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Memory loss in Alzheimer's disease: implications for development of therapeutics

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease marked by a constellation of cognitive disturbances, the earliest and most prominent being impaired episodic memory. Episodic memory refers to the memory system that allows an individual to consciously retrieve a previously experienced item or episode of life. Many recent studies have focused on characterizing how AD pathology impacts particular aspects of episodic memory and underlying mental and neural processes. This review summarizes the findings of those studies and discusses the effects of current and promising treatments for AD on episodic memory. The goal of this review is to raise awareness of the strides that cognitive neuroscientists have made in understanding intact and dysfunctional memory. Knowledge of the specific memorial processes that are impaired in AD may be of great value to basic scientists developing novel therapies and to clinical researchers assessing the efficacy of those therapies.

Keywords

Alzheimer's disease; memory; memory disorder

Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for more than two-thirds of all cases of dementia [1]. The most important risk factor for AD is age,

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followed by an APOE4 genotype. A 2007 report released by the Alzheimer's Association estimated that more than 5 million Americans are currently diagnosed with AD, while a Delphi consensus study projected that the global prevalence of AD will quadruple by the year 2040 to over 80 million cases in total [2,3]. Just as this disease is often devastating at the individual and family levels, the high prevalence of AD means that it is also economically and societally burdensome. Indeed, AD represented the third most costly health condition in the USA in 2000, and is of growing financial relevance for health policy planning in other industrialized and developing nations [4-6]. Perhaps due to mounting evidence regarding the gravity of the situation, there has been a crescendo of research interest in AD over the past decade, with 50% more papers published on the topic in the year 2007 than 1997 (Pubmed keyword search, MeSH term: Alzheimer disease). Throughout this period, one major area of research in AD has focused on the cognitive impairments exhibited by patients.

Clinicians and researchers have identified six cognitive domains that are commonly disturbed in patients suffering from AD: memory, executive functioning, language, visuospatial functioning, attention and affect. Of these disturbances, memory impairment is the central problem. Memory problems are among the most frequent reasons for admission to residential nursing facilities [7]. A recent prospective, longitudinal study reported that delaying the onset of nursing home care for elderly adults with dementing illnesses by 1 month would result in annual savings of US\$4 billion for the USA [8]. Moreover, it has been suggested that community-dwelling individuals diagnosed with AD score higher on scales of quality of life than institutionalized patients at every stage of the disease [9]. It has also been suggested that caregivers are more likely to avoid depression and to receive support from family and friends when patients exhibit fewer functional limitations [10]. While preventive, disease-modifying and curative therapies for AD must be aggressively pursued as the over-riding goals of pharmaceutical research, in the interim drugs that effectively treat the memory impairments associated with AD may benefit patients, their families and society at large.

Treatments for AD

Reversible acetylcholinesterase inhibitors represent the first and most widely prescribed class of pharmaceuticals approved by the US FDA for treatment of the cognitive disturbances caused by AD. Drugs in this class include donepezil, galantamine, rivastigmine and tacrine. Acetylcholinesterase inhibitors are thought to improve global cognitive functioning by increasing the neurotransmitter concentration at cholinergic synapses at many sites throughout the brain [11]. The only other FDA-approved treatment for the cognitive manifestations of AD is memantine, a noncompetitive, low-affinity NMDA receptor antagonist. It has been widely reported that memantine works by preventing excitotoxicity (the death of neurons resulting from over stimulation by glutamate), although this putative mechanism is unproven in humans. Memantine may also improve cognitive function by modulating NMDA receptors to sharpen the neural signal and decrease background noise. However, studies have suggested that the clinical effects of memantine may be due, at least in part, to its role as a dopaminergic agonist [12]. Acetylcholinesterase inhibitors and memantine are frequently prescribed in tandem, although memantine is only approved for the treatment of moderate and severe AD (Table 1) [13].

In addition to these two established therapies, dozens of possible drugs for AD are in various stages of development [14]. Many of the possible disease-modifying therapies are based on the amyloid hypothesis, which posits that the cognitive disturbances of AD result directly or indirectly from β -amyloid ($A\beta$), either soluble as dimers and oligomers, or deposited in amyloid plaques in particular regions of the CNS [15]. It should be noted that synaptic loss and cognitive dysfunction have been most closely associated with tau pathology in AD, and much less well correlated with amyloid pathology. Tau pathology and amyloid pathology are both thought to

disrupt neuroplasticity, the process of forming and removing synapses that is believed to underlie memory. Recently, both tramiprosate, designed to bind to and maintain A β peptides in their nontoxic soluble form, and tarenflurbil, designed to selectively lower the concentration of A β_{42} by modulating γ -secretase activity, have failed high-profile Phase III clinical trials [16,17]. With the failure of these drugs, one of the most prominent possible therapies for AD is administration of monoclonal antibodies or antibody fragments to A β peptides [18].

Memory systems

Understanding the specific memory deficits that AD patients experience is essential to designing and assessing the efficacy of novel pharmaceuticals for the treatment of memory impairments. Although once thought to be a simple concept, memory is now considered to be a collection of mental abilities that use different systems and components within the brain. Memory research that began with neuropsychological studies of patients with focal brain lesions and today includes techniques such as PET, functional MRI (fMRI) and event-related potentials (ERPs) has provided the rationale for a more refined and improved classification scheme [19]. Six major memory systems have been characterized (Figure 1):

- Episodic memory is the memory system employed when consciously remembering a particular episode of one's life, such as sharing a meal with a friend;
- Semantic memory represents the store of conceptual and factual knowledge that is not related to any specific memory, such as the color of broccoli or for what purpose a fork is used;
- Simple classical conditioning involves the pairing of two stimuli, an unconditioned stimulus and a conditioned stimulus. When paired together repeatedly, the response associated with the conditioned stimulus can be elicited by the unconditioned stimulus alone;
- Procedural memory is the ability to learn cognitive and behavioral skills that operate at an automatic and unconscious level, such as learning to ride a bicycle or to play the piano;
- Bringing together the traditional fields of attention, concentration and short-term memory, working memory refers to the ability to temporarily maintain and manipulate information that one needs to keep in mind;
- Priming occurs when a prior encounter with a particular item changes the response to the current item.

In studies of AD patients, cognitive neuroscientists have found some of the six major memory systems to be severely impaired and others to be relatively preserved [20]. Studies have consistently shown semantic memory to be disrupted in AD, with patients exhibiting particular deficits in naming categorized items [21]. The disruption of semantic memory in AD patients has often been attributed to pathology in the anterior and inferolateral temporal lobes, and the frontal lobes, which presumably causes a loss of neuronal dendritic trees in these cortical regions [22,23]. Studies indicate that several forms of classical conditioning may be impaired in AD patients, including amygdala-dependent fear conditioning and eyeblink conditioning that may be supported by inputs from the entorhinal cortex to the hippocampus [24,25]. Experiments testing procedural memory suggest that while this memory system is diminished compared with healthy age-matched controls, it may be relatively intact compared with other forms of memory in AD patients [26,27]. Findings from working memory paradigms indicate that the ability to keep information in mind is very vulnerable to manipulations that divide or interrupt attention in AD patients [28]. Deficits in working memory may reflect damage to the frontal lobes in AD patients [29,30].

Studies of priming have reported mixed findings in AD patients. In repetition priming experiments the participant studies a word or picture and is later presented with the identical stimulus. If priming is intact, then the stimulus should be processed more quickly when viewed for the second time than the first time. Several researchers have reported preserved repetition priming in AD patients [31-33]. Repetition priming is thought to be supported by the frontal lobes [34]. In its simplest form, semantic priming involves presentation of an item, such as the word 'dog', and subsequent presentation of a semantically related item, such as the word 'cat'. The experience of processing the original stimulus (dog) is expected to lead to faster processing of the semantically related stimulus (cat). In AD, some studies have reported semantic priming to be normal [35], while others have found diminished semantic priming [36], and still others have found greater-than-normal semantic priming [37].

Clinical importance of episodic memory in AD

Of the six major memory systems, episodic memory is the most clinically relevant for AD patients. Disruptions to the episodic memory system are among the earliest signs and symptoms of AD [38]. Early in the disease, such disruptions may result in misplaced keys, missed appointments and late bills. Individuals and their families may attribute these occasional and seemingly innocuous incidents of forgetfulness to fatigue, distraction or 'senior moments'. However, the episodic memory system is also essential for remembering more critical events, such as whether or not the stove has been turned off and if medications have been taken. Clinical observations suggest that potentially dangerous incidents of forgetfulness often precipitate the initial visit to a behavioral neurologist, geriatric- or neuropsychiatrist, geriatrician, neuropsychologist or other health professional with expertise in memory disorders. Making a confident clinical diagnosis of probable AD is a complex process that is based on patient history, a report from a family member or friend of the patient, physical examination, and laboratory and neuroimaging studies [39]. Standardized neuropsychological tests may be used to confirm the diagnosis of dementia and to assess the severity of the patient's cognitive impairments [40]. Brief neuropsychological tests used to directly assess episodic memory in the clinical setting include the Montreal cognitive assessment (MoCA [201]), the blessed information-memory-concentration test [41], the drilled word span test [42], the Mini-Cog [43], the mini-mental state examination [44], the 7-min screen [45], the three words-three shapes memory test [42] and the word list memory test of the Consortium to Establish a Registry for Alzheimer's Disease [46].

From a clinical perspective, episodic memory deficits continue to represent one of the most significant functional problems as a patient progresses through the mild and moderate stages of AD. Disruptions to the episodic memory system usually follow Ribot's law, which states that events and items experienced just prior to an ictus are more vulnerable to decay than remote memories [47]. Thus, as episodic memory abilities decline in AD patients, events from the distant past are relatively better remembered than events that occurred after or shortly before the onset of the disease [48]. Of benefit, this means that watching movies or discussing life events from youth or early adulthood may orient and soothe a patient with AD. However, vivid remote memories may sometimes be confused with psychotic delusions or hallucinations. For example, caregivers may become concerned when a patient claims to have recently seen and interacted with a long-dead friend or family member. Inevitably, the inability to remember recent events or learn new information leads to functional deficits that are devastating for the patient and the caregiver.

Episodic memory from a cognitive neuroscience perspective

Owing to its clinical importance, the episodic memory system is among the most thoroughly researched topics in cognitive neuroscience. From early lesion studies and more recent work

in neuroimaging, it is apparent that the episodic memory system is supported by the medial temporal lobes, especially the hippocampus (Figure 2) [49,50]. Other structures that appear to be involved in the episodic memory system in humans include the anterior and dorsomedial nuclei of the thalamus [51], the fornix [52], the mammillary bodies [53], the mammillothalamic tract [54] and the retrosplenial cortex [55]. Findings from animal studies suggest that several more structures may play roles in episodic memory, including the diagonal band of Broca's area [56] and the presubiculum [57].

Researchers have found evidence of changes in many of these anatomical areas in AD patients. The hippocampus has long been viewed as one of the sites most severely damaged in AD patients. Studies have demonstrated hippocampal atrophy, and alterations in hippocampal shape and surface structure in AD patients compared with nondemented older adults [58-60]. Neurons in the vertical limb of the diagonal band of Broca's area, a major source of innervation to the hippocampus, are paradoxically more metabolically active in AD patients than in age-matched controls [61].

MRI findings have suggested that the fornix and the mammillary bodies are atrophied in AD patients compared with healthy controls and with patients with mild cognitive impairment (MCI).[62], a condition thought to represent a transition state between healthy aging and AD [63]. Neuropathological studies have shown that regions including the entorhinal transition area and the presubiculum contain exceptionally high levels of amyloid plaques in AD patients [64].

Cognitive neuroscientists have not yet completely elucidated the mechanisms by which the medial temporal lobes store and retrieve memories of items and events. However, certain aspects of the neural processes underlying episodic memory are generally accepted [50]. Sensory information, emotions and thoughts present at the time of an event are processed in various regions of the cerebral cortex. The entorhinal cortex, located in the anterior portion of the parahippocampal gyrus, is in reciprocal communication with these cortical areas and serves to transmit information about organization relevance to other regions. From the entorhinal cortex, the signals are sent to the dentate gyrus and then to the CA3 region of the hippocampus via the mossy fiber pathway. Neurobiological and computational modeling studies support the theory that the CA3 region is essential for creating the so-called hippocampal index, the distinct record of an item or event that facilitates subsequent retrieval [65-67]. Studies have suggested that the entorhinal cortex [68], the dentate gyrus [69] and the CA3 region of the hippocampus [70] are all altered to some degree in AD patients.

Memory retrieval is often initiated by experiencing an environmental or internal cue that shares specific features with a stored memory. The cue, whether sensory, emotional or based in thought, travels from various cortical locations to the entorhinal cortex and then to the CA3 region of the hippocampus. By some mechanism, the cue activates the hippocampal index associated with the index of the original stored memory – not the memory itself – in the CA3 region. This activation leads to the reinstatement of much of the neural pattern of activity associated with the original event in the CA1 region of the hippocampus, the subiculum and various cortical regions [66,67]. This reinstatement of cortical activity leads to the experience of 'remembering' the sights, sounds, smells, tastes, emotions and thoughts that were present at the time of the original episode. It must be noted that reactivation of the hippocampal index may only be necessary for neural reinstatement of episodic memories that have not yet been consolidated [71]. Consolidation refers to the process by which the distributed pattern of cortical neural activity associated with a particular memory is directly linked together. It is thought that once consolidation has occurred, encountering an environmental or internal cue may lead to retrieval of the memory directly from cortical-cortical connections without the need for the hippocampus [72]. Studies indicate that sleep may be critical for consolidation

[73]. Sleep spindles, a defining feature of stage two sleep, are thought to be particularly important [74] and may be decreased in number in patients with AD compared with controls [75]. That AD patients retain the ability to recall remote memories, but are unable to learn new information or recall relatively recent events is consistent with impairments in medial temporal lobe function, consolidation or both.

Cognitive neuroscientists have explored several types of episodic memory supported by the medial temporal lobes. Recall and recognition represent the two quintessential tests of episodic memory. In a standard recall experiment, an individual studies a series of items (e.g., the words fence, kangaroo and truck) and is subsequently asked to recall the items without their re-presentation, and often without cues of any kind. In a typical recognition memory experiment, an individual is presented with a series of items (e.g., fence, kangaroo and truck) during the 'study phase'. In the 'test phase', the individual is presented with a randomly ordered series of items (e.g., truck, basketball, tree, fence, kangaroo and pencil), some studied and some unstudied. The individual is asked to declare each item to be 'old' (i.e., previously studied) or 'new' (i.e., novel). Both recall and recognition memory tests are used for assessing episodic memory in AD patients, and each has its strengths and weaknesses. Recall tests are quite sensitive for detecting memory deficits, but are not specific as recall is affected by many factors, including, for example, frontal lobe dysfunction. Although not very sensitive, performing poorly on a recognition memory test more specifically suggests a failure of the hippocampus or other medial temporal lobe structures that are affected in AD, provided that information has been successfully learned or encoded.

Box 1

Six reasons to consider cognitive neuroscience in the development of therapeutics for Alzheimer's disease

- Knowledge of the anatomical correlates of episodic memory may be critical to delivering anatomically targeted immunotherapies based on the amyloid hypothesis.
- Scientists developing new drugs for symptomatic relief of the cognitive disturbances associated with Alzheimer's disease (AD) would benefit from a detailed understanding of the neural correlates and neurochemistry of episodic memory in AD patients.
- Tests that measure particular aspects of episodic memory may be more useful tools in assessing the efficacy of new therapies for AD than current cognitive tests.
- Outcome measures that directly measure brain physiology while individuals are performing a memory task might reduce the costs and human risks associated with clinical trials.
- Measuring an AD patient's brain physiology during a memory task might also be a valuable tool for assessing the usefulness of approved therapies in that individual.
- Tests of episodic memory taking advantage of the discoveries of cognitive neuroscience may prove useful for the early diagnosis of mild cognitive impairment and mild AD.

Researchers have suggested that two distinct neural processes, recollection and familiarity, support recognition memory [76]. Recollection refers to the retrieval of specific context-bound information about an item or event, while familiarity is defined as a more general, acontextual sense that an item or event has been previously encountered. These two constructs are sometimes consciously experienced in daily life. For example, the unexpected sight of a

particular woman on a crowded city street may elicit an immediate feeling of knowing her without being able to produce any specific details about who she is or how she is known. After a moment of thought, these details may come into mind and the woman's identity – for example, the nice clerk at the record store you visited last Tuesday – becomes apparent. Familiarity describes the initial feeling of knowing the woman without being able to place her, while recollection captures the subsequent remembering of the specific details of her identity. Findings from a variety of recognition memory paradigms indicate that both processes are impaired in AD patients, with a greater decrement in recollection than familiarity reported by many researchers [77,78]. In theory, relying on one's sense of familiarity, and not on a firm recollection, would depress the hits (i.e., 'old' responses to studied items) and increase false alarms (i.e., 'old' responses to novel items). Indeed, this is exactly the pattern typically reported in recognition memory studies of AD patients [79]. Studies suggest that recollection requires an intact hippocampus, while familiarity appears to be supported by the perirhinal and lateral entorhinal cortex [80,81]. By carefully dissociating the processes underlying recognition memory, cognitive neuroscientists have gained insight into the patterns of medial temporal lobe dysfunction in AD patients.

In addition to the medial temporal lobes, the frontal lobes are also important for episodic memory. The frontal lobes play key roles in the acquisition and encoding of information, the retrieval of information in the absence of contextual cues, the recollection of the source of information, and the assessment of the temporal sequence and recency of events. Dysfunction of the frontal lobes can lead to distortions of episodic memory [82,83]. In mild cases, new information may become associated with the wrong context or incorrect specific details, a phenomenon that has been called both a provoked confabulation [84] and a false memory [79]. Studies have suggested that mild AD patients are more likely than healthy controls to exhibit false memories when tested on personal episodic memory [85-87]. More severe damage to the frontal lobes can lead to spontaneous confabulation [88]. Spontaneous confabulation refers to the formation of a 'memory' for an event that did not occur, but is merely consistent with current information. For example, an individual who spontaneously confabulates may not remember that she has rearranged the furniture in the living room. Upon seeing the furniture in locations that do not match her memory, she may create a new 'memory' that involves someone breaking into the house and rearranging the items. Such confabulations frequently occur in mild AD, even in the absence of frontal lobe pathology, simply because these patients cannot remember that their memory is impaired. They show inappropriately high confidence in their memory, and therefore assume that any discrepancy between their memory and the external world must be related to a problem in the world and not with their memory. Researchers have reported that some AD patients spontaneously confabulate as a result of their illness [89]. Spontaneous confabulation in AD may be associated with delusions and aggression [90], behaviors caused by frontal lobe dysfunction in AD patients [83,91,92].

Expert commentary

Deterioration of episodic memory is the central clinical feature of AD, a disease associated with tremendous personal suffering and financial costs. As the number of cases increases, research interest in therapies for AD is booming [14]. Many involved in the development of therapies for AD have focused their efforts on treating the neuropathology thought to be responsible for the progressive cognitive changes associated with the disease. It follows logically that diminishing the concentration of the A β plaques and neurofibrillary tangles commonly observed in the brains of AD patients at autopsy will lessen episodic memory impairments and other cognitive disturbances. Ultimately, the goal of treatment will be to prevent the formation of this pathology entirely. We offer six compelling, specific arguments for why it also may be useful for pharmaceutical scientists, directors of clinical trials involving

AD patients and clinicians to be aware of the strides that cognitive neuroscientists have made in understanding episodic memory in healthy and memory-impaired individuals (Box 1).

First, knowledge of the anatomical correlates of episodic memory may be critical to delivering anatomically targeted immunotherapies based on the amyloid hypothesis. Therapies based on the amyloid hypothesis have been designed to cross the BBB and then be distributed throughout the CNS, both to sites where plaques are present and to regions where they are absent. There is evidence that some anti-amyloid immunotherapies have caused deleterious effects when distributed throughout the brain and spinal cord. For example, the Phase IIa trial of an A β vaccine known as AN-1792 was terminated when several of the 360 patients who were given the vaccine developed meningoencephalitis [93]. Although the exact cause of the meningoencephalitis was never determined, some have suggested that it was due to an immune response not just to A β , but also to vascular amyloid [94]. Remarkably, autopsy of one of the AN-1792 clinical trial patients who developed meningoencephalitis revealed clearing of A β throughout the brain [95]. As mentioned earlier, administration of monoclonal antibodies or antibody fragments against A β is considered to be among the most promising potential therapies for AD [96]. However, it has been suggested that in high concentration, passive immunotherapy may also lead to brain inflammation and hemorrhage [18]. If passive immunotherapy proves to be an effective method of clearing A β , but is also dangerous when distributed throughout the CNS, then it may be beneficial to develop techniques for delivering antibodies or antibody fragments directly to the neuroanatomical sites where plaque deposition is contributing to cognitive impairment. Awareness of the neural correlates of episodic memory would be essential to any such effort.

Second, scientists developing new drugs for symptomatic relief of the cognitive disturbances associated with AD would benefit from a detailed understanding of the neural correlates and neurochemistry of episodic memory in AD patients. With increasing numbers of highly touted potential therapies failing clinical trials, it is possible that drugs based on the amyloid hypothesis (and other current theories of the basis of AD) will not have a major effect on the clinical course of AD. If this proves to be the case, then there may be renewed interest in developing treatments for episodic memory deficits and other cognitive impairments. Such drugs might augment the cholinergic system in new ways or more specifically target the glutamatergic NMDA and dopaminergic receptors that may be responsible for the cognitive benefits of memantine. Novel therapies based on additional neurotransmitter systems may be developed as neuroscientists learn more about the molecular underpinnings of various aspects of intact and impaired episodic memory.

Third, tests that measure particular aspects of episodic memory may be more useful tools in assessing the efficacy of new therapies for AD than current cognitive tests. Tramiprosate, the anti-amyloid therapy designed to maintain A β peptides in a nontoxic form, failed in a large multicenter Phase III trial in 2007. A press release issued by the manufacturer of tramiprosate suggested that very high statistical variance among centers on the primary behavioral end points, the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) [97] and the Clinical Dementia Rating-Sum of Boxes (CDR-SB) [98], may have been partly responsible for the failure of the trial [202]. The ADAS-cog and CDR-SB were designed to assess a broad assortment of cognitive abilities in AD patients, including episodic memory, through questions about activities of daily living and some cognitive testing. These scales are widely used in AD clinical trials. However, they are not designed to provide information about recollection and familiarity, false memories or other issues in episodic memory. Indeed, some cognitive neuroscientists have already proposed new versions of the recognition memory section of ADAS-cog that would take false memory into account [99]. It is possible that particular tests of episodic memory drawn from the cognitive neuroscience literature might have illuminated differences in the treatment group versus the placebo group in the tramiprosate trial, as well

as other recently failed trials. The feasibility of using an episodic memory paradigm as an outcome measure in a clinical trial has already been demonstrated [100]. In that clinical trial, researchers testing the efficacy of a substance known as AIT-082 assessed the performance of AD patients on a false-memory paradigm before and after treatment [100]. As more is learned about the details of episodic memory (e.g., the neural correlates of recollection vs familiarity), more specific tests and elements of larger scales such as the ADAS-cog can be devised, validated and implemented in clinical trials.

Fourth, outcome measures that directly measure brain physiology while individuals are performing a memory task might reduce the costs and human risks associated with clinical trials. Owing to the tremendous statistical variance associated with current outcome measures such as the ADAS-cog, AD clinical trials typically require enrollment of several hundred to more than 1000 patients to achieve statistical significance. Implementing a more specific test of episodic memory as an outcome measure, as discussed previously, might lead to somewhat lower variance. However, variance would likely be decreased to a much greater extent by using a specific test of episodic memory that is time-locked with a physiologic measure sensitive to improvements in memory, such as ERPs or fMRI, as an outcome measure. Researchers could design smaller, less costly clinical trials that would expose fewer AD patients to experimental medications if they had reasonable expectations of low statistical variance.

Fifth, measuring an AD patient's brain physiology during a memory task might also be a valuable tool for assessing the usefulness of approved therapies in that individual. It has been suggested that the cognitive response of individual AD patients to acetylcholinesterase inhibitor therapy varies from dramatic to minimal [101]. However, response to therapy cannot always be determined clinically. Studies have reported that AD patients who were thought not to have responded to acetylcholinesterase inhibitor therapy displayed a decline in function when the medication was discontinued [102]. Since the financial costs of acetylcholinesterase inhibitor therapy are not insignificant, a cost effective physiologic method for determining the response to therapy in individual patients would be helpful.

Event-related potentials may be able to serve as such a method to measure the brain physiology during the performance of a memory task for either an approved therapy as part of standard clinical care, or an experimental therapy as part of a clinical trial. Many ERP studies indicate that on a recognition memory test, studied words elicit a larger late positive component over parietal scalp areas than do unstudied words [103]. This parietal 'old/new effect' is of greater amplitude when test items are consciously remembered [104], when there are numerous study-test repetitions [105] and when correctly recognized items are subsequently recalled [106]. These findings have led researchers to associate the parietal old/new effect with the process of recollection. Previous research from our laboratory has suggested that the parietal effect amplitude is decreased in mild AD patients compared with controls, consistent with behavioral findings suggesting that recollection is markedly impaired in AD patients [79,107]. Thus, measuring parietal effect amplitude prior to initiating treatment and then again after some period of treatment might provide a physiologic measurement of episodic memory improvement. Future studies might assess the physiological effects of donepezil and other acetylcholinesterase inhibitors, memantine and combined acetylcholinesterase inhibitor, and memantine therapy in AD patients. Eventually, such testing might become routine in the clinical setting for devising individualized therapeutic protocols.

Sixth, tests of episodic memory taking advantage of the discoveries of cognitive neuroscience may prove useful for the early diagnosis of MCI and mild AD. At present, widespread screening of elderly adults for memory impairment is not typically recommended, as the social and financial costs are thought to outweigh the benefits of early diagnosis [108-110]. If more effective therapies for AD become available, then it may be advisable for most or all

community-dwelling elderly adults to be screened. Potential approaches to episodic memory-based screening include very brief neuropsychological tests administered by telephone [111] or in the primary care setting [43] and lengthier web-based assessments [112]. Testing by phone or in the primary care setting has the advantage of brevity (e.g., <3 min are required to administer the Mini-cog developed by Borson and colleagues) and easy access, but perhaps at the cost of specificity. Web-based cognitive tests require internet access and out-of-pocket payment. Moreover, such testing requires the elderly individual or a family member to actively pursue screening. Despite these drawbacks, web-based testing methods may eventually represent the most efficacious screening strategy, as they allow for longer tests drawn directly from the cognitive neuroscience literature.

Five-year view

Cognitive neuroscientists will continue to make refinements in their understanding of episodic memory in healthy individuals and in AD patients. We foresee particular advancements in delineating the neural correlates of episodic memory using electro physiological and neuroimaging techniques. Technological advances may allow multiple techniques (e.g., ERPs and fMRI) to be used simultaneously during memory tests, fostering insight into the temporal and spatial relationships of the neural regions involved. Future clinical trials may assess the efficacy of AD therapies using paradigms drawn from the cognitive neuroscience literature. Such trials may implement episodic memory tests as standalone outcome measures or time-locked with techniques that measure brain physiology. Finally, technologies that might aid memory-impaired patients with activities of daily living, such as paper organizers, personal digital assistants [113] and even neural prostheses [114], may be developed and offered to AD patients.

Key issues

- Alzheimer's disease (AD) is a progressive neurodegenerative illness that accounts for more than two-thirds of all cases of dementia and represents an increasingly important public health problem.
- Memory impairment is the most common and debilitating cognitive impairment associated with mild and moderate AD.
- Of the six major memory systems, the episodic memory system is the most clinically relevant for AD patients, as impairments in this system lead to poor memory for recent events, which results in functional deficits.
- The pattern of episodic memory impairments displayed by AD patients is consistent with damage to areas of the medial temporal and frontal lobes.
- Awareness of the neuroanatomical and physiological correlates of episodic memory may prove essential to pharmaceutical scientists developing targeted immunotherapies and other novel therapies for AD.
- Episodic memory tests drawn from the cognitive neuroscience literature may be implemented as outcome measures in future AD clinical trials.
- Physiologic techniques such as event-related potentials and functional MRI may allow for assessment of treatment-related memory improvements in individual AD patients.

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Episodic memory



“ Last night I saw the most wonderful one-man play at the Main Street Theatre. ”



Semantic memory

“ Who is this man on the one dollar bill? ”



“ That is George Washington. He was the first president of the United States. ”





Figure 1.
Major memory systems in everyday life.

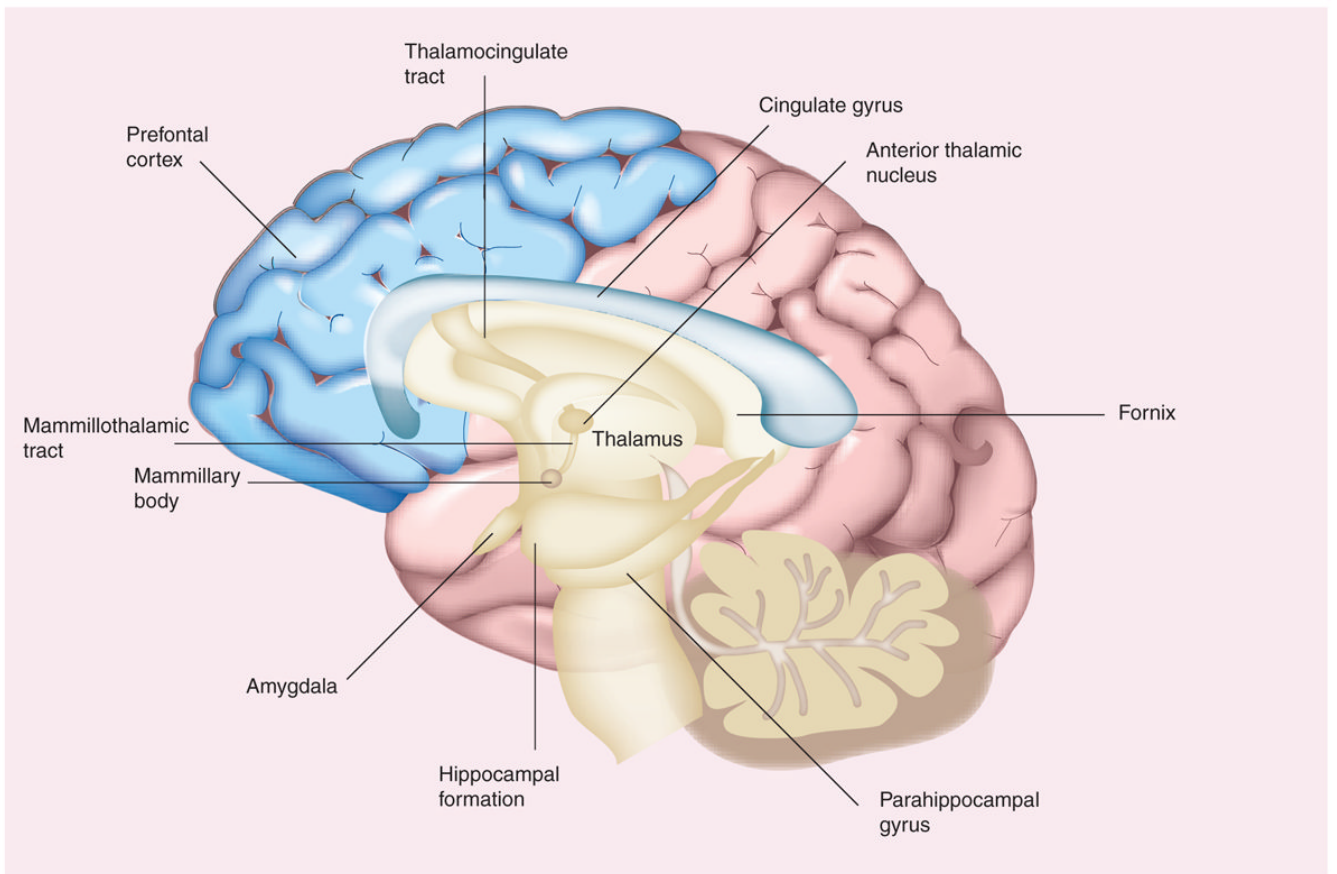


Figure 2.
Selected brain regions involved in episodic memory.

Table 1

Current therapies for Alzheimer's disease.

Drug(s)	Proposed mechanism(s)	Status
Donepezil; galantamine; rivastigmine; tacrine	Increasing the neurotransmitter concentration at cholinergic synapses at many sites throughout the brain	US FDA-approved for the symptomatic treatment of mild and moderate AD; donepezil is also approved for use in severe AD
Memantine	Preventing glutamate excitotoxicity and/or stimulating dopamine receptors	FDA approved for the symptomatic treatment of moderate and severe AD

AD: Alzheimer's disease.