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COGNITIVE FUNCTION AND AGING (DAVE MORGAN, SECTION EDITOR)

Neuroscience-based Tests for Assessing Cognitive Changes in Normal Aging and in the Prodromal Phase of Alzheimer's Disease

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Abstract Slow decline in cognition is key to the clinical diagnosis of Alzheimer's disease (AD). This diagnosis relies on screening tests insensitive to detection of prodromal AD, which occurs years before the appearance of clinical symptoms. Neuroscience-based tests of eyeblink classical conditioning, spatial navigation, and object recognition are associated with synaptic-level function. They show promise in detecting early changes in AD-impacted memory circuits. Eyeblink conditioning engages synapses dependent upon nicotinic acetylcholine receptors and medial septal cholinergic input to the hippocampus. Spatial navigation and object recognition engage perforant pathway entorhinal cortical input to the hippocampus. Synapses in these circuits are among the earliest impacted by beta amyloid. These three translational tests are well characterized in normal aging and AD in humans and pertinent animal models, including organisms expressing the AD risk factor apolipoprotein E4. They may detect cognitive decline in prodromal AD and prove useful for population screening and evaluation of therapeutic interventions.

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Introduction

Gradual memory loss and impairment in other cognitive functions used in the clinical diagnosis of Alzheimer's disease (AD) [1, 2] occur after neuropathology has caused irreversible deterioration in the brain [3]. Recent research advances led to recognition of a prodromal phase of AD that occurs years before the appearance of clinical symptoms [4, 5••, 6••]. Biomarkers identifiable in the cerebral spinal fluid (CSF) and brain demonstrate that beta amyloid (Aβ) aggregation and deposition increase slowly from cognitive normality in healthy adults to moderate severity in patients with clinically diagnosed AD. In humans, a slow accumulation of Aβ in the brain precedes cognitive impairment as measured by the brief neuropsychological screening tests that are currently used. These early changes are exacerbated in the presence of the apolipoprotein E (*APOE*) ε4 allele encoding apolipoprotein E4 (apoE4). However, longitudinal data indicate that cognitive decline is only weakly related to change in Aβ burden in the brain [7•]. Furthermore, the duration of the disease appears to be unaffected by genetic factors such as early onset in *APOE* ε4 carriers [8••].

The largest known genetic risk factor for sporadic AD is the ε4 allele of the apolipoprotein E gene [9]. The *APOE* ε4 allele markedly increases AD risk and decreases age of onset, likely through its strong effect on the accumulation of Aβ by impairing Aβ clearance from the brain [10••]. *APOE* ε4 carriers in the age decades of the 50s and 60s have more rapid memory loss and reduced learning efficiency than matched *APOE* ε4 noncarriers. Clinically healthy *APOE* ε4 carriers diverge from noncarriers before the age of 60 years [11].

The clinical assessment of cognitive changes in AD has traditionally relied on brief cognitive screening tests that are not sensitive to the earliest cognitive changes. Detecting these early cognitive changes before clinical AD symptoms develop is vital for the development and eventual success of therapeutic interventions. Biomarkers can involve invasive (eg, spinal tap) or expensive (positron-emission tomography [PET]) hospital-based procedures. Therefore, population-based cognitive screening with simpler, more accessible techniques is desirable as an initial step to detect prodromal AD and enhance the ability to treat the disease successfully before irreversible changes in the brain ensue.

Neuroscience-based translational cognitive tests of eyeblink classical conditioning, object recognition, and spatial navigation show promise in detecting early changes associated with risk factors of developing age-related cognitive decline in the absence of frank dementia and AD. Extensive knowledge on the neurobiological substrates of eyeblink classical conditioning, spatial navigation, and object recognition has been developed in nonhuman mammalian species and extended to humans. These tests are also well characterized in normal aging and in animal models of age-related cognitive decline and AD. These three neuroscience-based tests detect disruption in synapses in brain circuits impaired in prodromal AD.

For some years, impairment in acetylcholine neurotransmission was a major focus in AD research [12–14], and early treatment strategies aimed to ameliorate cholinergic function. More recently, studies indicate that neuron loss in the forebrain cholinergic system is associated with end-stage AD, whereas upregulation in the septohippocampal system occurs in the prodromal phase [15, 16]. Distinct Aβ oligomers and fibrils induce loss of nicotinic acetylcholine receptors (nAChRs) and interference with cholinergic neurotransmission [17•]. Disruption of the septohippocampal cholinergic system impairs delay eyeblink classical conditioning [18]. Lower numbers of nAChRs also have been associated with poor conditioning [19, 20•] as has knock out of α7 nAChRs [21]. Impairment resulting from septohippocampal cholinergic perturbations and loss of nAChRs are features of prodromal AD that may be detected by eyeblink classical conditioning.

The principal source of cortical input to the hippocampal formation is the perforant pathway, a large neuronal projection arising from layer II of the entorhinal cortex. Pathological changes in the perforant pathway occur early in disease progression in human AD as shown in histopathological [22, 23] and neuroimaging studies [24, 25]. Amyloid imaging demonstrates the selective vulnerability of the perforant pathway circuitry in human AD. Brain magnetic resonance imaging (MRI) and [^{11}C]Pittsburgh Compound B (PiB)–PET scans in 93 healthy elderly patients and 43 patients with mild cognitive impairment demonstrated that subtle deficits in episodic memory were closely related to Aβ deposition in the medial temporal neocortex, loss of white matter volume in the perforant pathway, and shrinkage of hippocampal volume [26].

Negative amyloid scans indicate the absence of AD with high accuracy, but some healthy elderly volunteers also have positive amyloid scans [27] in the seeming absence of cognitive impairment [28]. The value of biomarkers predicting conversion to clinical AD has limitations in the absence of tests sensitive to subtle cognitive changes in prodromal AD. Investigations using animal models of AD also indicate that the entorhinal cortex and perforant pathway input to the hippocampus are among the earliest affected and most vulnerable regions of Aβ pathology [29–31]. Spatial ability likely becomes affected in prodromal AD because Aβ selectively disrupts perforant pathway input to hippocampus from the entorhinal cortex. Together with the fact that eyeblink classical conditioning is sensitive to alterations in the cholinergic septohippocampal system and impairment and loss of nAChRs, the object recognition, spatial navigation, and eyeblink conditioning tests may help to identify at-risk individuals in the prodromal phase of AD and augment predictions about which biomarker-positive individuals are most likely to develop clinical AD symptoms (Fig. 1).

The Model System of Eyeblink Classical Conditioning

Based on a foundation of behavioral neuroscience research initiated in nonhuman mammals, classical conditioning of the eyeblink response has become one of the best-documented learning paradigms in all mammals, including humans. There is extensive evidence that the neural circuitry for classical eyeblink conditioning is similar in humans and nonhuman mammals. With regard to normal aging, it was suggested that classical conditioning may be the Rosetta stone for brain substrates of age-related deficits in learning and memory [32].

Ivan Petrovich Pavlov elucidated the phenomenon of classical conditioning in dogs and first observed that old dogs conditioned more slowly than young dogs. Russian scientists were also the first to discover age-related impairment in human eyeblink classical conditioning (reported in [33]). This observation of large effects of age on eyeblink

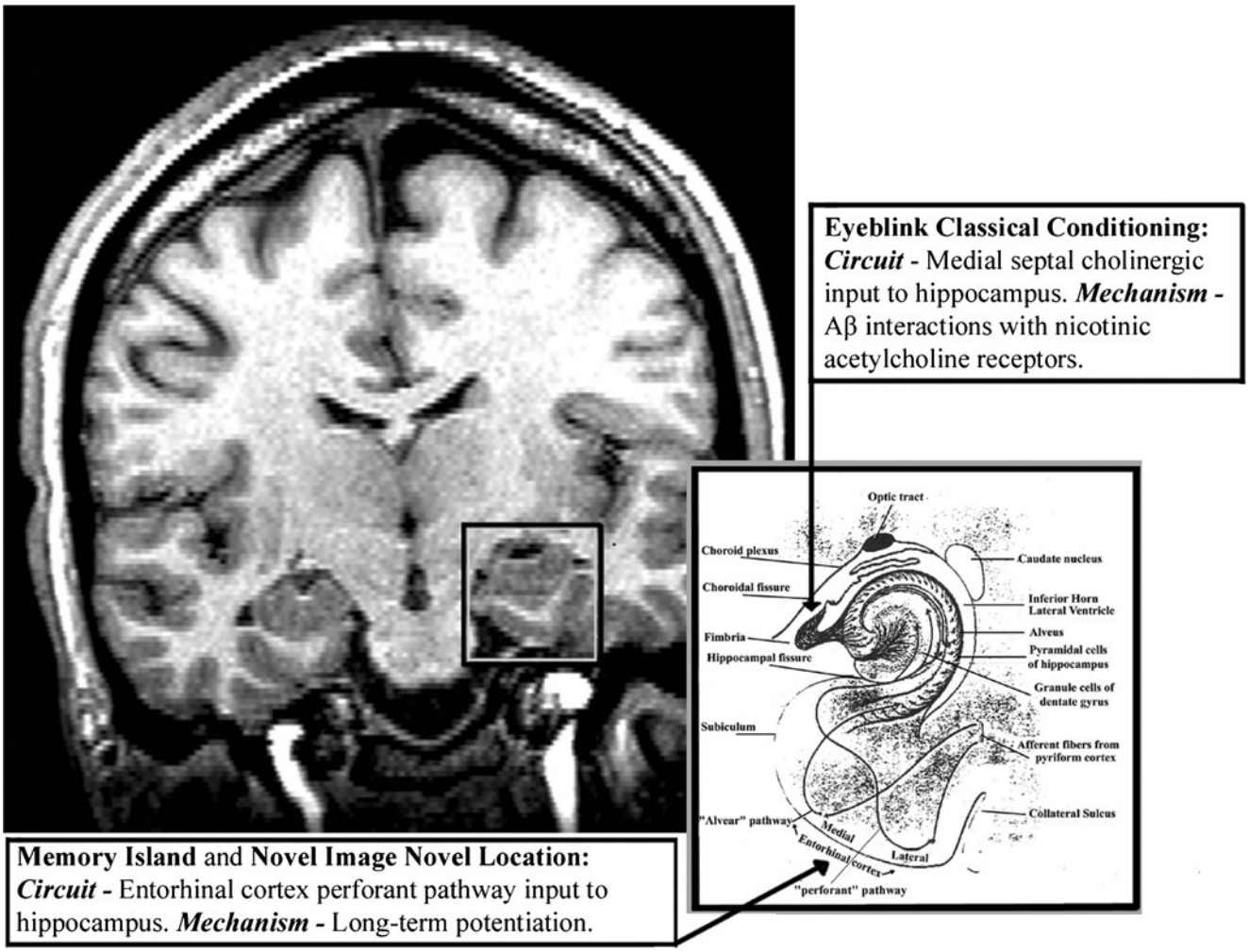

Fig. 1 Brain circuits affected in prodromal Alzheimer's disease (AD) that are engaged in three neuroscience-based tests. 3-Tesla coronal MRI of a healthy 33-year-old male is displayed on the *left*. The box on the MRI highlights the left medial temporal lobe including the hippocampus and associated structures. Illustration of medial temporal lobe structures highlighted in MRI is displayed on the *right*. Eyeblink classical conditioning engages medial septal cholinergic input into the hippocampus carried in the fimbria. Nicotinic acetylcholine receptors in this circuit are impaired by Aβ oligomers and fibrils early on in the early prodromal phase of AD. Memory Island and Novel Image Novel Location engage entorhinal cortex input to hippocampus via the perforant pathway. Long-term potentiation is disrupted in this circuit by early AD pathology Aβ— Beta amyloid; MRI—magnetic resonance imaging

classical conditioning has been replicated and extended in many laboratories (reviewed in [34]).

Eyeblink Classical Conditioning in Alzheimer's Disease

In eyeblink classical conditioning, a neutral stimulus such as a sound (that would not normally elicit a blink) is presented for about half a second before an air puff directed at the cornea (that by itself does elicit a blink) occurs. The sound (usually a pure tone of 1 KHz) and mild (3–5 psi) air puff are presented together in this manner: the tone is on for about 400 ms before the air puff comes on for 100 ms, and then they turn off together. With repeated presentations of the tone and air puff, called the conditioned and unconditioned stimulus (CS and US, respectively), the organism learns to blink to the tone before the air puff comes on. The learned blink that occurs before the air puff comes on is called the conditioned response (CR). Pavlov discovered that the neutral stimulus had to be on for a short while before the onset of the reflex-eliciting stimulus for learning to occur, and he called this timing of CS and US the "delay" classical conditioning paradigm.

Richard Thompson's group discovered that the hippocampus was activated in delay eyeblink classical conditioning in electrophysiological recording studies [35]. Human neuroimaging studies have found analogous hippocampal activation during eyeblink conditioning [36–38]. In the initial behavioral pharmacology studies, Moore et al. [39] reported that systemic administration of the muscarinic acetylcholine antagonist scopolamine disrupted acquisition,

and this result also has been reported in human eyeblink conditioning [40, 41]. Interestingly, compared to wild-type mice, mice lacking apoE (*Apoe*$^{-/-}$) had a reduced number of cortical and hippocampal muscarinic acetylcholine receptors. Whereas scopolamine had a small effect on delay eyeblink classical conditioning in wild-type mice, it had a large effect in *Apoe*$^{-/-}$mice, supporting a role for apoE in cholinergic function [42•]. Impaired apoE functioning may exacerbate cholinergic deficits that contribute to the cognitive impairments seen in AD. While muscarinic acetylcholine receptor number remains stable in late-onset sporadic AD [16], some subtypes of nAChRs are lost [43–45].

The septohippocampal acetylcholine system is much involved in delay eyeblink classical conditioning. The medial septum is the locus of neurons that release acetylcholine throughout the hippocampus. Medial septal multiple unit activity is elicited during delay eyeblink conditioning [46], and lesions of the medial septum [47] or infusion of scopolamine into the medial septum [18, 48] impair delay eyeblink conditioning. Hasselmo [49] suggested that one role of septohippocampal projections is to modulate processing in the hippocampus and that high levels of acetylcholine in the septohippocampal pathway may increase the rate at which new information is processed. Consistent with this notion is the fact that hippocampal acetylcholine increased during delay eyeblink conditioning [50].

As mentioned previously, the cholinergic system loses some classes of receptors in AD. Audioradiographic and histochemical studies of postmortem human brain tissue (eg, Perry et al. [51]) and brain imaging studies in living AD patients [52] demonstrated specific loss of nAChRs in AD. More specifically, the α4 subunit–bearing subtype is selectively lost in AD, whereas the α7 nAChR is retained [43–45]. An antagonist to nAChRs impairs acquisition of CRs [53], whereas agonists selective to nAChRs ameliorate eyeblink conditioning [54] and reverse antagonist effects [55]. Receptor binding studies demonstrated that poor conditioning is associated with lower numbers of nAChRs with the α4 subunit–bearing subtype [19, 20•].

The hippocampus is not the essential site for acquisition of CRs; the essential site is in the cerebellum. Disruption of the brain cholinergic system links AD to the model system of eyeblink conditioning in mammals, including humans [56]. Impairment resulting from septohippocampal cholinergic perturbations and impairment and loss of nAChRs are features of prodromal AD that may be detected by eyeblink classical conditioning.

We first demonstrated that 400-ms delay eyeblink classical conditioning was extremely disrupted in a sample of 20 individuals of a mean age of 82 years with moderate to severe AD [57]. Normal older adults are impaired in eyeblink classical conditioning compared to young adults, but all age groups of normal, nondemented adults, including adults in their 80s and 90s, show clear evidence of associative learning. In probable AD, there is very limited eyeblink conditioning in the first session of testing. However, when given a sufficient number of training trials (eg, 4 or 5 days of 90-trial presentations), patients diagnosed with probable AD acquire CRs [58, 59]. This slowing of the rate of acquisition occurs in animal models when antagonists to cholinergic neurotransmission are introduced [39, 60]. There is strong evidence that the site of interference of cholinergic antagonists in rabbits is the hippocampus [61, 62]. Thus, the results that patients with AD are slow to acquire CRs but eventually do acquire CRs parallels results in rabbits with disruption of the hippocampal cholinergic system. The fact that probable AD patients eventually acquire CRs suggests that the essential cerebellar circuitry for CR acquisition is intact, but that acquisition is disrupted in medial temporal lobe structures. These results parallel knowledge about human AD neuropathology: the cerebellum remains relatively intact.

Eyeblink conditioning had a sensitivity of 95% for AD in our initial study [57]. Solomon et al. [63] reported disruption of eyeblink conditioning in the 400-ms delay paradigm in a sample of probable AD patients in the early 70s, a decade younger than our first sample. An additional replication in which eyeblink conditioning was shown to differentiate some cerebrovascular dementia patients from patients with probable AD was performed [64]. Sensitivity for AD in that sample was 86%, and it was 100% in a sample of patients diagnosed with AD at an AD research center [65]. Eyeblink conditioning in adults with Down's syndrome and AD neuropathology over the age of 35 years was similar to conditioning in probable AD patients [66, 67]. Furthermore, eyeblink conditioning is selective to AD neuropathology. Eyeblink classical conditioning in patients with other neurodegenerative diseases such as Huntington's disease [68] and Parkinson's disease [69, 70] is relatively normal and clearly differentiated from eyeblink conditioning in AD.

Eyeblink Classical Conditioning and Early Detection of Alzheimer's Disease

Longitudinal results suggest that eyeblink conditioning has utility in early detection. Of the 20 age-matched control patients in the initial testing, 8 showed conditioning in the AD range [57]. Of the eight poor conditioning control patients, four developed dementia within 3 years and one died [71]. Thus, of eight nondemented patients age-matched to probable AD patients who scored on eyeblink conditioning in the AD range, only three remained cognitively normal. The 12 age-matched control patients scoring in the normal range remained cognitively intact. This 3-year longitudinal study of nondemented adults tested on eyeblink conditioning revealed that 63% of the cognitively

normal patients who were poor conditioners developed dementia within 3 years.

A second longitudinal study followed 20 cognitively normal elderly participants over a 2-year period (half good conditioners, half poor conditioners) [72]. A neuropsychological test battery administered 2 years after the initial eyeblink conditioning revealed significantly worse performance in poor conditioners on visuospatial abilities, semantic memory, and language, abilities showing early decline in AD. Over a 2-year period, two of the poor conditioners (and none of the good conditioners) failed significantly, and one was diagnosed with probable AD.

Results from a third follow-up study of older adults tested 5 to 8 years previously also indicated that poor-conditioning older adults scored significantly lower on neuropsychological tests used to characterize cognitive deficits in AD [65]. Among 59 patients over the age of 70 years, eyeblink conditioning scores less than 25% CRs were associated with significantly poorer performance on clock-drawing tests. All neuropsychological test scores were numerically lower in poor conditioners. These results suggest that poor performance on 400-ms delay eyeblink classical conditioning predicts subsequent cognitive impairment at a point in time when older adults are still cognitively intact.

400-ms Delay: Optimal Paradigm for Early Detection

Given that eyeblink conditioning may have utility in the early detection of AD, we sought to identify the eyeblink conditioning paradigm that would maximize early detection. We explored performance on the 750-ms trace paradigm with a 250-ms CS and a 500-ms trace period [73]. The 750-ms trace procedure did not improve AD detection. Whereas the 400-ms delay procedure had a sensitivity for AD of 95% [51], the 750-ms trace procedure had a sensitivity for AD of 54% [73]. Among the reasons that we suspected that the 750-ms trace eyeblink conditioning paradigm may have advantages for differentiating nondemented elderly patients from AD patients was that, in nonhuman animals, the hippocampus is essential in the trace procedure when the trace interval exceeds 300 ms [74]. More recently, it was demonstrated that in humans, the trace interval must be extended to 1000 ms for the hippocampus to be essential in trace eyeblink conditioning [75]. We have chosen not to explore a 1000-ms trace procedure in patients diagnosed with probable AD because of the difficulty of scoring CRs in long intervals that are within the spontaneous blink rate of humans.

Another feature of an optimal screening test is that it is relatively short. Many of our human eyeblink conditioning studies have used 90 trials and taken at least 45 min to complete. We correlated 10 to 80 total trials with the full 90-trial session in 240 patients and found that a session of 60 trials correlates 0.96 with 90 trials [76]. A 60-trial session lasts about 25 min. The data also indicated that performance variability increased in the last third of a 90-trial session, probably due to fatigue and/or boredom. A 25-min session provides a reliable assessment of eyeblink conditioning performance.

Because eyeblink conditioning is simple, nonthreatening, and noninvasive, it may be a useful addition to test batteries designed to detect AD in the prodromal phase. There are practical advantages to eyeblink conditioning as an assessment tool. With this test, the patients are not aware of the response that is being measured. They are able to watch an entertaining video throughout the test, making it a relaxing and enjoyable experience.

A Human Virtual Reality Version of the Morris Water Maze: Memory Island

Another neuroscience-based test that is enjoyable for participants is Memory Island, a spatial learning and memory task that is being assessed in a virtual reality environment [77]. Memory Island is based on the extensive use of water maze tests to assess mechanisms of spatial learning and memory in rodents. As a test of spatial ability, the water maze requires the rodent to navigate to the location of an escape platform that is hidden under water. This test was originally developed to examine the contribution of the hippocampus to navigation and place learning in the rat [78]. Subsequent research has confirmed the essential role of the hippocampus in this task and extended it from rats to mice. The water maze is one of the most widely used behavioral tests in studies of normal aging in rodents [79•]. It has been used extensively in studies of transgenic mouse models of AD and is thought to parallel the impaired spatial ability seen in human patients with AD. Spatial ability becomes affected in prodromal AD. In this condition, Aβ begins to disrupt perforant pathway input to hippocampus from the entorhinal cortex. Mechanisms of spatial learning associated with the water maze task include long-term potentiation (LTP) in the entorhinal cortex perforant pathway–hippocampus circuit. The first demonstration of synaptic potentiation in the hippocampus during learning about the environment was performed in Per Anderson's laboratory [80]. Synaptic field potentials were recorded in the dentate gyrus in response to stimulation of the perforant path in rats exploring a novel environment. Both the field excitatory postsynaptic potential and the population spike increased significantly early in the exploration in a time course similar to that of short-term potentiation. Subsequently, members of this group demonstrated an association between LTP in the perforant pathway input to hippocampus from entorhinal cortex and spatial

learning in the water maze [81, 82]. Furthermore, synthetic Aβ peptides inhibited LTP induction significantly in rat hippocampal slices without affecting the basal synaptic transmission and posttetanic potentiation in the dentate medial perforant path [83]. Such an effect may impair spatial learning in prodromal AD before actual loss of synapses and neurons has occurred.

The human virtual reality environment for the human task is an island comprising four quadrants, each containing a different target object (sculpture, seagull, seal, or fountain). Targets in all four quadrants are used for visible target training in distinct trials. The starting orientation of the participant is varied in each trial, but these variations are kept consistent across participants. These different orientations are intended to prevent using response strategies like always heading in one direction across trials. Participants practice this task using a joystick to a target location visibly marked with a flag adjacent to the target. After completing the visible target training, they navigate to a hidden target (ie, no flag located beside the target item). In this part of the test, the study participant has to remember where the hidden target is and how to get there. The location of the hidden target is kept constant for all participants. In each trial of the visible or hidden session, if the study participant is unable to locate the target within 2 min, a directional arrow appears to guide the participant to the target. after the last hidden target trial, the participant receives a 30-s probe trial with the target removed. In each trial, navigation is recorded in time-stamped coordinate files, which are used to calculate distance traveled (virtual units), cumulative distance to the target (virtual units), latency to reach the target (seconds), and speed (virtual units/sec). The primary outcome measures during the probe trial are the percent of time spent in each quadrant and the cumulative distance to the target.

Adults in the age range of 40 to 67 years perform worse on Memory Island in comparison to adolescents and young adults [84]. Previously, it had been shown that there was an effect of *APOE* ε4 on test performance among 116 non-demented older adults (mean age: 81 years) assessed on established tests of memory and on Memory Island and Novel Image Novel Location, with non-*APOE* ε4 carriers outperforming *APOE* ε4 carriers, but not in other cognitive tests [85].

In the Novel Image Novel Location test, a set of 12 panels, each containing three images in three of the four quadrants (one quadrant was empty), is presented to the participants to memorize. After no delay (immediate), participants are presented with a second set of panels that are either the same (no change), contain one novel image (novel image), or contain an image moved to the empty quadrant (novel location). Then after a delay (5 min) the participants are presented with a third set of panels that are either the same (no change), contain one novel image (novel image), or contain an image moved to the empty quadrant (novel location). The sequence of the panels is different in the second and third sets. The participants are asked to correctly identify if there was a change and, if so, how the panel changed (novel image/novel location) and what was the location of the change (quadrant). Memory Island and Novel Image Novel Location are especially sensitive to memory impairment in *APOE* ε4 carriers and, thus, sensitive to prodromal AD.

Comparing Memory Island to Traditional Spatial Tests of Human Cognition

Typically, human spatial ability is assessed with tests such as the Spatial Span Forward and Backward that use blocks attached to a tray [86]. The experimenter points to a series of blocks and asks the participant to repeat the order in which the blocks have been identified. Such a task is substantially different from spatial navigation in rodents as required by the water maze. The rodent navigation tasks are administered with an allocentric (or environment-centered) frame of reference in which the animal is required to use navigation to orient within a large space. Spatial Span and other human neuropsychological tests of spatial ability do not involve navigation. In traditional tests, all the information for the task is held within a single visual field or frame of reference, providing an egocentric (or self-centered) frame of reference. Banta Lavenex et al. [87] assessed human patients' reliance on sources of spatial information by testing four different conditions, controlling for participants' reliance on egocentric and/or allocentric frames of reference. Results demonstrated that changes in viewpoint produced by the movement of images placed in front of a stationary patient was not equivalent to the movement of the patient around stationary images. Studies using functional MRI (fMRI) demonstrate that egocentric and allocentric frames of reference engage different brain substrates of learning [88•]. Thus, traditional neuropsychological tests of spatial learning and memory in humans do not have the translational power that can be derived from building knowledge on animal models in which mechanisms of learning and memory have been elaborated at cellular and molecular levels.

Advances in technology have enabled the development of human tests of spatial navigation with the use of computerized virtual reality. The virtual testing environment of Memory Island simulates the water maze environment that rodents experience and requires navigation to a hidden location just as in the rodent water maze task. Virtual reality thus can help to bridge the gap between electrophysiological studies in rodents and brain imaging studies using fMRI in humans [89]. Using fMRI, Folley et al. [90] reported that temporal and frontal lobe regions were recruited by the hidden platform condition of a virtual water maze task, with

coupling between neural circuits, regional neuroanatomy, and behavior. The hippocampus and parahippocampal cortices exhibit theta oscillations during spatial navigation in rodents that are thought to mediate spatial memory formation. Neuromagnetic activity was recorded with a whole-head 275-channel magnetoencephalographic system as healthy participants navigated to a hidden platform in a virtual reality Morris water maze [91]. Analysis revealed greater theta activity in the left anterior hippocampus and parahippocampal cortices during goal-directed navigation relative to aimless movements in a sensorimotor control condition. Additional analyses showed that left anterior hippocampal activity was predominantly observed during the first half of training, pointing to a role for this region in early learning.

Object Recognition with a Spatial Component: Novel Image Novel Location

Neuroscience-based assessment of spatial learning and memory in animal models is also evaluated using object recognition tests containing a spatial component. Including the spatial component increases sensitivity compared to more traditional object recognition tasks and also provides direct application to early detection of AD. As emphasized previously, reduction in axons and synapses in the perforant pathway input into hippocampus from the entorhinal cortex is one of the earliest of the neural and synaptic changes in AD [22] and is associated with early Aβ accumulation. Following up 6 to 18 months later on the nondemented older adults assessed by Bertreau-Pavy et al. [85] on established tests of memory and on translational tests of spatial cognition, Haley et al. [92] assessed effects of *APOE* ε4 on study "dropouts" (participants that did not return for the second and/or third session[s]) and "finishers" (participants that returned for all sessions). There were effects of *APOE* ε4 on dropout rates and Novel Image Novel Location total scores as well as subscores in both dropouts and finishers. Novel Image Novel Location total score was a predictor of *APOE* ε4 participant dropout. Compared to non–*APOE* ε4 dropouts, *APOE* ε4 dropouts had lower Novel Image Novel Location scores. In contrast, *APOE* ε4 finishers had higher Novel Image Novel Location scores than non–*APOE* ε4 finishers. A 4-year follow-up of performance on the Mini-Mental State Examination (MMSE) [93] and the Novel Image Novel Location tests indicated that whereas MMSE scores did not change over the 4-year period, Novel Image Novel Location scores did change in some older adults [94•]. Novel Image Novel Location scores correlated with logical memory and word recall lists, cognitive tasks used to detect dementia in the clinic, as well as clinical dementia rating scales. Recent validation results from Steven Ferris' laboratory relating biomarker data in cognitively normal elderly participants to a task similar to Novel Image Novel Location demonstrated task sensitivity to higher levels of CSF Aβ and hippocampal atrophy [95].

Conclusions

There is an increasing need for assessment of cognition in early dementia [96••]. Based on animal models of neurological conditions, we developed sensitive neuroscience-based cognitive tests to detect early cognitive changes in prodromal AD in humans that are prime candidates. Therefore, increased efforts are warranted to use such translational cognitive assessments detecting synaptic changes as part of early diagnostic and subsequently intervention studies. As Dennis Selkoe [97] recently wrote, "Rigorous preclinical validation of mechanism-based therapeutic agents followed by meticulously designed trials that focus on the *cardinal cognitive symptoms* [emphasis is ours] and their associated biomarkers in the mild or presymptomatic phases of Alzheimer's disease are likely to lead to success, perhaps in the not-too-distant future" (p. 1060).

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Paper of particular interest, published recently,
have been highlighted as:
- • of importance
- •• of major importance

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