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Visual Spatial Cognition in Neurodegenerative Disease

Katherine L. Possin

Department of Neurology, University of California, San Francisco

Abstract

Visual spatial impairment is often an early symptom of neurodegenerative disease; however, this multi-faceted domain of cognition is not well-assessed by most typical dementia evaluations. Neurodegenerative diseases cause circumscribed atrophy in distinct neural networks, and accordingly, they impact visual spatial cognition in different and characteristic ways. Anatomically-focused visual spatial assessment can assist the clinician in making an early and accurate diagnosis. This article will review the literature on visual spatial cognition in neurodegenerative disease clinical syndromes, and where research is available, by neuropathologic diagnoses. Visual spatial cognition will be organized primarily according to the following schemes: bottom-up / top-down processing, dorsal / ventral stream processing, and egocentric / allocentric frames of reference.

Introduction

When we look at and interact with the visual world in all its detail, the process usually feels effortless, but in reality highly complex cognitive processes are occurring, enabling us to see, touch objects, navigate, and remember where we have been. Depending on our needs, we must quickly and accurately direct our attention to what is relevant while suppressing what is irrelevant, create brief or lasting visual representations in our minds, manipulate mental representations to guide our behavior, and find our way through familiar or new environments. Thinking about these many components of visual spatial cognition is not as intuitive as thinking about verbal cognition, but spatial cognition is at least as important for successful everyday functioning. Elderly persons with declines in spatial functioning frequently report difficulties, such as feeling unsafe when driving, having trouble navigating new routes, and forgetting where they placed their keys or parked their car. These subtle declines seen in the healthy elderly are even more pronounced and have a greater impact on function in most types of neurodegenerative disease (Amick, Grace, & Ott, 2007; F. K. Cormack, Tovee, & Ballard, 2000; Dawson, Anderson, Uc, Dastrup, & Rizzo, 2009).

In this review, I propose a multi-faceted model of visual spatial cognition that can help elucidate the specific patterns of visual spatial dysfunction associated with Alzheimer's disease, Parkinson's disease, Lewy Body Dementias, Corticobasal Syndrome, Progressive Supranuclear Palsy, and Frontotemporal Lobar Degeneration. These neurodegenerative disease syndromes impact the brain in characteristic topographic patterns of neuropathology, particularly during early stages (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Disease-related impairments in visual spatial cognition are manifestations of these anatomic patterns, and so performance on tests of spatial cognition can have implications for differential diagnosis and for monitoring disease progression. The purpose of this article is

to discuss how visual spatial cognition is impacted by neurodegenerative diseases, and how these impairments relate to the underlying pathology.

Facets of Visual Spatial Cognition

Visual spatial cognition is composed of a multi-faceted set of functions mediated by a predominantly right-hemisphere network of widely-distributed brain regions including the parietal lobes, lateral prefrontal cortex, medial temporal lobes, inferior temporal cortex, occipital cortex, basal ganglia, and white matter tracts. This domain of cognition includes skills as diverse as orienting attention and navigation learning. In this review visual spatial cognition is organized primarily according to 3 schemes: bottom-up / top-down cognition, dorsal / ventral stream processing, and egocentric / allocentric frames of reference.

Visual information is processed in both a bottom-up and top-down fashion. Bottom-up visual processing in the geniculostriate system follows a set anatomical and functional pathway from early sensory processing areas to progressively more specialized modules (Barton, 1998). Visual information enters the brain through the retina, passing through the axons of ganglion cells that form the optic nerve and optic tract. Cells in the geniculostriate system send information through the lateral geniculate body of the thalamus and then to the primary visual cortex. The primary visual cortex (V1) sends axons through secondary and tertiary processing areas (e.g., V2-V5) where cells respond to increasingly complex aspects of visual experience and have larger receptive fields (see Figure 1). Color and form information processing follows a ventral pathway through V2 and V4. V2 is tuned to simple attributes of visual experience such as orientation, spatial frequency, and color, whereas V4 is also tuned to object features of intermediate complexity such as geometric shapes. This pathway continues to inferior temporal cortex where progressively more complex aspects of visual object processing are accomplished, such as face perception. Bottom-up processing of motion and location information follows a dorsal pathway through V2 and V3. Dorsal V3 appears to be specialized for global motion detection (Braddick et al., 2001). V5, also called "MT," is specialized for local motion detection and receives some direct visual inputs that bypass V1 (Zeki, 2008). The dorsal pathway continues to posterior parietal cortex where complex aspects of space perception, such as perceiving details of a scene as an integrated percept, are accomplished. Lesions in the earliest visual processing areas, from the optic nerve to primary visual cortex, result in total blindness in all or part of the visual field (Stoerig & Cowey, 1997). In contrast, lesions in the visual association areas, where subsequent processing occurs, distort the attributes of visual experience processed by those areas.

Top-down visual processing refers to executive aspects, which are primarily mediated by lateral prefrontal cortex, parietal cortex, and frontal-striatal circuits (Kastner & Ungerleider, 2000; E. K. Miller & Cohen, 2001). These control system functions include selecting visual information for detailed processing, organizing complex visual information, mediating voluntary shifts of attention, inhibiting irrelevant information, planning how to use visual information to achieve behavioral goals, unifying percepts of ambiguous visual stimuli, and manipulating or updating visual information represented in the posterior cortex by bottom-up systems. Attentional enhancement appears to follow the reverse order of bottom-up systems; for example, earlier and larger responses to attended stimuli are seen in V4 than in V1 (Buffalo, Fries, Landman, Liang, & Desimone, 2009).

Top-down systems depend on the integrity of bottom-up systems. For example, if a patient's ability to perceive or mentally represent where objects are located in space is impaired due to bottom-up system compromise, the patient will not be able to manipulate that information in spatial working memory or utilize that information to plan a sequence of movements.

Performance on top-down tests should be interpreted relative to performance on tests of more fundamental visual processing, such as tests of simple figure copy, visual search, judgment of line orientation, and face perception (Strauss, Sherman, & Spreen, 2006). Newer test batteries such as the Delis-Kaplan Executive Function System include test conditions designed to parse out fundamental component skills and isolate executive processes (Delis, Kaplan, & Kramer, 2001). For example, performance on a test of complex visuomotor sequencing can be evaluated relative to performance on tests of motor speed, visual scanning, and simple sequencing.

A second distinction in visual cognition is dorsal and ventral stream processing. Visual processing pathways in the posterior cortex are segregated such that the dorsal regions process space-based “where” information, and the ventral regions process object-based “what” information (see Figure 1) (Ungerleider & Mishkin, 1982). The dorsal pathway projects rostrally via the superior longitudinal fasciculus from dorsal occipital cortex to posterior parietal cortex. The posterior parietal cortex in each hemisphere is organized primarily for contralateral spatial function, although there is a predominant role for the right hemisphere in dorsal stream spatial functions in general. The dorsal stream system has close ties with the motor system and codes the locations of objects and their movement in terms of how one would acquire or act upon them. For this reason, the dorsal stream has also been termed the “how” stream (Goodale & Milner, 1992). The ventral pathway projects rostrally via the inferior longitudinal fasciculus from ventral occipital cortex into inferior temporal cortex. This system codes non-spatial features of objects relevant to their identity, for example color and form. Inferior temporal cortex is organized for both contralateral and ipsilateral function, because inferior temporal areas receive heavy input from striate cortex via the corpus callosum representing the ipsilateral visual field. The Visual Object and Space Perception battery can be used to evaluate separately dorsal and ventral stream processing because it is divided into subtests that emphasize either object or space perception (Warrington & James, 1991).

The segregation of “where” and “what” information is not as clear in the prefrontal cortex, where there is evidence that the dorsal and ventral areas may be segregated by the type of processing required as well as the type of information to be processed (Courtney, 2004; Wager & Smith, 2003). Select deficits in top-down aspects of spatial (versus object-based or verbal) processing can be seen in some patients with Parkinson's disease, Corticobasal Syndrome, and Progressive Supranuclear Palsy, however, indicating some dissociation for space-based information in frontal-subcortical systems and the need to include executive function tests that utilize space-based information in dementia evaluations.

A third critical distinction in visual spatial cognition is that of egocentric and allocentric reference frames. In the egocentric reference frame, object locations are processed in reference to the self, and this self-based map is updated as we move through the environment. This reference frame is particularly important (1) when we need to update spatial information on a moment-to-moment basis as we move through the environment, and (2) when we have navigated along the same path so many times that our movement along that path becomes routine (Ball, Smith, Ellison, & Schenk, 2009; Postle & D'Esposito, 2003; Whishaw, 1985). In the allocentric reference frame, object locations are processed in reference to each other or fixed landmarks, independent of one's position in the environment. This reference frame is important for developing cognitive maps (O'Keefe & Nadel, 1978). The egocentric frame of reference relies critically on the dorsal caudate nucleus, the posterior parietal cortex, the precuneus, and the lateral frontal cortex (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; McDonald & White, 1994; Packard & McGaugh, 1992; Postle & D'Esposito, 2003; Spiers & Maguire, 2007; Weniger, Ruhleder, Wolf, Lange, & Irle, 2009) whereas the allocentric frame of reference relies on the medial temporal lobe,

including the hippocampus, and interactions with occipito-temporal (ventral stream) structures (Bohbot, Iaria, & Petrides, 2004; Bohbot, Lerch, Thorndyck, Iaria, & Zijdenbos, 2007; Byrne, Becker, & Burgess, 2007; Doeller, King, & Burgess, 2008; Gramann, Muller, Schonebeck, & Debus, 2006; Iaria, Chen, Guariglia, Ptito, & Petrides, 2007; Maguire et al., 1998). While parietal cortex is understood to play a critical role in the egocentric network, it has in some studies been implicated in the allocentric network (Burgess, 2008; Iaria et al., 2003), and is likely essential for integrating these frames of reference.

The vast majority of research on egocentric and allocentric navigation learning has been conducted with rodents, and many of these studies have used adaptations of the Morris Water Maze task (R. Morris, 1984). In the typical version of this paradigm, a rodent is placed in a pool of water with a hidden escape platform. By varying the presence and position of extra-maze (“distal”) cues or intra-maze (“proximal”) cues relative to where the rodent is placed in the pool, researchers can evaluate the integrity of different navigation strategies. For example, in one classic version of this task, a rat is placed in a pool that is surrounded by distal landmarks. After it learns the position of the platform, it is then placed back in the pool at a different starting point, relative to the platform. If the rat executes the same motor program (i.e., it swims in the same direction from the starting point regardless of the distal landmarks), it is using an egocentric navigation strategy. If the rat changes its motor program to find the platform based on the constellation of distal cues, it is using an allocentric strategy. Research studies using the Morris Water Maze have demonstrated a critical role for the hippocampus in allocentric navigation, and a critical role for the dorsal striatum in egocentric navigation (McDonald & White, 1994; Miranda, Blanco, Begega, Rubio, & Arias, 2006; Pearce, Roberts, & Good, 1998).

At present, there are no clinically available tests to measure allocentric and egocentric processing. New virtual reality techniques show promise for translating insights from studies of allocentric and egocentric navigation in rodents to the study of navigation in humans (Cushman, Stein, & Duffy, 2008; Weniger et al., 2009). These techniques combine the rigor and control of laboratory measures with the ecological validity of real life situations. For example, our laboratory evaluates allocentric navigation using a virtual reality version of the Morris Water Maze (Figure 2). Subjects are placed in a new starting position on each trial in a circular field, and search for a hidden treasure. The only stable referents relative to the treasure are the distal landmarks that surround the circular field. Thus, the subject must develop a cognitive map of the virtual environment to find the treasure and cannot rely on a route-based (egocentric) strategy. More work is needed to validate and standardize allocentric and egocentric tests for clinical purposes.

In this review, the constellations of visual spatial cognitive impairments in Alzheimer's disease, Parkinson's disease, Lewy Body Dementias, Corticobasal Syndrome, Progressive Supranuclear Palsy, and Frontotemporal Lobar Degeneration will be reviewed with a focus on the facets of visual spatial cognition, outlined above (see Table 1). It should be emphasized that in many respects, this research is in early stages. The impairments will be related to the topographic patterns of disease-related neuropathology. Careful evaluation of spatial cognitive functions using anatomically-specific methods can provide information about which neural networks are impacted by the disease, and therefore, can assist the clinician in making an accurate early diagnosis and monitoring disease progression and response to treatment.

Alzheimer's Disease

Cortical atrophy in Alzheimer's disease (AD) is most pronounced in the medial temporal and posterior temporoparietal regions (Ishii et al., 2005; Rabinovici et al., 2007). The primary

visual cortex tends to be more spared than the visual association areas. Neuropathologically, the earliest changes in the typical case occur in the hippocampus and entorhinal cortex and then progress to the parietal, temporal, and frontal lobes (Braak & Braak, 1998; Gomez-Isla et al., 1996). Early-onset cases tend to show less prominent hippocampal involvement, greater atrophy in parietal and occipital cortex, and in many cases more severe impairment on visual spatial testing that can present before memory impairment (Frisoni et al., 2007; Fujimori et al., 1998).

AD can impact most aspects of visual processing, consistent with the impact of the disease on both dorsal and ventral stream areas. Patients are impaired in dorsal stream functions such as angle discrimination and motion perception (Mapstone, Dickerson, & Duffy, 2008; Prvulovic et al., 2002; Rizzo, Anderson, Dawson, & Nawrot, 2000; Tippet & Black, 2008), and ventral stream functions such as the perceptual discrimination and recognition of faces, colors, and objects (Cronin-Golomb, Sugiura, Corkin, & Growdon, 1993; Kurylo et al., 1994; Rizzo et al., 2000). Contrast sensitivity deficits are also prominent in AD (Gilmore & Levy, 1991; Hutton, Morris, Elias, & Poston, 1993), and enhancing the strength of stimuli has been shown to ameliorate performance on tests of letter identification, word reading, picture naming, and face discrimination (Cronin-Golomb, Gilmore, Nearing, Morrison, & Laudate, 2007). Tests of visual cognition that require the integration of visual information processed by separate regions in visual association cortex can be particularly sensitive to the effects of AD (e.g., tests of complex figure copy, mental rotation, and visual organization; (Festa et al., 2005; Freeman et al., 2000; Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005; Paxton et al., 2007), perhaps due to the effects of the disease on multiple visual areas that are compounded by these integration tasks. Visual acuity, however, is relatively spared (Cronin-Golomb et al., 1991; Rizzo et al., 2000), except in patients who present with a Posterior Cortical Atrophy syndrome, discussed below.

A tendency to get lost is a common and often early symptom of AD (Monacelli, Cushman, Kavcic, & Duffy, 2003; Pai & Jacobs, 2004), consistent with the critical role of the medial temporal lobes and parietal cortex in navigation learning and spatial memory (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Burgess, 2008; R. G. Morris, Garrud, Rawlins, & O'Keefe, 1982). Navigation learning has been extensively studied in transgenic mouse models of AD; for example, transgenic hAPP mice with hippocampal damage are impaired in the use of allocentric cues on a Morris Water Maze task (Deipolyi et al., 2008). By translating findings from the rodent literature, researchers have been able to design tests to evaluate navigation learning in Alzheimer's disease in an anatomically-focused manner. DeIpolyi and colleagues (deIpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007) tested patients with mild AD on a real-world test of navigation learning. The patients were more likely to get lost than controls and were deficient at learning the locations of landmarks, and these impairments were associated with smaller right posterior hippocampal and parietal volumes. New virtual reality techniques are showing promise in translational research for refining our understanding of navigation impairments in AD, and tests that emphasize allocentric navigation may be particularly sensitive (Bohbot et al., 2007; Burgess, Trinkler, King, Kennedy, & Cipolotti, 2006; Cushman et al., 2008; Ishii et al., 2005).

Posterior Cortical Atrophy

Posterior Cortical Atrophy (PCA) is a clinical syndrome associated with prominent bottom-up visual spatial impairments and relative preservation of memory, insight, and judgment (Benson, Davis, & Snyder, 1988). PCA is associated with atrophy in the occipital, parietal, and posterior temporal lobes (Whitwell, Jack et al., 2007). Pathologically, PCA is usually a form of Alzheimer's disease with greater neurofibrillary tangle burden in the visual cortex and lower burden in the hippocampus (Alladi et al., 2007; Tang-Wai et al., 2004). In

comparison to typical AD cases, PCA patients show selective hypometabolism of the occipito-parietal regions, right worse than left (Nestor, Caine, Fryer, Clarke, & Hodges, 2003).

McMonagle and colleagues (McMonagle, Deering, Berliner, & Kertesz, 2006) characterized 19 patients with PCA. The most common clinical features were primarily dorsal stream (occipito-parietal) abnormalities and included features of Balint's syndrome including simultanagnosia and optic ataxia, and alexia and agraphia out of proportion to other language abnormalities that do not rely on visual processing. In addition, when presented with hierarchically constructed stimuli, the patients demonstrated impairments at processing the global features, which is consistent with right hemisphere dysfunction (Delis, Robertson, & Efron, 1986; Robertson, Lamb, & Knight, 1988). For example, when shown a complex picture, they would focus on individual elements and were poor at interpreting the overall scene. In addition, when shown Navon figures, which are compound figures in which a larger global letter is composed of a different, repeated, smaller letter (Navon, 1977), the patients were impaired in identifying the global letter even when cued to do so (see Figure 3 for an example of Navon figures). Ventral stream aspects of spatial cognition, such as recognizing objects, faces, and colors, tended to be less impacted than dorsal stream aspects (McMonagle et al., 2006; Nestor et al., 2003).

Parkinson's Disease

The primary neuropathological features of Parkinson's disease (PD) are the formation of alpha-synuclein inclusion body pathology (Lewy bodies and Lewy neurites) that are distributed throughout the nervous system (Braak & Del Tredici, 2008), and the degeneration of the dopamine producing cells of the substantia nigra pars compacta, which project to the striatum (i.e., the caudate nucleus and putamen; Agid, 1991). Dopamine depletion in the caudate nucleus and its impact on the frontal-striatal circuits is thought to be the primary substrate of cognitive sequelae (DeLong & Wichmann, 2007; Marie et al., 1999; Owen, 2004; Sawamoto et al., 2008). Circuits critical for top-down control and dorsal stream processing are particularly affected. Dopamine depletion in the caudate nucleus is uneven with the greatest loss in the anterodorsal extent of the head (Joyce, 1993; Kaufman & Madras, 1991; Kish, Shannak, & Hornykiewicz, 1988), a subregion which receives massive projections from the dorsolateral prefrontal cortex and posterior parietal cortex (Baizer, Desimone, & Ungerleider, 1993; Yeterian & Pandya, 1991, 1993).

Patients with PD without dementia typically show numerous strengths on neurocognitive testing. For example, these patients generally perform within normal limits or show very mild impairment on tests tapping language, episodic memory, abstract reasoning, problem solving, concept formation, and bottom-up visual cognition. PD has subtle and circumscribed effects on aspects of working memory and attention, however, that can impact everyday functioning (Salmon & Filoteo, 2007; Uc et al., 2007). Several studies have examined the nature of these impairments. In general, working memory for spatial information is more impaired than working memory for object-based or verbal information, particularly during early disease stages (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Postle, Jonides, Smith, Corkin, & Growdon, 1997). Whereas verbal working memory is often intact for simple span tasks but impaired for complex span tasks (e.g., involving the mental manipulation of memoranda), spatial working memory is impaired for both simple and complex span tasks (Siegert, Weatherall, Taylor, & Abernethy, 2008). The spatial working memory deficit appears to emerge after very brief maintenance intervals (e.g., 1s) and not worsen with increasing intervals, which suggests that the selective spatial impairment involves an early stage of working memory processing, such as encoding or attention (Possin, Filoteo, Song, & Salmon, 2008).

The nature of attentional impairment in PD has been examined, and there is some evidence that space-based aspects of attention are the most impacted, similar to the pattern of working memory deficits. For example, PD patients have shown a selective impairment in space-based inhibition of return (Possin, Filoteo, Song, & Salmon, 2009), an attentional phenomenon thought to be critical for efficient visual search (Posner & Cohen, 1984). Typically, when a person's attention is cued to a location in the periphery, a target presented in that location enjoys an immediate processing advantage as compared to a target presented in another location. However, if more than 300 ms elapses following the cue, attention is biased away from the cued location in favor of novel locations. This 'inhibition of return' can be directed at objects as well as locations; for example, inhibition is greater when objects surround the cues and targets, presumably because inhibition is directed to both the location of the cue and the object associated with the cued location (Leek, Reppa, & Tipper, 2003). PD patients have shown reduced inhibition of return associated with a cued location, but when the stimuli display was altered so that objects surrounded the cues and targets; the patients showed the same magnitude of inhibition of return as controls (Possin et al., 2009). These results suggest that the patients were impaired at inhibiting their attention in a space-based frame of reference but were able to overcome their impairment when they could direct their attention to objects.

Attention deficits in PD appear to be mediated by impaired inhibitory processes (Filoteo, Rilling, & Strayer, 2002; Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2007). Although nondemented PD patients often perform similarly to neurologically healthy individuals on tests that require the facilitatory aspects of orienting (Bennett, Waterman, Scarpa, & Castiello, 1995; Goldman, Baty, Buckles, Sahrman, & Morris, 1998), they frequently are impaired when conditions promote a conflict between task-relevant and irrelevant information, such as on tests of selective attention (Filoteo, Maddox, Ing, & Song, 2007), negative priming (Mari-Beffa, Hayes, Machado, & Hindle, 2005), set shifting (Downes et al., 1989), and inhibition of return. Inhibitory attention and working memory involve overlapping processes, and space-based and object-based aspects of these processes are functionally and neurally separable (Chou & Yeh, 2008; Simmonds, Pekar, & Mostofsky, 2008; Zhou & Chen, 2008). It may be at this intersection of working memory and inhibitory attention, for space-based information in particular, that PD patients can show their earliest cognitive impairments.

It is not known whether PD patients show more impairment in egocentric aspects of space-based processing than allocentric aspects, but there is reason to suspect based on the impact of PD pathology on caudate nucleus function that the disease may have a greater impact on egocentric processing. Packard & McGaugh (Packard & McGaugh, 1996) showed that when rats were given lidocaine injections to inactivate the hippocampus, allocentric place learning was impaired, i.e., the rats were not able to use the location of distal cues to choose the arm of a maze where food is located. In contrast, rats given injections to inactivate the dorsolateral caudate nucleus were impaired in using an egocentric response strategy, i.e., the rats could not learn to follow a path such as turning left irrespective of distal cues. A similar double dissociation has been shown using fMRI while human subjects performed a virtual reality navigation task (Iaria et al., 2003). Subjects who used distal cues to navigate showed increased activation in the right hippocampus, whereas subjects who used a response strategy showed increased activation in the caudate nucleus. Although research is needed to directly compare egocentric to allocentric spatial cognition in PD, these patients have shown evidence of disrupted egocentric cognition including constricted representations of the distances between their body and external space (Lee, Harris, Atkinson, & Fowler, 2001; Skidmore et al., 2009) and shifts in egocentric midline estimation such that patients with predominantly left-sided motor symptoms have shown a rightward shift, and patients with

predominantly right-sided motor symptoms have shown a leftward shift (Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008).

Lewy Body Dementias

Dementia is a frequent complication of Parkinson's disease. Prevalence estimates are about 30% in community based samples of individuals with Parkinson's disease (Aarsland, Zaccai, & Brayne, 2005), and recent longitudinal studies indicate that approximately 80% of Parkinson's patients develop dementia before death (Galvin, Pollack, & Morris, 2006; Hely, Reid, Adena, Halliday, & Morris, 2008). Onset of dementia in PD is more rapid in patients with a non-tremor dominant phenotype and in patients who show posterior cortical impairments on neuropsychological testing, including visual spatial construction impairment (Burn et al., 2006; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007).

In contrast to patients with Parkinson's disease with dementia (PDD), patients with Dementia with Lewy Bodies (DLB) show cognitive impairment prior to or within one year of extrapyramidal motor symptoms (Emre et al., 2007; McKeith et al., 2005). Other than the chronology of symptom progression, these disorders are much more similar than they are different. The DLB/PDD Working Group proposed the umbrella term "Lewy body dementias" to reflect the clinical and pathological convergence of these disorders and the value of treating them as overlapping entities when investigating and treating the underlying neurobiology (Lippa et al., 2007).

The neuropsychological phenotype of both PDD and DLB involves pronounced visual spatial, attention, and executive impairments (Metzler-Baddeley, 2007; Troster, 2008). According to most studies that have compared these disorders, when matched on overall severity of dementia, they differ minimally in their patterns of cognitive impairment and both disorders are associated with parkinsonism, attentional fluctuations, and visual hallucinations (Aarsland et al., 2003; Ballard et al., 2002; Janvin et al., 2006; Noe et al., 2004). Overlapping pathologic substrates of DLB and PDD include α -synuclein pathology, neuronal loss, and degeneration of the basal forebrain. Alpha-synuclein pathology in the central nervous system progresses in a characteristic and ascending pattern from the olfactory tract and the brainstem, to the nigrostriatal system, to cortex (Braak & Del Tredici, 2008). Cortical atrophy is less severe and widespread than in AD (Whitwell, Weigand et al., 2007). Cholinergic depletion is more severe in Lewy body dementias than in AD, and both DLB and PDD patients have shown improvements in attention after taking cholinesterase inhibitors (Emre et al., 2004; Giladi et al., 2003; Rowan et al., 2007). One difference in the neuropathology between DLB and PDD is that a co-association with Alzheimer's pathology is more common in DLB, which may contribute to the more rapid progression to dementia relative to the onset of motor symptoms (Edison et al., 2008; Gomperts et al., 2008).

Numerous studies have focused on identifying neuropsychological variables that allow discrimination between Lewy body dementias and AD (for a more comprehensive review on this topic, see (Troster, 2008). These studies are important because compared to patients with AD, patients with Lewy body dementia may show greater response to cholinesterase inhibitors (E. K. Perry et al., 1994; Tiraboschi et al., 2002) and abnormal sensitivity to neuroleptic drugs (Aarsland, Perry et al., 2005). The overall pattern emerging from these studies is that Lewy body dementia patients show more severe and pervasive visual spatial, attentional, and executive impairments than AD, whereas AD patients show more severe memory impairment. Visual spatial deficits are a particularly important component of differential diagnosis from AD (Aarsland et al., 2003; Collerton, Burn, McKeith, & O'Brien, 2003; Johnson, Morris, & Galvin, 2005). Although patients with AD are frequently impaired on tests of visual spatial construction, patients with Lewy body dementia are usually more

impaired on these tests early in the disease. For example, patients with DLB frequently fail to copy accurately the interlocking pentagons on the MMSE even when global cognitive impairment is mild (Hanyu et al., 2006; Tiraboschi et al., 2006). Tiraboschi and colleagues (2006) demonstrated that the presence of visual spatial impairment early in the course of dementia substantially improved the sensitivity of predicting pathology-proven DLB versus pure AD. An absence of visual spatial impairment had a negative predictive value of 90%, which was higher than visual hallucinations or extrapyramidal signs. Identification of visual spatial impairment is important not only for designating individuals whose clinical syndrome is impacted more by Lewy body formation than AD pathology, but also for predicting which patients with DLB will have a more malignant disease course (Hamilton et al., 2008).

Performance on construction tasks in Lewy body dementias is affected by impairments in visual perception and pre-attentive visual processing. These early aspects of bottom-up visual cognition are typically more impaired in Lewy Body dementias than AD, and likely play an important role in their more severe construction deficits. DLB patients are more impaired than AD patients on tests of visual search, with more severe relative impairment on parallel 'pop-out' search in contrast to top-down serial search (F. Cormack, Gray, Ballard, & Tovee, 2004; Noe et al., 2004). Calderon et al. (Calderon et al., 2001) compared patients with DLB to patients with AD on the Visual Object and Space Perception Battery (Warrington & James, 1991), a set of tasks that emphasize bottom-up aspects of visual cognition and place minimal demands on motor functions. DLB patients showed more severe impairments than AD patients on tests tapping both ventral stream (Fragmented Letters and Object Decision) and dorsal stream (Cube Analysis) aspects of visual perception. Similarly, Mosimann et al. (Mosimann et al., 2004) found that DLB and PDD patients showed more severe impairments than AD patients on tests tapping both ventral stream (tests of object and form perception) and dorsal stream function (tests of dot position and motion perception). These comparisons of bottom-up visual spatial processing suggest more severe posterior cortical dysfunction in Lewy body dementia. Consistent with these findings, both DLB and AD patients show hypoperfusion and hypometabolism in the parietal and temporal lobes, but only DLB patients show hypoperfusion and hypometabolism in the occipital lobes including the primary visual cortex (Lobotesis et al., 2001; Minoshima et al., 2001; Sato et al., 2007; Shimizu et al., 2008), which is the most critical cortical region for early aspects of bottom-up visual processing. Abnormalities in morphology and synuclein expression in the retina may also impact visual perception in DLB (Maurage, Ruchoux, de Vos, Surguchov, & Destee, 2003).

Visual hallucinations are common in Lewy body dementias, and appear to share an overlapping neural basis with visual perceptual disturbance. Both visual hallucinations and visual perceptual impairments have been related to Lewy body pathology in neocortex (Tiraboschi et al., 2006; Williams, Warren, & Lees, 2008), hypoperfusion and hypometabolism in the dorsal and ventral visual pathways (Matsui et al., 2007; Mori, Ikeda, Fukuhara, Nestor, & Tanabe, 2006; Perneczky et al., 2008), and cholinergic dysfunction (Bohnen et al., 2006; McKeith, Wesnes, Perry, & Ferrara, 2004). Visual hallucinations have been associated with Lewy body counts in the amygdala, parahippocampal, and inferior temporal cortices (Harding, Broe, & Halliday, 2002), which suggests a ventral stream basis for this clinical feature. In contrast, an inverse relationship between persistent visual hallucinations and tangle pathology has been reported (Ballard et al., 2004). Typically, hallucinations are complex visions of animals or people, occur daily for minutes at a time, and are experienced as unpleasant by the patient (Mosimann et al., 2006). Visual hallucinations, like visual spatial impairment, are useful for determining whether a patient's clinical syndrome is impacted by Lewy body pathology (Tiraboschi et al., 2006; Williams et al., 2008).

Corticobasal Syndrome

Corticobasal syndrome (CBS) characteristically presents with asymmetric rigidity and apraxia with additional cortical (e.g., alien limb, cortical sensory loss, myoclonus) and basal ganglia (e.g., bradykinesia, dystonia) dysfunction (Boeve, 2007b). Diagnostic criteria emphasize a motor disorder, but there is increasing recognition that cognitive impairment and even dementia can present before motor dysfunction (Litvan et al., 2003; Litvan et al., 1999). A recent CBD criteria consensus conference will soon propose new criteria that will need to be tested prospectively (personal communication). Cognitive impairment profiles are quite variable; for example, patients presenting with greater left hemisphere pathology show marked language impairment, whereas patients presenting with greater right hemisphere pathology show marked visual spatial dysfunction (Boeve, 2007b). This syndrome has been historically linked to other akinetic-rigid diseases like Parkinson's disease because of the presence of extrapyramidal features, but there is increasing recognition that this syndrome has more in common with a subset of frontotemporal lobar degeneration disorders (which are discussed below), both because of the frequency of tau pathology and because of the overlap of cognitive and behavioral features in some patients (Josephs, 2008; Mathuranath, Xuereb, Bak, & Hodges, 2000).

Corticobasal degeneration (CBD) is a neuropathologic diagnosis characterized by atrophy, gliosis, and tau-immunoreactive pathology in the neocortex, basal ganglia, and substantia nigra (Ludolph et al., 2009). Historically, CBD was considered to be a distinct clinico-pathologic entity presenting with CBS (Rebeiz, Kolodny, & Richardson, 1968), but it is now understood that CBD frequently presents in other clinical syndromes, most often bvFTD and PNFA (Boeve, 2007a). Further complicating the diagnostic picture, only about half of patients presenting with the clinical diagnosis of CBS have CBD pathologically, whereas other common neuropathologic diagnoses include Alzheimer's disease, progressive supranuclear palsy, and Pick's disease (Alladi et al., 2007). Although several neuropathologic diagnoses can cause CBS, there is a characteristic distribution of pathology associated with this syndrome, predominantly involving the frontal and parietal cortex and the basal ganglia and tending to start asymmetrically (Boeve et al., 1999; Boxer et al., 2006; Gibb, Luthert, & Marsden, 1989). The temporal cortex, including the medial temporal lobe, is relatively spared.

Visual spatial dysfunction can be a prominent component of the clinical presentation of CBS (Bak, Crawford, Hearn, Mathuranath, & Hodges, 2005; Tang-Wai et al., 2003), although it should be noted that many patients present without clear visual spatial impairment (Borroni et al., 2008; Murray et al., 2007). This heterogeneity in visual spatial function is a manifestation of the heterogeneous patterns of cortical dysfunction associated with the syndrome, including the side of the brain most affected by the disease and the degree of posterior involvement. Rare cases have been reported where visual spatial dysfunction appeared as the first symptom. Tang-Wai and colleagues (2003) described two such patients, one whose initial symptoms included difficulty following printed material from line to line, drawing simple configurations, and reading and writing despite a preserved ability to listen to books on tape and dictate her thoughts. A second patient's early symptoms included difficulty in identifying coins, writing and manipulating objects, telling time, and differentiating right from left. These patients showed a greater burden of tau pathology in the visual association (Case 1) and posterior parietal cortex (Case 2) than other patients with CBD. Although visual spatial dysfunction is rarely such a prominent feature of early CBS as it was in these cases, there is some evidence that when visual spatial impairments are apparent, they may tend to involve more dorsal stream than ventral stream functions. For example, Bak and colleagues (Bak, Caine, Hearn, & Hodges, 2006) found that CBS patients were more likely to be impaired on space-based than object-based subtests of the Visual

Object and Space Perception Battery. This pattern of greater dorsal stream impairment is consistent with the parietal and striatal dysfunction and relative preservation of the temporal cortex in CBS (Seeley et al., 2009).

CBS patients can show difficulty on tasks that require them to integrate spatial information with motor function. These patients can show impaired representation of how to use objects despite relatively intact object recognition (Silveri & Ciccirelli, 2007). In pre-dementia stages of the syndrome, gesture representation is typically intact and patients can comprehend gestures, but gesture production is frequently impaired; i.e., they know how to gesture but are unable to do it (Jacobs et al., 1999; Zadikoff & Lang, 2005). Similarly, Negash et al. (Negash et al., 2007) demonstrated that CBS patients were able to implicitly learn the structure of a spatial sequence that was visually presented to them, but they were unable to accurately execute that sequence. This pattern of impairment is consistent with the disproportionate effects of the disease on the dorsal stream regions in cortex, including the superior aspect of the parietal lobules (Boxer et al., 2006).

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), or Steele-Richardson-Olszewski syndrome, is characterized clinically by supranuclear gaze palsy, postural instability and falls, and akinetic-rigid features (Boeve, 2007b; Steele, Richardson, & Olszewski, 1964). The most striking pathologic feature of PSP is atrophy in the midbrain tegmentum, and atrophy is also seen in the pons, striatum, and frontal cortex (Boxer et al., 2006). Hypometabolism has been reported in the brainstem, medial thalamus, caudate nucleus, and medial frontal cortex (Eckert et al., 2008). PSP shares clinical features with CBD including atypical parkinsonism, and these disorders are genetically related and both associated with deposits of 4R tau. PSP is also pathologically distinct, however, and is associated with greater midbrain atrophy and less severe cortical atrophy than CBD (Boxer et al., 2006; Groschel, Kastrup, Litvan, & Schulz, 2006). PSP has historically been considered a classic example of “subcortical dementia” because the cognitive and behavioral features are attributed to the effects of the disease on subcortical regions and corresponding frontal lobe deafferentation whereas posterior cortex functions are relatively spared (Magherini & Litvan, 2005).

As compared to patients with CBS, patients with PSP in general show less severe impairments on tests of spatial cognition including visual construction tests, likely reflecting the relative preservation of posterior cortex in PSP (Bak et al., 2006; Bak et al., 2005; Garbutt et al., 2008). PSP patients can show marked impairments, however, on tests that rely on vertical eye movements, vertical shifts of covert attention, and on certain aspects of top-down spatial attention and working memory.

PSP is associated with dramatic eye movement abnormalities including impaired saccade velocity, saccade gain, and anti-saccades (Garbutt et al., 2008). Vertical saccades tend to be twice as slow as horizontal saccades (Bhidayasiri et al., 2001). Successful performance on many tests of spatial cognition relies on vertical saccades, for example, tests of figure copy, the Block Design subtest from the Wechsler Adult Intelligence Scale (Wechsler, 1997), the Benton Judgment of Line Orientation Test (Benton, Varney, & Hamsher, 1978), and the Number-Location subtest from the Visual Object Space Perception Battery. PSP patients can show deficits on these classic spatial tests (Bak et al., 2006; Garbutt et al., 2008; Soliveri et al., 2000), but these deficits may not reflect spatial impairment, per se. To properly evaluate spatial cognition in PSP, it is critical to select tests that allow the examiner to disentangle spatial cognition from ocular motility. For example, to assess visual construction, a PSP patient could be asked to draw a figure rather than copy a figure.

Using a paradigm that does not rely on oculomotor function, Posner and Rafal demonstrated that PSP patients show slowed covert orienting of attention and reduced inhibition of return that are most pronounced in the vertical plane (Posner, R.D., Choate, & Vaughan, 1985; Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988). In the orienting of attention task, a preparatory cue appeared in one of 4 squares that were positioned above, below, and on each side of a central fixation cross. After a brief delay, a target appeared in one of the 4 squares. Subjects were instructed to press a key as quickly as possible when the target appeared. Eye gaze was maintained on the fixation cross in the center of the display. Response times were faster for all subjects when the target appeared in the same square as the cue, but the response time advantage was reduced for PSP patients in the vertical plane. The vertical covert orienting and inhibition of return impairments could not be attributed to ocular dysfunction because in these tasks the display was small; eye movements were monitored; and the visual orienting deficits were present even at cue-target intervals as short as 50ms, which is much shorter than the latency for saccades in normal individuals. Robbins and colleagues (Robbins et al., 1994) examined attentional set-shifting in PSP using a task that required subjects to shift their attention between two superimposed figures. Because the figures were superimposed, eye movements were not required. Patients with PSP or PD were impaired on the task, but not patients with early AD, which suggests that the impairment was due to subcortical dysfunction. PSP patients can also show impairments on tests of spatial working memory, visual search, and the efficient use of spatial strategies (Robbins et al., 1994; Soliveri et al., 2000).

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disease that primarily affects the frontal and anterior temporal lobes. Critical visual spatial processing regions in cortex (the parietal, inferior temporal, and occipital cortex) are relatively spared. This pattern of sparing allows many FTLD patients to perform strikingly well on tests of visual spatial skills when other aspects of cognition and behavior are severely impaired. As compared to patients with AD matched on measures of global cognitive impairment, FTLD patients perform better on tests of visual spatial construction (Diehl & Kurz, 2002; Hutchinson & Mathias, 2008; Rascovsky, Salmon, Hansen, & Galasko, 2008; Katya's 2002). The differential diagnosis of FTLD from AD can in some cases be difficult, and assessment of this relative preservation of visual spatial function in FTLD patients can improve diagnostic accuracy (Harciarek & Jodzio, 2005; Thompson, Stopford, & Neary, 2008; Rascovsky et al., 2002). FTLD is a heterogeneous disorder, however, and so understanding spatial cognition in these patients requires consideration of the different neurobehavioral syndromes and neuropathologic subtypes.

Behavioral variant frontotemporal dementia

FTLD presents in 3 neurobehavioral syndromes depending on the distribution of pathology (Gorno-Tempini et al., 2004; Hodges, 2001; Neary et al., 1998; Snowden, Neary, & Mann, 2007), and these syndromes are associated with subtle differences in spatial cognitive functioning. The behavioral variant of frontotemporal dementia (bvFTD) is the most common of these 3 syndromes, and is associated with bilateral frontal, anterior insular, and anterior cingulate involvement with pronounced orbitofrontal atrophy early in the disease (R. J. Perry et al., 2006). Clinically, these patients show an early decline in social and personal conduct, emotional blunting, and loss of insight. Consistent with the relative preservation of the posterior cortex, mild bvFTD patients usually perform normally on tests that assess “bottom-up” visual spatial perception, such as the subtests of the Visual Object and Spatial Perception Battery (R. J. Perry & Hodges, 2000; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Thompson, Stopford, Snowden, & Neary, 2005). Deficits on tests of spatial cognition can be seen in bvFTD when the test relies on certain aspects of top down

control. Visual discrimination reversal learning and inhibition of spatial attention, in particular, can be impaired even early in the disease when the site of pathology involves predominantly ventral and medial aspects of prefrontal cortex (Krueger et al., 2009; Rahman et al., 1999). Patients with bvFTD often make numerous repetition errors on tests of design fluency, even in early stage disease, and the propensity to make these errors has been associated with orbitofrontal atrophy (Chester et al., 2009). As the disease progresses and there is more substantial dorsolateral prefrontal cortex and striatal dysfunction, executive dysfunction and its impacts on spatial cognition become even more prominent. Although bvFTD patients generally outperform AD patients on figure copy tests (Diehl & Kurz, 2002; Elfgrén et al., 1994; Mendez et al., 1996; Rascovsky, Salmon, Hansen, & Galasko, 2008; Rascovsky et al., 2002), they have been equally impaired in some studies when the figure to be copied is quite complex (Frisoni et al., 1995; Kramer et al., 2003; Lindau, Almkvist, Johansson, & Wahlund, 1998; Pachana, Boone, Miller, Cummings, & Berman, 1996; R. J. Perry & Hodges, 2000). On these tests, such as the Rey-Osterrieth Complex Figure, performance is known to be influenced by frontally-mediated executive skills such as organization, strategic processing, and working memory (Choi et al., 2004; Freeman et al., 2000; Hernandez et al., 2003; Varma et al., 1999) in addition to bottom up visual-spatial perception and integration skills. Whereas AD patients are more likely to make spatial errors on these tests, suggesting an underlying impairment in visual spatial processing, bvFTD patients are more likely to make organizational or perseverative errors with preserved spatial configuration, suggesting an underlying impairment in executive functioning (Thompson et al., 2005).

Semantic dementia and progressive nonfluent aphasia

The two aphasic variants of FTLN syndromes are semantic dementia (SD) and progressive nonfluent aphasia (PNFA). SD is associated with pronounced anterior temporal lobe atrophy and often begins unilaterally. When the disease begins in the left hemisphere, the patients show a progressive loss of knowledge about words and objects (Amici, Gorno-Tempini, Ogar, Dronkers, & Miller, 2006). When the disease begins in the right hemisphere, patients may show relatively subtle language deficits, loss of semantic information about visual information such as faces, and more pronounced behavioral dysfunction such as loss of empathy, compulsive behavior, or behavioral disinhibition (Rankin et al., 2006; Rosen et al., 2006). Progressive nonfluent aphasia (PNFA) is associated with pronounced left inferior frontal and insular atrophy. PNFA is characterized by hesitant, effortful, and apraxic speech, agrammatism, and early preservation of word meaning (Amici et al., 2006). PNFA patients are more behaviorally appropriate than the other variants (Rosen et al., 2006). Patients with SD and PNFA rarely show any impairment on spatial cognitive tasks that do not rely on language skills; for example, they can normally copy complex figures (Gorno-Tempini et al., 2004). When SD patients do show difficulty with the naming of visually-presented objects, this is attributed to their semantic knowledge impairment rather than a perceptual problem, *per se* (Woollams, Cooper-Pye, Hodges, & Patterson, 2008).

Some patients with SD or PNFA have developed a novel interest in producing art that seems to be triggered by the illness, as reported in several case studies (B. L. Miller et al., 1998; B. L. Miller, Ponton, Benson, Cummings, & Mena, 1996; Seeley et al., 2008). This art can take on a compulsive quality: patients may repeat the same painting several times, photograph the same subject from multiple angles, or take hours to complete single lines in each painting (B. L. Miller et al., 1998; B. L. Miller & Hou, 2004). In SD, distortions of space, color, faces, and other aspects of composition are prominent (Finney & Heilman, 2007; Rankin et al., 2007), and significant symbolism or abstraction is typically lacking, consistent with the left anterior temporal lobe degeneration that is the hallmark of this disease (B. L. Miller & Hou, 2004).

The neural mechanism underlying these bursts of artwork and alterations in visual creativity is controversial. In these patients, brain disease is initially focal, anterior, and left-hemisphere predominant. The posterior cortex, and notably the right posterior cortex, is relatively preserved. These patients may develop visual spatial creative skills because they practice using these skills to compensate for their impaired linguistic functions. Some have argued that perceived increases in visual creativity may be due to emerging dysfunction in the visual cortical system (i.e., visual distortions that may be artistically appealing were not done for effect; Finney & Heilman, 2007). Others have argued that the emergence of artwork in these patients may represent released inhibition of right posterior cortex, such that the disease process paradoxically facilitates a more vivid and connected perception of the visual world (B. L. Miller, Boone, Cummings, Read, & Mishkin, 2000; B. L. Miller & Hou, 2004; Seeley et al., 2008).

Neuropathologic subtypes of frontotemporal lobar degeneration

The majority of FTL spectrum disorders are defined according to 2 neuropathologic subtypes: one with tau positive inclusions (most commonly CBD, PSP, or Picks) and one with inclusions that stain positively for TDP-43. BvFTD patients are about evenly split according to these neuropathologic subtypes, whereas the majority of PNFA patients are tau positive and the majority of SD patients are tau negative (Josephs, Petersen et al., 2006; Kertesz, 2009; Llado et al., 2008). A third less common subtype that presents as bvFTD was recently discovered with fused in sarcoma (FUS) positive TDP-43-negative inclusions (Neumann et al., 2009). Studies that compare antemortem cognitive profiles of neuropathologic subtypes are critically important because scientists are developing promising new treatments that target specific molecules. Grossman and colleagues (Grossman et al., 2007) compared tau positive and tau negative patients, and showed that the tau positive patients were more impaired, on average, on a figure copy test. Clinical syndromes were mixed in the tau positive group; the most common presentations were CBS (8), social or executive disorder (7), and PNFA (5). As discussed above, CBS can be associated with profound spatial impairment, and so this group difference in spatial function may have been driven by the large number of CBS patients in the tau-positive group.

Within a clinical syndrome, patients may differ in their clinical presentation depending on the underlying neuropathology. Tau-positive and FUS-positive bvFTD has been associated with more severe striatal atrophy (Kim et al., 2007; Neumann et al., 2009; Seelaar et al., 2009) and tau-positive bvFTD has been associated with dorsolateral bifrontal atrophy (Whitwell et al., 2005) whereas TDP-positive FTL spectrum disorders often show hippocampal sclerosis (Josephs & Dickson, 2007; Josephs, Whitwell, Jack, Parisi, & Dickson, 2006). Based on these topographic patterns of pathology, one might hypothesize that tau- or FUS-positive bvFTD patients might show more impairment in spatial functions mediated by frontal-striatal systems such as spatial working memory and attention, whereas TDP-43 positive patients might show more difficulty on hippocampally-mediated functions such as spatial orientation and allocentric aspects of navigation. As large enough multi-center samples become available, it will be critical for future studies to report the antemortem profiles of patients according to both clinical syndrome and pathologic subtype.

Conclusion

Visual spatial cognition involves the perception, selection, organization, and utilization of location and object-based information, and provides a structure for how we interact with our physical environments. This multi-faceted domain of cognition depends on a widely-distributed and predominantly right hemisphere network of brain regions. As mental representations of the visual world move anteriorly from primary visual cortex through bottom-up systems, progressively more complex and integrated aspects are processed.

Representations in posterior cortex are selected “top-down” for further processing by frontal systems. Dorsal regions of cortex are specialized for processing the locations of objects and how to act on them, whereas ventral regions are specialized for processing features of objects relevant to their identity. This dorsal / ventral distinction is particularly relevant to bottom-up systems, but top-down aspects of spatial processing can be selectively affected in patients with frontal-subcortical system compromise (eg, PD). Separable frames of reference for processing self-based (egocentric) and world-based (allocentric) information have been well-elucidated by cognitive neuroscience; the egocentric network is anchored by the dorsal striatum and the allocentric by the medial temporal lobe. Standardized tests to evaluate this distinction in humans are not yet clinically available.

The effects of neurodegenerative disease syndromes on visual spatial cognition depend on topographic patterns of brain pathology, and so it is important that visual spatial cognitive evaluations use anatomically-specific methods for diagnosis and for monitoring disease progression. In most cases, however, dementia evaluations do not measure spatial cognition in a comprehensive or anatomically-specific manner. For example, these evaluations often include only a test of figure copy to assess this cognitive domain. Although including a test of figure copy is an excellent screen for visual spatial dysfunction and can provide some diagnostic information (e.g., a patient with LBD is likely to show more severe impairment than a patient with AD), patients can fail the test for several reasons. For example, a patient with bvFTD may fail a test of figure copy due to impairments in top-down control processes; a patient with PSP may fail the test due to oculomotor dysfunction; and a patient with posterior cortical atrophy may fail the test due to simultagnosia. Visual spatial evaluations should be designed to specifically evaluate the facets of visual spatial cognition that may be disrupted by the syndromes on the differential. In most cases the battery should include some evaluation of top-down spatial processing, and both dorsal and ventral aspects of bottom-up systems.

At present, pharmacologic treatments for neurodegenerative diseases are limited, but scientists are on the verge of developing promising new treatments including molecule-specific therapies. As these treatments become available, it will become critically important to identify accurately patients early in the disease course. Neurocognitive evaluations should aspire to diagnose not only clinical syndromes but also neuropathologic subtypes, which will ultimately be the target of treatments. Methods developed in a cognitive neuroscience framework that can tease apart the integrity of neural systems can be adapted for clinical use. Refinement of visual spatial evaluation methods is a promising avenue for improving early diagnostic accuracy and treatment monitoring.

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Figure 1.

As visual information travels from primary visual cortex (V1) through secondary and tertiary processing areas (V2-V5), increasingly more complex aspects of visual experience are processed and cells are tuned to larger receptive fields. Color and form information is processed by a ventral pathway via V2, V4, and inferior temporal cortex. Location and motion information is processed by a dorsal pathway via dorsal V2 and V3, V5, and posterior parietal cortex.

Figure 2.

A screen shot from an allocentric virtual navigation task we are using in our laboratory that is based on the Morris Water Maze. Subjects are virtually placed in a new starting position on each trial and navigate through the circular field to find a hidden treasure. The subjects must develop a cognitive map of the treasure's position relative to the distal cues to find the treasure because the route changes on each trial.

Figure 3.

Navon figures. Patients with impaired global processing will identify the smaller letters but will fail to identify the global letters (i.e., in this example, they would report seeing only an E in the first figure and an A in the second figure).

Table 1
Typical Constellation of Visual Spatial Impairments in the Early Stages of Neurodegenerative Diseases

	Bottom-up / top-down	Dorsal / ventral	Allocentric / egocentric
Alzheimer's disease	Bottom-up most patients, although some patients show top-down	Both are often affected	Allocentric
Posterior cortical atrophy	Bottom-up, all patients	Dorsal more than ventral, although both are affected with disease progression	Patients cannot use either frame of reference well due to severe bottom-up impairments
Parkinson's disease	Top-down	Dorsal	Egocentric
Lewy body dementias	Both, nearly all patients	Both, nearly all patients	Unknown, likely both in most patients
Corticobasal syndrome	Variable, top-down likely more common but in some patients bottom-up can be prominent, as discussed in text	When visual spatial processing is affected, dorsal impairments are usually more severe	Unknown, likely egocentric
Progressive supranuclear palsy	Top-down attentional impairment is common	Patients have difficulty orienting spatial attention, but cortical dorsal / ventral streams are usually intact	Unknown, likely egocentric
Behavioral variant frontotemporal dementia	Top-down, most patients, although in early stages no visual spatial impairment may be evident	Not impaired	Unknown, may vary with pathologic subtypes
Semantic dementia and Progressive nonfluent aphasia	Not impaired	Neither impaired early, although SD may affect ventral stream processing with disease progression	Not impaired