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The Effect of Delay on Conceptual and Perceptual Priming in Alzheimer's Disease: Relationship to Attention and Cortical Activation

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

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Clinical Psychology

by

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2009

DEDICATION

For my mother and father,

my greatest source of inspiration and support.

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ABSTRACT OF THE DISSERTATION

The Effect of Delay on Conceptual and Perceptual Priming in Alzheimer's Disease: Relationship to Attention and Cortical Activation

by

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Doctor of Philosophy in Clinical Psychology

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Repetition priming in which the initial presentation of a stimulus facilitates its subsequent processing through activation of its visual/auditory form (perceptual priming) is often normal in Alzheimer's disease (AD), whereas priming that depends upon activation of lexical/semantic associations (conceptual priming) is often impaired. This pattern of implicit memory deficits could reflect differential degradation of cortically-mediated conceptual versus perceptual representations, a general deficit in attention/alerting, or cortical activation deficiencies that interact with the integrity of representations. To explore these possibilities, the present study compared the performances of 20 AD and 20 normal elderly control (EC) subjects on word-stem

completion (WSC) and perceptual identification (PI) priming tasks with either no delay or a 10-minute delay between study and test phases. Explicit memory, visual attention, and phasic alerting (i.e., stimulus-driven enhancement of sensory processing that may reflect cortical activation) were also assessed. Results showed that AD patients were impaired in both delay conditions of the WSC test, but had a normal rate of decay of priming. The magnitude and rate of decay of priming in the PI task was normal in the AD patients. As expected, AD patients were impaired and exhibited abnormally rapid forgetting on explicit memory measures, but these effects did not correlate with the magnitude or rate of decay of WSC or PI priming. Alerting and orienting of attention was normal in AD patients and did not correlate with WSC or PI priming effects. WSC priming correlated with performance on a language/semantic memory test. These results confirm previously observed dissociations between impaired conceptual and preserved perceptual priming in AD and further show that priming in both tasks dissipates at a normal rate. This normal rate of decay of priming, along with normal attention and alerting effects, suggests that insufficient cortical activation does not underlie the priming deficit in AD. Rather, impaired conceptual priming may be better explained by degradation of cortically-mediated conceptual representations that must be activated in the WSC task but not in the PI task. Thus, the integrity of priming in AD may depend upon the nature of the representation rather than the fate of cortical activation.

Introduction

A considerable amount of evidence has accrued over the past two decades to indicate that human memory is not mediated by a single neuroanatomical system, but instead relies on distinct, interacting subsystems that differ in the information they process and in their underlying neurobiological mechanisms. A major memory subsystem dichotomy that captures this view is the distinction between explicit (or declarative; Schacter, 1992; Squire 1987) and implicit (or non-declarative; Tulving & Schacter, 1990; Squire 1987) forms of memory. Explicit memory refers to the ability to consciously and directly recall or recognize previous events (episodic memory) and facts (semantic memory). Implicit memory, in contrast, does not require conscious recollection and refers to the facilitation of performance on some task due to prior exposure to stimulus materials (i.e., priming) or through improvement in performance on a particular motor or cognitive task with repeated practice (i.e., skill learning).

The distinction that has been drawn between explicit and implicit memory is based not only on conceptual grounds but also on the dissociation of these two forms of memory in patients with circumscribed amnesia arising from damage to medial temporal lobe (i.e., the hippocampus and related structures) or midline diencephalic (e.g., the Wernicke-Korsakoff syndrome) brain structures. Despite severe deficits in explicit memory, amnesic patients demonstrate relatively normal lexical and semantic priming and a preserved ability to learn and retain a variety of motor, perceptual, and cognitive skills (e.g., Graf et al., 1984; Shimamura & Squire, 1984; Warrington & Weiskrantz, 1968, 1970; for review, see Squire, 1987). For example, Graf and colleagues (1984) examined the ability of amnesic patients and normal control subjects to perform an implicit word-stem completion task.

In this task, subjects were first exposed to a list of 10 target words (e.g., motel, abstain) and asked to rate each word in terms of "likeability." Following two presentations and ratings of the entire list, the subjects were shown three-letter stems (e.g., mot, abs) of words that were and were not on the presentation list, and were asked to complete the stems with the "first word that comes to mind." Half of the stems could be completed with previously presented words, while the other half were used to assess baseline guessing rates. Priming was indicated by an increased propensity to complete stems with the previously presented words even though the previous words were not consciously remembered. The subjects' ability at free recall and recognition (i.e., explicit memory) were assessed with other list of words. Despite severe deficits in the ability to explicitly recall and recognize presented words, the amnesic patients exhibited as strong a tendency (relative to chance guessing rates) as normal control subjects to complete word stems with previously presented words (for similar results, see Butters, 1985; Shimamura, 1989; Squire, 1987, 1992).

While the preservation of implicit memory in patients with circumscribed amnesia indicates that this form of memory does not rely on the same medial temporal and diencephalic brain structures that are thought to mediate explicit memory, it does not shed light on the neurobiological systems that do underlie this form of memory. Some researchers have proposed that brain regions involved in the initial processing and performance of a particular task may underlie performance on implicit memory measures (Cohen & Squire, 1980). For example, damage to the corticostriatal system may be responsible for impaired motor skill learning, whereas verbal priming may be mediated by cortical association areas involved in the processing and storage of semantic

knowledge. It is only through studying patients with more widespread damage that affects these and other brain regions that the psychobiological bases of implicit memory might be elucidated. Thus, a number of researchers have examined implicit memory in patients with Alzheimer's disease (AD) because the widespread cortical damage that occurs in the disease suggests that these patients may present with a unique pattern of preserved and impaired implicit memory abilities.

Alzheimer's disease is an age-associated neurodegenerative disorder characterized by neuronal atrophy, synapse loss, and the abnormal accumulation of neuritic plaques and neurofibrillary tangles within widespread regions of the cortex (Terry, 1994). A growing body of evidence suggests that the hippocampus and entorhinal cortex are involved in the earliest stage of the disease with frontal, temporal, and parietal association cortices becoming increasingly involved as the disease progresses (Arriagada, et al., 1992; Bancher, et al., 1993; Braak & Braak, 1991; Hyman, et al., 1984; Pearson, et al., 1985). In general, primary motor and sensory cortices and most subcortical structures are spared. However, neurodegeneration does occur in the basal forebrain (e.g., the nucleus basalis of Meynert) producing a major decrement in neocortical and hippocampal levels of the neurotransmitter acetylcholine (Whitehouse, et al., 1982). In some cases, the nucleus locus ceruleus is also affected resulting in a reduced level of neocortical norepinephrine (Bondareff, et al., 1982).

Consistent with the pattern of neurodegenerative changes described above, AD results in a global dementia syndrome that affects many aspects of cognition. The dementia associated with AD is broadly characterized by prominent amnesia with additional deficits in language and semantic knowledge (i.e., aphasia), abstract reasoning

and other "executive" functions, attention, and constructional and visuospatial abilities (Corkin, 1982; Moss & Albert, 1988). The severe amnesia of AD has been attributed to the early and pronounced damage that occurs in the hippocampus and related structures (e.g., the entorhinal cortex; Hyman et al., 1984), whereas the deficits in language and semantic knowledge are thought to result from deterioration of the neocortical association areas of the temporal and parietal lobes (Hodges, Patterson & Tyler, 1994). The "executive" dysfunction (e.g., the inability to monitor two cognitive tasks simultaneously) and deficits in abstract reasoning that are associated with AD have been attributed to neocortical degeneration in the frontal lobes (Morris, 1996), and damage to this brain region may also contribute to the impairment of attention that is often evident in the disease (Parasuraman & Haxby, 1993). The visuospatial and visuoconstructional deficits that typically occur in AD are thought to be mediated by neocortical deterioration in the parietal lobe (Martin, 1987), but may also be influenced by damage in the frontal cortex and in the occipital cortex (Nielson, Cummings & Cotman, 1996).

Specific aspects of the effects of AD on explicit and implicit memory are described below.

Explicit Memory in Alzheimer's Disease

Like the neurobiologically-based distinction between explicit and implicit memory, explicit memory has been further dichotomized into episodic and semantic forms (Tulving, 1983). Episodic memory refers to the storage and recollection of temporally dated autobiographical events which depend upon temporal and/or spatial contextual cues for their retrieval. Examples of episodic memory include the ability to

recall our activities from the previous day and the ability to remember a list of words presented 10 minutes earlier. In a typical test of episodic memory, subjects study information (e.g., a list of words) and are subsequently asked to recall that information either without cues (free recall) or with cues (cued recall), or to judge whether an item was presented previously or not (recognition). The subject must remember the specific study list to respond correctly. Semantic memory, in contrast, refers to our general fund of knowledge which consists of over-learned facts and concepts that are not dependent upon contextual cues for retrieval. Knowledge of the meanings of words, the ability to name common objects, or to recollect well-known geographical, historical, and arithmetical facts are all examples of semantic memory.

As with explicit and implicit memory, episodic and semantic memory can be neurobiologically and neuropsychologically distinguished by the differential impairment of these two forms of memory in patients with circumscribed amnesia. Patients with damage to medial temporal lobe or midline diencephalic brain structures exhibit a severe deficit in their ability to learn or retain new, contextually-tagged information (episodic memory), but typically display intact vocabulary skills and retain various aspects of general knowledge (semantic memory). Thus, these patients are characterized by a severe loss of episodic memory combined with preserved semantic memory (for review, see Squire 1987, 1992).

A severe memory disorder is clearly the most prevalent and striking feature in the early stages of AD (Salmon & Bondi, 1999). Given the prominence of medial temporal lobe damage in AD, it is not surprising that researchers have consistently shown that, like patients with circumscribed amnesia, individuals with AD suffer from prominent explicit

memory impairment. In addition to complaints of forgetfulness in every day life, patients with AD show deficits on tests of episodic memory, including inefficient learning of new information (Buschke & Fuld, 1974; Delis et al., 1991; Masur et al., 1989; Moss et al., 1986; Wilson et al., 1983) and an inability to retain information over time (Butters et al., 1988; Delis et al., 1991; Moss et al., 1986; Troster et al., 1993; Welsh et al., 1991). Numerous studies provide support for the idea that the episodic memory impairment in AD is due to inefficient consolidation of information during learning. For example, Delis and colleagues (1991) compared AD patients' performance to normal controls on the California Verbal Learning Test (CVLT; Delis et al., 1987). AD patients demonstrated inefficient learning across the five learning trials, a heightened recency effect on recall measures, equivalent deficits on recognition and free recall, and an abnormally rapid rate of forgetting.

Unlike patients with circumscribed amnesia, patients with AD also typically demonstrate explicit semantic memory deficits in remembering conceptual information such as the meaning of words, names of common objects, and over-learned facts (Hodges et al., 1992; Norton et al., 1997). Semantic memory loss is particularly evident in evaluation of patients' language abilities. In addition to word finding difficulties in normal speech, AD patients show prominent deficits on measures of verbal fluency (Ober et al., 1986, 1991) and confrontation naming (Hodges et al., 1991). In verbal fluency testing, subjects are asked to generate as many words as possible in one-minute trials, which either begin with a particular letter or are members of a particular category (e.g., fruits). Patients with AD are generally impaired on both letter and category fluency tasks, but they show disproportionately more impairment on the category fluency trials

that place greater demand on semantic memory (Monsch et al., 1992, 1994; Salmon et al., 1991). Qualitative analysis of AD patients' impaired performance on confrontation naming tests reveals that word-finding errors are often semantically- and lexically-based (e.g., naming an apple a fruit; Cahn et al., 1997; Hodges et al., 1991). Performance on these and similar language tasks provides evidence supporting the hypothesis that patients with AD suffer a breakdown in the organization and structure of semantic knowledge rather than simply a failure to access items in memory (Hodges et al., 1992).

Implicit Memory in Alzheimer's Disease

Studies examining the performance of patients with AD on implicit memory tasks have shown that some, but not all, aspects of implicit memory are adversely affected by the disease (for reviews, see Meiran & Jelicic, 1995; Salmon & Fennema-Notestine, 2004). Mildly demented patients with AD demonstrate normal performance on implicit motor skill learning, some aspects of cognitive skill learning, and some forms of classical conditioning (for review, see Salmon & Fennema-Notestine, 2004). The preservation of these abilities is consistent with neuropathological findings of intact primary motor cortices and subcortical brain structures in AD. In contrast, some (but not all) forms of implicit priming are impaired in patients with AD.

Many studies of priming in patients with AD have employed the methodology of repetition priming (for review, see Fleischman & Gabrieli, 1998). Repetition priming refers to a procedure in which a stimulus is presented and after some interval (ranging from milliseconds to days) the original stimulus, or some degraded form of the original stimulus, is presented again. The initial presentation of the stimulus is assumed to

produce some activation that facilitates its subsequent processing. This facilitation is reflected by faster processing of the stimulus on its second presentation or by an enhanced ability to identify the stimulus in a degraded form. Some investigators have further divided repetition priming into perceptual (or data-driven) and conceptual (or concept-driven) types (Blaxton 1989; Roediger & Blaxton, 1987). Perceptual priming involves processes that operate at the level of the visual or auditory form of a target stimulus. This type of priming is not affected by the particular meaning or content of the stimulus, but can be influenced by manipulations of its surface features (e.g., changes in modality or type face). Conceptual priming, in contrast, does involve processes that operate at the level of meaning or content of a target stimulus, and is influenced by manipulations of the depth of conceptual analysis of the stimulus.

The various tasks that have been used to assess priming in patients with AD often do not exclusively engage either conceptual or perceptual processes. Rather, both types of processing may contribute to priming performance, with the relative contribution of each depending on the specific features of the task. Keeping in mind the caveat that both conceptual and perceptual processes may contribute to priming effects in many tasks, certain measures have been shown to be more heavily weighted towards conceptual processes (e.g., word-stem completion task) whereas others rely primarily on perceptual processes (e.g., perceptual identification task). The impact of AD on conceptual-level and perceptual-level priming will be discussed in turn.

Conceptual level priming in AD. Conceptual-level priming is reflected in the unconscious facilitation of performance on a test (e.g., speeded processing of a target item) by previously presented information that was semantically or associatively related

to the target item. Thus, this form of priming relies on the analysis or activation of pre-existing representations (i.e., meanings and associations) within semantic memory to influence the retrieval of a target item. Two of the first studies to examine priming in patients with AD used the word-stem completion task previously used by Graf and colleagues (1984) to study patients with circumscribed amnesia (Salmon et al., 1988; Shimamura et al., 1987). This lexical priming task has a strong conceptual component because it presumably engenders priming for the association in semantic memory between the word stem (e.g., MOT) and the word (MOTEL). These studies compared the stem completion priming performance of patients with AD to those of demented patients with Huntington's disease (HD; a neurodenegerative disorder that primarily affects the basal ganglia) or circumscribed amnesia due to alcoholic Korsakoff's (AK) syndrome. Although all three patient groups were severely and equally impaired on free recall and recognition of presented words, only patients with AD exhibited impaired stem completion priming.

These studies were among the first to demonstrate significant deficiencies in long-term priming in any neurologically impaired patient group and have been replicated by many investigators (for review, see Meiran & Jelicic, 1995). The unique deficit exhibited by patients with AD on the stem-completion task suggests that this form of priming may be mediated by neural substrates that are selectively disrupted in AD. Since AD patients, and not HD or amnesic patients, evidence marked pathology in temporal, parietal, and frontal association cortices (Brun, 1983; Terry & Katzman, 1983), impaired priming may be the result of damage to those neocortical association areas which are presumed to store the representations of semantic memory. This cortical damage in AD patients may result

in a breakdown in the organization of semantic knowledge that is necessary to support conceptual level priming. The association in semantic memory between the word stem (e.g., MOT) and the word (MOTEL) on the lexical priming task may be sufficiently disrupted to negate the facilitating effect of the word's presentation.

Numerous studies have provided support for the notion that abnormal priming in AD patients is related to their semantic memory deficit. Salmon and colleagues (1988) employed a paired associate priming procedure (e.g., BIRD – ROBIN) and found that AD patients were significantly less likely to produce the second word of a semantically related pair than were HD patients or normal control subjects. A similar free-association procedure was used by Brandt and colleagues (1988) that yielded parallel findings; AD patients demonstrated less of a priming effect relative to normal controls. Impaired priming in AD patients was also shown on a category exemplar generation task in which subjects were first exposed to target words in a simple decision task and then later asked to generate words orally that were members of a specific semantic category (Lazzara et al., 2001). Normal control subjects were more likely than AD patients to include target words when freely generating category exemplars. Taken together, these results are consistent with the possibility that the hierarchical associative network underlying semantic knowledge may have deteriorated sufficiently in AD patients to greatly limit the capacity of available cues to activate traces of previously presented stimuli. Numerous studies provide evidence of semantic impairment in AD that includes a significant loss of semantic knowledge (Chertkow & Bub, 1990; Hodges et al., 1992) and disruption of semantic organization (Chan et al., 1993a, b, 1995; Salmon & Chan, 1994).

In contrast to the view that the conceptual priming deficit in patients with AD is related to semantic deterioration, some investigators suggest that previous findings of impaired priming may be related to a deficiency in controlled, effortful retrieval processes (for review, see Nebes 1989). According to this view, semantic knowledge is relatively intact in patients with AD, but can only be accessed in a normal fashion through automatic retrieval processes. Several investigators have found normal rates of conceptual level priming in AD patients when assessed using tasks that involve automatic cognitive processes such as naming or pronunciation, or that measure priming over extremely short time intervals (e.g., less than 400ms; Albert & Milberg, 1989; Nebes et al., 1984; Ober et al., 1991). However, methodological issues such as failure to demonstrate priming in normal control subjects and significant differences between the AD group and normal control group on measures of baseline reaction time make these results difficult to interpret. Other studies that were not plagued by such issues, found abnormally low semantic priming in patients with AD on lexical decision or word-reading tasks that used a very short, 250ms time lag between the prime and target stimuli (Bell et al., 2001; Knight 1996; Ober et al., 1991; Silveri et al., 1996).

Another possible mechanism underlying the conceptual priming deficit in AD patients is a generalized disturbance in attention, arousal, or activation, which could lead to an inability to activate an otherwise intact representation in semantic memory at a level that would be sufficient to support long-term priming (Bell et al., 2001; Salmon & Heindel, 1992). Traces may still be sufficiently activated, however, to support intact priming over the very short delay intervals used, for example, in the Nebes et al. (1984) paradigm. Results from a study conducted by Partridge and colleagues (1990) in which

they changed the study phase of the word-stem completion task to increase the likelihood of semantic processing (i.e., asked subjects to provide a definition of the word), thus increasing the proportion of attentional resources allocated to the task, provides further evidence for this theory. When the subjects were asked to provide a definition of the word (rather than simply rate the likeability of the word as in studies by Shimamura et al., 1987 and Salmon et al., 1988) AD patients demonstrated normal levels of stem-completion priming. It should be noted, however, the interpretation of the results of this study is complicated by several methodological issues. First, patients with AD who were unable to perform the semantic encoding task were eliminated from the Partridge et al. study, and these may have been the very subjects with semantic memory deterioration who would have exhibited impaired priming on the stem-completion task. Second, the semantic orienting task resulted in considerably less priming in NC subjects than usually observed in other studies that have used the stem-completion procedure. Third, the study did not directly compare the 'likability judgment' and 'semantic processing' orienting tasks, so alternative explanations (e.g., subject differences) for the differences in Partridge et al.'s results and those of Shimamura et al. (1987) and Salmon et al. (1988) cannot be ruled out. Thus, the underlying cause of the conceptual priming deficit exhibited by patients with AD remains unknown.

Perceptual level priming in AD. In contrast to conceptual level priming, studies consistently demonstrate normal perceptual level repetition priming in patients with AD (for review, see Salmon & Fennema-Notestine, 2004). Perceptual priming is reflected in the facilitated visual identification of a stimulus upon its second presentation (Schacter, 1992; Tulving & Schacter, 1990). This perceptual repetition priming seems to depend on

the analysis of particular perceptual features of the stimulus (e.g., form and structure) and does not require the analysis of its meaning. As suggest by Schacter (1992), perceptual repetition priming may be mediated by activation within a presemantic perceptual system localized in the parieto-occipital association cortex (for visually presented information), a brain region that remains relatively intact in patients with circumscribed amnesia or AD.

Consistent with this notion, Keane and colleagues (1991) found normal repetition priming in patients with AD on a task in which subjects were required to identify briefly presented words, half of which had been presented previously in an unrelated reading task. That is, patients with AD and normal control subjects had equivalently reduced thresholds (on the order of about 20 msec faster) for identifying those briefly presented words that had been previously exposed compared to those words that had not been previously exposed. The AD patients' normal perceptual repetition priming ability occurred despite their impairment on a stem-completion task that was similar to that employed by Shimamura et al. (1987). The preservation of perceptually-based repetition priming in patients with AD suggests that this form of priming occurs independently of the brain regions that are damaged by the disease. Keane and colleagues (1991) attributed its preservation to the fact that parieto-occipital association cortex is relatively unaffected in early AD. Evidence to support the notion that perceptual level priming is mediated by a pre-semantic perceptual system is provided by a case study that showed impaired perceptual identification priming, but normal stem-completion priming, in a patient (M.S.) with a left homonymous hemianopsia due to a right hemisphere temporal lobectomy (Fleischman et al., 1995; Gabrieli et al., 1995; Tulving & Schacter, 1990). The impaired perceptual priming exhibited by this patient was not the result of ineffective

visual processing as his performance on a visually-based explicit recognition memory test was normal.

Mechanisms of priming in AD

The results of the studies reviewed above suggest that patients with AD generally exhibit abnormal performance when priming is primarily mediated by conceptual processes as in a word-stem completion task, but normal performance when priming is primarily mediated by perceptual processes as in a perceptual identification task. The neuropsychological mechanisms that underlie this pattern of performance are presently unknown, although several possibilities have been identified. As previously discussed, there is evidence that the conceptual priming deficit in AD patients may be related to the deterioration of semantic memory (for review, see Salmon & Fennema-Notestine, 2004), but other factors such as deficient effortful retrieval processes (Nebes et al., 1984) or a deficit in attention (Bell et al., 2001) could be involved.

Another possible explanation of the pattern of priming performance seen in AD patients is a general decline in the ability to activate cortical representations (Salmon & Heindel, 1992). There is evidence that the noradrenergic system involved in maintaining vigilance and alertness (Posner & Peterson, 1990) is deficient in patients with AD (Freed et al., 1989), most likely resulting from locus coeruleus neuropathology (Zweig et al., 1988). It has been suggested that the noradrenergic innervation provided by the locus coeruleus modulates selective attention by enhancing the level of steady-state cortical activation, or "cortical tonus," which increases the efficiency of cortical information processing (Sara, 1985). Salmon & Heindel (1992) raised the possibility that during the

priming task, the noradrenergic system provides a level of "cortical tonus" necessary to initiate and maintain activation of a representation. When this system is damaged in AD, stimuli presented in a priming task may be processed at a semantic level, but the representation of the stimulus cannot be normally activated (or the activation cannot be maintained), and that is why priming does not occur.

One way to further explore the possibility that abnormal cortical activation contributes to the priming deficit in AD is to examine the rate at which priming effects decay over time. Although few studies have examined both immediate and delayed priming within the same paradigm (Fennema-Notestine et al., 1994; Heindel, et al., 1998; Mitchell & Schmitt, 2006), the results suggest that priming effects do decay more rapidly in AD patients than in normal controls. This was true for both lexical (Fennema-Notestine et al., 1994) and non-lexical information (Heindel et al., 1998; Mitchell & Schmitt, 2006) suggesting that the observed decay of priming effects in AD cannot be fully explained by cortical semantic/lexical representation damage alone. It may be that a rapid dissipation of cortical activation, or perhaps an interaction between abnormal cortical activation and degradation of semantic/lexical representations, is responsible for the pattern of priming performance in AD. The current project will attempt to address these possibilities by examining conceptual and perceptual priming under both immediate and delayed conditions.

Another way to explore the possibility that abnormal cortical activation contributes to the priming deficit in AD is to examine the relationship between priming and other measures of cortical activation such spatial orienting and phasic alerting. As described below, recent studies suggest that these abilities may be impaired in patients

with AD, and their impairment could reflect decreased cortical activation that also underlies the priming deficit they exhibit. If so, deficits on priming and phasic alerting tasks should be correlated in AD patients.

Spatial orienting and phasic alerting in AD

The possibility that attention and/or cortical activation plays a role in the pattern of priming deficits observed in patients with AD is consistent with evidence that certain aspects of attention are affected relatively early in the disease's course (for reviews, see Parasuraman & Haxby, 1993; Perry & Hodges, 1999). The majority of studies that have examined attention in AD have been concerned with the orienting of spatial attention using modifications of the pre-cuing paradigm developed by Posner and colleagues (Posner, 1980; Posner & Cohen, 1984; Posner, Cohen, & Rafal, 1982). In this paradigm, a cuing signal is presented prior to the presentation of a target, with the cue providing valid, invalid, or neutral information about the probable location of the target. The difference between response times (RTs) to the invalidly cued and validly cued targets, referred to as the orienting effect, reflects how efficiently observers engage, move, and disengage attention from one location to another. The orienting effect reflects both the cost of switching from an invalidly cued position and the benefit of attending to a validly cued position. However, the cues not only denote the possible location of the target but also signal that the target is imminent. Fernandez-Duque & Posner (1997) demonstrated that even when the cue does not provide any information about the location of the target (i.e., spatially neutral), it can still enhance the processing of the target stimulus. This is referred to as the phasic alerting effect.

Festa-Martino and colleagues (2004) added a no cue condition to the Posner pre-cuing attention task to simultaneously assess spatial orientation and the effect of phasic alerting in AD patients. The phasic alerting effect was determined by the difference between RTs on trials with neutral cues and trials with no cue. Consistent with the results from an earlier study (Tales et al., 2002), Festa-Martino et al. (2004) found that the spatial orienting effect elicited in response to an exogenous cue (e.g., the brightening of a box surrounding the potential location of a target) was normal in AD patients. In contrast, the phasic alerting effects of the cue were diminished in patients with AD (Tales et al., 2002; Festa-Martino et al., 2004). In light of these findings, Festa-Martino et al. suggested that damage to the noradrenergic system in AD could result in decreased cortical activation which would diminish the phasic alerting effect in this population. To the extent that phasic alerting deficits in AD reflect decreased cortical activation, such deficits should correlate with impaired priming if cortical activation is a neurophysiologic process that critically drives the priming effect.

Summary and Specific Hypotheses

As the above review attests, AD results in deficits in some forms of implicit priming that are not observed in patients with circumscribed amnesia due to medial temporal lobe or diencephalic brain damage. This appears to be particularly true for priming tasks that require relatively long-term activation (on the order of seconds or minutes) of conceptual representations. These findings suggest that some aspect of the neurological damage in AD, other than medial temporal lobe damage, is critically important for this implicit memory deficit. Identification of this factor would improve

our knowledge of the neurobiological basis of priming. Potential contributors to the conceptual priming deficit evident in patients with AD are degradation of cortically-mediated conceptual representations and associations (i.e., semantic memory) that are activated in priming tasks, dysfunction of cortical activation (i.e., attention and arousal) that is needed to produce priming, or an interaction between these two deficits.

To evaluate these possibilities, the present project will examine conceptually-based (i.e., stem completion) and perceptually-based (i.e., perceptual identification) priming under immediate (i.e., no delay between exposure and test) and delayed (10-minutes between exposure and test) conditions in patients with AD. In addition, cortical activation as indexed by the phasic alerting effect will be examined in these same patients. The performance of the patients on traditional neuropsychological tests of episodic memory, semantic memory, attention, executive functions, and visuospatial abilities will also be examined.

These procedures will allow the following hypotheses to be addressed. First, if the conceptual priming deficit in AD is due primarily to degraded semantic representations, one would expect to see impaired immediate and delayed stem completion priming (compared to normal control subjects) but normal perceptual identification priming (since perceptual representation are presumed to be intact in AD patients), and the decay in the priming effect over the delay interval would be similar for the patients and controls. In addition, the magnitude of the conceptual, but not perceptual, priming effect in AD patients should correlate with other explicit measures of the integrity of semantic memory (e.g. confrontation naming, verbal fluency for semantic categories). Second, if the conceptual priming deficit in AD is due to abnormal cortical activation, AD patients

should demonstrate a greater rate of decay in priming over the delay period relative to normal control subjects on both the word-stem completion task and the perceptual identification task. Furthermore, the magnitude of priming in AD patients on both types of tasks should correlate with the level of phasic alerting and not spatial attention. On the other hand, if an attention deficit is the primary cause of impaired priming in AD, then the magnitude of priming in both types of tasks should correlate with spatial orienting and not phasic alerting.

General Methods

The present investigation examined the performance of AD patients and elderly normal control subjects on word-stem completion and perceptual identification (PI) priming measures of implicit memory, corresponding measures of episodic memory, a modified pre-cuing attention task that provided measures of exogenous covert orienting and phasic alerting, and traditional neuropsychological measures of memory, attention, language, executive functions, and visuospatial abilities. This battery was given within one group of patients with AD to decrease the variability in patient selection and diagnosis that may have been responsible for previous discrepant findings across studies. Word-stem completion priming (Experiment 1) and PI priming (Experiment 2) tasks were administered under an immediate and a delay condition to examine the rate and decay of conceptual and perceptual priming, respectively. The pre-cuing attention task was administered (Experiment 3) to examine basic components of attention and alerting. Performance on traditional neuropsychological measures was also examined to confirm the representativeness of our AD sample and to allow examination of relationships among priming and other cognitive domains. Taken together, these experiments allowed the direct investigation of competing theories of semantic degradation, attention deficits, abnormal cortical activation, or some interaction among them, to explain AD patients' profile of spared and impaired priming performance. The use of multiple tasks within the same patients allowed us to examine the relationships among different memory measures, to suggest mechanisms responsible for priming performance through correlational analyses, and to understand which mechanisms might be deficient in AD.

Subjects

Twenty-three patients with mild to moderate AD and 20 healthy elderly normal control subjects (EC) participated in this project. Written informed consent was obtained from each participant. The AD patients and EC subjects were recruited from the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC) through which they receive annual medical, neurological, and neuropsychological evaluations. The diagnosis of probable AD was made by a senior staff neurologist according to criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984). The Dementia Rating Scale (DRS; Mattis, 1976) was used to determine overall severity of dementia. To ensure that patients were able to comprehend and follow task instructions, only those patients with DRS scores above 110 were included in the study. The elderly normal control group consisted of neurologically intact individuals recruited through the ADRC and were selected to match the AD patient group in terms of age, education and gender distribution. Subjects were excluded if English was not their first language or if they reported a history of stroke, brain tumor, brain surgery, head injury with loss of consciousness greater than 5 minutes, or substance abuse/dependence within the past year.

Demographic characteristics for both groups are presented in Table 1. The groups did not differ significantly in age, education, or gender distribution. As expected, the AD patients scored significantly lower on the DRS compared to the EC group. The mean AD DRS score of 124.1 is indicative of a mild to moderate level of dementia.

Table 0.1

Demographic Characteristics of Subject Groups

	AD (n = 23)	EC (n = 20)	p-value
Age, y	80.2 (6.1)	78.7 (6.6)	.43
Male/Female	15/8	9/11	.18
Education, y	15.1 (2.0)	15.4 (3.1)	.69
DRS score	124.1 (6.9)	140.4 (3.3)	< .001

Note. Values are mean with standard deviation in parentheses. DRS = Mattis Dementia Rating Scale total score. AD = patients with Alzheimer's disease, EC = elderly normal controls.

General Procedure

Each subject was administered a test battery that included the word-stem completion priming task (immediate and delay condition), the perceptual identification priming task (immediate and delay condition), measures of recall and recognition memory associated with each priming task, and an attention task assessing both spatial orienting and phasic alerting. The attention task was administered during the 10-minute delay period for both types of priming tasks. The order of administration of the word-stem completion and the perceptual identification priming tasks was counterbalanced across subjects within each group. The battery took approximately two hours to administer and was completed in one testing session whenever possible, although two sessions were required for some subjects due to fatigue or other time constraints. In such cases, testing was completed within one week of the original testing session.

A comprehensive battery of neuropsychological tests was completed by all subjects within approximately 6 months (M = 4.8) of the implicit memory and attention test battery. The individual neuropsychological tests and their administration procedures have been described previously (Salmon & Butters, 1992). Scores on the various neuropsychological measures for both groups are presented in Table 2. All subjects were tested individually by a trained psychometrist in a quiet, well-illuminated room at the UCSD ADRC.

Table 0.2

Neuropsychological Test Scores of Subject Groups

Test	EC subjects			AD subjects			Group Comparisons
	N	M	SE	N	M	SE	
LANGUAGE							
Category Fluency	20	47.6	2.9	23	27.9	1.7	t(41) = 6.04, p < .001
Letter Fluency	20	45.3	3.0	23	33.5	2.3	t(41) = 3.20, p < .01
Boston Naming Test	20	28.0	0.4	23	24.5	0.8	t(41) = 3.51, p < .01
ANART Errors	15	7.8	1.1	23	13.5	1.9	t(36) = -2.31, p < .05
WAIS-R Vocabulary	15	58.7	1.9	23	50.5	1.8	t(36) = 3.03, p < .01
VISUOSPATIAL ABILITY							
WISC-R Block Design	15	46.7	2.5	23	33.0	2.9	t(36) = 3.34, p < .01
WMS-R Visual Reproduction Test - (VRT) Copy	15	16.1	0.2	23	15.5	0.4	t(36) = 1.29, p = .21
ATTENTION							
WAIS-R Digit Span	15	15.5	1.0	23	13.4	0.6	t(36) = 1.96, p = .06
WAIS-R Digit Symbol	15	45.1	2.8	23	30.5	1.6	t(36) = 4.84, p < .001
EXECUTIVE FUNCTION							
WCST Errors	15	8.3	1.7	21	16.3	2.1	t(34) = -2.76, p < .01
Trail Making Test - A	20	37.3	2.9	23	61.6	4.6	t(41) = -4.35, p < .001
Trail Making Test - B	20	81.9`	7.1	22	172.9	15.6	t(40) = -5.14, p < .001

Table 0.2 continued

Test	EC subjects			AD subjects			Group Comparisons
	N	M	SE	N	M	SE	
MEMORY							
WMS-R VRT - Immediate Recall	15	13.1	0.6	23	7.1	0.8	t(36) = 5.83, p < .001
WMS-R VRT - Delayed Recall	15	12.0	0.9	23	2.0	0.5	t(36) = 10.73, p < .001
WMS-R VRT - Savings	15	0.9	0.1	23	0.3	0.1	t(36) = 9.56, p < .001
Logical Memory I	18	32.9	1.6	23	11.8	1.1	t(39) = 11.02, p < .001
Logical Memory II	18	29.5	2.1	23	3.7	1.0	t(39) = 12.24, p < .001
Logical Memory Savings	18	88.3	2.4	23	28.4	6.4	t(39) = 7.90, p < .001
CVLT Trials 1-5	20	55.6	2.7	23	23.5	2.0	t(41) = 9.72, p < .001
CVLT Short Delay Free Recall	20	11.3	0.7	23	2.0	0.5	t(41) = 11.40, p < .001
CVLT Short Delay Cued Recall	20	12.3	0.5	23	4.1	0.5	t(41) = 11.17, p < .001
CVLT Long Delay Free Recall	20	11.3	0.7	23	1.5	0.5	t(41) = 11.56, p < .001
CVLT Long Delay Cued Recall	20	12.2	0.5	23	3.5	0.6	t(41) = 10.58, p < .001
CVLT Recognition	20	15.3	0.2	23	11.4	0.7	t(41) = 4.89, p < .001
CERAD Savings	15	88.5	7.4	23	26.9	5.3	t(36) = 6.93, p < .001
CERAD Recognition	15	19.9	0.1	23	15.8	0.6	t(36) = 5.55, p < .001

Note. Values are mean (M) and standard error of the mean (SE) for each subject group.

AD = patients with Alzheimer's disease, EC = elderly normal controls.

EXPERIMENT 1: THE EFFECT OF DELAY ON WORD-STEM COMPLETION PRIMING IN AD

As mentioned previously, a number of studies have shown that patients with AD are impaired on implicit word-stem completion priming tasks that are performed normally by patients with circumscribed amnesia arising from medial temporal lobe or diencephalic brain damage. In two of the first studies to examine priming in patients with AD (Shimamura, Salmon, Squire, et al., 1987; Salmon et al., 1988), the performance of AD patients was compared to that of elderly NC subjects, demented patients with HD, and patients with circumscribed amnesia associated with the AK syndrome on the word-stem completion task previously used by Graf and colleagues (Graf et al., 1984). In this task, subjects were first exposed to a list of 10 target words (e.g., MOTEL, ABSTAIN) and asked to rate each word in terms of its "likeability." Immediately following two presentations and ratings of the entire list, the subjects were shown three-letter stems (e.g., MOT, ABS) of words that were and were not on the presentation list and asked to complete the stems with the "first word that comes to mind." Half of the stems could be completed with previously presented words, while the other half were used to assess baseline guessing rates. Although all three patient groups were severely and equally impaired on free recall and recognition of presented words, the groups differed with regard to their ability to prime. The stem-completion priming of the AK and HD patients was comparable to that of the NC subjects. The patients with AD, in contrast, exhibited impaired priming relative to the NC subjects and the other two patient groups. It should be noted, however, that patients with AD primed

significantly above chance guessing rates even though the level of priming they exhibited was impaired.

Although many subsequent studies have confirmed this deficit in word-stem completion priming in patients with AD (for review, see Meiran & Jelicic, 1995), all examined the magnitude of priming only immediately after the initial exposure of the target words. It is not known if the stem completion priming effect in patients with AD decays in a normal or abnormal fashion. There is some evidence that priming in the stem completion task decays at a normal rate (over a two-hour delay) in patients with circumscribed amnesia (Squire et al., 1987), in contrast to the rapid forgetting they exhibit on explicit memory tasks. This dissociation has been taken as further evidence that implicit memory assessed by priming is dissociable from explicit memory and not dependent upon the medial temporal lobe or diencephalic structures impaired in those patients. It is not known, however, if the additional neurological damage that occurs in AD leads to an abnormally rapid decay of the priming effect, or what the nature of that additional damage might be if abnormally rapid decay is evident.

To address these issues, the present experiment was designed to examine the magnitude of immediate and delayed conceptual priming in patients with AD and EC subjects using a word-stem completion task similar to the one used by Shimamura and colleagues (1987). In this task, subjects first rated the likeability of words, and then performed a stem completion task where they were asked to complete three-letter word stems with the first word that came to mind. The task was modified to include a 10-minute delay condition so that the rate of decay in priming could also be assessed.

Immediate and delayed explicit recall and recognition memory for the words presented in the task were also measured.

The following hypotheses were formulated to examine the integrity of immediate and delayed conceptual priming in AD: (1) AD patients will demonstrate impaired performance relative to EC subjects on both conditions of the word-stem completion task (i.e., immediate and delayed). (2) If the observed conceptual priming deficit in AD is due to abnormal cortical activation, AD patients will demonstrate a greater decline in priming over the delay period (i.e., a faster rate of decay of activation) than EC subjects. (3) If the conceptual priming deficit in AD is due to degraded semantic/lexical representations, immediate and delayed priming will be impaired in the AD group, but the rate of decay in priming will be similar to that of EC subjects. (4) AD patients will be impaired on explicit memory measures (i.e., recall and recognition) and demonstrate a faster rate of forgetting over the delay period (i.e., exhibit rapid forgetting) than will EC subjects.

Method

Subjects

The 23 AD patients and 20 EC subjects described in the General Methods participated in the present experiment.

Measures

Word-Stem Completion Task. A word-stem completion task similar to the one used by Shimamura and colleagues (1987) was employed. In this task, subjects first rated the likeability of words, and then performed a stem completion task where they were

asked to complete three-letter word stems with the first word that came to mind. Half of the stems could be completed with previously presented words, while the other half were used to assess baseline guessing rates.

A total of 112 words were used in the stem completion task. Words included nouns and verbs ranging in length from four to eight letters. The first three letters of each word (e.g., CLA__ for CLASS) could be completed to make at least ten different words as designated by the number of dictionary entries. Eighty of these words were selected to be target or distractor words for the priming task while 12 of the words were selected to be filler words placed at the beginning and end of the study word lists to reduce primacy and recency effects. In each condition, 20 words were used as targets for the word-stem completion task (presented during the rating task), and 20 words were used as distractors (not shown during the study phase). The assignment of words as targets and distractors was counterbalanced across forms and delay conditions.

Free Recall and Forced-Choice Recognition Tasks. Target words for the free recall portion of the task were the same as the target words for the corresponding priming task. That is, subjects were asked to recall as many words as they could from the rating task. Twenty word pairs were used for the forced-choice recognition test. The word pairs consisted of a target word (previously seen in the rating task) and a distractor word. The 20 distractor words used in this task were different from those used for the priming task.

Procedure

The word-stem completion task consisted of three phases, an exposure phase where target words were presented, a stem completion phase, and a recall and recognition phase.

Exposure Phase. Each subject was exposed to a list of 26 words including 20 target items (e.g., MOTEL) and 6 filler items. Three filler words were placed at the beginning of the set and three were placed at the end to reduce primacy and recency effects. The words were presented on separate 3 x 5 inch cards one at a time. To ensure a deep (i.e., semantic) level of processing, subjects were asked to rate how much they liked each word on a scale from 1 to 5 (1 = extremely dislike, 5 = extremely like). After the subjects completed the initial rating of the entire set of words, they were asked to perform a second rating of the same words presented in a different order. The rating scale was drawn on a 3 x 5 inch card and remained visible to the subjects during the entire rating task.

Word-Stem Completion Task. Either immediately following the rating task (immediate condition), or after a 10-minute delay filled with non-verbal testing (delay condition), the subjects were shown 40 three-letter word stems (e.g., MOT) and asked to complete each stem with the first word that came to mind. The task was presented as an unrelated word puzzle and no reference was made to the previous presentation of words. Half of the stems could be completed with the previously presented words while the other half were used to assess baseline guessing rates. This task was presented twice: (1) immediate condition, where the rating task was immediately followed by the stem completion task, and (2) delay condition, where the stem completion task was completed after a 10-minute filled delay period. The order of the delay conditions was

counterbalanced (i.e., half of the subjects received the immediate condition first and the other half received the delay condition first). Thus, both immediate and delayed word-stem completion priming were assessed in each subject using two different word lists.

Free Recall and Forced-Choice Recognition. Following the second word-stem completion task (either delayed or immediate), recall and recognition were assessed. The subject was asked to recall as many words as possible from the latest rating task and then was given a two-alternative, forced-choice recognition test. In order to minimize the effect of explicit memory on the task, each subject was given recall and recognition tests only once (i.e., half of the subjects were assessed on immediate recall and recognition and half were assessed on delayed recall and recognition).

Results

Stem Completion Priming Effects

Stem completion priming and baseline guessing rates of the two subject groups are shown in Figure 1.1. There was no significant difference in baseline guessing rates between the groups for either the immediate [$t(41) = 1.17$, $p=.25$] or the delay condition [$t(41) = -1.28$, $p=.21$]. Furthermore, baseline guessing rates in each condition were approximately 10% to 20% for both groups as would be expected since each stem could be completed by at least 10 different words. Thus, there were no differences in the ability of the subject groups to perform the basic task of completing 3-letter stems with words.

A 2 x 2 x 2 mixed-model analysis of variance (ANOVA) was performed with group (AD, EC) as the between-subjects factor and word type (studied, unstudied) and delay (immediate, 10-minute delay) as within-subjects factors. The analysis revealed a

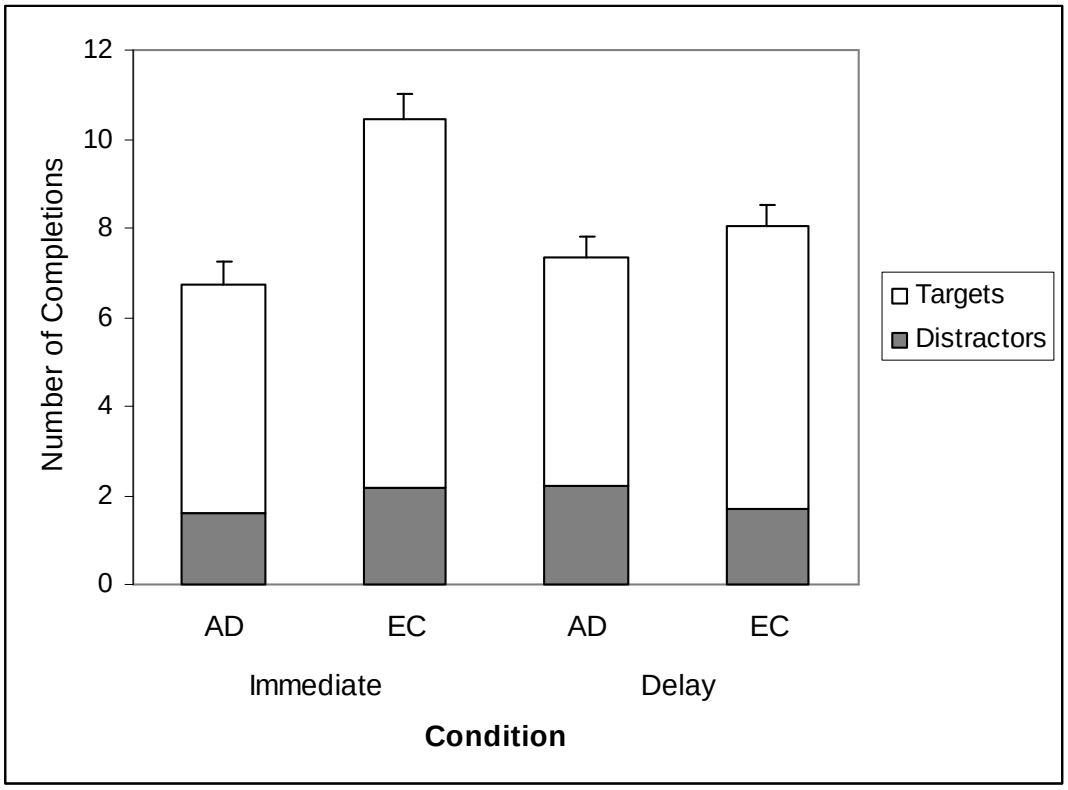

Figure 1.1. Number of stems completed with previously presented target words versus the number of distractor words completed. The number of distractor items represented chance or baseline guessing rates. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

significant group by word type interaction [F (1, 41) = 13.82, p<.01], indicating significantly greater priming in EC subjects than in AD patients. It should be noted, however, that planned comparisons showed that both groups exhibited priming with target hit rates significantly greater than baseline guessing rates for the immediate condition [AD: t (22) = 6.19, p<.001; EC: t (19) = 10.19, p<.001] and the delay condition [AD: t (22) = 7.07, p<.001; EC: t (19) = 7.20, p<.001]. There was also a difference in performance across delays between the subject groups (collapsed across studied and unstudied words), as evidenced by a significant group by delay interaction [F (1, 41) = 8.37, p<.01], with EC subjects showing faster decline than patients with AD. A marginally significant word type by delay interaction effect [F (1,41) = 7.31, p = .05] indicated that there was a decline in priming over the delay in both groups. However, the three-way group by word type by delay interaction effect was not significant suggesting that the decay of priming was similar in the two groups. The lack of the three-way interaction is illustrated in Figure 1.2, which shows similar rates of decline in priming (i.e., the difference between the number of stems completed with target words from the previously studied list and the number of stems completed with distractor words) across the delay interval for the AD patients and EC subjects.

Recall and Recognition Performance

The AD patients performance was at floor on the free recall test for both the immediate condition (M = 0) and the delay condition (M = .45). Therefore, no further analyses were conducted using the recall data. Performance on the recognition task was used as a measure of explicit memory.

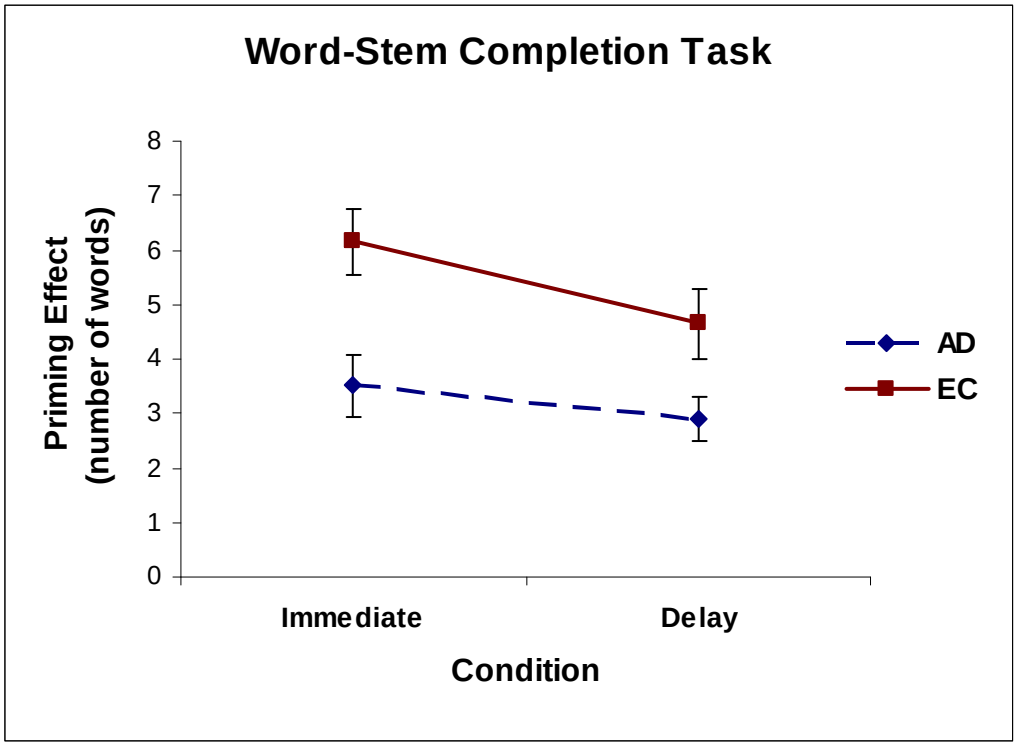

Figure 1.2. Word-stem completion priming effect (i.e., target-distractor rates) for both immediate and delay conditions. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

Recognition memory was measured with a two-alternative, forced-choice task that consisted of 20 pairs of items. Chance performance under these conditions would be 50% correct, or 10 out of 20 items. Both groups performed above chance on this measure under the immediate condition [AD: $t(11) = 7.61$, $p<.001$; EC: $t(10) = 80.50$, $p<.001$] and the delay condition [AD: $t(10) = 10.75$, $p<.001$; EC: $t(8) = 28.00$, $p<.001$]. However, AD patients performed worse than EC subjects on both immediate and delayed recognition (Figure 1.3). Univariate ANOVA with group and delay as between-subjects factors revealed a statistically significant difference between AD and EC subjects' performance [$F(1, 39) = 48.93$, $p<.001$] demonstrating that AD patients were impaired on this measure of episodic memory relative to the normal control group. However, the effect of delay and the group by delay interaction were not significant.

The apparent lack of forgetting across the 10-minute delay in the AD patient group is somewhat surprising, but as previously discussed, half of the subject group performed immediate recall and recognition and half of the group performed delayed recall and recognition. This was done to reduce the likelihood of explicit memory contamination in the priming tasks. Using different subject groups to assess immediate and delayed recall and recognition does not lend itself to examining rate of decay of explicit memory over time because of the possible impact of differences in subject characteristics in the two groups. Therefore, the California Verbal Learning Test (CVLT) was used to examine rate of forgetting (Figure 1.4). A group by delay (number of words recalled on CVLT trial 5 vs. the number of words recalled on short delay free recall) ANOVA revealed a significant interaction effect [$F(1, 41) = 15.26$, $p<.01$] indicating that AD patients exhibited faster forgetting over the delay period than did the EC subjects.

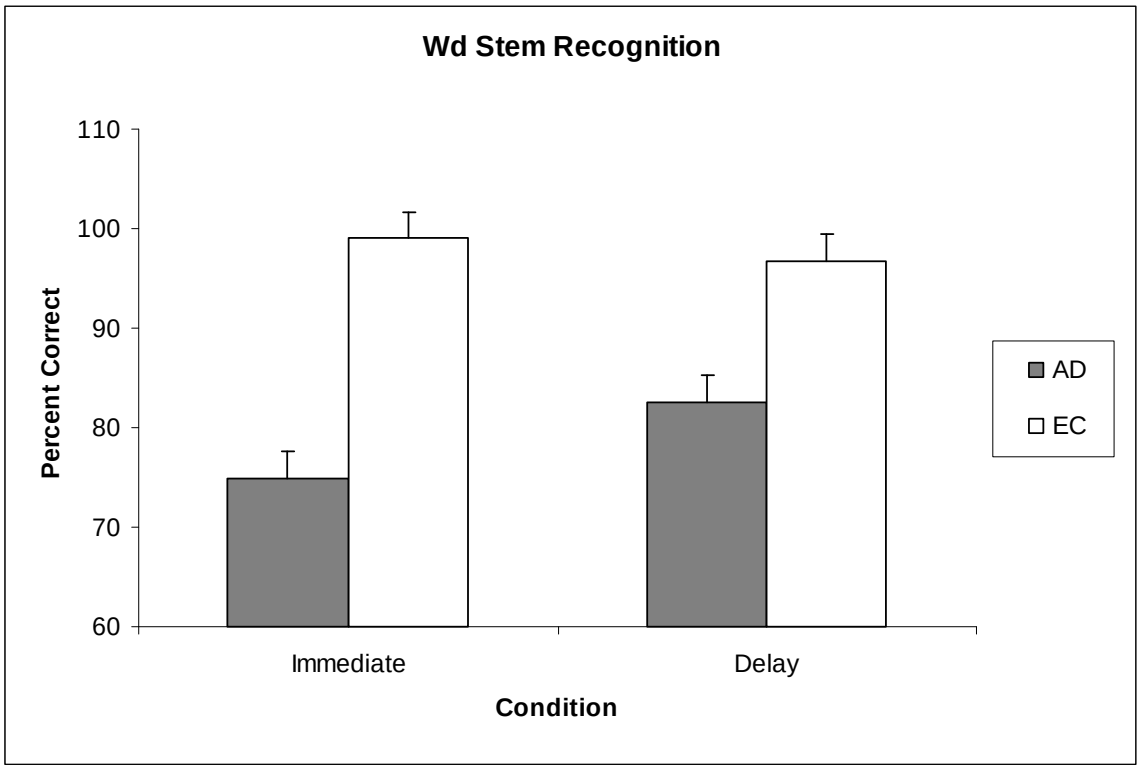

Figure 1.3. Percentage of correct responses on the word-stem completion recognition test. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

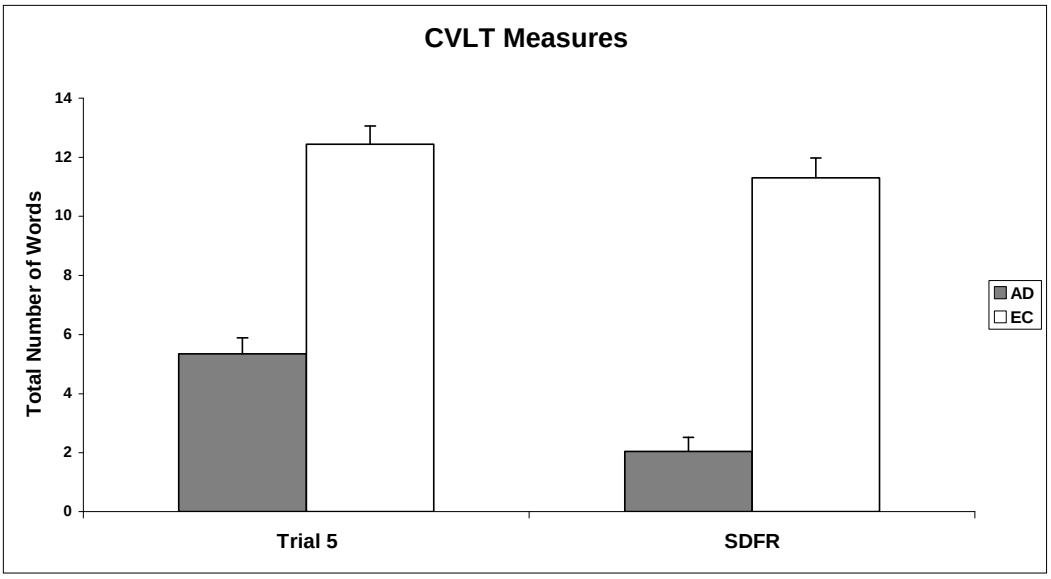

Figure 1.4. Total number of words recalled on Trial 5 and short delay free recall (SDFR) on the California Verbal Learning Test (CVLT). Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

Discussion

The results of Experiment 1 are consistent with previous reports of impaired immediate stem-completion priming in patients with AD (e.g., Heindel et al., 1989; Salmon et al., 1988). Although the AD patients were impaired on the stem-completion task relative to their matched controls, both groups primed significantly above baseline guessing rates (and showed equivalent baseline guessing rates) in both delay conditions. The manipulation of the delay between the study and the test lists extended these findings by revealing a normal rate of decay of the priming effect across a 10-minute delay period for patients with AD (i.e., there was no significant group by word type by condition interaction). That is, the magnitude of the priming deficit exhibited by the AD patients relative to EC subjects was similar in the immediate and delayed conditions. Both groups showed a decline in the magnitude of priming across the delay, but this was slightly larger (although not statistically significant) in EC patients than in AD patients.

The observed similarity in rates of decay in conceptual priming in AD patients and EC subjects suggest that the priming deficit of the patients is not likely to be due to abnormally rapid dissipation of cortical activation. If cortical activation is necessary for priming and it dissipated rapidly in patients with AD, then their priming performance should have declined more rapidly than that of the EC subjects. The observed pattern of results does not, however, rule out the possibility that the conceptual priming deficit exhibited by patients with AD on the stem completion task is due to degraded semantic/lexical representations that need to be activated to support priming. A deficit in semantic/lexical memory would equally influence priming in the immediate and 10-minute delay conditions. This possibility was marginally supported by an examination of

the correlations between stem completion priming and traditional neuropsychological test performance. Only the relationship between stem completion priming performance (in either delay condition) and performance on the Boston Naming Test, a test of language and semantic memory, approached significance ($r=.40$, $p=.06$) in the AD patient group. The magnitude of stem completion priming was not correlated with performance on any other cognitive measure.

A relationship between conceptual priming and semantic memory deficits in patients with AD could be mediated by the selective disruption of neural substrates of semantic memory that include temporal, parietal, and frontal association cortices. Because of this disruption, the hierarchical associative network underlying semantic knowledge may have deteriorated sufficiently in patients with AD to greatly limit the capacity of available cues to activate traces of previously presented stimuli (Salmon et al. 1988). For example, the representation of the concept MOTEL may be degraded to such an extent that it cannot be activated by its prior presentation in the stem-completion task to a level that facilitates its subsequent identification in a degraded form.

The patients with AD in the present study demonstrated significant impairment on explicit recall and recognition tests that followed the stem completion tasks in each delay condition. Indeed, when asked to freely recall words from the previous study list, AD patients typically performed at floor (i.e., they either did not remember the rating task or simply could not recall any of the words). Forced-choice recognition of the words was not at floor levels for the AD patients but was significantly impaired compared to the EC subjects. The severe explicit memory deficits exhibited by the patients with AD is consistent with many previous studies and is a hallmark of the AD dementia syndrome.

It was somewhat surprising, however, that there was no significant difference between recognition performance in the immediate and delay conditions of this explicit memory task for patients with AD. In the usual case, patients with AD exhibit rapid forgetting of information over a 10-minute delay interval. The failure to observe rapid forgetting may be because different AD patient subgroups were used to assess immediate and delayed recognition in the priming task due to efforts to maintain the implicit nature of the task. To assess this possibility, the decline in free recall performance over a short delay period on a list-learning task (i.e., CVLT) was examined in the entire AD patient group. Consistent with previous findings (e.g., Delis et al., 1991), the AD patients exhibited abnormally rapid forgetting on this rigorous explicit memory test. Importantly, there was no significant correlation between performance on any of these explicit memory measures and the magnitude and rate of decay of priming (r's ranged from .02 to .20). Thus, the impaired conceptual priming of patients with AD was independent of their marked explicit memory deficit.

EXPERIMENT 2: THE EFFECT OF DELAY ON PERCEPTUAL PRIMING IN AD

In contrast to the conceptual/lexical priming deficit that has been demonstrated in patients with AD using the stem completion priming task (see Experiment 1), perceptual priming remains intact in these patients (for review, see Fleischman & Gabrieli, 1998). One of the most important studies to demonstrate preserved perceptual priming in AD used a perceptual identification (PI) task that required subjects to identify briefly-exposed words that had or had not been previously exposed in an unrelated reading task (Keane et al., 1991). Both AD patients and normal EC subjects were able to identify previously read words at a faster presentation rate than words that were not previously read (i.e., exhibited perceptual priming), and the magnitude of this effect was equivalent in the two groups. Importantly, these same AD patients were impaired relative to the EC subjects on a conceptually-based stem completion priming task demonstrating an apparent dissociation between the two forms of priming.

While the preservation of perceptual priming in early AD is well established (for review, see Fleischman & Gabrieli, 1998), it is less clear whether of not perceptual priming decays at a normal rate. Only a few studies have examined both immediate and delayed perceptual priming within the same paradigm (Heindel, et al., 1998; Mitchell & Schmitt, 2006). Although these studies suggest that perceptual priming effects decay more rapidly in AD patients than in normal controls, the results are inconclusive. In one of these studies, Heindel et al. (1998) examined immediate and delayed perceptual priming using a continuous stimulus presentation method in which a series of visual

stimuli (abstract forms) were presented with some items repeated immediately or after a lag of 3 intervening items. Subjects were simply required to make a decision about whether the form was "open" or "closed" as each one was presented. Patients with AD exhibited normal priming when stimuli were immediately repeated (i.e. faster RT for the decision than on their first presentation), but impaired priming (relative to normal controls) when stimuli were repeated after a delay. However, it is not known if the decrement in priming was due simply to the delay or to interference from the intervening visual stimuli. In a study by Mitchell & Schmidt (2006), AD patients showed normal immediate priming (i.e., a reduction in naming time), but impaired delayed priming, on a picture naming task in which some pictures were repeated immediately and some after a 3-day delay. Whether priming after three days reflects an implicit process or a residual (and unintended) explicit process is not clear, however, since patients with circumscribed amnesia do not show normal priming after a delay of that length (e.g., Squire et al., 1987). Given the inconclusive findings from these studies, it remains unknown whether or not perceptual priming decays abnormally rapidly in patients with AD as would be expected if they have a general deficit in maintaining cortical activation.

In the present experiment, the perceptual priming ability of patients with AD and normal elderly control subjects was examined using a perceptual identification task similar to the one used by Keane and colleagues (1991). In this task, subjects first read a list of words aloud, and then performed a perceptual identification task in which they attempted to read aloud very briefly flashed words, half of which were from the initial reading list and half of which had not been previously seen. The task was modified to include a 10-minute delay condition so that the rate of decay in priming could be

assessed. Immediate and delayed explicit recall and recognition memory for the words presented in the task were also measured.

The following hypotheses were formulated to examine the integrity of immediate and delayed perceptual priming in AD: (1) Consistent with previous findings, AD patients will demonstrate intact performance relative to elderly normal control subjects in the immediate condition of the perceptual identification task. (2) If abnormal dissipation of cortical activation underlies the priming deficit in AD, patients will exhibit normal perceptual priming in the immediate condition, but will show faster decline in priming over the delay period than will EC subjects. (3) However, if the priming deficit in AD is limited to conceptually-based processes due to degradation of cortical semantic representations, AD patients and EC subjects will demonstrate equivalent performance on the perceptual identification task with similar rates of decay over the delay period. (4) AD patients will be impaired on explicit memory measures (i.e., recall and recognition) and demonstrate a faster rate of forgetting over the delay period (i.e., exhibit rapid forgetting) than will EC subjects.

Method

Subjects

Twenty of the 23 AD patients and the 20 EC subjects described in the General Methods participated in the present experiment. Data from one AD patient was excluded due to the patient's refusal to guess or say the word until she could clearly read it on the computer screen. In addition, two of the AD patients were unable to complete the perceptual identification task due to poor vision. Demographic characteristics of the AD

group changed only slightly and the groups remained matched on age, education, and gender.

Measures

Perceptual Identification Task. A perceptual identification (PI) priming task similar to the one used by Keane and colleagues (1991) was employed. In this task, subjects first read a list of words aloud, and then performed a perceptual identification task in which they attempted to read aloud very briefly flashed words, half of which were from the initial reading list and half that had not been previously seen.

The stimuli included 140 four- and five-letter low frequency words (with no more than 10 occurrences per million) as listed in the Kucera and Francis (1967) word frequency count. Twelve of these words were used as filler items. The remaining 128 words were divided into four lists, which were used to create four distinct, balanced forms of the test. Each 32-word list included: 16 low-frequency four-letter words and 16 low-frequency five-letter words. The mean frequency of words for each of the four lists was similar. In each of the test forms, half of the 32 words were presented in an initial reading list and in the subsequent perceptual identification or recognition task (targets), and the other half appeared only in the perceptual identification or recognition task (distractors). Of the words that appeared in the initial reading list, each word was presented twice. The target and distractor word sets each included equal numbers of four- and five-letter words. The assignment of words as targets and distractors was counterbalanced across forms and delay conditions.

Free Recall and Forced-Choice Recognition Tasks. Target words for the free recall task were the same as the target words for the corresponding priming task. That is, subjects were asked to recall as many words as they could from the initial reading task. The yes-no recognition task contained the 16 target words from the initial reading task as well as 16 distractor words not previously seen.

Procedure

In the PI task, each subject read a list of words one at a time on a computer screen, and then performed a perceptual identification task with studied and unstudied words either immediately following the study list or after a 10-minute delay. In the explicit memory task, each subject recalled as many words as they could think of from the reading task, and then performed a yes-no recognition task with studied and unstudied words. All stimuli were presented on a 12-inch Dell Inspiron computer screen. Subjects were asked to sit approximately 20 inches from the screen.

Exposure Phase. Subjects were told they would see a series of words presented one at a time on the computer screen and were asked to read each word aloud. They were not told to try to remember the words. Sixteen different words were presented singly on the computer screen. In addition to these 16 trials, three filler words were presented at the beginning and end of the list yielding a total of 22 trials. At the initiation of the examiner, each word was presented on the computer screen for 4 seconds. The subject saw each list twice.

Perceptual Identification Task. The exposure phase was followed by a perceptual-identification task, either immediately or after a 10-minute delay. A series of

words were presented very briefly on the computer screen and subjects were asked to identify (i.e., read aloud) each word. Each trial was preceded by the appearance of a fixation character (+) in the middle of the screen. Subjects were instructed to fixate on this character in preparation for the brief appearance of a word. On each trial, a word flashed on the computer screen and then was replaced by a backward mask of random numbers of 250ms duration. The initial presentation time was 17ms. If the subject was unable to identify the word at that exposure time, the examiner pressed the "2" key which set off a 700ms pause and then the next trial began with the fixation point. The same word was presented in the next trial for 34ms. The same word was presented in additional increments of 17 ms on successive trials until the subject correctly identified it. Guessing was encouraged. When the examiner entered the subject's correct response ("1"), the computer recorded the number of presentations (i.e., the exposure time) required to correctly identify that particular item. A set of practice trials was administered prior to the first identification task to familiarize each subject with the task. Thirty-two different words were presented in the perceptual-identification task. Sixteen of these words had been previously seen in the reading task. The other 16 words had not been previously seen. The order in which the subject performed the immediate and delayed tasks was counterbalanced (i.e., half of the subjects received the immediate condition first and the other half received the delay condition first). Thus, both immediate and delayed perceptual identification priming was assessed in each subject using two different word lists.

Free Recall and Forced-Choice Recognition. Following the second identification task (either immediate or delayed PI), recall and recognition were assessed.

Subjects were asked to recall words from the reading task and were then given a yes-no recognition task. The recognition test list was presented one word at a time on the computer screen. Participants were asked to respond "yes" if they saw the word during either the reading or identification task or "no" if they did not. Guessing was encouraged. Each item remained on the screen until the participant supplied a verbal response. Presentation of items and recording of responses were controlled by the examiner. In order to minimize the effect of explicit memory on the identification task, each subject was given recall and recognition measures only once (i.e., half of the subjects were assessed on immediate recall and recognition and half were assessed on delayed recall and recognition).

Results

Perceptual Identification Priming Effects

For each subject group, the mean identification time for studied and unstudied words, for both delays, are shown in Table 3. There was no significant difference in baseline performance between the groups for either the immediate [$t(38) = -0.59$, $p=.56$] or the delay condition [$t(38) = -0.75$, $p=.46$]. Thus, there were no differences in the ability of the subject groups to perform the basic task of identifying briefly flashed words.

A 2 x 2 x 2 mixed-model analysis of variance (ANOVA) was performed on identification times with group (AD, EC) as the between-subjects factor and word type (studied, unstudied) and delay (immediate, 10-minute delay) as within-subjects factors. The analysis revealed a significant effect of word type [$F(1, 38) = 136.99$, $p<.001$],

Table 2.1

Mean Identification Time by Word Type

	IMMEDIATE CONDITION		**DELAY CONDITION**	
	Unstudied	**Studied**	**Unstudied**	**Studied**
AD	64.9 (13.4)	54.2 (10.4)	62.5 (12.8)	52.7 (10.0)
EC	62.1 (16.0)	49.4 (12.6)	59.3 (14.4)	50.1 (14.1)

Note. Data are presented as mean number of milliseconds (standard deviation). AD = patients with Alzheimer's disease, EC = elderly normal controls.

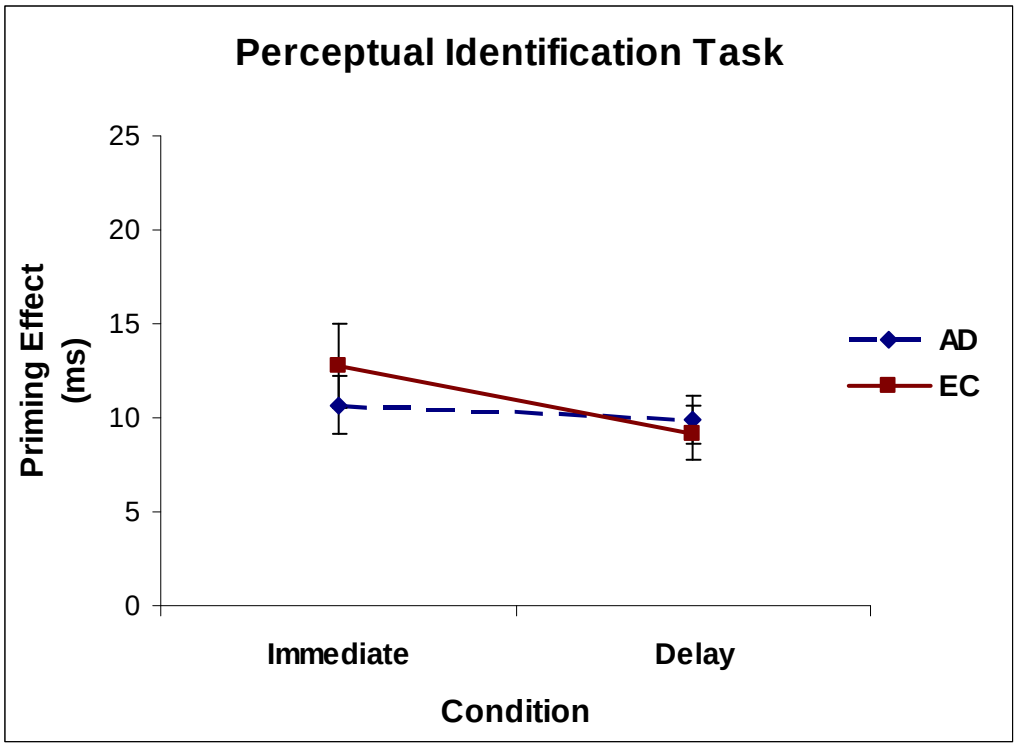

Figure 2.1. PI priming effect (RT difference between studied and unstudied words) for both immediate and delay conditions. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

however there was no significant group by word type interaction (p=.71) indicating equivalent priming performance across groups. No other main effects or interactions were significant including the three-way group by word type by delay interaction. Neither the AD patients nor the EC subjects showed a significant decay in priming over the 10-minute delay period. The perceptual identification priming effect (i.e., the difference between the mean identification time for distractor words and previously seen target words) in the immediate and delayed conditions is shown in Figure 2.1. Although the magnitude of the priming effect on this task was small for both the immediate and delay conditions, the effect was fairly robust and similar in magnitude to the effect observed by Keane et al. (1991). Thirty-nine of the 40 subjects showed a mean priming effect in the predicted direction for the immediate condition and 38 out of 40 for the delay condition.

Recall and Recognition Performance

The AD patients' performance was at floor on the free recall portion of this task for both the immediate condition (M = .30) and the delay condition (M = .10). Therefore, no further analyses were conducted using the recall data. Performance on the recognition task was used as a measure of explicit memory.

AD patients performed worse than EC subjects on both immediate and delayed recognition (Figure 2.2). Recognition performance was measured with a yes-no forced-choice task consisting of 32 words (16 from the previous study list and 16 distractor words not previously seen). Chance performance under these conditions would be 50% correct. Both groups performed above chance on this measure under the immediate

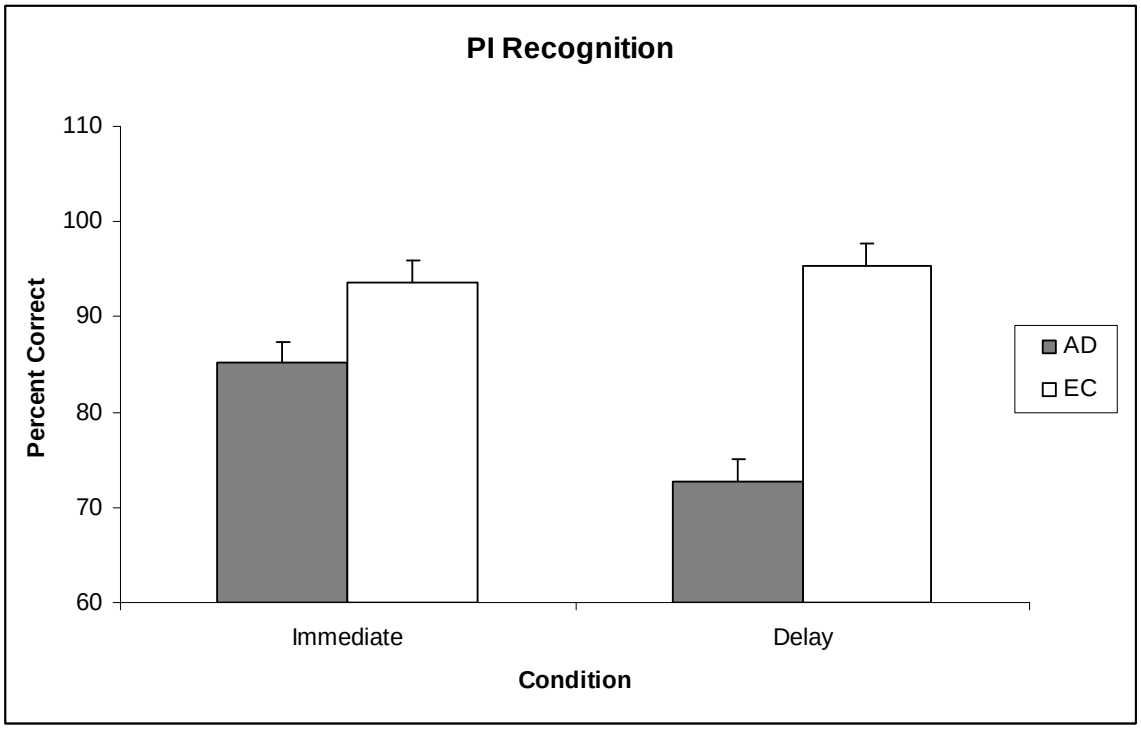

Figure 2.2. Percentage of correct responses on the PI recognition test. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

condition [AD: t (9) = 12.69, p<.001; EC: t (8) = 17.99, p<.001] and the delay condition [AD: t (9) = 8.61, p<.001; EC: t (10) = 44.45, p<.001]. Univariate ANOVA with group and delay as between-subjects factors revealed a statistically significant difference between AD and EC subjects' performance on the recognition test [F (1, 36) = 46.83, p<.001] demonstrating that AD patients were impaired on this measure of episodic memory relative to the normal control group. Additionally, a significant group by delay interaction [F (1,36) = 9.76, p<.01] was revealed, indicating that AD patients had a faster rate of decline over the delay period than did the EC subjects. This finding is consistent with the prominent explicit memory deficit seen in AD. However, as mentioned previously, using different subject groups to assess immediate and delayed recall and recognition does not lend itself to examining rate of decay of explicit memory over time because of the possible impact of differences in subject characteristics in the two groups. Therefore, it should be noted that AD patients exhibited faster forgetting than EC subjects on the CVLT measure of forgetting as discussed in Experiment 1 (i.e., CVLT trial 5 minus the number of words recalled on short delay free recall).

Discussion

The results of Experiment 2 replicate previous findings (e.g., Keane et al., 1991) of preservation of normal immediate perceptually-based repetition priming effects in patients with AD. This finding is consistent with the notion that this form of repetition priming is not dependent upon medial temporal lobe structures (e.g., hippocampus, entorhinal cortex) or temporal, frontal, or parietal association cortices that are affected in AD. The pattern of intact immediate perceptual priming in this experiment, but impaired

immediate conceptual/lexical priming in Experiment 1 in the same AD patients, also replicates the results of Keane et al. (1991) and provides further support for the notion that these are dissociable forms of priming that may be mediated by distinct neural systems. As Schacter (1992) has proposed, perceptual priming may be mediated by activation within a pre-semantic perceptual system localized in the parieto-occipital association cortex, a brain region that is relatively unaffected early in AD.

The present results extend previous findings to show that the perceptual priming effect does not decay abnormally rapidly over a 10-minute delay interval in patients with AD. There was no significant difference in the perceptual priming performance of the AD patients and EC subjects at the 10-minute delay and there was no evidence that either group's priming declined over the interval. These findings suggest that the priming deficits that are observed in patients with AD (such as the immediate and delayed stem completion priming deficit seen in Experiment 1) are not due to a general inability to initially activate or maintain activation of cortical representations in these patients. This interpretation is consistent with the normal rate of decay of stem completion priming observed in these same patients in Experiment 1.

In contrast to their normal perceptual priming, AD patients demonstrated impaired performance on related measures of explicit memory. The AD patients were impaired on both the immediate and delayed components of the recognition memory test and their deficit worsened from the immediate to the delay condition (i.e., they exhibited rapid forgetting). As mentioned previously (see Experiment 1), this same pattern of abnormally rapid forgetting was observed when examined with a test (the CVLT) that was completed by all of the AD patients and EC subjects. Consistent with previous

findings (e.g., Delis et al., 1991), the AD patients exhibited abnormally rapid forgetting on this rigorous explicit memory test. The dissociation between intact perceptual priming and impaired explicit recall and recognition memory in the AD patients supports the notion that these two forms of memory are mediated by distinct neural systems. There is considerable evidence that medial temporal lobe structures damaged in AD such as the hippocampus and entorhinal cortex are critical for explicit memory (for review, Squire, 1991), but these structures are apparently not necessary for perceptual priming.

It should be noted, however, that there was at least a marginal relationship between perceptual priming and explicit memory performance in the patients with AD. The rate of forgetting on the CVLT (i.e., the difference between number of words recalled on Trial 5 and short delay free recall) was significantly correlated with AD patients' immediate PI priming performance ($r=.45$, $p=.048$). In contrast, the number of words recalled on Trial 5 of the CVLT was negatively correlated with delayed PI priming performance in the AD patients ($r=-.52$, $p=.02$). Several other CVLT measures were correlated with rate of decay of the priming effect, but these relationships are difficult to interpret since there was no significant decay of PI priming over the 10-minute interval. These findings suggest that performance of the PI priming and explicit memory tasks by the AD patients may engage some shared processes. Whether this shared variance is indicative of contamination of priming performance by explicit memory (unlikely since explicit memory is impaired in these patients), or the use of preserved implicit memory processes to perform the explicit memory tasks, remains to be determined. In contrast to these significant correlations, there were no significant correlations between performance

on the perceptual priming task and other neuropsychological measures for the AD patients.

EXPERIMENT 3: SPATIAL ORIENTING AND PHASIC ALERTING IN AD: RELATIONSHIP TO PRIMING PERFORMACE

As discussed earlier, a decrease in the level or maintenance of cortical activation resulting from damage to the noradrenergic system (Freed et al., 1989) has been proposed as a possible mechanism underlying the priming deficits that have been observed in patients with AD. According to this view, the noradrenergic system provides a level of "cortical tonus" necessary to initiate and maintain activation of a representation. When this system is damaged in AD, stimuli presented in a priming task may be processed at a semantic or perceptual level, but the representation of the stimulus cannot be normally activated (or the activation cannot be maintained), and that is why priming may not occur. If this hypothesis is correct, any priming that does occur in patients with AD, whether mediated by activation of semantic or perceptual representations, might be expected to decline abnormally rapidly over a delay interval. The results of Experiments 1 and 2 did not support this hypothesis. The priming effects exhibited by patients with AD, whether normal or abnormal in the immediate condition, declined at a normal rate on both the stem completion and perceptual identification priming tasks.

The normal rate of decay of priming observed in Experiments 1 and 2 provides only indirect evidence against the possibility that decreased cortical activation underlies the priming deficit in AD. A more direct examination of cortical activation and its relationship to priming performance in these patients might strengthen this conclusion. One method of assessing the integrity of cortical activation in AD is to measure a "phasic

alerting" effect within an orienting of spatial attention task that uses a pre-cuing paradigm developed by Posner and colleagues (Posner, 1980; Posner & Cohen, 1984; Posner, Cohen, & Rafal, 1982). In the pre-cuing paradigm, an exogenous or endogenous cue provides valid, invalid, or neutral information about the probable spatial location of a soon-to-be-presented target stimulus. The subject must respond as quickly as possible to the presentation of the target. The efficiency with which observers engage, move, and disengage attention from one spatial location to another can be determined by examining differences in response times to validly-cued, invalidly-cued, and non-cued (or neutrally-cued) targets. Attention can be evaluated in terms of the cost of switching from an invalidly-cued position and the benefit of attending to a validly cued position. It has also been noted, however, that the processing of the target stimulus can be enhanced even when the cue does not provide any information about the location of the target (i.e., spatially neutral) because any of the three cue types (i.e., valid, invalid, or neutral) provides a warning signal that the target will appear within a short period of time (Fernandez-Duque & Posner, 1997). This phenomenon is a phasic alerting effect that is presumably produced by a general increase in cortical activation that enhances stimulus processing. A number of studies have shown that the phasic alerting effect is mediated in part by the ascending noradrenergic system (see Foote & Morrison, 1987).

A number of studies have examined attention in patients with AD using pre-cuing, orienting of spatial attention tasks. The results have been mixed when endogenous cues (e.g., target location is cued by a centrally-located arrow that points to a potential target location) have been used to cue spatial locations, with some studies showing impairment and others intact performance in patients with AD (see Parasuraman &

Haxby, 1993; Perry & Hodges, 1999). In contrast, studies are consistent in showing normal attention processes in patients with AD when exogenous cues (e.g., target location is cued by brightening of a box that surrounds a potential target location) have been used to cue spatial locations (see Parasuraman & Haxby, 1993; Perry & Hodges, 1999). Only a few studies have examined the phasic alerting effect in AD within the pre-cuing paradigm. In one of these studies, Festa-Martino and colleagues (2004) added a no cue condition to the pre-cuing attention task to simultaneously assess spatial orientation and the effect of phasic alerting in AD patients. The phasic alerting effect was determined by the difference between response times (RTs) on trials with neutral cues and trials with no cue. Consistent with the results from an earlier study (Tales et al., 2002), these investigators found relatively normal spatial orienting effects to an exogenous cue, but a greatly diminished phasic alerting effect.

The present experiment was designed to examine the relationship between phasic alerting, spatial attention processes, and priming in patients with AD. The pre-cuing spatial orienting task with the phasic alerting modification of Festa-Martino et al. (2004) was administered to the same AD patients and EC subjects that completed the priming tasks in Experiments 1 and 2. To the extent that phasic alerting deficits in AD reflect decreased cortical activation, such deficits should correlate with impaired priming if this is a neurophysiologic process that critically drives the priming effect. Thus, the following hypotheses were formulated to examine the integrity of attention and cortical activation in AD and their relationship to priming: (1) AD patients will demonstrate a normal spatial orienting effect. (2) AD patients will demonstrate a decreased phasic alerting effect relative to EC subjects. (3) If the stem completion priming deficit in AD is

due to deficits in attention, priming performance will correlate with spatial orienting and not phasic alerting. (4) If, on the other hand, the stem completion priming deficit in AD is due to diminished cortical activation, priming performance will correlate with phasic alerting and not spatial orienting.

Method

Subjects

The 20 AD patients and 20 EC subjects described in the General Methods and Experiment 2 participated in the present experiment.

Measures

The spatial orienting task described by Festa-Martino and colleagues (2004) was used in the current study. In this task, subjects are asked to indicate whether a target stimulus (i.e., black circle) appears in a box on the right or left of a central fixation point as quickly and as accurately as possible. Based on the pre-cuing paradigm developed by Posner and colleagues (Posner, 1980; Posner & Cohen, 1984; Posner, et al., 1982), an exogenous cue (e.g., brightening of a box that surrounds a potential target location) is presented prior to the presentation of the target, with the cue providing valid, invalid, or neutral information about the probable location of the target. Festa-Martino and colleagues included double-cue (i.e., both boxes brightened) and no-cue conditions to assess alerting effects separately from orienting effects. That is, the difference in RT between the double-cue condition and no-cue condition provides a measure of phasic

alerting, whereas the difference in RT between the valid and invalid conditions provides a measure of the spatial orienting effect.

A second condition was added in an attempt to elicit maximal phasic alerting effects. In one condition, the task as described by Festa-Martino et al. was presented so that the boxes that will be brightened as cues stay on the screen throughout the entire experiment (i.e., the "no-blank" condition). In the second condition, the boxes disappear after each response and then reappear to start the next trial (i.e., the "blank" condition). The novel blank condition was added because it was thought that the disappearance and reappearance of the boxes between each trial could increase the phasic alerting effect. The order in which the blank and no blank conditions were presented as the filler task in the two priming tasks of Experiments 1 and 2 was counterbalanced across subjects.

The stimuli were displayed on a 12-inch computer monitor at a viewing distance of approximately 50 cm. Participants were asked to focus on a fixation point at the center of the screen flanked on the left and right by two square boxes that measure 3^{o} of visual angle on each side. The center of the box was 5.3^{o} of visual angle from fixation. After a variable delay interval between 1000 and 1500ms, the outline of one, both, or neither of the boxes thickened for 100ms. After a variable inter-stimulus interval (ISI) ranging from 160 to 240 ms (mean ISI = 200 ms ± 20%), the warning cue was followed by the presentation of a target at the center of one of the two boxes. This arrangement yielded a mean stimulus onset asynchrony (SOA) between the cue and the target of 300ms, a value that has been shown to elicit maximal phasic alertness for both groups of participants (Nebes & Brady, 1993; Rabbitt, 1984). The target was a black circle with a diameter of 0.7^{o} of visual angle. Participants were asked to indicate which box contained the target

by pressing one of two response keys with their left or right index fingers as quickly as possible. Reaction time (RT) and accuracy was recorded.

Procedure

Participants were given a practice block of 8 trials, followed by a block of 104 trials in which the following four trial types were presented 26 times each in a randomized order: (a) double cue trials, in which both boxes brightened simultaneously; (b) no cue trials, in which neither of the boxes brightened; (c) valid cue trials, in which the box correctly predicting the location of the target brightened; and (d) invalid cue trials, in which the box opposite the subsequent target brightened. Because there was an equal number of each trial type, all cue conditions were equally probable and therefore of no predictive value. Moreover, the target appeared equally often in the left and right boxes across trials.

Results

Preliminary examination of the data showed that there were no differences in spatial orienting or phasic alerting effects in the “blank” and “no-blank” conditions for either group, so only the results of the no-blank condition (i.e., the identical task used in Festa et al.) are reported.

Response Accuracy. The error rates associated with the four cue conditions for both groups are shown in Table 4. Overall, both groups displayed similar and extremely low error rates (means of less than one error) in all four conditions.

Reaction Time. The mean RTs associated with the four cue conditions for each group are shown in Figure 3.1. A two-way mixed-model ANOVA revealed significant main effects of group, $F(1, 38) = 5.40$, $p < .03$, and cue condition, $F(3, 36) = 72.86$, $p < .001$, but no Group x Cue Condition interaction, $F(3, 36) = .77$, $p = .52$. The main effect of group indicates that the EC group was significantly faster than the AD group. The main effect of Cue Condition indicates that both AD patients and EC subjects responded faster on some trial types than others, and the non-significant Group x Cue Condition interaction effect indicates that the pattern of RTs across the various cue types was similar for AD patients and EC subjects. Thus, the effects in each group are examined separately.

Post-hoc examination of the RTs for the EC group using paired t-tests revealed that (a) RTs in the double cue condition were significantly faster than in the no cue condition ($p < .001$), indicating a significant phasic alerting effect; (b) RTs in the valid cue condition were significantly faster than in the invalid cue condition ($p < .001$), indicating a significant spatial orienting effect; (c) RTs in the valid cue condition were significantly faster than in the no cue condition ($p < .001$) and the double cue condition ($p < .01$), indicating a benefit of spatial orienting beyond that obtained from nonselective phasic alerting; (d) RTs in the invalid cue condition were significantly slower than in the double cue condition ($p < .001$) but still significantly faster than in the no cue condition ($p < .001$), indicating a cost associated with invalid spatial orienting that was counteracted in part by a benefit of nonselective phasic alerting provided by the presentation of the cue.

Post-hoc examination of the RTs for the AD group using paired t-tests revealed that (a) RTs in the double cue condition were significantly faster than in the no cue condition ($p < .001$), indicating a significant phasic alerting effect; (b) RTs in the valid cue condition were significantly faster than in the invalid cue condition ($p < .001$),

Table 3.1

Mean Error Rates for the Four Cue Conditions

	Double Cue		No Cue		Valid Cue		Invalid Cue	
Group	M	SD	M	SD	M	SD	M	SD
EC	.05	.22	0	0	0	0	.30	.57
AD	.10	.31	.10	.31	.10	.31	.45	.69

Note. Data are presented as mean number of errors (standard deviation). AD = patients with Alzheimer's disease, EC = elderly normal controls.

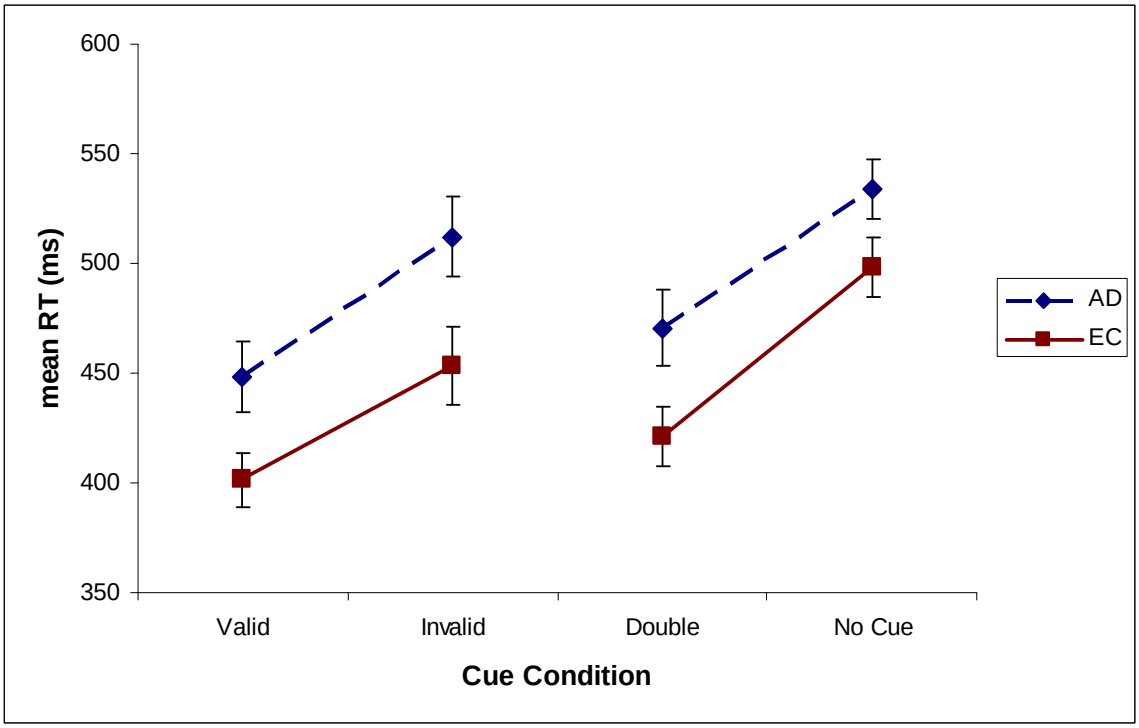

Figure 3.1. Mean reaction times (RTs) for each cue condition across the two groups. The differences in RT between the double cue and no cue conditions and the valid cue and invalid cue conditions reflect the magnitude of phasic alerting and spatial orienting within each group, respectively. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

indicating a significant spatial orienting effect; (c) RTs in the valid cue condition were significantly faster than in the no cue condition ($p < .001$) and the double cue condition ($p < .01$), indicating a benefit of spatial orienting beyond that obtained from nonselective phasic alerting; and (d) RTs in the invalid cue condition were significantly slower than in the double cue condition ($p < .001$), indicating a cost associated with invalid spatial orienting. Unlike in the EC group, however, RTs in the invalid cue condition in the AD patients was not significantly faster than in the no cue condition ($p = .08$), indicating that the cost of invalid orienting outweighed the benefit of nonselective phasic alerting provided by the cue.

Proportion Scores. To better compare the effects of the different cue conditions across the two groups, the RTs were transformed into proportion scores by dividing the mean RT in each condition for each observer by their overall RT. These proportion scores were then used to compute four index scores corresponding to the different attentional component processes contributing to performance on this task. Specifically, an alerting index was calculated by taking the difference between the proportion scores in the double cue and no cue conditions (i.e., no cue – double cue), and an orienting index was calculated by taking the difference between the proportion scores in the invalid cue and valid cue conditions (i.e., invalid cue – valid cue). The overall orienting index was further separated into cost and benefit indices by computing the differences between the proportion scores in the invalid cue and double cue conditions (i.e., invalid cue – double cue) and between the proportion scores in the valid cue and double cue conditions (i.e., double cue – valid cue), respectively. The alerting and orienting indices for each group

are shown in Figure 3.2, and the cost and benefit indices for each group are shown in Figure 3.3.

Alerting and Orienting Indices. A two-way mixed-model ANOVA with group (AD, EC) and index (alerting, orienting) as factors, revealed no significant main effects and no significant interaction effect, indicating that the alerting and orienting indices were not different across groups.

Cost and Benefit Indices. A two-way mixed-model ANOVA with group (AD,EC) and index (cost, benefit) as factors revealed a significant main effect of index, $F(1, 38) = 7.67$, $p < .01$. The cost index was significantly larger than the benefit index across both groups. No other effects were significant.

Relationship between Priming and the Phasic Alerting and Spatial Orienting Indices. Pearson product moment correlations were carried out to examine the relationship between the magnitude of the priming effect (immediate and delayed conditions), and the rate of decline of priming, exhibited by patients with AD in the stem completion and perceptual identification tasks on the one hand, and the magnitude of the phasic alerting and spatial orienting indices on the other (Table 5). The results showed that there were no significant relationships between measures of priming and the magnitude of phasic alerting. Delayed priming in the perceptual identification task was significantly correlated with spatial orienting, but no other priming measures were significantly correlated with this measure of attention.

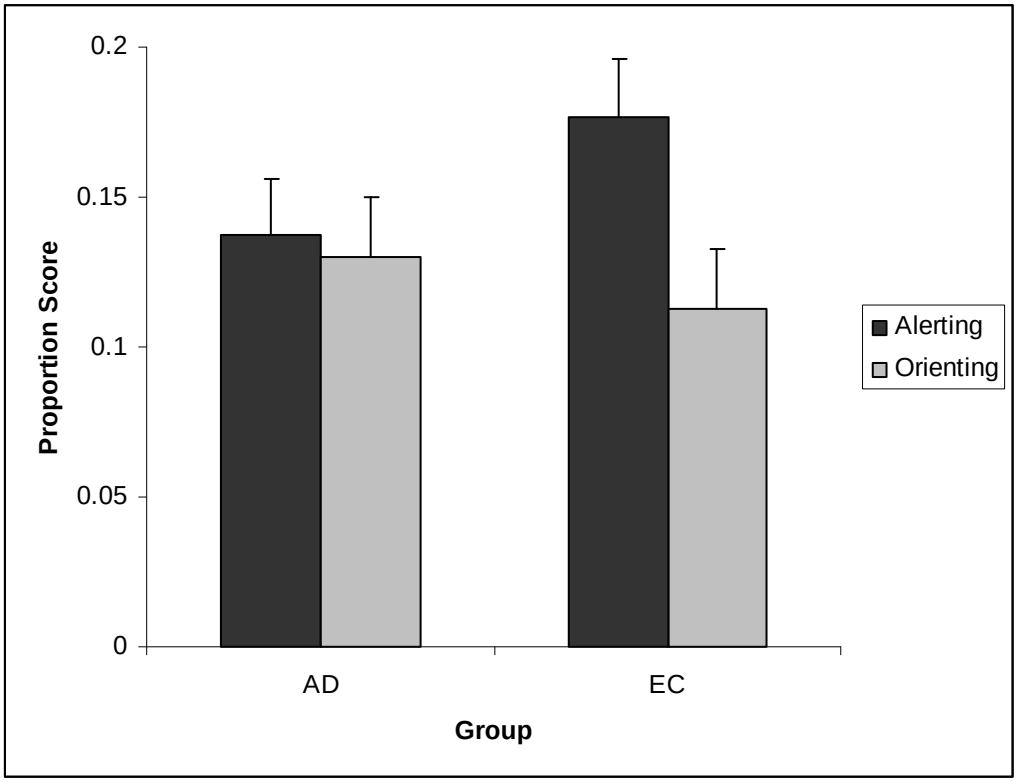

Figure 3.2. Mean alerting and orienting indices for each group. The alerting index was defined as the difference between the proportion scores in the double cue and no cue conditions. The orienting index was defined as the difference between the proportion scores in the invalid cue and valid cue conditions. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

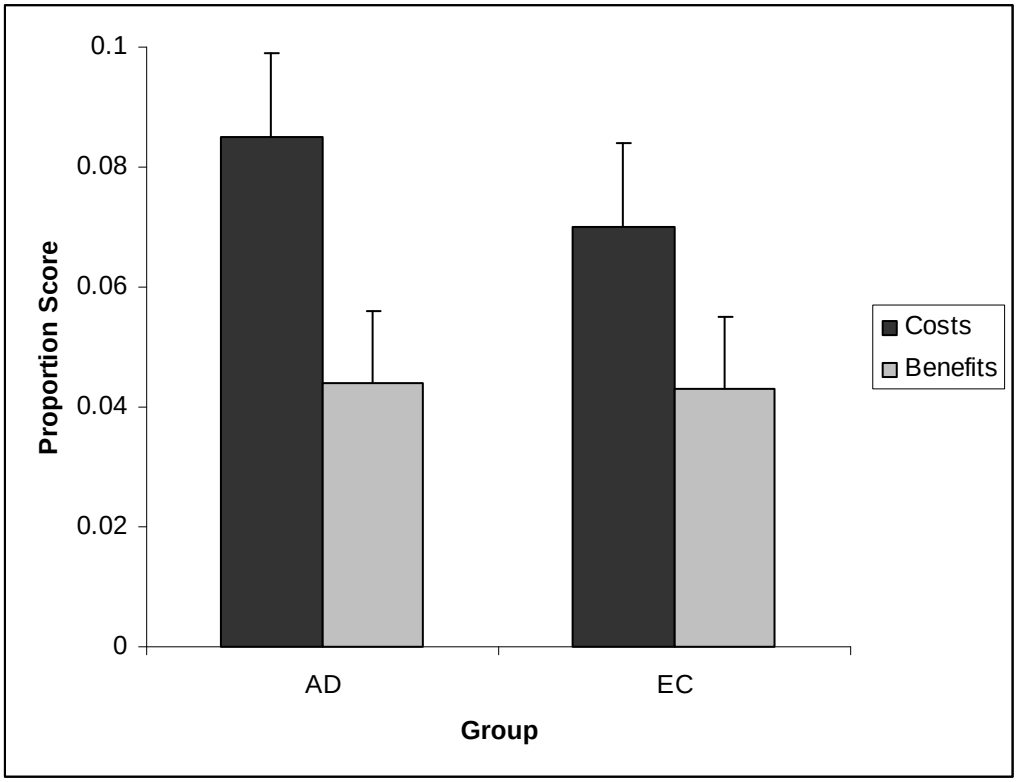

Figure 3.3. Mean cost and benefit indices for each group. The cost index was defined as the difference between the proportion scores in the invalid cue and double cue conditions. The benefit index was defined as the difference between the proportion scores in the double cue and valid cue conditions. Error bars reflect the standard error of the mean. AD = patients with Alzheimer's disease, EC = elderly normal control subjects.

Table 3.2

Correlations (Pearson's r) among Priming, Phasic Alerting and Orienting Indices in the AD Patient Group

	Stem Completion Priming Task			PI Priming Task		
Measure	**Immediate**	**Delayed**	**Rate**	**Immediate**	**Delayed**	**Rate**
Phasic Alerting	-.07	-.31	.12	-.12	.12	-.16
Spatial Orienting	.22	.41	-.04	-.13	-.50*	.20

Note. *p<.05

Discussion

The results of Experiment 3 showed no significant deficit in phasic alerting or spatial orienting effects in the same mildly demented patients with AD that were impaired on the stem completion priming test in Experiment 1. Although the AD patients were significantly slower than EC subjects, the magnitude of the orienting and phasic alerting effects they exhibited were the same as those in EC subjects. The normal spatial orienting effect that was observed using endogenous cues in the pre-cuing paradigm is consistent with previous findings, including those of Festa-Martino and colleagues (2004), and suggests that at least this aspect of attention is intact in the early stages of the AD. In contrast to the findings of Festa-Martino et al. (2004) and Tales et al. (2002), phasic alerting was also not impaired in the AD patients examined in the present experiment. The differences in the phasic alerting results obtained in the present study and previous studies may be due to the inclusion of globally less impaired patients in the present study. For example, although measures of global dementia (i.e., MMSE or DRS) were similar in the AD patients included in the two studies, patients in the present experiment had faster RTs and a much lower error rate in the spatial orienting task than those in the Festa-Martino et al. study. This suggests that neither spatial orienting nor phasic alerting deficits are a particularly early consequence of AD.

Despite normal phasic alerting that is presumably mediated by cortical activation driven by the ascending noradrenergic system, the AD patients in the present experiment were impaired on the stem completion priming test in Experiment 1. Furthermore, there was no significant correlation between the magnitude of the stem completion priming effect in the immediate and delayed condition, or the rate of decay of priming over the

10-minute delay interval, and the magnitude of the phasic alerting effect. These findings suggest that the decrement in stem completion priming observed in AD patients in Experiment 1 is independent of phasic alerting and the cortical activation that it purports to measure. There was also no significant relationship between spatial orienting ability and the stem completion priming deficit observed in Experiment 1, suggesting that the priming deficit of patients with AD is not mediated by impaired attention. Although spatial orienting of attention in AD patients was correlated with one measure of priming in the perceptual identification task, it is difficult to determine if this reflects a true relationship between this form of priming and attention since neither of the cognitive processes was impaired in patients with AD.

When viewed in conjunction with the lack of abnormal decay of the priming effect over time in patients with AD, the lack of a relationship between phasic alerting and priming observed in this experiment provides relatively strong support for the argument that the stem completion priming deficit exhibited by patients with AD is not due to a decline in the ability to activate and maintain activation of cortical representations. The possibility remains, however, that a level of activation necessary to produce the phasic alerting effect may be less than required to fully activate a degraded representation in semantic memory. Thus, there could be an interaction between these factors such that activation of representations within an intact cortical system (e.g., the perceptual representation system) can be achieved with a level of activation sufficient to produce the phasic alerting effect in AD, whereas activation of representations within a degraded cortical system (e.g., semantic memory) requires a level of cortical activation more than required for phasic alerting, and more than AD patients can achieve. This

possibility will need to be addressed in further studies, perhaps using direct measures of cortical activation such as electroencephalography or functional magnetic resonance imaging.

General Discussion

The three experiments presented above were designed to explore the neuropsychological processes underlying the deficit in some aspects of implicit priming that have been observed in patients with AD. Specifically, they sought to determine whether or not the pattern of impaired and preserved priming abilities in patients with AD was more likely a reflection of differential degradation of cortically-mediated conceptual (i.e., semantic memory) versus visual perceptual (i.e., visual forms) representations, a general deficit in attention processes that are differentially required by various priming tasks, or cortical activation deficits that interact with the integrity of different types of cortical representations. To examine these questions, the magnitude and rate of decline in conceptual/lexical (i.e., word stem completion) and perceptual (i.e, perceptual identification) priming effects were compared, and the relationship between these priming effects and explicit memory, visual attention, and phasic alerting (i.e., a nonselective, stimulus-driven enhancement of sensory processing that may reflect cortical activation) were explored.

The results of the present experiments (particularly Experiments 1 and 2) are consistent with previous studies that have shown a dissociation between impaired conceptual/lexical (e.g., Shimamura et al., 1987) and preserved perceptual priming in patients with AD (e.g., Keane et al., 1991). The same AD patients were impaired in both the immediate and delayed conditions of the stem completion priming task (relative to EC subjects), but intact in both delay conditions of the perceptual identification task. This pattern of impaired and spared priming abilities has been attributed to degradation of

the semantic representations that are primed in the stem completion (and similar) priming tasks, and intact pre-semantic visual perceptual representations that are primed in perceptually-based, repetition priming tasks such as the perceptual identification task.

The possibility that the conceptual/lexical priming deficit observed in Experiment 1 is mediated by the degradation of semantic memory in these patients is consistent with numerous studies that have used a variety of experimental tasks and procedures to demonstrate semantic memory deterioration in AD patients (for review, see Salmon & Bondi, 1999). As the neuropathology of AD spreads into the association cortices of the temporal, frontal and parietal lobes, patients develop a semantic memory deficit that manifests itself as a loss of general semantic knowledge and impairment of language abilities (i.e., aphasia). They are often impaired on tests of confrontation naming, verbal fluency, and semantic categorization, and have a reduced ability to recall over-learned facts (e.g., the number of days in a year) (for review, see Salmon & Bondi, 1999). Patients with AD are highly consistent in the individual items they miss across different semantic memory tests that employ unique modes of access and output (e.g., fluency versus confrontation naming; Hodges et al., 1992). This suggests that AD results in a true degradation of semantic knowledge rather than only an impaired ability to retrieve information from intact semantic memory stores. The finding in Experiment 1 that the stem completion priming deficit exhibited by patients with AD is marginally correlated with performance on a test of language and semantic memory (i.e., Boston Naming Test), and not with performance on traditional neuropsychological tests in any other cognitive domain, suggests similar underlying mechanisms may be responsible for performance on both types of tasks.

In contrast, the results of the present experiments do not provide support for the notion that the priming deficit exhibited by patients with AD is mediated by deficits in the development and maintenance of cortical activation or deficits in attention. First, the rate of decay of the conceptual and perceptual priming effects dissipated at a normal rate in patients with AD. This finding is in stark contrast to the abnormally rapid decay of explicit episodic memory exhibited by these patients. Second, the AD patients that exhibited impaired stem completion priming in Experiment 1 showed normal attention and phasic alerting, a purported measure of cortical activation, in Experiment 3. If the stem completion priming deficit in AD is due to decreased cortical activation, phasic alerting would also be expected to be impaired. Third, there was no significant correlation between phasic alerting and either form of priming as would be expected if these two processes were driven by the same cortical activation mechanism. Fourth, the same arguments can be drawn between spatial attention and priming in AD since no attention deficits were observed in the AD patients with impaired stem completion priming, and there were no significant correlations between this form of priming and the attention measures. Taken together, these findings suggest that the integrity of priming in patients with AD may depend upon the nature of the representation (e.g., semantic vs. perceptual) rather than the fate of cortical activation.

Although suggestive, the present results do not directly address the possibility that impaired priming in AD is due to degradation of the cortically-mediated semantic representations that must be activated for priming to occur. Future studies should further explore this hypothesis by examining immediate and delayed priming using tasks that are more semantically- than lexically-based (e.g., the free association priming task used by

Salmon et al., 1988) in larger groups of AD patients who have also been tested on a battery of neuropsychological tests that probe the integrity of the structure and organization of semantic memory. Characterizing the relationship between priming and semantic memory impairments in these patients may shed light on the neuropsychological basis of the priming deficit. In addition, more direct measurement of the integrity of cortical activation would allow better assessment of whether or not dissipation of cortical activation directly contributes to the priming deficit in patients with AD or interacts with semantic memory deterioration to exacerbate their priming impairment. This possibility will need to be addressed in future studies, perhaps using direct measures of cortical activation such as electroencephalography or functional magnetic resonance imaging.

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