

VISUOSPATIAL DYSFUNCTION IN THE NEURODEGENERATIVE DISEASES

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1. ABSTRACT

Visuospatial dysfunction is not generally considered a cardinal feature of the common neurodegenerative disorders of late life like Alzheimer's disease (AD), Parkinson's disease (PD), and Dementia with Lewy bodies (DLB). However, a large number of research studies have shown visually related disorders to be surprisingly pervasive among these disease states. Broader recognition of the problems is hindered by a complex literature, which suffers from a lack of uniform definitions of what constitutes "visuospatial" dysfunction and few commonly accepted theoretical models for interpreting results. The interface between visual-spatial function and other variably-defined constructs such as attention and executive function further complicates experimental approaches to this construct. Nonetheless, this review addresses both theoretical and practical issues regarding the presence, importance, and correlates of visual dysfunction associated with neurodegeneration. In addition, the functional impact of the deficits is addressed.

2. INTRODUCTION

The neurodegenerative diseases of late life represent a growing area of clinical awareness, in part because of their increased prevalence with the aging of the population. Despite a burgeoning literature on the clinical identification, neuropsychological expression, and pathological underpinnings of the common syndromes associated with Alzheimer's disease (AD), Parkinson's disease (PD) and dementia with Lewy bodies (DLB), the visual and spatial dysfunction intrinsic to these illnesses remains underrecognized in general practice. This article will address key areas of visual and spatial dysfunction in these syndromes, as well as other neurodegenerative illnesses in which visual or spatial dysfunction can be prominent.

The literature in this area can be very confusing. Like "attention," "visuospatial" is a term that everyone understands, but for which there is no unified definition. The definition for visuospatial dysfunction proposed by

Boller *et al.* (1), “difficulty in appreciating the position of stimulus-objects in space, difficulty in integrating those objects into a coherent spatial framework, and difficulty in performing mental operations involving spatial concepts,” is perhaps the most appropriate for these populations. However, because these specific spatial functions depend on perceptual inputs and are demonstrated with motor outputs, the contributions of these related nonspatial phenomena cannot be ignored. Unfortunately, many investigators do not report how they have defined their constructs, nor the use of related terms in their experimental designs and research communications.

Three major realms of function emerge as common themes in experimental approaches to visual and spatial dysfunction in neurodegeneration. These are 1) perceptual, 2) spatial, and 3) visuomotor. This organizational scheme is based on the classification suggested by Benton and Tranel (2) and the reader is referred to their work for a detailed review of the extensive literature that supports distinguishing visual processes in this way. Attention and executive function are additional supervening constructs that may also influence task performance and interpretation of results in visual and spatial research. Interpretation of these factors and their confounds is further complicated in the neurodegenerative diseases because of concomitant factors like multifocal declines in cognition and significant motor dysfunction that can substantially vary between individuals with the same diagnosis. Furthermore the illnesses have widely distributed anatomical and neurochemical pathology.

3. DISEASE STATE INFLUENCES ON VISUAL AND SPATIAL DEFICITS

3.1. Alzheimer’s disease

3.1.1. Pathophysiology

Alzheimer’s disease is the most common late-life brain degenerative disorder. It is also the most common cause of dementia in the overwhelming majority of populations that have been studied. Although it is often characterized as a memory disorder, a broad range of neuropsychological deficits is typically evident. Many practitioners view typical AD as a diffuse disease of the brain, but current evidence suggests that cortical pathology selectively involves sensory and polymodal association cortices, including a large area from the ventral temporal lobe through the parietal lobes bilaterally (3). Neurofibrillary tangles and neuritic plaques increase 20-40 fold from primary visual cortex (Area 17) through visual association areas 18-20 (4). Not surprisingly AD cases with prominent pathology in visual association cortex had significant disorders in object recognition (5). In addition, individuals with profound disorders of visuospatial processing associated with pathologic changes in occipitoparietal connections have also been reported (6). The localized aspects of cortical dysfunction in AD are also evident on functional imaging tests during life. Studies consistently show hypometabolism or hypoperfusion through the temporal and parietal association cortices in association with visual symptoms in AD (7-10).

3.1.2. Neurotransmitter factors

Loss of acetylcholine (ACh) activity in the cortex is well recognized in AD. Several lines of evidence from both animals and humans suggest a potent role for cholinergic neurotransmission in visual attention. Using models of excitotoxin-induced basal forebrain damage, Hodges and colleagues (11) demonstrated that lesioned rats do not process visuospatial information relevant to solution of a radial arm maze task. They concluded that cholinergic deficits were responsible for attentional impairments associated with a loss of visual stimulus detection. Criticisms that this lesion model was not specific to cholinergic deficits were addressed by Muir and co-workers (12), who used a more ACh-selective toxin that also demonstrated attentional effects.

ACh appears to mediate attentional function by regulating the degree of cerebral responsiveness to sensory stimuli. It has been shown to alter the general responsiveness and firing patterns of both large and small groups of neurons (13). Cholinergic stimulation also increases excitatory responses to sensory stimuli (14). Warburton (15) has argued that ACh serves in a primary control mechanism for information processing. It may accomplish this by narrowing the focus of visuospatial attention (16). Callaway and colleagues (17) further refine the role of ACh as one of increasing constraints on information processing, based on findings such as increased distractibility and decreased task persistence with the anticholinergic agent scopolamine.

Attention and other cognitive functions are enhanced in AD subjects by the cholinomimetic action of the acetylcholinesterase inhibitor tacrine (18). Physostigmine, another cholinesterase inhibitor, has also been found to reduce attentional problems in visuoconstructive tasks (19). Intravenous nicotine (a potent ACh agonist) administered to AD patients improved visual attention on some tasks, perhaps by enhancing the acquisition or encoding of information (20). Attentional errors on a rapid visual information processing task were also reduced in AD subjects following subcutaneous nicotine administration (21). Nonspecific muscarinic receptor stimulation with arecoline has also been shown to improve visual processing on facial recognition tasks in AD patients (22-23). Visuospatial function, as measured on figure copying tasks, also responds to arecoline infusions in some AD patients (24).

3.1.3. Clinical features

In clinical settings, estimates of the frequency of AD related deficits in complex visual function vary widely depending on which tests are used to define visual performance. About half of AD patients will complain of the problem or acknowledge it when questioned (25). Cummings and Benson (26) identify four main areas of visual and spatial dysfunction that generate complaints among AD patients. They are: 1) becoming lost in familiar settings, 2) getting lost while driving, 3) disorientation in their own home, and 4) difficulty recognizing familiar faces.

A number of factors contribute to the underestimation and under recognition of visual problems in AD patients when such overt problems are not reported. Visual difficulties evolve gradually and occur in individuals who typically have deficits in verbal expression, limiting their ability to communicate subtle dysfunction. Families may also be unable to disassociate memory, behavioral, and language disturbances from visual disorders. For instance, a patient with prosopagnosia may be described to have “forgotten” the faces of family members. Anosognosia is commonly associated with visual problems in AD and right hemispheric dysfunction has been suggested as the substrate for their concurrence (27). In most circumstances, the amount of visual dysfunction is closely related to overall AD severity, but in some individuals, disturbances in complex visual function are the earliest and most prominent sign of the illness (28). This syndrome has been called posterior cortical atrophy or, more rarely, the “visual variant” of AD.

3.1.4. Perceptually mediated deficits

Visual acuity is the most common screening test for vision, but it is not preferentially affected by AD (29). Among other common visual screening tests, AD patients are impaired on pseudoisochromatic color discrimination tasks (30). Additional deficits may be evident on tasks of object naming (31), facial discrimination, and facial recognition (32). A number of investigators have found decreased sensitivity to visual contrast in AD using different experimental paradigms (30, 33-35). Deficits in contrast sensitivity function in AD are especially prominent at low spatial frequencies and worsen over time (35). The loss of low spatial frequency vision is particularly important because it is the low and medium spatial frequencies which provide basic visual form information with the higher frequencies adding fine details to the percept (34). As a result, removing low spatial frequencies from visual stimuli impairs control subjects ability to recognize and discriminate images. Conversely, improving contrast enhances cognitive performance in AD subjects. AD subjects who were noted to have slow reading speed read briefly presented letters as quickly as healthy elderly subjects when the stimulus contrast was increased (36). Turner (37) also demonstrated that naming time in AD patients could be improved with even modest increases in visual contrast.

3.1.5. Spatial processing deficits

Mendez *et al* (25) reported that spatially related difficulties were the most common visual problem in their series of 30 AD patients. Although several studies show impaired mean performance by AD patients on the Benton Line Orientation task, there is often overlap between some healthy controls and some AD patients, providing the test with low discriminative value (e.g., 32). Spatial disorientation likely reflects impaired visuospatial processing in AD patients. Trobe and Butter (38) found that AD subjects were very sensitive to confusing elements in visual arrays and attributed their deficits to a failure of integrating visual information across space. The overall severity of visuospatial impairments in AD can be quite similar to acute right hemisphere damage, though the

pattern differs somewhat between the two disease states (39).

3.1.6. Visuomotor and constructional deficits

Constructional praxis, or design copying, is often considered a marker of visuospatial ability in clinical settings. However, it is strongly dependent on visuomotor processes. It is commonly impaired in AD. Spatial errors occurred nearly twice as frequently in AD subjects when compared to controls on a design-copying task (40). Clinical experience suggests that three-dimensional figures, like a closed cube figure are especially sensitive to this effect. Another characteristic of visuomotor impairment in AD is the “closing-in” phenomenon, by which patients tend to trace the model figure or otherwise attach their copy to the model. The clock drawing test, in which a patient is asked to draw a clock and hands set to a specific time, also depends on constructional ability, but semantic knowledge and executive function components are prominent. Clock drawing generally deteriorates with overall AD severity. Its utility for detecting mild cases of AD is controversial (41-42).

3.1.7. Visual attention

Deficits in visual attention are a major contributor to cognitive impairment in AD. Impaired attention leads to dementia subjects' poor ability to acquire information during brief visual stimulus presentations (43). The spatial aspects of selective attention, such as redirecting the focus of attention, are particularly affected in individuals with AD (8). This can lead to narrowing of the functional visual field (44) and the useful field of view (45). Nebes and Brady (46) reported that although AD patients can adequately focus their attention, they show impairments on tasks which require them to divide their attention across multiple stimuli. Their finding is supported by the subsequent demonstration that mild and moderately affected AD patients are impaired in reorienting (disengaging) attention away from initial stimuli and that visuospatial ability in AD subjects was adversely affected by automatic redirections of attention toward peripherally occurring invalid cues (8). When severe, these deficits can take the form of Balint's syndrome, a classically described symptom complex. Balint's syndrome is characterized by simultanagnosia (an inability to simultaneously perceive or attend to multiple visual stimuli), “optic ataxia” (a disorder of visually guided reaching), and “ocular apraxia” (an inability to move the eyes voluntarily to a visual target).

3.1.8. Behavioral eye-movements in AD

Although the individuals with Balint's syndrome represent the extreme case, multiple deficits in elementary oculomotor function are associated with AD. These include impaired oculomotor reaction time, saccade and pursuit generation, and target tracking (47-48). It is unclear how these changes impact upon visual information processing, but primary ocular motility deficits probably do not account for visuocognitive impairments observed in AD subjects (49).

Analyses of the ocular scan path have demonstrated perseveration in the oculomotor programming of AD subjects (47). A more recent study

also reported that perseverations, as well as intrusions, such as returning to previously fixated locations, were the most common scanning errors among individuals with AD (50). It can be argued however that these behaviors do not represent frontally-mediated perseverations, but rather indicate poor organization of visual search, akin to what has been described with parietal lobe lesions (51-52). In another study implicating frontal dysfunction as a source of scanning abnormalities, AD patients showed diminished overall exploration, especially to novelty and visual incongruities (49). Unlike controls, AD patients' fixations do not increase in duration over the time course of visual inspection; this suggests that they do not acquire necessary information early in the course of viewing or that they have difficulty identifying informative aspects of visual scenes (48). Moser and colleagues subsequently reported that impaired environmental scanning in AD subjects with complex visual dysfunction was the result of "motivational and perceptual deficits," but did not identify which differences in performance might relate specifically to motivation or spatial perception (53).

The available literature on behavioral eye movements in AD lacks an explicit theoretical framework to guide a consistent approach to analysis and interpretation. Consequently, a clear consensus regarding the practical implications of scanning disturbances as a contributor to functional impairment in AD has not arisen.

3.2. Parkinson's Disease

3.2.1. Background

PD is characterized by a progressive akinetic-rigid movement disorder associated with disordered function in subcortical motor circuits. The neuropathological basis is marked cell loss and accumulation of intracytoplasmic neuronal inclusions, known as Lewy bodies, in the substantia nigra. Neuronal dysfunction and death in the substantia nigra deprives the basal ganglia of inhibitory dopaminergic inputs, resulting in increased motor tone in skeletal muscles. Bradykinesia and bradyphrenia are intrinsic to the basal ganglia dysfunction characteristic of the illness as well, and significantly complicate the interpretation of visuospatial deficits.

Many studies report visuospatial deficits in PD, but concomitant neuropsychological and motor deficits appear to be important mediators of their expression. Brown and Marsden (54) reviewed the available literature and identified limited evidence for an isolated visuospatial deficit in PD. Instead, they interpreted the reports to indicate a common theme of impaired shifting of perceptual sets, consistent with the impaired frontal-subcortical circuit function characteristic of PD. Waterfall and Crowe (55) performed an extensive review of the literature in this area and found 70 studies suitable for including in a meta-analysis. Extensive differences in methods, demographics, and illness-related factors precluded inclusion and reliable interpretation of the rest of this complicated literature in their analysis. They suggested that low level perceptual deficits and compromised executive function contribute to the observed visuospatial dysfunction. Overall motor severity is closely associated with the severity of the

visuospatial problems in PD (56). Regardless of the origins of the complaints, a high proportion of PD patients report problems with space and depth perception (57).

Functional imaging studies of the source of visuospatial complaints in PD are equally confusing. When dementia in PD contributes to visuospatial impairments, parietal hypometabolism resembling that of AD may be seen. However, when dementia is excluded, frontal and temporal deficits are most prominent (58).

3.2.2. Neurotransmitter factors

PD is strongly associated with loss of dopaminergic inputs to the basal ganglia, but other dopamine pathways that regulate frontal function either directly, or via the caudate nucleus, may be similarly affected (59). However, the influence of these inputs is likely to be small. The observation that withdrawal of antiparkinsonian medication did not lead to decreased performance on basic perceptual tasks in PD is therefore not surprising (60). It is more likely that nigrostriatal dysfunction exerts its influence via frontal subcortical pathways, such as the "dorsolateral" and "orbitofrontal" circuits (61). Dopamine deficiency has been associated with significant degrees of retinal dysfunction and may contribute to some of the more basic perceptual problems in PD, like impaired acuity and contrast sensitivity (62).

3.2.3. Perceptual dysfunction

Unlike AD, some investigators have found up to 25% mean reductions in visual acuity in PD, but there is extensive variability in the severity of the effect across individuals (60). Further analysis of the same data set suggests, however, that even when controlling for poor acuity, other perceptual abilities are reduced in PD (60). This is supported by the observation of impaired contrast sensitivity among PD patients (63), which may account for deficits in tasks such as face recognition (56). Among 30 PD subjects and 30 controls on a battery of visually-loaded psychometric tasks, factor analysis identified a that a presumably perceptual component contributed prominently to impaired visual performance among the PD group (1).

3.2.4. Spatial processing

Nondemented PD patients performed significantly worse than controls on a battery of visual tests that assessed figure-ground discrimination, spatial position, perceptive constancy, and spatial relationships (64). Mental rotation tasks are also impaired (65). Deficits in spatial memory also appear to be an important contributor to poor spatial ability in PD patients (66-67).

3.2.5. Visuomotor and constructive tasks

Boller *et al's* (1) factor analysis of visuospatial impairments identified that in addition to a perceptual factor, a (presumably) motor component also contributed to impaired performance on a battery of perceptual and constructive tasks in PD. Methodological problems common to factor analysis, especially regarding cognitive data not included in the analysis, limit the interpretation and generalizability of their findings. Timed motor

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elements probably contribute to the relative deficits in the performance IQ of PD patients on the Wechsler Adult Intelligence Scale (68). However, simple motor effects may not account for all of the differences between performance IQ and verbal IQ. For instance, a comparison of reaction time on verbal and visuospatial tasks among PD patients revealed a significant relative penalty for reaction time on the visuospatial tasks (69). Design copying is a constructional task impaired in PD (70), but the complex motor sequencing required for executing the copies also draws on executive function.

3.2.6. Visual attention and executive control

Simple visual attentional tasks, like the covert orienting of attention appear to be preserved in mildly affected PD patients, but their performance declines relative to controls as the attentional demands of the task are increased. (71). The link between visuospatial deficits and executive dysfunction in PD is supported by Bondi *et al* (72), who found that covarying for executive function eliminated visuospatial deficits. In support of this, PD patients were found to inappropriately use visual cues in the performance of the Water Jar Test of spatial perception (73). The support for dysexecutive contributions to the visuospatial problems in PD led Dubois and Pillon (61), in their seminal review of cognitive deficits in PD, to conclude that “visuospatial disorders in PD result more from a decrease in central processing resources than from a specific alteration of visuospatial function.”

This viewpoint is not, however, universally accepted. For instance, Cronin-Golomb and Braun (74) found PD-related visuospatial deficits beyond those that could be attributed to executive dysfunction. In addition, Crucian *et al* (73) found that common measures of executive dysfunction were not related to visuospatial performance. Perhaps because of difficulties in defining both “executive function” and “visuospatial function,” the exact relationship between these domains in PD remains to be determined.

3.3. Dementia with Lewy Bodies

Although parkinsonism frequently complicates Alzheimer’s disease and dementia frequently complicates parkinsonism, the recognition of a distinct clinical syndrome associated with both is relatively recent. Current terminology generally refers to this as “Dementia with Lewy Bodies,” and consensus criteria have been developed (75). Key features of this illness include relatively concomitant development of parkinsonism and overt cognitive impairments with a progressive course over years. There are often marked fluctuations in cognition and attentiveness that may be based in disordered regulation of arousal.

Early visual hallucinations are a characteristic neuropsychiatric feature. Unlike pure AD, hallucinations frequently develop while the dementia is quite mild. For many DLB patients these are benign, well-formed, and nonthreatening visions of people or animals. The character of the hallucinations suggests that they may be linked to

deficits in processing complex visual information. For instance, micropsia of the hallucinated elements is common, suggesting a disorder of size constancy.

Not surprisingly, there is an emerging understanding that visual and spatial deficits are also characteristic of DLB and may appear early in the disease course. Visuo-perceptual tasks, such as size discrimination, form discrimination, overlapping figure identification and visual counting, were impaired in DLB relative to patients with AD (76). The deficits relative to AD also extend to spatial and visuomotor realms, on tasks like picture arrangement, block design, object assembly, digit symbol substitution, and Raven Colored Progressive Matrices, even though the DLB group performed better on the Mini-Mental State Examination and a word recall task (77). These more detailed investigations support a smaller, earlier series with similar findings (78).

The clinical patterns are supported by observations on functional imaging studies that identify a somewhat more posterior distribution of cortical hypometabolism in DLB in comparison to AD, particularly in the occipital lobe (79). Furthermore, the prominence of visual hallucinations has been directly linked with hypometabolism in the occipital lobe (80).

3.4. Other Neurodegenerative Syndromes

None of the other neurodegenerative syndromes has as extensive a literature on visual and spatial impairment, though symptoms may be evident. In many cases, prominent dysexecutive states in these illnesses lead to impairments on neuropsychological tests that include visuoconstructive performance. Huntington’s disease (HD) is perhaps the best studied of the other illness in regard to visuospatial deficits. HD patients show particular deficits in spatial learning and memory, and appear to have visuomotor impairments on visual search tasks (81). The amount of impairment on visuospatial and visuomotor tasks increases with overall disease severity, but is not present in asymptomatic carriers of the illness (82). Corticobasal degeneration (CBD) is characterized by a prominent apraxia and concomitant visuoconstructive problems. In CBD patients, diminution in cerebral blood flow is observed in several brain regions, including the temporal and parietal association cortices, as measured by single photon emission computed tomography. Perfusion deficits were asymmetric, occurring contralateral to clinically evident apraxia (83). However, systematic manipulation visual inputs did not alter the expression of ideomotor apraxia in one carefully studied patient (84). Genetic studies suggest that progressive supranuclear palsy (PSP) is closely related to CBD, and many patients with PSP will complain of visual symptoms. These appear to be primarily linked to oculomotor, postural, and executive function disturbances characteristic of the disease. There is little systematic investigation of visuospatial deficits in PSP reported in the literature. Patients early in the course of amyotrophic lateral sclerosis demonstrate problems on visuo-perceptual tasks as well as visuospatial reasoning (85).

4. FUNCTIONAL IMPACT OF VISUAL AND SPATIAL DYSFUNCTION

The clinical pictures of the neurodegenerative diseases are dominated by functional disability. One reason for the lack of broad understanding of the visuospatial impairments in these illness states may be an underappreciation of the role of low vision as a contributor to the functional disability. In the case of parkinsonian disorders, for example, problems with gait or visually guided behaviors are often attributed directly to the extrapyramidal motor dysfunction rather than to more cognitively mediated deficits.

However, the pervasiveness and character of visual dysfunction in these illnesses suggests it has a clinically meaningful role. While this has not been well segregated in the neurodegenerative illnesses, there is an extensive literature on the role of visual abilities in daily function in aging, as well as in ocular disease.

Among healthy elderly, there can be very little correlation between self-reported quality of vision and results of vision testing (86), suggesting that elders under-report their actual degree of visual disability. Among those who do report visual problems, there is an increased risk for falls (87). Dependence in ADL's was also strongly associated with reduced visual function in both community-dwelling and nursing home samples (88-89). In addition, persons with self-reported visual disability were 1.37 times more likely to be dependent in ADL's (90).

Impaired visual function also has impacts on behavior and quality of life. A decreased sense of psychologic and social well-being was found among individuals self-reporting poor vision (91). In addition to decreased self-sufficiency in ADL's, persons with visual problems had a higher risk for depression and decreased social relationships (92).

Visual acuity is overemphasized as a measure of visual function in clinical settings. It is usually preserved in AD and markedly variable in PD (29, 60). Nonetheless, healthy elders frequently report changes in vision that are not assessed by acuity (45). For ocular disease states, like cataracts, contrast sensitivity (CS) function impairments probably more accurately represents "real-world" everyday vision (93). It is therefore important that investigators have found decreased CS in AD and PD using different experimental paradigms (33-35, 94). Interestingly, CS impairments and acuity were independently associated with self-reported visual difficulty (95). Glaucoma is also associated with decreased CS, which may precede declines in acuity or visual fields in 30% of cases (96). Given the prominence of CS changes in both AD and PD, it is significant that CS declines in glaucoma have a negative impact on activities of daily living (ADL) even prior to the development of overt symptoms (96).

5. PERSPECTIVE

Visual and spatial problems are common in the neurodegenerative diseases of late life. The pattern of these

changes differs across the illnesses, and interpretation of the literature is complicated by the lack of common definitions. Defining the boundaries of visuospatial dysfunction and testing them is complicated by the central role vision plays in human behavior. Elemental perceptual changes influence inputs into visual processing in the cortex, and executive dysfunction is an important mediator of visual and spatial behaviors on neuropsychological tests and in everyday life. The functional implications of visual and spatial dysfunction in the context of other disabling features of these illnesses remain largely unexplored.

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