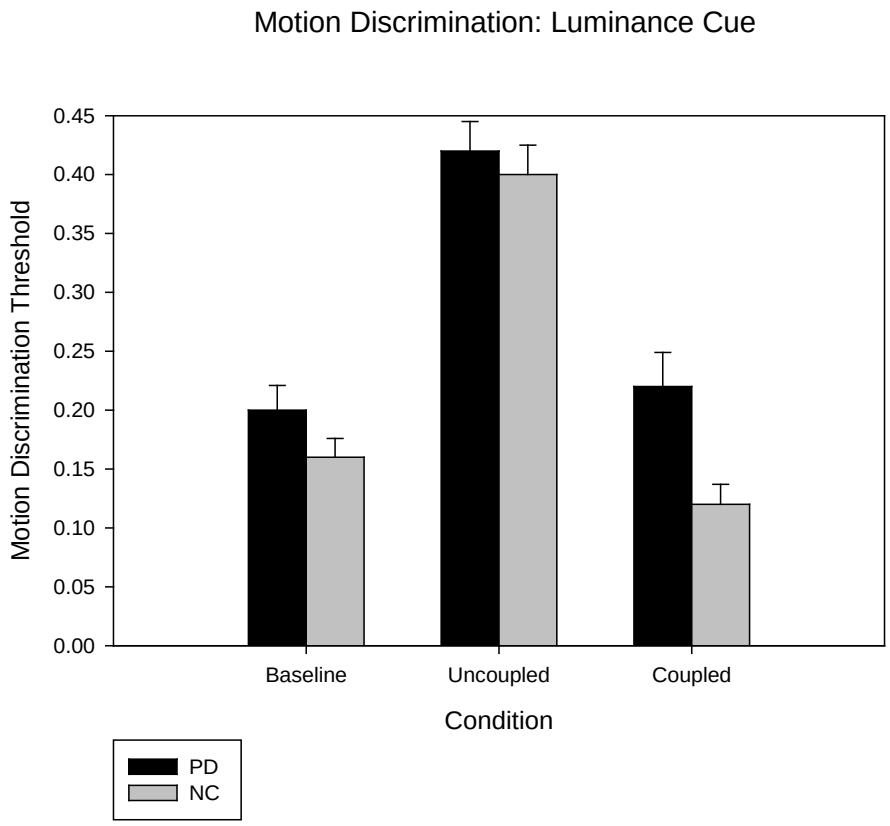

Figure 4.8: Mean threshold scores (with standard error bars) produced by the Normal Control (NC) Participants and Patients with Parkinson's Disease (PD) in the baseline condition and the two integration conditions (uncoupled and coupled) of a sensory integration task with a luminance cue.

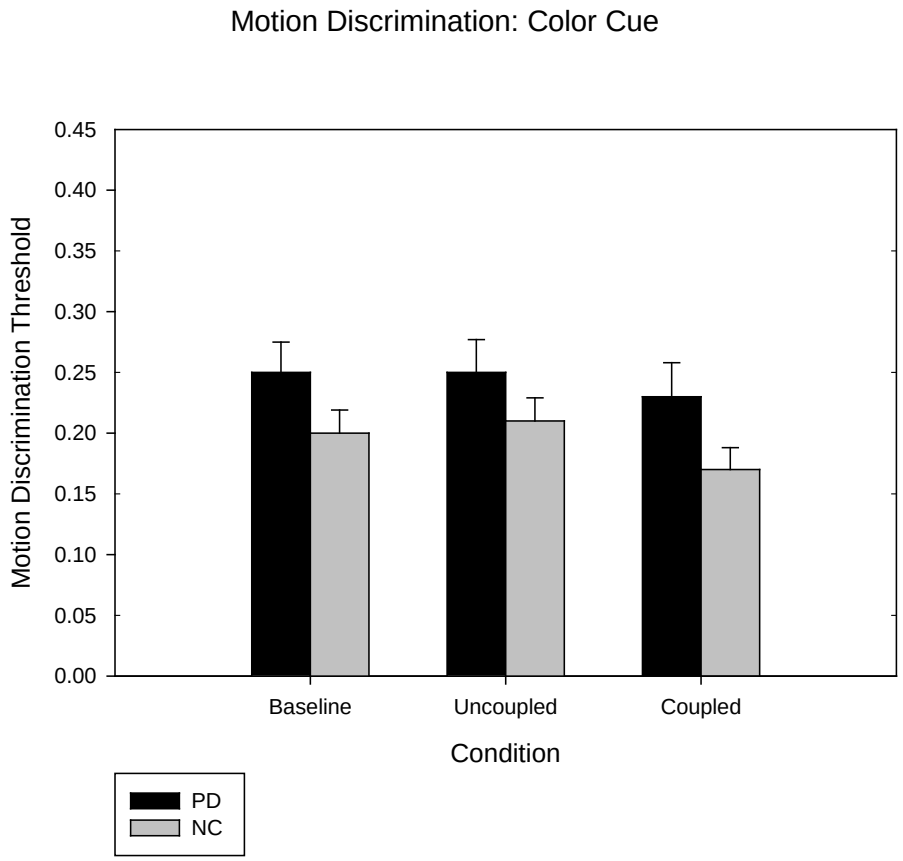

Figure 4.9: Mean threshold scores (with standard error bars) produced by Normal Control (NC) Participants and Patients with Parkinson's Disease (PD) in the baseline condition and the two integration conditions (uncoupled and coupled) of a sensory integration task with a color cue.

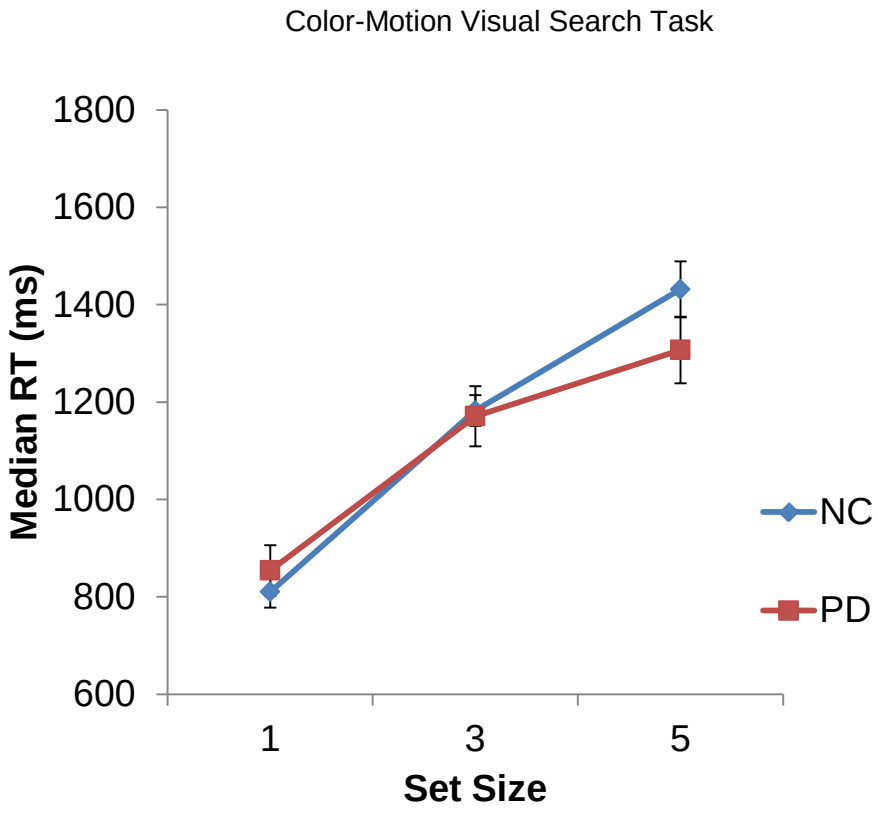

Figure 4.10: Mean (with standard error bars) of median reaction times to the presentation of a color-motion visual search task as a function of set size for Normal Control (NC) Participants and Patients with Parkinson's Disease (PD).

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Chapter 5

Conclusions

The studies described in this dissertation examined visual cognition across a spectrum of Lewy body disorders. The experiments included a study of the ability of DLB patients to discriminate simple horizontal motion, and a study of their ability to perform visual search tasks. Additional studies investigated visual cognition in non-demented patients with PD to determine if significant visual cognition deficits occurred in individuals who have Lewy body pathology largely restricted to subcortical structures. Because PD shares Lewy body pathology with DLB but has less cortical Lewy bodies or AD pathology, the pattern of performance produced by PD patients on tests of visual cognition can help elucidate the neurological bases of the visuospatial impairment in DLB. If non-demented PD patients display deficits similar to those of patients with DLB, those particular visual cognition deficits might be related to subcortical Lewy body pathology (and the various striato-cortical connections it disrupts) common to the two disorders. However, if a particular aspect of visual cognition is normal in non-demented patients with PD but markedly impaired in DLB, it is likely that the deficit is due to cortical Lewy body pathology, cortical AD pathology, or their interaction.

The results of the study of simple motion discrimination in DLB (Chapter 2) supported our hypothesis that DLB patients display severe deficits in the ability to detect simple horizontal motion. This deficit was not an artifact of dementia alone, as AD patients performed the task at the same level as healthy older adults. The results

of the study of visual search in patients with DLB were somewhat unexpected. Previous research suggested that patients with DLB are impaired in performing single-feature search (Cormack, Gray, Ballard, & Tovee, 2004). Our results showed that patients with DLB were slower than NC participants and other neurologically impaired groups in detecting visual targets, but showed the same amount of increase in reaction time with increasing numbers of distractors as NC participants and the other patient groups. The DLB patients also showed normal performance on a dual-feature visual search task that required the integration of visual information processed in different visual processing streams. In fact, it was the AD group in the dual-feature search task who showed a slight (but significant) increase in reaction time as the number of distractors increased in dual-feature search. We speculate that this difficulty in AD patients occurred because information about the target and the distractors had to be processed in two distinct cortical processing streams (with luminance information processed in the dorsal stream, and shape information in the ventral processing stream (Ungerleider & Haxby, 1994)). In addition, a breakdown in cortico-cortical connectivity that results from the neurodegenerative processes of AD may be responsible for this deficit.

Because patients with DLB showed a severe deficit in motion discrimination in previous studies, the studies described in Chapter 4 were conducted to determine if this was an early feature of PD or a deficit that evolved as pathology involved neocortical brain regions. Thus, PD patients were tested on a motion discrimination task in which either luminance or color cues could be used to segregate coherently

moving stimuli from those moving randomly and thus aid in motion discrimination. The performance of patients with PD on this task was consistent with an emerging deficit in the ability to integrate motion and luminance information. Both of these types of visual information are predominantly processed in the dorsal visual stream. Although PD patients did not differ from normal controls in the ability to detect motion in the baseline condition of the luminance and color cue conditions, they were impaired when using luminance as a cue to segment motion direction. It appears that PD patients are not able to use luminance as a cue to the same extent as their NC counterparts. When luminance could be used as a cue to segment the direction of motion, the motion thresholds of NC participants decreased considerably, indicating that their performance was better when they used the cue. Patients with PD appeared to be able to use the luminance cue to some extent, but were not able to use it to the same extent as NC participants. Their motion threshold scores never improved as much as those of the NC participants. Thus, there may be a deficit in PD patients' ability to integrate luminance and motion information when the dorsal visual processing stream is taxed.

This does not seem to be the case when the ventral visual processing stream is taxed, or when the dorsal and ventral streams are used together. Results from the color cue condition of the sensory integration task remain difficult to interpret for both PD patients and NC participants. This is because the task was not particularly sensitive to normal controls' ability to use color as a cue to segment motion. In this task, we assume that the dorsal and ventral streams must process and integrate color and

motion information in order for the participant to identify the direction of motion and segment the motion using the color cue. The NC group did not demonstrate the expected improvement in motion discrimination ability in the coupled condition (which would indicate that they were using color as a cue to segment motion), so it is difficult to make any claims about the ability of PD patients to use a color cue to segment motion.

However, results from a second task used in the studies described in Chapter 4 suggest that patients with PD do not suffer from a deficit in the ability to integrate color and motion. A visual search task in which the participant needed to use color and motion information concurrently to identify the target did not reveal group differences in the distribution of hits, misses, false alarms, or correct rejections. Unexpectedly, the slope of the reaction time by stimulus set size function in this dual-feature attention task was significantly shallower for PD patients than for NC participants (i.e., they performed search task more efficiently than the NC participants). This strongly supports the notion that PD patients do not suffer a deficit in the ability to integrate color and motion in a visual search task. This may be a spurious result and should be replicated in a larger sample of participants. At the least, these results strongly suggest that PD patients do not display a deficit in the ability to combine information about motion and color to enhance their performance in a visual search task. The finding that there were no differences across groups in reaction times at each distinct set size in this task also suggests that this aspect of attention remains intact in patients with PD,

contrary to some studies that report attentional deficits in these patients (G. S. Watson & Leverenz, 2010).

The shape-based and motion-based search efficiency tasks used to assess patients with PD and NC participants produced somewhat unexpected results (described in Chapter 4). Each of these tasks had 3 discrete levels of complexity where the salience of the target against background distractors was systematically varied. Patients with PD performed at the same level as NC participants on both tasks. In addition, performance declined to the same degree in the two participant groups as task difficulty increased. It is particularly notable that PD patients were not impaired on the motion-based search efficiency task. This finding shows that the presence of Lewy body pathology alone does not confer a deficit in the ability to detect motion. This is important to note in light of the findings from Chapter 2 which describe a striking impairment in the ability of DLB patients to detect simple horizontal motion. PD patients were very competent at detecting differences in speed, and this search efficiency task used real motion as opposed to the apparent motion in the sensory integration tasks.

Taken together, the results presented here suggest that Lewy body pathology is associated with specific deficits in visual cognition, but that these deficits may only be evident in non-demented patients with PD when the dorsal processing stream is taxed. Prominent deficits in motion perception were found in patients with DLB (Chapter 2), and these are consistent with reported neuroanatomical changes. For example, a recent study examined the correlation between scores on visual tasks and the integrity

of white matter in fiber tracts that approximated the dorsal and ventral visual processing streams. The study found that areas of reduced white matter integrity in DLB were primarily in parieto-occipital areas, whereas white matter damage in AD had a more diffuse pattern (R. Watson et al., 2012).

Although the present results do not support a true double dissociation between visual cognition deficits associated with Lewy body disorders and AD, the pattern of impairment in the sensory integration task in PD is different from the pattern of impairment in AD patients (Festa et al., 2005). Patients with PD in the present study had a deficit in the ability to use luminance cues to segment motion. In contrast, patients with AD in a previous study (Festa et al., 2005) used luminance cues in a normal fashion to segment motion. That is, they could integrate information at the level of a healthy older adult when demands were placed solely on the dorsal stream. These results suggest that DLB and other Lewy body disorders may have a particularly harsh impact on the dorsal visual processing stream.

In summary, the results of the present studies suggest that Lewy body pathology does not cause a uniform deficit in all areas of visual cognition. While motion discrimination was severely impaired in patients with DLB, there was no deficit in their ability to carry out visual search (other than general slowing). Non-demented patients with PD showed few deficits in visual cognition on a variety of processing tasks that systematically manipulated task difficulty. The observed deficits appeared to be isolated to situations where demands were high on the dorsal visual processing stream. This deficit was evident, for example, on a sensory integration task

that required integration of luminance and motion information that are both processed in the dorsal visual processing stream.

The clinical and neuropsychological profile of patients with DLB suggests that the disease strikes areas that are particularly important for visual cognition. However, the specific kind of pathology that affects the visual processing regions of the brain in this disorder remains unknown. Future research that incorporates neuropathological analysis would be immensely informative for determining if the striking visual cognition deficits in DLB are associated with Lewy body pathology, concomitant AD pathology, or some combination of the two. Imaging studies may help in this regard, particularly if methods to visualize alpha-synuclein pathology *in vivo* are eventually developed to the same level as *in vivo* amyloid imaging. Other imaging modalities that can assist in visualizing the integrity of white matter tracts in the brain or cortical integrity could also shed light on the neuroanatomical basis of visual cognition deficits in Lewy body disorders. Combining neuroanatomical, neuropathological, and behavioral approaches may prove to be a very powerful way to determine the neural underpinnings of the deficits in visual cognition that are such a prominent feature of Lewy body disorders.

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