Over a century ago, Alois Alzheimer published a case description of a 51-year-old woman whose initial behavioral abnormality was pathological jealousy of her husband. Her condition rapidly deteriorated with the accumulation of behavioral symptoms that constitute the syndrome of dementia. Besides memory loss, personality change, and agnosia, the woman described in the report exhibited visuospatial symptoms including perceptual abnormalities and dysfunction of spatial localization:

(S)he could not find her way about her home . . . She was disoriented as to time and place . . . She suffered from serious perceptual disorders . . . While reading she would omit sentences . . . “ (Alzheimer, 1907).

Though the young age of the woman in the report and her initial symptom of jealousy might cause today’s neurologist to pause before offering a diagnosis of “typical” Alzheimer’s disease (AD), the changes over time in memory, object recognition, and visuospatial function would lend confidence to the diagnosis. Among the cortical areas usually affected early in the disease course are the posterior regions, including the parietal lobes, which are of critical importance for normal visuospatial abilities, with involvement of the occipital lobes as well (Arnold et al., 1991; Beach & McGeer, 1988; Braak et al., 1989; Grady et al., 1993; Lewis et al., 1987; McKee et al., 2006; Pietrini et al., 1996).

The topic of the present chapter is visuospatial function in AD and related disorders. With reference to the symptoms reported in Alzheimer’s original case, the focus is on spatial localization and on perceptual disorders that are related to spatial
dysfunction. We have reviewed this topic extensively in the past (Cronin-Golomb, 2001; Cronin-Golomb & Amick, 2001; Cronin-Golomb et al., 1993; Cronin-Golomb & Gilmore, 2003) and other reviews are also available (Geldmacher, 2003). Spatial memory, itself a large topic, is not discussed in detail here (see Iachini et al., 2009, for a review). The goal of this chapter is to report the most recent literature (since 2000) and to describe current conceptualizations of spatial disability in AD. These conceptualizations arise from careful behavioral and imaging studies that together permit a fresh view of spatial function in those afflicted by AD and related neurodegenerative conditions.

Before proceeding with a discussion of the literature on spatial function, it should be noted that the potentially important factor of gender continues to be given short shrift in research studies. Gender differences are understood to be robust for certain spatial tasks (Hampson, 2000) yet are rarely examined in AD despite the fact that they have been documented for motion perception (Andersen & Atchley, 1995; Atchley & Andersen, 1998; Gilmore et al., 1994), which as shown later in the chapter is associated with visuospatial dysfunction. One more recent study has shown poorer performance by women than men with AD on a task of mental pathway generation (Millet et al., 2009) and another has shown that men and women with AD differed in predictors of navigational performance (Cushman & Duffy, 2007), providing an impetus for further investigation of potential gender differences.

In most studies of visuospatial function, individuals with AD exhibit impaired task performance relative to matched control participants. The end result of poor visuospatial function may arise from problems along several different pathways to performance, such as degraded or otherwise non-salient stimulus input, narrowing of attentional focus, suboptimal visual search strategies, and higher order cognitive disturbance. Different domains of impairment may respond to different therapeutic interventions (e.g., environmental, pharmacological), lending importance to the identification of specific causes of spatial dysfunction in individuals with AD.

The chapter sections are organized as follows:

1 Neuropsychology: findings from studies using neuropsychological, cognitive neuroscience, and imaging techniques
2 Potential causes of visuospatial disorders:
   (a) Stimulus salience
   (b) Motion perception
   (c) Spatial exploration: scanning and attentional focus
   (d) Visual search
3 Heterogeneity of AD presentation: visual variant
4 Interventions to improve visuospatial function:
   (a) Environmental interventions
   (b) Pharmacological interventions
5 Visuospatial dysfunction arising from conditions other than AD:
   (a) Dementia with Lewy bodies
   (b) Parkinson's disease
Neuropsychology

An important problem in AD is topographic disorientation, which leads to becoming lost in familiar or unfamiliar surroundings. Cherrier and colleagues (Cherrier et al., 2001) applied a route-learning test to patients with AD who did not differ significantly from a control group on performance of a number of standard neuropsychological measures of spatial function, though they differed on memory measures. Only performance on the Standardized Road-Map Test of Direction Sense (also known as the Money Road Map) predicted the total score on the route-learning test. A novel finding of the study is that the AD patients performed relatively well on the route-learning subtest of landmark recognition, suggesting that fundamental spatial disorientation rather than failure of memory for landmarks (topographic agnosia) was the principal dysfunction leading to topographic disorientation in this sample. A similar conclusion was drawn by Monacelli and colleagues in their examination of a route-learning task, the total score on which was predicted better by map location ability than by landmark recall, though performance on both subtests was impaired in their sample of patients with AD (Monacelli et al., 2003).

Topographic orientation is especially critical for driving. Brown and Ott reviewed the literature on the use of neuropsychological measures as predictors of driving ability in demented patients and found that performance on visuospatial tasks was a factor to consider in regard to fitness to drive (Brown & Ott, 2004). Studies conducted since this review, including those of Uc and colleagues (Uc et al., 2006) and Grace and colleagues (Grace et al., 2005), are in accord with this point. In the first study (Uc et al., 2006), predictors of unsafe outcomes in a driving simulator included visual psychophysical measures (acuity, contrast sensitivity, visual attention) and measures of spatial function (Judgment of Line Orientation and visuoconstructive tests). The AD group was more likely than the control group to engage in abrupt or premature slowing, though there was no group difference for actual collisions. The second study (Grace et al., 2005) measured driving performance directly during on-road assessment rather than with a simulator, comparing performance in AD and Parkinson's disease (PD). Whereas both patient groups made more tactical driving errors than did the control group (i.e., obeying rules of the road, choice of driving speed, basic driving maneuvers), the AD group additionally committed more operational errors (such as timing of reactions to changing driving environment) and strategic errors (such as mistakes in cognitive reactions and reasoning). Unsafe drivers performed more poorly on a number of neuropsychological measures than did their safe-driving counterparts, with impaired driving predicted best by cognitive tests assessing spatial and executive function (Trail Making Test,
Rey-Osterrieth Complex Figure). Current efforts include the development of neuropsychological tests that correlate well with on-road driving skills, such as the Neuropsychological Assessment Battery’s Driving Scenes test of visual attention (Brown et al., 2005), and a composite score from standardized neuropsychological tests across cognitive domains (including visuospatial and visuomotor) that identifies those patients with AD who perform poorly on on-road driving assessment (Dawson et al., 2009).

Studies combining traditional neuropsychological measures with neuroimaging are becoming increasingly common and offer new insights into the brain bases of cognitive change in AD. In a functional magnetic resonance imaging (fMRI) study, Prvulovic and colleagues (Prvulovic et al., 2002) showed patients with AD and a matched control group pairs of angles (clock hands). The task was to indicate whenever an acute angle appeared in a series of oblique angles. The AD group’s performance did not differ overall from that of the control group, though it was characterized by a high variance in error rate. Despite the similarity in mean performance (and even when controlling for accuracy and reaction time of behavioral performance), imaging revealed group differences in brain processes, with the AD group showing relatively low activation of the dorsal stream’s superior parietal lobule bilaterally as well as of frontal areas, basal ganglia, and thalamus. The patients also showed relatively high activation of the ventral stream’s left fusiform gyrus, suggesting a reorganization of activation pattern in AD – possibly a compensatory mechanism. An important further point was that this pattern was associated with the degree of atrophy of the superior parietal lobules. That is, it is likely that the reduced parietal activation followed from parietal atrophy. This finding is further supported by a more recent fMRI study of angle judgment in AD in which it was found that dorsal pathway function was altered, indicating a failure to modulate neural responses to increasing demands of the task (Vannini et al., 2009).

A somewhat different picture was obtained through study of a visuoconstructive task, complex figure drawing (Rey-Osterrieth), performance on which was used to separate patients with AD into two groups who were otherwise matched for neuropsychological performance (Boxer et al., 2003). The more impaired group showed greater atrophy of the right inferior temporal gyrus on structural MRI than did the better-performing group. Presumably figure copying, because of its demands on form (object) perception, engages temporal cortex to a greater extent than would a test of angle orientation, which would rely more heavily on parietal-mediated processes.

Fujimori and colleagues (Fujimori et al., 2000) used positron emission tomography (PET) to measure regional cerebral glucose utilization during performance of tasks of dorsal-stream visuospatial processing (number counting) and ventral-stream object identification (overlapping figures, visual form discrimination). There were significant correlations between the metabolic rate of the bilateral inferior parietal lobules and visuospatial performance, and between the metabolic rate of the right middle temporal and right inferior parietal and object identification.
Though the AD sample size (49) was large for this type of study, there was minimal information provided on the control group (no sample characteristics or PET findings; descriptive statistics were provided for the neuropsychological tests only). The control information would have permitted comparison of the results of this study with that of Prvulovic and colleagues (2002), above, with their demonstration of reorganized activation patterns in dorsal and ventral streams in AD relative to a matched control group.

The clock drawing test (CDT) is a standard neuropsychological measure that is commonly applied to a wide variety of clinical populations. It is a sensitive index of the integrity of several cognitive domains, including spatial abilities, semantic abilities, and executive function. Its multifactorial nature makes it useful clinically but difficult to interpret in terms of brain–behavior relations. Ueda and colleagues (Ueda et al., 2002) attempted to determine the neural substrates of clock drawing in patients with AD using single photon emission computed tomography (SPECT). They used the Rouleau scoring system, which appears to be sensitive to semantic memory as well as to other cognitive abilities. Their report of a correlation of test score with left posterior temporal blood flow is consistent with the sensitivity of the scoring system to semantic dysfunction. In an fMRI study, healthy older adults showed cortical activation of intraparietal, inferior temporal, and occipital cortex during clock-time identification tasks, implicating both ventral and dorsal visual processing pathways (Leyhe et al., 2009). The task requiring identification of the placement of the clock's minute hand elicited activation of parietal areas that the investigators associated with spatial mental imagery. In patients with early AD, impaired performance on the clock tasks was associated with reduced activation of the occipital lobes and the left fusiform gyrus, the latter possibly related to this area's role in conceptual processing. Another study of AD patients, using PET and multiple CDT scoring systems, revealed consistent correlations between clock drawing performance and regional cerebral glucose metabolism in the right inferior parietal lobule (Lee et al., 2008). It is unclear why this group found right parietal to be the area correlating with test performance whereas, as noted above, Ueda et al. found the correlation with left posterior temporal, especially since both studies had a CDT scoring system in common (Rouleau).

In a qualitative assessment of clock drawing comparing individuals with AD to those with frontotemporal dementia, Blair and colleagues found the AD group committed more spatial errors as well as more stimulus-bound responses, conceptual deficits, and planning errors (Blair et al., 2006). In another study, qualitative analysis of the error patterns of patients with AD versus vascular dementia showed that it was the vascular group that made more spatial and planning errors (Kitabayashi et al., 2001), a finding that may be supported by findings from Fukui and colleagues, who reported that a group of patients with subcortical cognitive impairment (including subcortical vascular lesions, Parkinson's disease, progressive supranuclear palsy, dementia with Lewy bodies, and corticobasal degeneration) performed more poorly than patients with AD on clock tasks (drawing, reading,
and matching) and figure copying (Fukui et al., 2009). This finding applied to patients with moderate to severe overall cognitive impairment. Small sample sizes did not permit subgroup analysis within the non-AD group.

A very informative approach was taken by Mosimann and colleagues (Mosimann et al., 2004), who examined eye movements in AD patients during clock reading. They found that relative to healthy age-matched adults, visual exploration in the AD group was less tightly focused on the ends of the clock hands, and fixation latency and duration were increased. The latency and duration results indicate a probable difficulty in disengaging attention from one area to move the eyes to a region of interest. Such impairments in disengagement suggest parietal dysfunction. Impaired clock reading has also been associated with poor functional status as indexed by activities of daily living scales, underscoring the importance of visuospatial ability to everyday function (Fukui & Lee, 2009).

**Potential Causes of Visuospatial Disorders in AD**

**Stimulus salience**

Stimulus salience may be reduced in AD because of impairments at the levels of basic vision (reduced signal strength leading to degraded perceptual input) and attention.

**Reduced visual signal strength**

A growing number of research studies are focusing on the impact of deficiencies in lower level visual processes upon higher order visuospatial function. Dysfunction occurs in multiple visual capacities in AD, including contrast sensitivity, color discrimination, depth perception, and motion perception (Cronin-Golomb, 1995). Contrast sensitivity is especially important to stimulus salience, with reductions leading to degraded perceptual input. An example may be seen in Figure 15.1. The image has been passed through an “Alzheimer filter,” developed by Grover C. Gilmore and colleagues. The filter simulates the spatial contrast sensitivity deficit of a person with AD relative to a normal adult through digital reduction, thereby reflecting the proportional difference in contrast sensitivity between AD and normal groups. The image suggests how difficult spatial navigation in an environment may be for an individual with a contrast sensitivity deficit of the magnitude commonly seen in AD.

More recent work on the relation of contrast sensitivity to higher order visuo-perceptual and spatial function has come mainly from our laboratory together with that of Gilmore and his colleagues. Deficient contrast sensitivity occurs across the frequency range in AD (Neargarder et al., 2003), with low-frequency impairments especially affecting the ability to discriminate faces (Cronin-Golomb et al., 2000). We have been extending our work in the direction of enhancing stimulus strength in order to improve visual cognition in aging and AD. In one study (Cronin-
Golomb et al., 2007), increased signal strength was related to improved performance by the patients with AD and by healthy age-matched adults, relative to their baseline performance with stimuli of lower signal strength. This result pertained to letter and word reading, picture identification, and face discrimination. Most promising were the results with reading and picture naming. For reading, we found that increasing signal strength beyond normal levels improved AD performance to the extent that it was indistinguishable from that of healthy elderly adults. This result was similar to what was found for letter reading in a separate study (Gilmore et al., 2005). For picture naming, the percentage of perceptual-type errors (as opposed to semantic errors, or errors with no discernible basis known as “no-content” errors) decreased with increased signal strength, both for healthy elderly adults and patients with AD (Figure 15.2). It would be enlightening to examine the effect of signal strength on other standard measures of visuospatial ability, especially those that longitudinal studies suggest are sensitive to decline over the course of AD (e.g., Paxton et al., 2007, with the Hooper Visual Organization Test).

Reduced attentional salience

Traditional measures of spatial attention have used emotionally neutral stimuli that are either abstract, such as lines, letters or symbol cancellation (Liu et al., 2004) or concrete pictures that elicit verbal description, such as Cookie Theft from the Boston Diagnostic Aphasia Examination, or the Picture Description Test as in the study by Meguro and colleagues (Meguro et al., 2001). A growing trend is to examine the effect on spatial exploration of more specific stimulus components. Daffner et al. (1992) varied the novelty and complexity of emotionally neutral

Figure 15.1 The image on the left is of a concrete staircase seen from above under normal viewing conditions. The image on the right is the same staircase passed through the “Alzheimer filter,” which simulates the spatial contrast sensitivity deficit of a person with Alzheimer’s disease. Source: Photographs courtesy of Thomas M. Laudate. Image filtering courtesy of Grover C. Gilmore and Cecil W. Thomas.
stimuli and found that healthy adults, but not patients with AD, spent more time looking at incongruous or irregular objects and scenes than at their more congruous or regular counterparts (Daffner et al., 1992). By contrast, LaBar and colleagues (LaBar et al., 2000) varied the emotional salience of pictures (neutral-negative) and found that patients with AD were similar to healthy older adults and to young adults in the location and duration of fixations. It is unclear whether the difference in the results of the two studies arose from sample differences (with small sample sizes), from slight differences in overall cognitive status, or from a genuine difference in spatial attention as a function of the emotional salience of the viewed stimuli.

Of relevance here is the study from our laboratory of facial emotion (Wong et al., 2005), in which we found that older and younger adults showed different topographical distributions of fixations. Older adults exhibited fewer fixations on the face overall but proportionately more fixations to the lower half of the display, with implications for accuracy of identification of specific facial emotions (Figure 15.3). Relative to the younger adults, the older adults were less accurate in identifying fear and anger in the visual modality but performed at the same level as the younger adults on an auditory test of emotion (prosody). Though this study did not examine patients with AD, the implication is that investigations of emotional salience in visual search should focus on individual emotions and should attend to where in the visual display the fixations occur. A word of caution is in order here, however, as there is a paucity of work examining facial emotion that simultaneously assesses the spatial demands of facial discrimination or recognition. A study showing
poor performance by AD patients in the perception of rotated (different orientation) or inverted faces, suggesting viewpoint dependency in AD (Adduri & Marotta, 2009), speaks to the need to address this issue more fully.

Motion perception

Mapstone, Duffy, and their colleagues have conducted a series of careful studies of the relation of deficits in motion perception to visuospatial impairments (Duffy et al., 2004; Mapstone & Weintraub, 2004; see Duffy, 2009, for a review). A specific focus of their work has been the perception of optic flow, or the apparent motion of objects in the environment as one is moving in relation to them. As an example, when we are walking, we have the sense that the visual world is moving from in front of us to behind us, on both left and right sides, which provides...
information on the direction in which we are headed. Beginning with a linkage of optic flow thresholds to open-field navigational capacity in AD, Duffy et al. (2000) went on to report a correlation of optic flow thresholds and performance on both the Money Road-Map Test of Direction Sense and an on-road driving test, though not with tests of memory (O’Brien et al., 2001). Cherrier and colleagues (2001) suggested that their route-finding results described above were consistent with these findings of environmental navigation being related to the integrity of optic flow perception (Tetewsky & Duffy, 1999).

A third study (Mapstone et al., 2003) extended the scope of the others by assessing individuals with mild cognitive impairment (MCI) as well as patients with AD. The AD and MCI groups performed well on a test of planar (horizontal) motion relative to one of radial motion (simulated optic flow). Those in the AD, MCI, or age-matched control group who had problems with optic flow perception were also impaired on the Road-Map Test, with much weaker correlations between optic flow performance and neuropsychological measures of memory. The implication of the results of the latter two studies is that topographical disorientation in AD arises from visuoperceptual impairments independent of memory difficulties. In addition, the studies suggest that some older normal individuals with elevated optic flow thresholds may be at risk for AD. Optic flow thresholds are correlated with temporal factors in AD, as shown through application of rapid serial visual presentation, suggesting that the temporal dynamics of perception may contribute to spatial disorientation in this disorder (Kavcic & Duffy, 2003). In further studies, this group has found that patients with AD, with their deficits in object motion and optic flow perception, were impaired at pointing or steering accurately in the direction of simulated heading (Mapstone et al., 2006), and that men and women with AD were different in regard to predictors of navigational performance (Cushman & Duffy, 2007). Though men and women were equally impaired in navigation, performance was predicted by visual motion processing in men and by verbal capacities in women.

Festa and colleagues (Festa et al., 2005) used motion perception to investigate the role of cortical connectivity in sensory integration in AD. There were two conditions within a single integration task. For one (motion and color), feature binding required more cross-cortical integration than for the other (motion and luminance). AD patients were impaired on the former but not the latter condition, whereas healthy adults as well as patients with Huntington’s disease were able to effect binding under both conditions. The result accords with the disruption of cortico-cortical connections that characterizes AD.

A more recent fMRI study provides information on the neural bases of impairments in depth and motion perception, which to date had not been available in reference to AD (Thiyagesh et al., 2009). These investigators examined stereomotion and radial motion and found reduced activation in the AD group for regions that were active in the control group (e.g., V5, superior parietal lobule, parieto-occipito junction). The reductions were accompanied by greater activation for AD in inferior parietal lobule and other regions, possibly reflecting recruitment compensation.
The authors noted that the findings with stereomotion and radial motion may be relevant to understanding visuospatial disorientation, a common and debilitating visuospatial symptom of AD.

**Spatial exploration: scanning and attentional focus**

Spatial exploration refers to the ability to scan and search the environment, to attend to areas of interest, and to orient the body in preparation for action in this spatial realm. Neuropsychological disorders in which spatial exploration is impaired include hemineglect (unilateral) and Balint’s syndrome (bilateral). Spatial exploration is conceptualized as comprising a number of abilities, including scanning or searching the environment and focusing attention on areas of interest.

**Scanning**

Thulborn and colleagues (Thulborn et al., 2000) administered a visually guided saccade task while recording activation patterns with fMRI. Relative to the control group, patients with AD exhibited less right parietal activation and more prefrontal activation. Whereas the age-matched control group showed right-hemisphere dominance in the intraparietal sulcus for the task (as do young adults, it is reported), the majority of the AD group showed relatively great left-parietal activation. No volumetric differences between groups were noted, by contrast with the findings of Prvulovic and colleagues (2002) described above, in which parietal deactivation was associated with regional atrophy. Other studies that used eye movement recording are described in the next section on attentional focus.

**Attentional focus**

Meguro and colleagues (2001) related cerebral blood flow in AD with performance on the Picture Description Test, a complex scene that has been used in studies of aphasia and verbal description capacities in AD. These investigators reported that about equal numbers of AD patients who showed some hemispatial neglect were affected on the right or left side, with 12 patients neglecting items on the right and 14 on the left. Another eight patients described elements only in the central area of the picture, neglecting both right and left peripheral regions. Frequency analysis indicated an interaction of side of hemispatial inattention and the side of the parietal lobe with relatively low blood flow as exhibited on SPECT scanning, such that the group with decreased left hemispatial attention had low flow in the right parietal whereas those with low right hemispatial attention had relatively low flow in the left parietal lobe.

There appears to be substantial heterogeneity across patients, as other investigators have reported either hemispatial neglect (Liu et al., 2004; Mendez et al., 1997) (more in left than right hemispace) or more general inattention, conceptualized as a narrowing of the zone of attentional spotlight or reduction in the useful field of view (Rösler et al., 2005). With a narrowing of the central area that one can attend...
to without eye movements, it becomes necessary to increase the number of relatively peripheral eye movements in order to attend across a large field, such as that presented during driving. This increase in peripheral eye movements is in fact what is seen in older relative to younger adults and in AD (Mapstone et al., 2001; Rösl er et al., 2005). The findings of Mosimann and colleagues in regard to clock reading, described above, may be related to these results, in that AD patients in that study had eye movements that were less tightly focused on an area of interest (ends of clock hands) than were the eye movements of a control group (Mosimann et al., 2004).

Visual search

Liu and colleagues (Liu et al., 2004) found that patients with AD were impaired on cancellation tasks, with some patients showing unilateral and others bilateral neglect. There was a significant correlation of visual inattention on the standard measures with performance on a questionnaire of behavioral inattention, though not with other questionnaire measures of daily function, pointing perhaps to unequal sensitivity of the questionnaire measures to aspects of spatial exploration in AD. Supporting the idea of the fundamental relation of visual search to activities of daily living, it was found that impairments in visual search appeared to account for poor performance by AD patients relative to a control group on a landmark and traffic sign identification task during on-road driving assessment (Uç et al., 2005). These investigators also found a relation between scores on tests of visual perception, visual attention, visuoconstruction and other cognitive domains and the ability of AD patients to perform an on-road route-finding task, as indexed by the number of driving errors including incorrect turns, times lost, and at-fault safety errors (Uç et al., 2004).

Our laboratory has examined the influence of lower level visual characteristics of the target on the ability to search for and detect differences between naturalistic scenes in AD (Neargarder & Cronin-Golomb, 2005). We found that both reaction time and change-detection accuracy were adversely affected with increased scene complexity, and that variations in gray scale (white vs. gray vs. black) were much more difficult to detect than were changes in hue (red/green, blue/yellow). Changes in hue detection were relatively preserved in older adults as well as in patients with AD relative to a young adult group, as was the ability to note the presence of a target in one scene and its absence in an otherwise-identical scene. These findings are in line with the conceptualization of Tales and colleagues (Tales et al., 2004), who noted that targets with larger discernible differences may be processed preattentively whereas those with smaller differences may require more attention. In our study, the gray-scale changes were more difficult to discern and invoked a higher attentional load for the healthy elderly adults (targets never detected in up to 38% of trials) and especially for those with AD (targets never detected in up to 62% of trials) relative to the young adults (7% of trials). As noted earlier, visual input (e.g.,
contrast sensitivity) is compromised in aging and especially in AD, which may well relate to reduced ability to successfully search for items differing only in gray-scale contrast. In another study, degradation of signal strength was associated with impairments in visual search for objects in unexpected locations in AD (Stehli et al., 2003).

Applying cognitive neuroscience techniques, other groups have focused on various aspects of visual search and spatial attention. Vecera and Rizzo (2004) have invoked impairments in visual short-term memory as an important contributor to observed deficits in spatial attention. Tales and colleagues (Tales et al., 2002) examined spatial cuing with exogenous cues versus endogenous cues, with the former attracting attention automatically and the latter requiring voluntary shifting of attention. They found that patients with AD showed strong effects for exogenous cues but did not differ from a control group for endogenous cues, meaning that AD is associated with an impairment of automatic but not controlled visuospatial attention. They acknowledged that under other experimental conditions, controlled visuospatial attention may also be compromised. In an intriguing extension of this type of work, Greenwood, Parasuraman and colleagues (Greenwood et al., 2005) reported that apolipoprotein E (ApoE) genotype is related to cued visual search, noting that the presence of the epsilon-4 allele was associated with cognitive decline in midlife that was consistent with prodromal AD. They further found that the CHRNA4 gene is associated with attentional cuing whereas the DBH gene is associated with spatial working memory (Parasuraman & Greenwood, 2004; Parasuraman et al. 2005).

**Heterogeneity of AD Presentation: Visual Variant**

There is substantial heterogeneity in the symptom profile of individuals with AD, with even Alzheimer’s original case being today considered atypical in presentation. Even with “typical” AD, there is extensive heterogeneity in the severity of problems that lead to visuospatial dysfunction, such as disorders of basic vision (Cronin-Golomb, 2004), as well as in extent of visuospatial difficulty (Caine & Hodges, 2001).

A subset of patients with AD present with relatively severe disorders of basic visual function (such as restricted visual fields and abnormal color discrimination and depth perception), visuoperceptual and visuocognitive problems (e.g., associative agnosia) and a variety of spatial difficulties, some of which constitute Balint’s syndrome. In these individuals, impairments in the visual and spatial domains usually precede semantic deficits (Caine & Hodges, 2001; Suzuki et al., 2003). These cases are referred to as “visual variant” or posterior cortical atrophy, with AD being the usual cause. The symptoms correspond to glucose hypometabolism in the occipito-parietal regions, especially in the right hemisphere, consistent with damage to the dorsal visual processing stream (Nestor et al., 2003). It has been proposed that visual motion evoked potentials may be useful in distinguishing AD patients with more pathology in visual cortex, who showed relatively low sensitivity on a
task of visual attention, from those with more pathology in higher order areas, for whom the attentional performance was relatively spared. Of note, the low-sensitivity group also had relatively impaired contrast sensitivity (Fernandez et al., 2007).

The neural substrates of atypical presentations in AD, with special emphasis on the visual variant, have been reviewed by von Gunten and colleagues (von Gunten et al., 2006) and interested readers are urged to consult this excellent reference as well as previous thorough reviews from this group (von Gunten et al., 2004) as well as from Mendez (2004).

Interventions to Improve Visuospatial Function

Environmental interventions

In an applied study, we set the goal of improving daily function in patients with AD by enhancing signal strength and thereby directing their visual attention to the important task of eating and drinking at mealtime (Dunne et al., 2004). In a dining setting of a long-term care facility, we conducted a pre-post intervention study using standard (white) and high-contrast tableware and measured the amount of food and beverage that were consumed. The intervention resulted in significant increases in ingestion of food (25% increase) and beverage (84% increase) in a severely demented AD sample (Figure 15.4). Follow-up testing indicated that the salience of the signal was of critical importance whereas hue itself was not. Specifically, red and blue tableware of saturated hues worked equally well relative to white, but pastel shades (pink, light blue) were ineffective in providing sufficient signal strength to effect behavioral change. These results are in accord with those of Koss and Gilmore, who found that modifications of the visual contrast environment improved nutritional intake in AD patients (Koss & Gilmore, 1998). An important further finding of Koss and Gilmore was that the environmental manipulation decreased agitated nighttime behavior (“sundowning”) in this sample of patients.

There has been substantial interest in more general modification of the visual environment of patients with AD in order to enhance the success of spatial navigation as well as safety. Dunne has described simple environmental modifications, room by room, that are based on empirical research on visual and visuospatial dysfunction in AD, with an emphasis on color discrimination and contrast sensitivity. This review is particular helpful as it is written as a practical guide for the lay reader (Dunne, 2004).

Pharmacological interventions

Although the cholinergic hypothesis has been driving research studies of AD for many years, little attention has been paid to the cholinergic system in primary visual areas until relatively recently. Ikonomovic and colleagues examined choline...
Visuospatial Function in Alzheimer’s Disease and Related Disorders

Acetyltransferase (ChAT) activity in the primary visual cortex of the brains of 54 individuals with and without AD who had been enrolled in the longitudinal Religious Orders Study, who had had clinical examination within 12 months of death (Ikonomovic et al., 2005). The AD brains showed significantly less ChAT activity in this region than did brains from those with no or mild cognitive impairment. The amount of ChAT in primary visual cortex correlated significantly with the group’s overall mental status as indexed by the Mini-Mental State Examination (MMSE), even when restricting AD group membership to those with only mild to moderate symptoms. As well, there was a trend for ChAT activity to correlate with an index of visuospatial ability (z score of Standard Progressive Matrices and Standard Line Orientation). The authors interpreted their results to mean that ChAT activity in primary visual cortex not only affects visuospatial function but

**Figure 15.4** Food and liquid intake was measured under baseline and post-intervention conditions using white background (luminance 45.0 fl) and under the intervention condition using high-contrast red background (luminance 7.1 fl). Mean percent food (top) and liquid (bottom) intake is shown for the baseline, intervention, and post-intervention conditions for lunch (left) and supper (right). Error bars represent the standard error of the mean for each condition.

also might interfere with the integration of visual processing to affect global cognition.

Some studies indicate the usefulness of cholinergic treatment, such as cholinesterase inhibitors, in the preservation of higher order visuospatial function in AD (clock drawing) (Almkvist et al., 2004; Fukui & Taguchi, 2005) and in improvement of performance of healthy older adults on tasks with significant visual scanning demands (tangled lines, Symbol Digit Substitution) (Wezenberg et al., 2005).

**Visuospatial Dysfunction Arising from Conditions Other Than AD**

**Dementia with Lewy bodies**

The principal dementing disorder besides AD that is associated with visuospatial impairment is Dementia with Lewy bodies (DLB). Whereas significant visual and visuospatial impairment as a prominent presenting feature is relatively rare in AD, such presentation is common in DLB. Pertinent symptoms of DLB include visual hallucinations, agnosia, delusional misidentification, and constructional impairments (Geldmacher, 2003; Kao et al., 2009; Stavitsky et al., 2006). Holroyd has effectively made the point that despite shared features such as visual hallucinations that can make differential diagnosis difficult, AD and DLB are likely distinct disorders (Holroyd, 2004).

Most studies of visual and spatial abilities in DLB provide an AD control group and regularly find that patients with AD outperform those with DLB. Developing latent constructs of verbal memory and visuospatial abilities from a comprehensive neuropsychological assessment, Johnson and colleagues found that patients with AD ($n=66$) performed more poorly than did patients with DLB ($n=9$) on verbal memory, whereas the opposite pattern prevailed for visuospatial ability. DLB that was co-morbid with AD, in 57 patients, was associated with poor visuospatial ability specifically (Johnson et al., 2005). In regard to spatial tests, DLB patients have been reported to perform more poorly on constructional praxis (Ala et al., 2001; Guidi et al., 2006; Stavitsky et al., 2006), size and form discrimination, identification of overlapping figures (Mori et al., 2000), and visual counting (Guidi et al., 2006; Mori et al., 2000). Those with DLB who also had visual hallucinations were especially impaired on the visuoperceptual tasks (Mori et al., 2000). These findings are consistent with AD–DLB differences in regional cerebral blood flow (Colloby et al., 2002). The latter study showed that a DLB group exhibited hypoperfusion relative to an AD group in primary visual and visual association cortices and parietal cortex (Brodmann areas 17, 18, and 7, respectively). Relative to a healthy control group, temporal perfusion deficits were seen only in AD, occipito-parietal deficits only in DLB, and frontal and parietal hypoperfusion in both groups. The importance of examining visuospatial function is underscored by a retrospective study that reported that deficits in this domain predicted the rate of cognitive decline in 22...
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autopsy-confirmed cases of DLB but not in AD alone (44 cases). Specifically, poor baseline performance on visuospatial tests (Block Design, Clock Drawing Copy) was associated with more rapid cognitive decline as well as with visual hallucinations (Hamilton et al., 2008).

One study has compared visuospatial performance across patients with three disorders that share the neuropathological feature of α-synuclein immunoreactivity: DLB, Parkinson’s disease, and multiple system atrophy (MSA) (Kao et al., 2009). All participants in this study scored 23 or higher on the MMSE. The DLB and MSA groups performed significantly more poorly than those with PD on copying a complex figure, and the DLB group was additionally significantly worse than the others on a number location task.

Parkinson’s disease

Parkinson’s disease (PD) is related to DLB in that Lewy bodies are present in both disorders. Whereas in DLB these pathological entities appear in the subcortex and cortex, in PD they are mainly restricted to the subcortex. There appears to be much overlap in symptoms between DLB and PD with dementia, the criterion for differential diagnosis being whether or not motor symptoms were the presenting symptom, as they are in PD. Accordingly, one might expect similar cognitive profiles in the two disorders, including the presence of visual and visuospatial impairments. This is indeed what is found. PD is associated with multiple visual and spatial impairments, in demented patients and in those without dementia. Because the PD literature is extensive and the issue of differential diagnosis vis-à-vis AD is not as prominent as it is for vascular dementia and frontotemporal dementia, the present chapter has concentrated on the non-PD disorders. Reviews of the visual and spatial literature in PD appear in Cronin-Golomb (2010) and Cronin-Golomb and Amick (2001), with specific findings reported in a number of papers on vision and visuospatial function, including their relation to participant characteristics such as side of disease onset and gender (e.g., Amick et al., 2006; Clark et al., 2008 and 2010; Davidsdottir et al., 2005; Davidsdottir et al., 2008; Miller and Cronin-Golomb, 2010; Schendan et al., 2009; Young et al., 2010) as well as their relation to important daily functions such as driving (Uc, Rizzo, Anderson et al., 2009; Uc, Rizzo, Johnson et al., 2009). A neuroimaging study has linked reduction in gray matter in posterior cortices (temporal, parietal, occipital) to impaired performance on visuospatial and visuoperceptual measures (Pereira et al., 2009).

Vascular dementia

Less work has been done in the study of vascular and frontotemporal dementia than in DLB, particularly in comparison with AD. Moretti and colleagues examined clock
drawing in a large sample of individuals with subcortical vascular dementia \( (n = 144) \) or AD \( (n = 150) \) (Moretti et al., 2005). The vascular group performed more poorly than did the AD group at baseline, and declined further over a 24-month period. The clock-drawing score correlated with performance on visuospatial measures, especially right–left discrimination, as well as on measures of executive function (verbal fluency). It is noteworthy that the patient group included individuals with only subcortical dementia without apparent infarcts in strategic cortical areas responsible for visuospatial abilities. As already described above, Kitabayashi and colleagues conducted a qualitative analysis of clock-drawing errors and found that patients with vascular dementia made more spatial and planning errors than did patients with AD (Kitabayashi et al., 2001).

**Frontotemporal dementia**

Frontotemporal dementia (FTD) is usually characterized by preservation of visuospatial abilities relative to what is commonly seen in AD. Chow and colleagues examined annualized rate of decline in both groups on subtests of the MMSE (Chow et al., 2006). They found that whereas the FTD group declined more quickly on the language subtest, the AD group showed accelerated decline on the visuospatial subtest (figure copy). The results accorded with practiced criteria for differential diagnosis of FTD and AD. As noted above, Blair and colleagues (2006) performed a qualitative assessment of clock drawing and found that a group with FTD committed fewer spatial errors as well as fewer stimulus-bound responses, conceptual deficits, and planning errors than did a group with AD.

**Summary**

Visuospatial dysfunction in AD is reflected in perceptual impairments as well as in deficits in higher order aspects of spatial orientation and navigation. In AD as it typically presents, visuospatial difficulties are revealed through behavioral assessments using standard neuropsychological measures and by newer tools made available by cognitive neuroscience. Neuroimaging has provided complementary findings, extending our knowledge of the relation of visuospatial behavior to particular brain areas and systems, including the possibility of compensatory mechanisms in AD relative to healthy aging.

Current studies focus not only on the phenomenology of visuospatial dysfunction but also on its sources. In regard to stimulus salience, there are some studies on aspects of stimulus novelty and incongruity as well as on emotional arousal, and there is considerable room for more work in this area. A stronger research focus in recent years is on lower level perceptual components of the stimulus, focusing either on overall visual input (e.g., contrast sensitivity, motion perception) or on actual stimulus features, especially in relation to visual search and spatial cuing. Eye-
movement recording is another technique that is finding increasing use in studies of spatial function in AD, with reports of abnormal search patterns being related to general spatial abilities. An important further point of entry to understanding visuospatial problems is through study of patients with the visual variant of AD. The exceptionally severe visual and spatial disorders of this subset of patients provide more broadly relevant information on regional pathological change and its behavioral consequences. Identifying the sources of spatial dysfunction is of great importance, as it leads us to consider rational environmental and pharmacological interventions targeting one or more of the causes of impairment. Finally, it is useful to study visuospatial dysfunction in disorders besides AD, as such study helps us to narrow our hypotheses about the most likely candidate brain regions and consequent treatment strategies. Whereas there is growing interest in assessment of dementia with Lewy bodies and Parkinson’s disease, a great deal more work needs to be done in the study of frontotemporal dementia, vascular dementia, and other dementing disorders.

Despite the need for more research, the current emphases on new assessment techniques, identifying the specific sources of visual, perceptual and spatial impairments, and studying the visual variant of AD and related disorders hold promise for enhancing our understanding of visuospatial dysfunction and in developing effective interventions to improve the quality of life of individuals with AD.

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References


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