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Visual Cognition in Alzheimer's Disease and Its Functional Implications

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1. Introduction

Alzheimer's disease (AD) is a common form of neurodegeneration that entails a progressive breakdown of cognitive functions. Cognitive impairments commonly begin with noticeable difficulties in remembering recent events (Gold & Budson, 2008; Ally, Gold & Budson, 2009), as well as spatial disorientation (Duffy, Cushman & Kavcic, 2004) and semantic memory impairments (Milberg, McGlinchey-Berroth, Duncan & Higgins, 1999). As the disease progresses, AD also entails impairments to visual cognition, which encompasses processes that help us to understand what we see (Cronin-Golomb, 1995). The purpose of this chapter is to review recent progress towards understanding aspects of visual cognition in AD, including visual memory and visual attention, and then explore how this research can be applied to assist in the daily living of AD patients.

Humans normally rely tremendously on vision for interacting with the world. Therefore, there is a profound impact on everyday activities when visual impairments develop. For example, Perry and Hodges (2000) showed that measures of visuospatial functions, semantic memory, and attention correlated significantly with measures of daily living in patients with AD, but measures of episodic and verbal short-term memory did not. Further, impairments to visual attention and memory in patients with mild-to-moderate AD lead to poor performance in complex situations like driving (Rizzo, Sparks, McEvoy, Viamonte, Kellison & Vecera, 2009) and measures of financial responsibility (Sherod, Griffith, Copeland, Belue, Krzywanski et al., 2009). Finally, certain visual abilities, like assembling an image from its parts, deteriorate as AD progresses, providing a reliable means of tracking the progress of AD in a given patient (Paxton, Peavy, Jenkins, Rice, Heindel & Salmon, 2007). Changes in everyday visual abilities can be observed very early in the disease, even in patients with mild cognitive impairment (MCI), which is thought to be a precursor to AD (Farias, Mungas, Reed, Harvey et al., 2006). Together, these studies suggest that measurable visual impairments in AD are strongly related to deterioration in everyday activities.

Since the decline of visual abilities can have a very profound effect on daily living, a better understanding of AD-related changes to visual cognition, and the development of subsequent interventional strategies, promise to lead to improvements in patients' quality of life. This chapter will place an emphasis on visual short-term memory (VSTM) in patients with AD, which has only recently been investigated. We will first describe the basic process of VSTM and then review the changes known to occur in AD. Then, we will review the interaction between visual attention and VSTM in AD patients and indicate how these two

processes have sometimes been confounded with each other in the literature regarding AD patients. Finally, we will discuss possible functional interventions to improve daily living in AD patients based on findings in visual cognition.

2. Visual short-term memory

Visual memory is extremely important in normal daily functioning. Consider how one navigates a room during a sudden blackout or how one recalls the color of a pill he or she just ingested. More fundamentally, visual memory is crucial for one's basic understanding of the visual environment. Objects often become occluded, like when a person walks behind a tall bookshelf. Visual processing is also suppressed during saccadic eye movements, when one's eyes suddenly move from one position to another. The situations described above are discontinuous visual events: the bookshelf disrupts the image of a person in the former situation, and the saccadic suppression disrupts the image of the entire world in the latter. Such discontinuities introduce a problem of correspondence to the visual system. In the first situation, how do we know that the person walking behind the bookshelf is the same person that emerges from behind that bookshelf? In the second situation, the image of an object will project to different regions of the retina before and after the saccadic eye movement. Given that visual information is unavailable during saccadic suppression, how are the images matched across saccades? Both solutions require visual memory.

Several forms of visual memory are available to the visual system following the offset of a visual stimulus, including visible persistence, iconic memory and visual short-term memory (VSTM). Visible persistence refers to the subjective impression of an image remaining visible after it has offset. For example, lightning is only physically present for less than 100 milliseconds (ms), but we perceive it to last much longer. Iconic memory is a highly detailed representation of an image, but only lasts for 300 - 500 ms (Sperling, 1960). Unlike visible persistence, iconic memory does not necessarily involve an impression that the stimulus is still present (Coltheart, 1980; Irwin & Yeomans, 1991), and the information extracted from iconic memory has undergone some higher-level processing, such as rapid matching to long-term memory representations (Chun & Potter, 1995). Another form of memory is visual short-term memory. VSTM involves a less detailed representation of an image compared to iconic memory, but it can endure for up to nine seconds or longer (Phillips, 1974). In relation to models of cognition, VSTM is similar to the visuospatial sketchpad of Baddeley's multi-component model of working memory (Baddeley & Hitch, 1974).

Phillips (1974) first distinguished iconic memory from VSTM with a change detection task. A typical trial in this task entails presenting observers with a brief visual pattern, followed by a blank interval of a specified duration, and then another visual pattern. The observer's task is to report whether the two patterns are the same. It is assumed that the ability to detect whether a change has occurred is mediated by comparing the memory of the first pattern to the perception of the second pattern (Figure 1). Using this task, Phillips (1974) discovered that visual memory exhibited different properties depending on how much time intervened between the visual patterns. The early memory was related to iconic memory, and the late memory eventually became known as VSTM. These memories differed in two important ways. First, unlike iconic memory, VSTM is not tied to the retinotopic region upon which the image was projected. Second, VSTM is resistant to backward masking, which is erasure that could occur due to visual stimulation occurring after a stimulus has

been encoded in memory. In contrast, iconic memory is not resistant to backward masking, so it can be erased by subsequent visual stimulation.

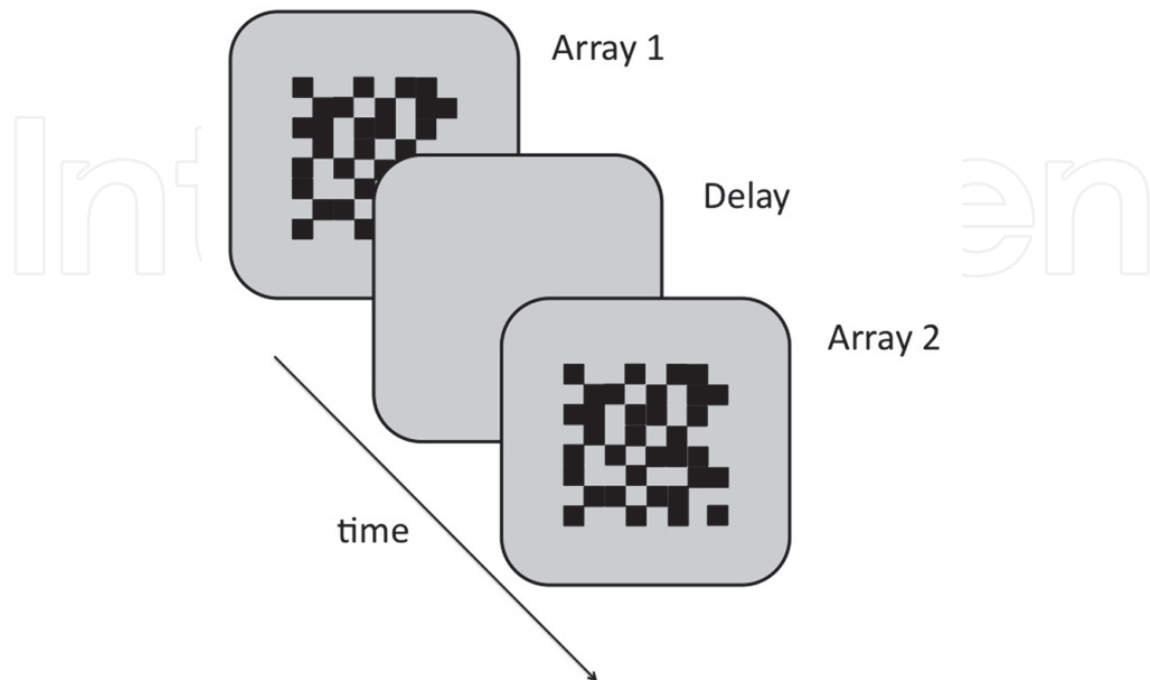


Fig. 1. One trial of a change detection task, adapted from Phillips (1974)

Two visual patterns appear sequentially and separated by a blank screen enduring for a certain amount of time. The ability to detect any difference between the patterns is assumed to depend on a form of memory that must span the delay interval. This delay could be between 100 – 500 ms to capture iconic memory. Delay intervals of longer than 500 ms could capture VSTM.

The properties of VSTM discovered by Phillips (1974) make it an ideal component in performing everyday activities. The finding that VSTM is not retinotopic suggests that it plays a role in resolving the correspondence of images across saccadic eye movements. Irwin (1991) showed that subjects were able to detect changes between the visual patterns, even when they made eye movements during the inter-pattern interval. Irwin's (1991) results closely resembled those of Phillips' (1974) study, suggesting that VSTM mediated the retention of visual information across saccadic eye movements. VSTM is also vital in correcting eye movement errors (Hollingworth, Richard & Luck, 2008; Hollingworth & Luck, 2009). Eye movements often land inaccurately and miss their targets, especially in crowded situations where one must perform a visual search and move the eyes frequently. Hollingworth and colleagues (2008) showed that the ability to correct saccadic eye movement errors was significantly slowed when subjects concurrently maintained information in VSTM, but not when they held information in verbal short-term memory. The use of VSTM in eye movements is also suggested by the finding that it is not susceptible to backward masking. Some theories propose that finding an object during visual search is facilitated by keeping the target in VSTM (Desimone & Duncan, 1995). It would then be important that contents of VSTM are not easily erased as the eyes land on different objects in the scene during the search.

The differing properties of iconic memory and VSTM suggest a possible transformation of information between the two systems. This transformation of information is referred to as consolidation (Chun, 1997; Jolicoeur & Dell'Acqua, 1998). Consolidation of an item into short-term memory is cognitively demanding, so that the performance of other tasks is delayed until it concludes (Jolicoeur & Dell'Acqua, 1998). The time that is required for consolidation to conclude depends on the amount of information being transitioned between iconic memory and VSTM (Vogel, Woodman & Luck, 2006), as well as difficulties in target identification caused by low-level factors, such as backward masking (Seiffert & Di Lollo, 1997).

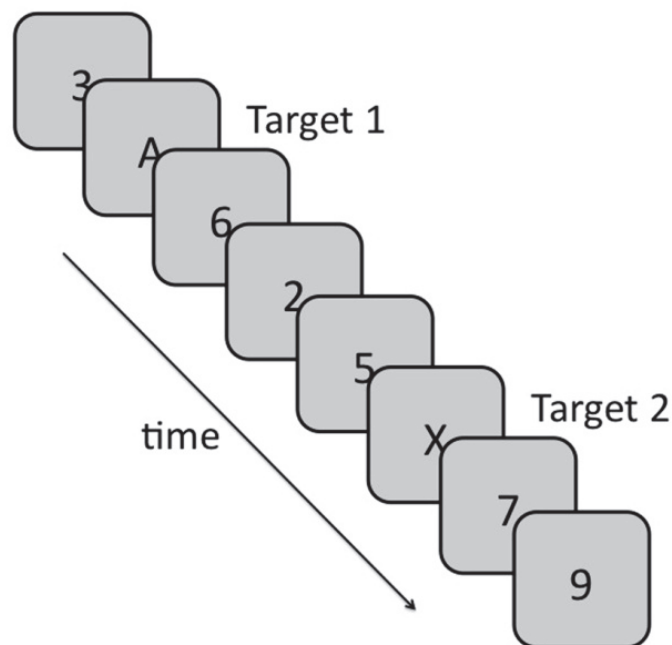


Fig. 2. One trial of a target discrimination task using RSVP.

A schematic of a typical multiple target discrimination task using rapid serial visual presentation (RSVP). The stimuli are typically presented at a rate of 100 ms per item, although this varies across studies. The task is to report the identities of items belonging to a target category, in this case letters. The attentional blink refers to the difficulty of reporting the second target if it appears too closely to the first target in the sequence. However, accuracy of reporting the second target is often high when it immediately follows the first, a phenomenon called “Lag-1 sparing” (Chun & Potter, 1995).

One paradigm that nicely illustrates the consolidation process is multiple target discrimination during a rapid serial visual presentation (RSVP; see Figure 2). In this task, participants view several items in rapid succession, and are required to identify two items belonging to a specific target category, such as letters appearing among digits. One well-known phenomenon that occurs in this paradigm is the attentional blink (Raymond, Shapiro & Arnell, 1992). When participants correctly identify the first target, they are often impaired at identifying the second one if it follows the first target too closely in the sequence. It is thought that the processing of the first target delays the processing of other incoming

information. If the second target falls within this window of time, it cannot be reported. The processing during the attentional blink is thought to include the consolidation of the first target from iconic memory to VSTM (Chun & Potter, 1995). The actual processing of the first target may entail binding its features together as it is encoded in VSTM (Chun, 1997). Together, visible persistence, iconic memory, and consolidation can be conceptualized as progressive stages of encoding information into VSTM. A rough schematic of this process is shown in Figure 3.

What determines the limit of VSTM storage capacity? Using change detection tasks, Luck and Vogel (1997) found similar VSTM capacity when memorized items differed from each other by a single feature, as well as when the items differed from each other by a specific conjunction of color and orientation. In other words, they found that change detection of conjunctions was just as good as that of basic features. This result showed that VSTM capacity was not defined by the total amount of differing information available to the observer. Instead, the basic unit of VSTM is not individual features, but rather integrated objects. This may have occurred because each item underwent processing that integrated their component features. Another important result was that VSTM capacity had an upper limit of about four objects, which resembled the capacity of several short-term memory studies (Cowan, 2001).

To illustrate this finding, imagine that a person with a VSTM capacity of 2 objects must remember to take two pills. This person would have the same capability to remember to take two red and blue circular pills, and to take a red circular pill and blue cylindrical pill. In the first case, there are only two pieces of differing information, being the colors. In the second case, there are four pieces of differing information, being the colors and the shapes. This person would have adequate memory in both cases since they both involve only two objects, which fits the person's VSTM capacity. With some modification, Luck and Vogel's (1997) results have been replicated many times (Vogel, Woodman & Luck, 2001; Olson & Jiang, 2002; Xu, 2002; Alvarez & Cavanagh, 2004; although see Wilken & Ma, 2004).

However, an important debate in the VSTM literature has regarded exactly how objects are represented in VSTM. Luck and Vogel (1997) proposed that the objects of VSTM were fully integrated, such that no other process but VSTM storage was necessary to maintain them. Alternatively, Wheeler and Treisman (2002) proposed that sustained visual attention was necessary to keep the features of each object bound together. Treisman had shown years earlier that visual attention plays a similar role in visual perception (Treisman & Gelade, 1980), thus providing a parsimonious theory of how objects are represented in visual cognition: in both perception and memory, objects are comprised of separate features bound together by visual attention. Studies have examined Wheeler and Treisman's (2002) binding account of VSTM by having participants perform a visual attention task during VSTM retention. The binding account predicts that, in such conditions, VSTM for features would be unaffected by the intervening task, but VSTM for conjunctions would be profoundly impaired since visual attention would be occupied with the intervening task. Many studies failed to show any differences in VSTM for features and conjunctions (Yeh, Yang & Chun, 2005; Allen, Baddeley & Hitch, 2006; Johnson, Hollingworth & Luck, 2008). However, when Fougny and Marois (2008) used a multiple-object tracking task during VSTM maintenance, which places heavier demand on visual attention than the previous studies, they showed significant impairments in VSTM for conjunctions, but not for features. In further support for a bound feature-based representation in VSTM, it has been shown that participants can selectively encode specific features of an object in memory (Woodman & Vogel, 2008).

Furthermore, participants can selectively update a specific feature of an object in VSTM, while leaving the other features of that object unchanged (Ko & Seiffert, 2009).

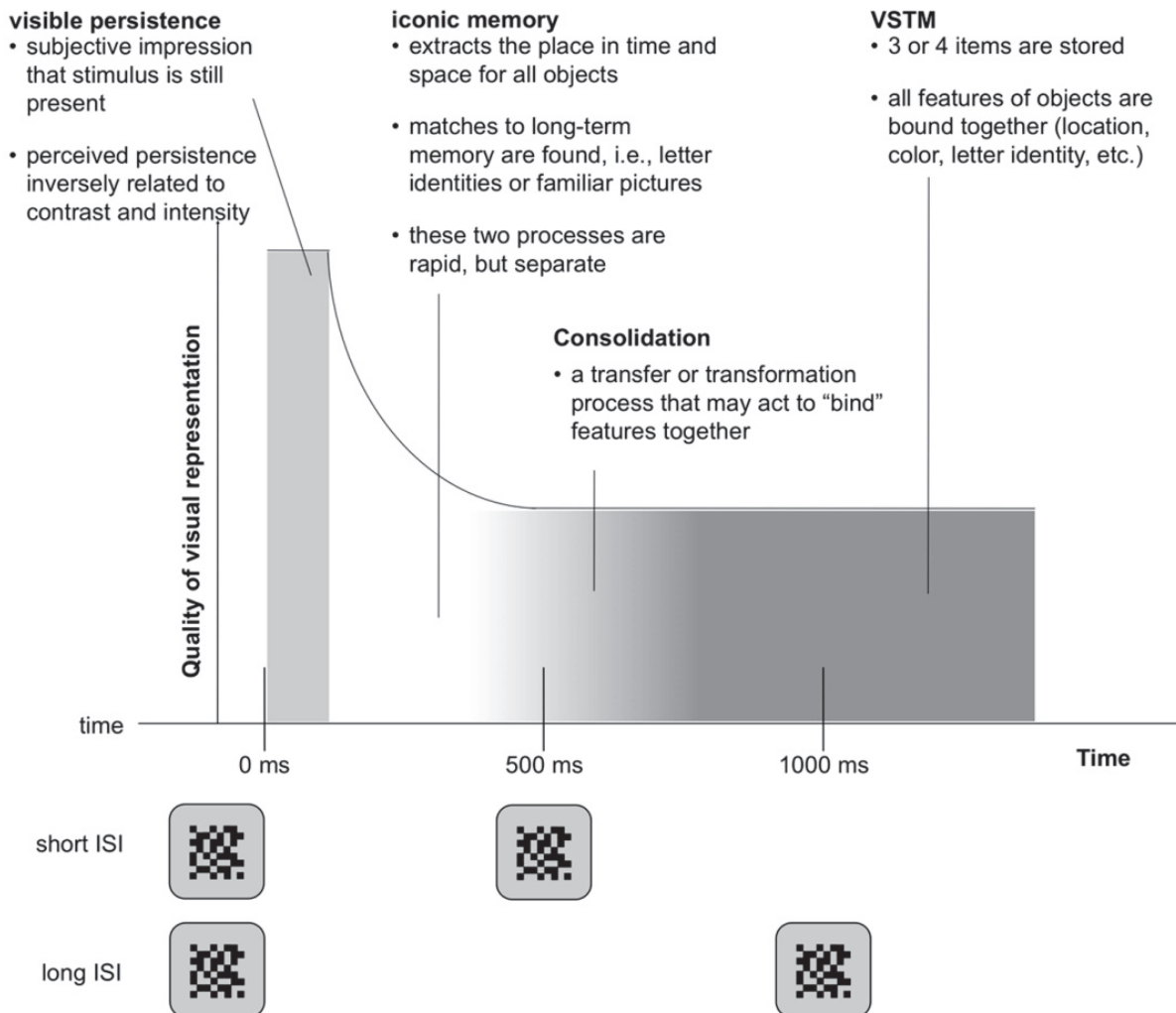


Fig. 3. A schematic of visual memory stages.

The y-axis depicts a vague concept of “quality”, indicating how similar the memory representation is to the original perceptual representation. This visual quality is plotted as a function of time on the x-axis. In visible persistence, quality is high because the subjective percept is identical to the stimulus. Iconic memory marks the exponential decay of visual quality over time. The gradient between the iconic memory stage (white) and VSTM stage (dark gray) represents the time of consolidation. The decay in quality plateaus as the information is being consolidated into VSTM and then there is no further loss of information. This decay in visual quality trades off with the level of abstraction from the original stimulus, so by the time information is consolidated into VSTM, it is processed at a high-level. Below the x-axis, the stimuli for change detection are depicted as they would appear in time. This illustrates how manipulating the time interval between the two arrays captures different kinds of visual memory. It should be noted that this summary of findings is specific to change detection and RSVP methods. Other psychophysical methods, like method of adjustment, capture important details of VSTM not usually found by change detection (Zhang & Luck, 2008; Bays & Husain, 2009).

What are the neural correlates of VSTM? Studies using functional magnetic resonance imaging (fMRI) have related activity in the posterior parietal cortex to VSTM capacity (Todd & Marois, 2004). However, there may be multiple sites of neural representation related to VSTM. For example, different regions of the parietal cortex have been related to the number of items stored in VSTM and the visual complexity of the items (Xu & Chun, 2006). Recent studies using sensitive multivoxel pattern analyses have shown evidence that primary visual cortex and extrastriate areas are also involved in VSTM representation (Harrison & Tong, 2009; Serences, Ester, Vogel & Awh, 2009). Studies using electroencephalograms (EEG) have identified an event-related potential (ERP), recorded from posterior electrodes in the hemisphere contralateral to the stimulus, that modulates with VSTM capacity (Vogel & Machizawa, 2004). This ERP, called the contralateral delay activity (CDA), originates from activity recorded by posterior electrodes contralateral to the stimulus location. It emerges 200 ms after stimulus onset, and remains active during VSTM maintenance.

In summary, VSTM emerges from earlier stages of visual memory. Visual information is initially available in high resolution visual memories, including visible persistence and iconic memory. Visual information then must undergo a time-consuming, cognitively demanding process of transfer or transformation into VSTM, during a stage called consolidation. These early stages of visible persistence, iconic memory, and consolidation can be conceived of as progressive stages of VSTM encoding. Information is properly stored in VSTM, which exhibits three important properties:

1. It is not tied to the original retinotopic location of the perceptual image being stored.
2. It is resistant to incoming visual stimulation, so one can hold information in VSTM while looking at other things.
3. VSTM stores relatively complex objects; the mechanism by which this is possible may be sustained visual attention that binds the features of each object together.

These properties indicate that VSTM is critical in common tasks that involve frequent eye movements around a scene, such as visual search. VSTM enables people to match images across saccades, correct saccadic eye movement errors, and keep a target item in memory during a search process. Understanding this system in AD patients is important when considering changes to visual cognition associated with the disease. In the next section, we will examine what is known about visual memory and VSTM in AD patients.

3. VSTM in Alzheimer's disease

There has been relatively little direct investigation of VSTM in patients with AD. However, examining VSTM in AD patients is potentially important for several reasons. First, methods that tap into VSTM processing are relatively simple, sensitive, and inexpensive, providing a means to detect early signs of AD-related changes to VSTM. Second, AD may also involve specific changes to VSTM that can be measured to distinguish AD from other neurodegenerative diseases and memory disorders. Finally, understanding changes in VSTM in patients with AD can help lay the groundwork for developing meaningful behavioral strategies and interventions that can be easily implemented in the clinic or home. In this next section of the chapter, we will first review early research on visual memory in AD and its relationship with visual perception and long-term memory. Then, we will review more recent research on VSTM in AD, and emphasize AD-related changes to VSTM encoding and storage.

Various techniques in neuroscience have revealed deficits in functions that may overlap with VSTM in AD patients. fMRI has shown that when encoding visual information, medial

temporal activity that is typically observed in normal adults is absent in patients with AD (Kato, Knopman & Liu, 2001). However, this finding may be specific to encoding information into long-term memory. AD-related differences in neural activity during working memory may suggest that AD patients use different cognitive strategies than controls to accomplish such tasks (Yetkin, Rosenberg, Weiner, Purdy & Cullum, 2006). Animal models of AD using non-human primates have shown that lesions to the cholinergic and noradrenergic systems impair VSTM (Dudkin, Chueva, Makarov, Bich & Roer, 2005), suggesting that deficits in visual memory can be related to pathology in areas such as the nucleus basalis of Meynert and the locus coeruleus.

Early studies suggested that AD-related impairments in visual memory were independent of problems with visual perception. Grossi, Becker, Smith and Trojano (1993) showed that AD patients had impaired short-term memory for movement patterns and visual patterns, without showing impairments of visual perception. Similarly, Trojano, Chiacchio, De Luca and Grossi (1994) demonstrated that AD patients had impaired short-term memory for abstract visual patterns, while exhibiting no deficits in visual perception. More recently, Rizzo and colleagues (2000) showed that while AD patients exhibited intact performance on tasks measuring low-level perceptual functions like motion discrimination and visual acuity, they were impaired on higher-level visual processes, such as divided attention, selective attention, and visual memory. Together, these early findings suggested that patients with AD have impairments in VSTM, while their visual perception remains intact.

However, not all low-level perceptual functions are left intact by AD. Rizzo et al. (2000) showed that contrast sensitivity was impaired in AD patients. This perceptual impairment in AD has profound effects on higher-level visual tasks. Supporting this idea, Cronin-Golomb and colleagues (2007) showed that enhancing the contrast of visual stimuli facilitated the performance of AD patients to match that of healthy older adults on several tasks of high-level visual cognition. This finding is remarkable, because it indicates a simple solution to significant visual problems in AD patients. Interestingly, although the enhanced stimuli aided AD patients on several visual-based tasks, it did not help them on the Raven's Progressive Matrices task. This task requires viewing a patterned sequence of abstract images and choosing another abstract image to complete the sequence. Their impairment on the matrix task was remarkable, because enhanced contrast did benefit them on a face-matching task that was arguably equal in task demands – both required multiple fixations, and both entailed a form of matching a target to a sample. In other words, both had similar oculomotor demands, and both likely required visual memory. The crucial difference between the tasks could have been that the abstract visual patterns contained no semantic information, in contrast to the stimuli in the face-matching task. This suggests that compensating for low-level impairments in contrast sensitivity effectively enhances retention of images containing familiar semantic information but not images devoid of semantic content.

This idea is supported by results from Ally, Gold and Budson (2009), who showed that mild AD patients have a relatively preserved long-term memory for real-world pictures compared to memory for the verbal referents of those pictures. Pictures of real objects produce a great deal of semantic or conceptual activation, in addition to the rich amount of perceptual information that they contain. To follow-up on this finding, Ally, McKeever, Waring and Budson (2009) found that ERP components related to memorial familiarity were preserved in amnesic MCI patients when they memorized pictures, but were diminished when they memorized words. Familiarity can be rooted in the ease at which both perceptual

and conceptual information related to the test item is processed. Since MCI patients demonstrated intact familiarity for visual stimuli compared to verbal stimuli, Ally, McKeever, et al. (2009) suggested that implicit or stored visual representations were responsible for the increased familiarity and discrimination for pictures. Further, O'Connor and Ally (2010) found that recognition memory in amnesic MCI and mild AD patients was superior when the perceptual and conceptual aspects of studied items were preserved from study to test, compared to when only the conceptual aspects were preserved from study to test. Importantly, this advantage was much greater when the stimuli were pictures rather than words.

Together, these findings show that storing information as pictures leads to greater success of long-term memory retrieval in AD patients. This might stem from the rich retrieval cue provided by the combination of visual and semantic information in pictures compared to words alone. Another likely hypothesis is that neural regions dedicated to VSTM remain intact, allowing for storage of visual representations that can be used for subsequent retrieval. In support of this idea is evidence that similar neural regions are activated during retrieval from VSTM and visual long-term memory (Ranganath, Cohen, Dam & D'Esposito, 2004).

Direct investigation of AD-related changes in properties of VSTM has become more popular in the last decade. In an initial study, Vecera and Rizzo (2004) used change detection tasks to show that AD patients exhibit a decreased VSTM capacity. What is the root of this decreased VSTM capacity? Subsequent research has shown AD-related deficits in at least three important stages of the VSTM process. First, iconic memory decays much faster in patients with MCI compared to healthy controls. Second, the consolidation of information in VSTM may be impaired in AD patients. These first two findings suggest that the encoding of information into VSTM from earlier memory representations may be corrupted. Third, VSTM storage itself is changed in patients with AD. Specifically, AD patients appear to have a specific deficit in how features of objects in VSTM are bound together.

Lu, Nuese, Madigan and Doshier (2005) showed that patients with MCI exhibited much faster decay of iconic memory than healthy younger and older adult controls. In this particular visual task, the duration of iconic memory was calculated to be approximately 70 ms in patients with MCI, while younger and older adults showed durations of nearly 340 ms and 300 ms, respectively. This accelerated decay of iconic memory could potentially lead to fewer items being transferred to VSTM, especially as MCI patients develop AD.

In addition to iconic memory being shorter in duration for patients with very mild AD, the consolidation of information from iconic memory into VSTM appears to be somewhat impaired. Kavcic and Duffy (2003) showed that the attentional blink window was much more severe and longer enduring for AD patients than for healthy older adults. Furthermore, the authors noticed that AD patients tended to report the second target correctly while failing to identify the first target. This impairment was attenuated when 5 or more intervening distractors appeared between the first and second target. In other words, the identification of the second target seemed to retroactively mask identification of the first target, analogous to perceptual backward-masking effects. However, this effect was attentional in nature because it occurred between items belonging to the target category. This effect may stem from the same mechanism responsible for object substitution masking, a phenomenon thought to reflect the overwriting of one visual object by another (Enns & Di Lollo, 1997). An object may be susceptible to this overwriting if there is a failure to encode it into VSTM (Prime, Pluchino, Eimer, Dell'Acqua & Jolicoeur, 2010). Interestingly, this

alteration to the attentional blink may explain some results in a study directly examining VSTM in AD patients. Alescio-Lautier and colleagues (2007) had AD patients report any changes between a visual image in memory and three sequentially presented probe images. AD patients failed to detect changes in the first of the three probe images but successfully detected changes in the second and third image. This temporary failure to detect changes between the image in memory and a subsequent probe image is consistent with Kavcic and Duffy's (2003) finding of a prolonged attentional blink in AD.

The finding of AD-related changes to the attentional blink (Kavcic & Duffy, 2003) differs from the results of two studies with MCI patients. Perry and Hodges (2003) found that patients with MCI did not show alterations to the time-course of the attentional blink. Also, Lu et al. (2005) found that, although MCI patients have shortened duration of iconic memory, they have normal transfer of items from iconic memory into VSTM. Together, these results could reflect the natural course of AD, such that the consolidation process from iconic memory to VSTM is still intact in MCI patients but becomes corrupted once MCI patients develop into AD patients. Alternatively, they could reflect the methodological differences between the studies. For example, the stimuli used by Perry and Hodges (2003) and Lu et al. (2005) were spatially distributed, but the stimuli used by Kavcic and Duffy (2003) were all centrally presented. Subjects could therefore use the spatial pattern formed by multiple items as a memory cue (Jiang, Olson & Chun, 2000).

AD patients have also been shown to exhibit changes in VSTM storage. These studies suggest that AD patients do not have impaired VSTM storage per se, but rather have a specific problem in maintaining how features of objects are bound together. For example, Parra and colleagues (2009a) had AD patients and healthy older adults view visual arrays of multiple items. Each item was either distinguishable by a single feature, like color or shape, or by a specific conjunction of color and shape. Participants then provided a free recall of the items after the array was removed. AD patients did not differ from controls in their memory accuracy for features, but showed significantly worse accuracy for conjunctions. This suggested that short-term memory deficits in AD might not involve a decreased capacity per se, but a specific impairment in maintaining the relationship between the component features of each object. However, since the participants provided verbal reports, the authors did not claim that these short-term memory deficits were specifically visual.

Further studies from the same group have supported the idea that patients with AD have specific problems keeping information bound in VSTM. These results have practical applications, such as early detection of AD onset and distinguishing AD from other memory disorders. Parra et al. (2009b) measured VSTM for features and conjunctions in patients with familial AD caused by mutation of the presenilin-1 gene. Binding deficits were detected in patients with early onset AD, as well as asymptomatic carriers of the gene, when compared to non-carriers of the same families. This suggests that measuring a specific impairment in VSTM can be used as a means for detecting AD early in the course of the disease, perhaps prior to the onset of noticeable symptoms. Parra and colleagues (2010) also showed VSTM binding deficits to be specific to patients with AD compared to depressed patients, who also suffer from poor memory. The detection of VSTM binding deficits is more accurate than other binding problems in distinguishing AD patients from healthy older adults. Healthy older adults show deficits in binding features in long-term memory (Chalfonte & Johnson, 1996), but AD patients show this deficit as well (Dierckx, Engelborghs, De, et al., 2007; Swainson, Hodges, Galton et al., 2001). However, healthy older adults do not show deficits in VSTM bindings (Brockmole, Parra, Della Sala, & Logie, 2008; Parra et al., 2009c).

Together, these studies show that deficits in VSTM binding could better distinguish AD from healthy aging compared to other impairments in memory.

In summary, important findings have begun to reveal AD-related changes in certain VSTM processes. Changes to visual encoding can be detected early in the course of AD, as suggested by shortened iconic memory in MCI patients. While consolidation may remain intact in MCI, it becomes corrupted as MCI patients convert into patients with AD. As information is consolidated from iconic memory to VSTM, AD patients have trouble preventing incoming information from interfering with representations already in VSTM, sometimes resulting in the overwriting of information in VSTM. This impairment would subsequently interfere with normal cognitive processes, such as making correspondence between images across eye movements. Imagine that, in such a situation, rather than being able to compare the images across an eye movement, the new information acquired once the eye has landed subsequently erases the memory of information acquired before the saccade. This would greatly impair common activities, like trying to find one's wallet on a crowded countertop.

Finally, the storage of information in VSTM is changed in AD. AD patients have a specific difficulty retaining the relationship between features of objects in VSTM. For example, if a patient kept the image of two parking lot symbols in VSTM, such as a red square and blue oval, a potential problem might be that he or she could falsely recognize a blue square or red oval. It is important to note that this finding indicates information in VSTM is still preserved in AD patients. The key to helping patients could be to adapt their environment according to this preservation.

4. Visual attention and memory in Alzheimer's disease

Attention is considered to be involved in the high-level processing of information in a manner that is limited in capacity (Pashler, 1998). This capacity limitation has many consequences, including the processing of some information at the cost of neglecting other information (James, 1890) and the inability to adequately perform two tasks simultaneously (Pashler, 1994). Visual attention refers to when an aspect of vision is the basis of this capacity limitation. For example, visual attention may select and process a small region of visual space at the cost of processing surrounding regions. In this section, we will examine the relationship between visual attention and VSTM in AD. Although some researchers consider visual attention and VSTM to be synonymous (Cowan, 2001), some research suggests that there is only a partial overlap in these processes and at least some important distinction exists between them (Fougnie & Marois, 2006; Ko & Seiffert, 2006). It is important to understand this relationship in the context of AD, because AD-related impairments in visual attention could actually be rooted in changes to VSTM (Vecera & Rizzo, 2004). For example, one early study by Simone and Baylis (1997) suggested that AD-related problems with selective attention could be significantly alleviated once memory demands had been removed. However, removing such demands did not relieve all attention-related impairments.

AD patients have long been known to have disturbances in visual attention. Extensive reviews on this topic have been recently published (Vecera & Rizzo, 2004; Iachini, Iavarone, Senese Ruotolo & Ruggiero, 2009; Tales & Porter, 2009), so this section will not provide an exhaustive review. Instead, we will examine whether AD-related problems in visual attention could be re-interpreted as problems with VSTM, as first proposed by Vecera and

Rizzo (2004), prior to much of the research conducted on VSTM in AD patients. We will show that, although there is some evidence to support Vecera and Rizzo's (2004) theory in regards to selective attention, visual search, and eye movements, there is also evidence to support the opposing theory – problems with VSTM could be rooted in deficits of visual attention.

Selective attention processes must enhance or facilitate relevant information while also filtering or inhibiting irrelevant information (Neill, 1977). Priming measures have been used to examine selective attention in AD patients. In these studies, participants attend to one stimulus while concurrently ignoring another stimulus. Effects of this selection can be observed by subsequently measuring responses to a quality of the attended or ignored stimulus, such as a color, a location, or a name. Faster responses, or positive priming, are predicted to occur for a feature of the attended stimulus, indicating facilitated processing of that stimulus. Slower responses, or negative priming (Tipper, 1985), are predicted to occur for features of the ignored stimulus, indicating inhibited processing of that stimulus. Research using priming has suggested that AD patients have trouble inhibiting irrelevant information (for a review, see Amieva Phillips, Della Sala & Henry, 2004). For example, Grande, McGlinchey-Berroth, Milberg and D'Esposito (1996) demonstrated that AD patients not only failed to suppress information to be ignored, but that such information was actually enhanced, as if it were attended. Similar studies have shown that AD patients fail to suppress the visual image of an object that should have been ignored (Sullivan, Faust & Balota, 1995; Amieva, Lafont, Auriacombe, Le Carret, Dartigues et al., 2002). Together, these studies suggest that AD patients are impaired at inhibiting irrelevant information. Impaired filtering of irrelevant information becomes particularly problematic for AD patients because once they attend to something like a spatial location, they have trouble disengaging from that location (Parasuraman, Greenwood, Haxby & Grady, 1992), especially if their attention has been captured in an exogenous manner (Tales, Muir, Bayer & Snowden, 2002).

Visual selective attention to spatial locations in AD patients has also been investigated with priming. Vaughan, Hughes, Jones, Woods and Tipper (2006) presented participants with two ovals of different sizes that could each appear in one of four possible locations in space and instructed them to attend to the location occupied by the larger oval. AD patients did not behave differently for ignored locations and baseline conditions, suggesting that they failed to inhibit ignored locations. In contrast, Ko, Higgins, Kilduff, Milberg and McGlinchey (2005) used a similar task and showed that both the facilitative and inhibitive components of spatial attention were intact in AD patients. One reason for this discrepancy may stem from task-related differences across the studies. Vaughan et al.'s (2006) targets and distractors were defined by a rule: the larger stimulus was the target, so that the appearance of the target could have changed across trials. In contrast, Ko et al. (2005) used the same visual identities for targets and distractors throughout the experiment, thereby allowing participants to habituate to their appearance. Could this difference account for intact selective attention in AD patients? Recently, Fernandez-Duque and Black (2008) also demonstrated intact selective attention in AD patients, but they found severe performance costs in conditions when the targets and distractors could switch identities across trials. In support of this, Langley, Overmier, Knopman and Prod'Homme (1998) also found intact selective attention when the identities and locations of targets and distractors were kept constant. Together, these results suggest that habituation may be important in preserving visual selective attention in AD. Dynamically changing the appearance of what is to be attended or ignored, and therefore requiring a memory system like VSTM, could severely impair AD patients in ways that obscure the benefits of selective attention.

The shifting of visual attention, as assessed by visual search, could also be interpreted as a VSTM deficit in AD patients. Many studies of visual search in AD have been conducted under the framework of Treisman and Gelade's (1980) feature integration theory, whereby search for targets differing from distractors by a single feature requires little attention because they can be found primarily by bottom-up processes. However, search for targets differing by distractors by a conjunction of features requires attention to bind the features of a single object in order to discriminate targets from distractors. Foster, Behrmann and Stuss (1999) showed that AD patients were impaired at finding targets defined by conjunctions compared to those defined by single features, especially as set-size increased, indicating an attentional binding problem during search. Tales, Butler, Fossey, Gilchrist, Jones and Troscianko (2002) also showed that AD patients were selectively impaired at conjunction search, even though feature search was equated for attentional demands. More recently, AD patients were shown to have increased pupil dilation during visual search for conjunctions rather than features, suggesting increased effort during such conditions (Porter, Leonards, Wilcock, Haworth, Troscianko & Tales, 2010). Together, these results show that AD patients have specific impairments search for objects defined by conjunctions of features rather than single features.

Some neural models of visual search require VSTM for the control of attention, such as biased competition theory (Desimone & Duncan, 1995). This model proposes that visual search for a target requires a "template" of that target be stored in VSTM during the search. This target-to-template theory of visual search is supported by behavioral evidence (Soto, Heinke, Humphreys & Blanco, 2005; Soto, Hodsoll, Rothshtein & Humphreys, 2008; Olivers, Meijer & Theeuwes, 2006) and electrophysiological evidence (Woodman & Arita, 2011). This may help to explain AD patients' specific impairment at conjunction searches. It is possible that conjunction search is supported by attentional binding of perceptual information (Treisman & Gelade, 1980), as well as a memory template for the conjunction target. AD patients may be missing the search template, since they have a specific impairment at maintaining feature bindings in memory (Parra et al., 2009a, 2009b). This would leave search for conjunctions possible for AD patients, but severely impaired compared to the healthy older adults.

Like visual search, eye movements provide a measure of spatial shifting in attention, albeit in an overt manner. Early research suggested that AD patients have abnormal smooth pursuit eye movements (Hutton, 1985). Bylsma and colleagues (1995) found that AD patients also made saccadic eye movements when they were supposed to fixate, and the increase in these intrusive saccades correlated with lower scores on the Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975). AD patients also exhibit neural changes with abnormal eye movement behavior. Using fMRI, Thulborn, Martin and Voyvodic (2000) showed that right-parietal dominance during a saccadic eye movement task was reversed to left-parietal dominance in AD patients.

Some research has shown that AD patients show relatively intact performance when asked to make saccadic eye movements towards a visual target, or pro-saccades, but they are error-prone when instructed to make a saccade away from a target, or an anti-saccades (Crawford, Higham, Renvoize, Patel, Dale et al., 2005; Boxer, Garbutt, Rankin, Hellmuth, Neuhaus et al., 2006; Kaufman, Pratt, Levine & Black, 2010). AD patients make fewer spontaneous self-corrections after anti-saccade errors, while other types of dementia patients readily make corrections as well as normals (Garbutt, Matlin, Hellmuth, Schenk, Johnson et al., 2007). This is consistent with the finding that AD patients have trouble disengaging after

being exogenously drawn towards a location (Tales, Muir et al., 2002). Together, these results may reflect impairments in inhibiting overt attention.

Another possibility regarding antisaccades in AD is that their high error rate reflects a working memory deficit. For example, AD patients could have simply forgotten the task instruction to saccade away from the target rather than saccade to it. Performance on antisaccade tasks have been linked to working memory (Mitchell, Macrae & Gilchrist, 2002) and measures of working memory have correlated with antisaccade performance in AD (Boxer et al., 2006). However, this theory remains controversial (Crawford, Parker, Solis-Trapela & Mayes, 2011). Oddly, there is no research on memory-guided saccadic eye movements in AD to our knowledge. In this paradigm, a participant must hold target location in VSTM prior to making a saccade toward that location. VSTM is not only important in guiding such saccades (Desimone & Duncan, 1995), but also in correcting them in case of errors (Hollingworth et al., 2008). The memory-guided saccade task has been shown to be a useful biomarker for Huntington's disease (Blehker, Weaver, Cai, Hui, Marshall et al., 2009). Exploring memory-guided saccades in AD would provide a better understanding of how VSTM could guide overt shifts of attention.

In contrast to Vecera and Rizzo's (2004) theory that AD-related attentional impairments actually stem from deficits in VSTM, a more recent study has suggested the opposite: deficits in VSTM could be traced to an underlying deficit in visual attention. Alescio-Lautier, Michel, Herrera, Elahmadi, Chambon et al. (2007) examined VSTM in patients with probable AD and MCI. In their task, participants memorized multiple real-world objects presented in one image, followed by a variable delay, and then three probe images that could be either the same or different than the sample image. AD patients showed impaired task performance at 30-second delay intervals, but strangely, these impairments were restricted to the first probe image, and not the second or third probe. High performance on the later images suggested that VSTM is intact in AD. The authors speculated that the AD patients' performance suffered during the first probe due to an attentional blink (as discussed above; see Kavcic & Duffy, 2003). In contrast, AD patients' performance on a task requiring only memory for spatial location decreased as the time interval increased. Together, these results suggest that VSTM for appearance may stem from an attentional deficit, while VSTM for spatial locations stem from a memory deficit. The fact that the stimuli were real-world images may also be important; as discussed above, memory tests using real-world images have shown high rates of successful retrieval in AD patients (Ally et al., 2009a, 2009b; O'Connor & Ally, 2010).

Additionally, the finding that AD patients have a specific deficit in maintaining feature bindings in VSTM (Parra et al., 2009a; 2009b) could be interpreted as a deficit of attention at its core. One prominent theory proposes that maintaining conjunctions in VSTM relies on sustained visual attention to keep the separate features of the conjunctions bound together (Wheeler & Treisman, 2002; Fougny & Marois, 2008). AD patients in the studies by Parra and colleagues may not have suffered from a memory failure per se, since they showed normal VSTM for features. Instead, they showed VSTM binding deficits because they lacked the attention to sustain those bindings.

Do these results imply a dissociation between AD patients with visual attention deficits and those with VSTM deficits? Research examining neurotransmitter systems suggests that this is a possibility. One hallmark of AD is the breakdown of the cholinergic system, which has profound effects on attention (Contestabile, 2010) and inhibiting the processing of irrelevant sensory stimuli (Ally, Jones, Cole & Budson, 2007). Studies have also shown acetylcholine to

play a role in working memory (Furey, Peitriini & Haxby, 2000). However, acetylcholine may only have similar effects on stages of memory that are shared by attention. Consistent with this, Bentley, Husain and Dolan (2004) found that pharmaceutically induced cholinergic enhancement increased activity in extrastriate regions while suppressing parietal activity during spatial attention and spatial memory encoding. However, this effect was absent during the spatial memory delay. This showed that acetylcholine has distinct effects on attention and memory. Importantly, Voytko and colleagues (1994) found deficits in visual attention, but not VSTM, after lesioning cholinergic neurons in crab-eating macaques. Together, these studies suggest that acetylcholine may play a specific role in visual attention, but not VSTM.

In contrast to results by Voytko et al. (1994), Dudkin and colleagues (2005) found that by lesioning both cholinergic and noradrenergic neurons in rhesus macaques, VSTM was impaired. Related to this finding, one theory proposes that dynamics of norepinephrine activity in the forebrain is the primary mechanism behind the attentional blink (Warren, Breuer, Kantner, Fiset, Blais & Masson, 2009), supporting the role of the noradrenergic system in VSTM encoding. Together, these results highlight the importance of understanding, not only cholinergic systems in AD, but also noradrenergic systems. AD has long been known to affect the noradrenergic system (Bondareff, Mountjoy, Roth, Rossor, Iversen et al., 1987). Besides the cognitive consequences, norepinephrine plays a mechanistic role in the pathology of AD. Recent work has shown that norepinephrine activity from the locus coeruleus is critical in clearing beta-amyloid plaques in the brain (Heneke et al., 2010). Together, these studies suggest that AD patients could be split into cognitive subtypes, some with more severe impairments in visual attention, and others with more severe impairments in VSTM, depending on how the pathology has affected specific neurotransmitter systems. However, this possibility has not been investigated to our knowledge. Possible research could include the use of pharmacological agents, such as donepezil (Rokem, Landau, Garg, Prinzmetal & Silver, 2010; Dickerson, 2010) and clonidine (Coull, Nobre & Frith, 2001) to manipulate levels of acetylcholine and norepinephrine, respectively, and observe the effects on visual attention and VSTM.

In summary, the literature indicates several areas of visual attention that could be recast as impairments with VSTM, including selective attention, visual search, and eye movement behavior. However, some findings in the VSTM literature could also be re-interpreted as impairments of visual attention. This possibly reflects the difficulty in teasing apart the effects of visual attention and memory. Since these processes are closely interrelated, it may be better to always consider both visual attention and VSTM in investigations of visual cognition in AD. Findings that could not link visual attention to problems of daily living may have ignored memory systems like VSTM (Liu, McDowd & Lin, 2004). In contrast, research that has integrated measures of visual attention and VSTM in formal computational models, such as Bundesen's Theory of Visual Attention (Bundesen, 1990) have had success in creating a more full picture of changes to visual cognition in AD (Bublak, Redel, Sorg, Kurz, Forstl et al., 2009; Redel, Bublak, Sorg, Kurz et al., 2010). Alternatively, the discrepant findings in visual attention and VSTM of AD patients may be rooted in distinct subtypes of AD. One possible reason for differences in patients could be how AD pathology affects different neurotransmitter systems, including those mediating acetylcholine and norepinephrine activity. This could possibly lead to differences in pharmacological treatments of AD, depending on the specific nature of changes to visual cognition.

5. Functional implications on daily living

A better understanding of visual cognition in AD patients potentially leads to inexpensive alterations of their visual environment that could prolong a high quality of patients' lives. In this section, we speculate on such alterations based on the known research. Understanding changes in visual processing in AD has been shown to be clearly effective. For example, Dunne, Nearing, Cipolloni and Cronin-Golomb (2004) applied the finding of low contrast sensitivity in AD patients (Cronin-Golomb et al., 2007) to known problems with food intake in AD patients. By using high contrast plates, cups and utensils, they were able to increase food intake by 25% and liquid intake by 84%. We believe that similarly effective applications can be inspired by basic research in visual cognition to improve the lives of AD patients. In this section, we focus on how the following findings can lead to improved daily living for AD patients:

1. Visual perception and VSTM for feature bindings is impaired in AD patients.
2. AD patients have impaired mechanisms of encoding visual information into VSTM.
3. "Enhancing" visual stimuli for AD patients facilitates performance in higher-level visual cognition, but only for real-world pictures.
4. Visual selective attention in AD may be intact, but only for overlearned, habituated stimuli.

It must be noted that each of these findings requires further verification with basic research involving AD patients. Further basic research will also provide psychological and physiological explanations in understanding why the proposed applications may work. However, there is no reason to refrain from testing the effectiveness of these proposed applications until the theoretical verification is exhausted. Testing the impact of inexpensive ideas now could lead to tremendous savings in healthcare costs in the near future. One study by the Department of Veteran's Affairs found that delaying nursing home placement by only one month could realize a \$4 billion annual savings to the healthcare system (Clipp, 2005). Below, we will discuss two potential applications to the benefit of AD patients: First, we provide suggestions on organizing patients' visual environment and how they interact with it. Second, we suggest that a visual mnemonic, in the form of a cheap booklet of pictures, would facilitate several everyday abilities.

AD patients are impaired at perceiving and remembering feature bindings. Everyday objects are generally composed of several different features, such as color and shape, and often the objects in a given scene share many visual features. For example, many objects on your desk, like a computer mouse, cell phone, and pen, could be colored black or white, and shaped as a rectangle or oval. Binding is necessary when you must find the black-oval object, like the computer mouse. This attentional process is impaired in AD (Foster et al., 1999; Porter et al., 2010), and even when they successfully find such items, they cannot remember them well (Parra et al., 2009). It would therefore benefit AD patients if the objects in their surroundings were distinguishable by a single, salient feature, such as color. If the objects all appeared in different colors, the attentional cost of finding them in a cluttered scene would be significantly reduced. Since visual search is likely to be facilitated by VSTM contents (Woodman & Arita, 2011), patients with AD would be better able to maintain their search target in memory, and therefore find the target sooner. Instead of having to find the "black-oval" object, they just have to find the "black" object.

Additionally, with regards to AD patients' environments, it is important to consider impairments to their visual selective attention. It has been shown that selective attention in

AD may be intact when aspects of targets and distractors are fixed (Ko et al., 2005), rather than dynamic and changing (Vaughan et al., 2006; Fernandez-Duque & Black, 2008). It may be damaging for a patient to perform too many attentive tasks in succession. For example, if a patient must quickly find her keys and then her cell phone, the search for these items may be impaired due to the rapid switching of the search target. Also, if too many people are addressing them at a time, the focus of their attention will rapidly switch, introducing confusion that could obscure otherwise intact selective attention. Related to this notion is that AD patients have trouble disengaging from an attended object or location (Parasuraman et al., 1992). This is most problematic when their attention has been captured in a bottom-up manner (Tales, Muir, et al., 2002). Therefore, it is important to reduce sudden loud noises or visual transients in their environment. For example, if a telephone rings or the television suddenly turns on while a patient with AD is being addressed by a family member, the patient could suddenly attend to the phone or television and subsequently fail to return attention to the family member. The flow of the conversation could easily be lost by these sudden interruptions.

Keeping in mind that VSTM helps to guide visual search and that VSTM is impaired in AD, it may be useful for AD patients to keep a booklet containing pictures of common targets of their visual search. Such objects could be a patient's wallet, cell phone, or keychain. While a patient searches for a specific object, like her keys, she could visually consult this booklet repeatedly during the search. The booklet image would effectively serve as the search template, alleviating the need to use an impaired VSTM system, and potentially facilitating the search. This booklet might also be useful because AD patients have trouble encoding information into VSTM. This impaired encoding not only prevents a normal range of information to be stored in VSTM, but information already in storage will be vulnerable to incoming perceptual information. This scenario is relevant to eye movements made in perceptual comparisons – information stored prior to a saccade could be fragile and may be prone to erasure once the saccade is complete, since the observer is looking at a new visual scene after the eye movement. A booklet of objects would also be useful in this situation. It can be held next to objects of the comparison to reduce eye movements. For example, if a patient is looking for his wallet, he could hold up a picture of his wallet from the booklet next to each object that could potentially be the wallet. The spatial proximity of the picture to each candidate object would minimize eye movements and the need for VSTM.

The use of real-world pictures, collected into a handy booklet, may also be useful in recognizing other important information, like the faces of family members. Writing family members' names underneath each picture would maximize the perceptual and conceptual information that could trigger familiarity processes. AD patients could use these pictures to rehearse the information and potentially reduce the amount of retrieval failures when encountering those faces in person.

In summary, changing the visual environment of AD patients can potentially facilitate their performance on everyday visual tasks. Our suggestion is to essentially simplify the objects in their environment, so that each object is defined by a single, salient feature. Keeping the appearance of their objects as stable as possible may also help their selective attention. Finally, the use of a visual mnemonic, like a booklet of pictures, is potentially useful in activities involving visual attention and VSTM, including search and perceptual comparisons. It could also help AD patients rehearse the names and faces of friends and family who interact with them regularly. It is important to note two factors in the use of such a booklet: (1) AD patients have low-level perceptual impairments, so the pictures must

be high contrast and devoid of visual clutter; (2) Enhancing the quality of visual aids may only help when the images carry semantic information. So, real-world pictures should be used as opposed abstracted icons.

6. Conclusions

AD patients experience changes to processes that enable them to understand what they see. In this chapter, we have referred to such processes as visual cognition, which includes visual attention and VSTM. Although much research has been conducted in understanding visual attention in AD, less research has examined changes in other components, like VSTM. Further examination of this component of visual cognition could reveal a greater understanding of everyday visual abilities in AD patients. The relationship between visual attention and VSTM remains unclear, so future research may benefit from always considering both components. It is also important to understand how these short-term processes relate to long-term memory and visual perception.

Understanding visual cognition in AD patients leads to ideas of how their visual environment could be optimized to suit their psychological changes. Such inexpensive visual alterations could enhance patients' quality of life and save the healthcare industry billions of dollars. Here, we provide some suggestions on changing AD patients' visual environment, as well as a possible mnemonic that could be used to aid patients in everyday tasks.

7. Acknowledgments

This work was supported by National Institutes on Aging grants K23 AG031925 and R01 AG038471 to BAA.

8. References

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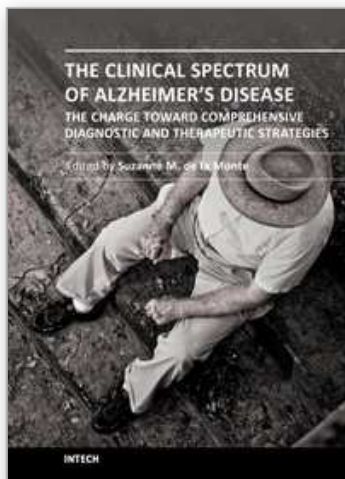
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The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

Edited by Dr. Suzanne De La Monte

ISBN 978-953-307-993-6

Hard cover, 362 pages

Publisher InTech

Published online 06, September, 2011

Published in print edition September, 2011

The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

How to reference

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Philip C. Ko and Brandon A. Ally (2011). Visual Cognition in Alzheimer's Disease and Its Functional Implications, The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies, Dr. Suzanne De La Monte (Ed.), ISBN: 978-953-307-993-6, InTech, Available from: <http://www.intechopen.com/books/the-clinical-spectrum-of-alzheimer-s-disease-the-charge-toward-comprehensive-diagnostic-and-therapeutic-strategies/visual-cognition-in-alzheimer-s-disease-and-its-functional-implications>

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