

# Long-term memory in Alzheimer's disease

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Recent findings have further characterized the neural and psychological bases of long-term memory failure in Alzheimer's disease. Convergent volumetric neuroimaging studies indicate that loss of episodic memory is specifically related to early-stage limbic–diencephalic pathology, and that non-mnemonic impairment is specifically related to later-stage temporal–neocortical pathology. Recent studies of Alzheimer's disease have also reported informative cognitive dissociations in semantic memory and implicit memory.

## Addresses

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## Abbreviations

**AD** Alzheimer's disease  
**PET** positron emission tomography  
**SPECT** single-photon emission computed tomography

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the most common cause of age-related intellectual decline [1••]. The hallmark, and typically the initial, cognitive symptom is a profound amnesia for recently experienced events [2]. Later stages of the disease are characterized by debilitating deficits in multiple cognitive domains such as language, attention, reasoning, and visuospatial function [3].

The cognitive neuroscience of AD has two fundamental goals. The first goal is to deepen our understanding of the disease by linking specific psychological declines to specific structural, metabolic, and neurochemical brain pathologies. The second goal is to deepen our understanding of the functional and neural architecture of normal human cognition by examining brain–behavior relationships in AD. There are significant challenges to these goals. First, it is difficult to analyze AD in terms of cognitive neuroscience because the neuropathology is multi-focal and causes deficits in multiple cognitive domains. Nonetheless, there are systematic patterns of cognitive failure and preservation in AD that can be related to biological changes in the brain, particularly in the early stages of the disease. These patterns have yielded important clues about fundamental cognitive processes. Second, there is substantial inter-individual heterogeneity

in both the neural and the cognitive manifestations of the disease. Recently, however, investigators in the cognitive neuroscience of AD have begun to view this heterogeneity not as a problem but as fertile ground for experimentation [4••]. Third, neuroimaging techniques that are critical for advancing cognitive neuroscience are difficult to perform with AD patients. For example, AD patients often require re-instruction while performing a cognitive task, but verbal communication with the patient is not possible during the course of a neuroimaging activation experiment. Thus, activation studies, although potentially of great value, have been slow to appear in the literature.

The present review summarizes recent findings examining the neural and psychological bases of long-term memory impairment in AD. We begin with episodic memory — memory for events in recent personal history. Impairment in this form of memory is required for a diagnosis of probable AD [5]. Several recent studies have correlated performance on measures of episodic memory with volumetric measurements of various brain regions, in particular, structures within the mesial aspect of the temporal lobe. Neuroimaging studies that include episodic memory correlates have provided important convergent information, as well as new insights regarding neural changes that take place before a diagnosis of clinical AD can be made. Next, we turn to semantic memory — the storehouse of world knowledge. Interesting new AD studies demonstrate how a multi-focal disease can cause very specific deficits in the categorization of object knowledge. Finally, we discuss new findings in studies of implicit memory — memory for recent events measured indirectly through a change in behavior — which offer further hints about the brain correlates of long-term memory, and how it changes in the face of healthy aging and AD.

## Episodic memory

Long-term memory of events within specific spatiotemporal contexts is referred to as episodic memory [6]. Studies of patients with focal amnesia indicate that this form of memory is profoundly impaired as a consequence of circumscribed, bilateral lesions to the mesial–temporal (e.g. hippocampus and parahippocampal cortices) and/or diencephalic (e.g. thalamus) regions of the brain [7,8]. Similar to patients with focal amnesia, a profound episodic memory impairment is the defining feature of AD [2]. Early in the course of the disease, AD patients have extensive mesial–temporal damage that is concentrated in the hippocampal formation and surrounding structures (i.e. input pathways in the entorhinal cortex and output pathways in the subiculum) [9••,10]. On the basis of work linking episodic memory and mesial–temporal structures in amnesic patients and in nonhuman primates [11], damage to these structures is thought to be responsible for the profound episodic memory deficit in AD.

Wilson *et al.* [12] recently reported a link between episodic memory impairment in AD and structural change in the mesial-temporal lobe. In this study, hippocampal formation volume, calculated from the reconstruction of three-dimensional magnetic resonance images, was positively correlated with a measure of verbal long-term memory (delayed story recall). Hippocampal formation volume did not, however, correlate with performance on a measure of verbal short-term memory (immediate story recall). Furthermore, in patients with mild to moderate AD, performance on measures of language and constructional praxis was related to temporal-neocortical volume, but was not correlated with hippocampal formation volume. This cross-sectional finding suggests that the episodic memory disorder of AD is related to mesial-temporal pathology, and that the non-mnemonic features of AD dementia may emerge with the spread of pathology into the lateral aspects of the temporal lobe. Other recent volumetric studies [13,14,15\*,16] support and extend the findings of Wilson *et al.* [12]. In particular, one recent study [17\*] has extended the association between verbal episodic memory and mesial-temporal shrinkage in AD to include regions of the diencephalon, specifically the thalamus. In combination, these studies document a specific, quantitative relation between episodic memory failure in AD and reduced volume of mesial-temporal and diencephalic regions.

An important area of AD research is the preclinical prediction of the disease. One recent study [18\*] has used regional cerebral perfusion rates at baseline as a predictor of subsequent development of AD. Single-photon emission computed tomography (SPECT) and neuropsychological testing were performed on subjects with normal cognition, questionable AD, mild AD, and moderate AD. Subjects with questionable AD that developed clinical AD over the next year and a half were distinguished from normal subjects at the initial evaluation by decreased perfusion rates in the posterior and anterior cingulate, hippocampal-amygdaloid complex, and anterior thalamus. The investigators noted that these brain regions (with the exception of the anterior cingulate) have been shown to comprise a network that is critical to episodic memory. Indeed, perfusion rates in these brain regions were positively correlated with performance on tests of verbal and nonverbal episodic memory. Both the SPECT measures and the neuropsychological measures were reliable predictors of the development of AD. Another important finding from this study was that perfusion abnormalities were seen in the temporoparietal regions in moderate AD patients, but not seen in subjects with pre-clinical AD. This suggests that the association cortex is not involved substantially until the later stages of the disease.

### Semantic memory

Semantic memory is the long-term repository of context-free memories—a storehouse of concepts, rules, associations, and general world knowledge [6]. Studies of patients with focal brain damage have been helpful in understanding the functional and neural organization of

semantic memory. Of particular interest are studies that have shown selective loss in the ability to name certain categories of objects, such as natural kinds (living things) versus artifacts (nonliving things) [19,20]. Patients with herpes simplex encephalitis have focal damage to temporolimbic structures and often have selective deficits in naming living things [21]. In contrast, patients with frontoparietal damage have more difficulty naming nonliving things [22]. The living/nonliving distinction is thought to reflect the organization of object knowledge according to perceptual or functional attributes, respectively [20,23].

There is large-scale damage of temporolimbic structures in AD, and there is evidence that AD patients have a selective deficit in naming living versus nonliving things [24,25\*]. Other studies, however, have reported that AD naming ability is no more impaired, on average, for naming living things than it is for naming nonliving things [26,27\*]. In the study reported by Gonnerman *et al.* [27\*], an analysis of individual differences in naming ability within the AD sample revealed two cases that represented a double dissociation between naming living and nonliving things, suggesting a heterogeneity of naming ability in AD that is not easily accommodated by a locus of neuropathology hypothesis. The investigators suggested that category-specific deficits in AD reflect differential vulnerability of object knowledge systems to the effects of a diffuse and progressive disease process. In a second experiment with an independent sample of AD patients [27\*], it was found that patients in the mildest stage of the disease had more difficulty naming nonliving than living things. As the cognitive impairment worsened, however, the pattern reversed, and patients began having more difficulty naming living things.

Gonnerman *et al.* [27\*] proposed a model of semantic memory organization that is based on differences between object knowledge networks in the density of their intercorrelated and distinguishing features. Nonliving things are distinguished often by a single functional feature. Degradation of that feature results in the inability to distinguish one nonliving thing from another nonliving thing. With few intercorrelated features to compensate for the loss of distinguishing features, naming of nonliving things fails even with relatively mild disease, and continues to fail over the course of the disease in a linear fashion. Networks supporting naming of living things, in contrast, decline in a nonlinear fashion across the course of the disease. These networks are characterized by numerous intercorrelated (usually perceptual) features and can tolerate the loss of features for some time before a threshold is reached and naming fails. Further support for this model has been obtained using a computational modeling approach [28\*].

### Implicit memory

Implicit memory tasks measure memory indirectly as a change in performance upon the repeated presentation of previously studied material. This is in contrast to explicit memory tasks that measure memory directly by requiring

the conscious recall or recognition of previously studied material [29]. One widely studied form of implicit memory is repetition priming. To measure repetition priming, stimuli (usually a word or a picture) are processed in a study phase, and subsequently the same or related stimuli are processed in a test phase along with unstudied, baseline stimuli. Repetition priming is calculated as the difference in performance with studied and unstudied stimuli. That difference reflects memory acquired in the study phase and retrieved in the test phase.

Patients with focal amnesia as a result of damage in mesial-temporal and/or diencephalic regions have profoundly impaired explicit memory, but generally preserved repetition priming [30\*\*]. Patients with AD have similarly impaired explicit memory, but a more varied pattern of preserved and impaired priming [4\*\*]. Thus, AD provides an opportunity in which to explore the functional and neural boundaries of this form of implicit memory.

Numerous AD studies have suggested that repetition priming is supported by neurally and psychologically separable neocortical memory systems devoted to the processing of perceptual and conceptual information. AD patients most often fail on priming tasks that draw upon conceptual processes, such as word-association [31,32] and category exemplar production [33,34]. In contrast, AD patients most often succeed on priming tasks that draw upon perceptual processes in vision, such as word-identification [35,36], lexical decision [37,38], and picture naming [39,40]. Neuroimaging [41–44] and lesion [36,45,46] studies have demonstrated a posterior cortical locus for visual perceptual priming, and have implicated regions of left frontal [47] and left frontal and left temporal cortex [41] in conceptual priming.

A new study, however, suggests that the fundamental distinction between processes in priming may take place between identification and production [48\*]. In this study, the same AD patients showed intact priming on both perceptual and conceptual tasks that required test-phase identification of a response, but impaired priming on both perceptual and conceptual tasks that required test-phase production of a response. The results suggest a new distinction in AD priming that may be related to attention-driven dissociations in young people and to dissociations recently reported between various forms of priming in normal aging [49].

A recently published study of word-stem completion priming offers hints regarding brain changes that occur in healthy aging and AD [50\*]. In this study, healthy old subjects and AD patients were distinguished by the AD impairment on multiple measures of explicit memory and a measure of global cognitive status. Both groups, however, demonstrated a reduction in word-stem completion priming. As dementia severity increased, there were further reductions in AD priming beyond that of even the

oldest healthy subjects. On the basis of these results, it could be speculated that cortical compromise occurs to some degree in all but the most successful healthy agers (see e.g. [49]), some of whom may go on to develop additional compromise in medial-temporal function, and be diagnosed with clinical AD. Initially, the cortical compromise in these early AD patients may be no worse than some of their healthy aged counterparts, but as the disease progresses, cortical function may continue to deteriorate, culminating in the profound dementia that characterizes the disease. The idea that changes in the mesial-temporal lobe may be the first signal that an elderly individual has AD, and that additional cortical compromise signals progression of the disease, dovetails with the findings of Wilson *et al.* [12] and Johnson *et al.* [18\*] discussed above.

## Conclusions

Evidence from volumetric, neuroimaging, and cognitive studies of AD has converged on a pattern of disease progression that initially involves the limbic-diencephalic regions and disrupts episodic memory, and later involves temporal-neocortical regions and disrupts some forms of repetition priming and non-mnemonic function. AD is a progressive disease, however, and definitive results can only come from well-designed studies that incorporate advances in brain measurement technology and cognitive psychology, with longitudinal design. Although AD is a multi-focal neural disease, cognitive neuroscience studies have successfully demonstrated dissociations within both semantic and implicit memory that have contributed important information about the psychological and neural organization of these long-term memory systems.

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