Insights About Learning in Alzheimer’s Disease From the Animal Model

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Elga had been athletic throughout her life. Relatively tall, blonde, and deeply tanned, she epitomized the image of the Californian she had been for 75 years. Throughout her adult years, Elga remained an active golfer while raising her children and helping her husband with the expanding family business. In her 70s, she was still a scratch golfer. Indeed, in later life there were days when Elga’s golf score and her age were identical.

However, to her dismay, Elga began to notice her memory problems on the golf course. She couldn’t keep track of her strokes and thus had difficulty scoring her game. Her golf partners even accused her of cheating. Her daughter insisted that Elga see her physician about these memory problems. After an extensive physical examination including a brain scan (magnetic resonance imaging, or MRI) and neuropsychological tests, Elga’s physician diagnosed possible Alzheimer’s disease and prescribed Aricept. This drug improves the function of the acetylcholine neurotransmitter system in the brain, and it was identified as a treatment for Alzheimer’s disease through animal research.

Aricept is not effective in all patients with Alzheimer’s disease, but Elga was fortunate. Not only did Aricept ameliorate some of her confusion, but it reduced the emotional toll caused by the cognitive impairment.

Pavlovian conditioning of the eyeblink response engages the medial–temporal lobe memory system that uses the neurotransmitter acetylcholine, and this memory system is severely disrupted in Alzheimer’s disease. Knowing on the basis of animal models the medial–temporal lobe and acetylcholine neurotransmitter involvement in this form of associative learning, I predicted that classical eyeblink conditioning would be extremely impaired in patients with Alzheimer’s disease. Because of the striking similarities in all mammals in the brain circuitry and behavioral response in eyeblink conditioning, tests of cognition-enhancing drugs in animals are directly relevant to the treatment of memory impairment in Alzheimer’s disease. Aricept is one of only several drugs currently approved early in the 21st century by the Food and Drug Administration. It
is available in the United States through a physician's prescription for the
treatment of memory impairment in Alzheimer's disease. Aricept (under
its generic name donepezil) was tested in my laboratory using the rabbit
eyeblink classical conditioning paradigm, demonstrating that learning
improved in older rabbits at a dose of 3.0 mg/kg (see Figure 21.1). There are
dramatic neurobiological and behavioral parallels in eyeblink conditioning
in humans and animals, including mice, rats, cats, rabbits, and monkeys.
Parallels in the impairment of eyeblink conditioning in normal aging have
been demonstrated in rats, rabbits, cats, and humans. The striking similari-
ties in this behavior and its neural substrates among all mammals
make results observed in animals directly relevant to humans.

Before drugs can be tested in humans, they must be screened for
safety and effectiveness in other species. One insight about learning in
Alzheimer’s disease provided by animal models in general and the rabbit
eyeblink classical conditioning model specifically is that certain drugs are
effective in ameliorating deficits in learning and memory. Eyeblink clas-
sical conditioning is an excellent paradigm for pharmaceutical tests of
cognition-enhancing drugs because of behavioral and neurobiological simi-
larities among species in this model.

Research in my laboratory testing patients diagnosed with Alzhei-
mer’s disease began with an idea based on results from the rabbit eyeblink
conditioning experiments. My laboratory staff and I knew from the animal
studies that acetylcholine neurotransmission in the medial–temporal
lobes (specifically, the pathway from the medial septum into the hippocam-
pus) was activated during eyeblink conditioning. On the basis of the re-
results with the animal model, we hypothesized that patients with a diag-
nosis of probable Alzheimer’s disease would be impaired in eyeblink
conditioning beyond the deficit due to normal aging because the disease
damages the cholinergic system of the human brain (Woodruff-Pak, Fink-
biner, & Katz, 1989). The hypothesis that eyeblink conditioning would be
severely impaired in patients with Alzheimer’s disease was confirmed and
replicated (e.g., Woodruff-Pak, Papka, Romano, & Li, 1996) and indepen-
dently replicated (Solomon, Levine, Bein, & Pendlebury, 1991).

Classical or Pavlovian conditioning is considered a simple form of as-
sociative learning. In the delay procedure in which the conditioned and
unconditioned stimuli overlap, classical conditioning is classified as a non-
declarative form of learning and memory. It was surprising from some
perspectives that this simple, nondeclarative form of learning and memory
would be impaired in Alzheimer’s disease, but it was predictable from the
perspective of the rabbit eyeblink classical conditioning model and the
demonstrated involvement of the medial–temporal lobe cholinergic neural
circuits.

Yet another insight about learning in Alzheimer’s disease provided by
animal models is that eyeblink classical conditioning is a possible diag-
nostic tool for the early detection of the disease. I anticipated that patients
with Alzheimer’s disease would be impaired in eyeblink conditioning, but
I did not anticipate that impaired eyeblink conditioning might be one of
the markers for the earliest stages of the disease. The possibility that
Figure 21.1. (A) Trials to a learning criterion of eight conditioned responses (CRs) in 9 consecutive trials in the 750-ms delay eyelink classical conditioning procedure for female retired breeder rabbits of a mean age of 29 months. (B) Percentage of CRs per 90-trial session for 15 daily sessions for the three groups of rabbits. In A, Eight rabbits in each group were treated with 0.0 (sterile-saline vehicle), 0.3, or 3.0 mg/kg donepezil (Ariacta). Rabbits treated with the 3.0-mg/kg dose acquired CRs significantly faster than vehicle-treated rabbits. Error bars are standard deviation.
eyeblink conditioning detected the disease early became evident in longitudinal studies of normal older adults. Ferrante and Woodruff-Pak (1995) reported that the older adults who served as normal control participants in our initial studies and scored in the disease's range in eyeblink classical conditioning (below 25% conditioned responses, CRs) developed dementia or died within 3 years of testing. In another sample of normal elderly adults, those individuals producing less than 25% CRs were impaired on neuropsychological tests in a pattern characteristic of patients with Alzheimer's disease (Downey-Lamb & Woodruff-Pak, 1999). These results indicated that eyeblink conditioning might serve to detect the disease early. With the advent of cognition-enhancing drugs, the early identification of people at risk for the disease is increasingly important. As medications become available, effective treatment will depend on early intervention. Cognition-enhancing drugs are effective only if sufficient numbers of neurons remain to respond. Not only do some cognition-enhancing drugs ameliorate the impaired neuronal function, but the drugs may preserve remaining neurons and slow cognitive decline. Unfortunately, by the time most cognitive deficits are apparent in patients in the early stages of Alzheimer's disease, significant neuronal damage (up to 50% loss) has occurred in brain regions that are essential for memory (Gomez-Isla et al., 1996).

There are a number of additional insights researchers have gained about Alzheimer's disease in working with the rabbit model of eyeblink classical conditioning. However, I focus in this chapter on the three insights I have highlighted. Neurobiological and behavioral studies of young and older rabbits tested with eyeblink classical conditioning have identified (a) cognition-enhancing drugs that are most likely to have therapeutic effects on memory impairment in Alzheimer's disease, (b) possible mechanisms by which the disease affects learning and memory in patients, and (c) new ways to detect the disease early in its course when therapies can be most effective.

This chapter's focus is primarily with the role of the hippocampus in eyeblink classical conditioning. The neural circuitry underlying this form of associative learning is probably better understood than any other form of learning in mammals. Studies using rabbits have identified the cerebellum on the same side (ipsilateral) as the conditioned eye as the essential site for the neural and molecular changes that occur ("plasticity") for learning. If an airpuff is aimed at the left eye in the rabbit, the left cerebellum is the site of the plasticity for learning to produce CRs. The hippocampal formation is not essential in the "delay" eyeblink classical conditioning procedure. In the delay procedure, a tone is the conditioned stimulus (CS), and it overlaps with a corneal airpuff, which is the unconditioned stimulus (US). The interval between the CS and US is the same for every trial of a session, and the CS-US intervals discussed in this chapter range between 400 and 750 ms. In the delay classical conditioning procedure, the CS and US overlap. Pavlov used the term delay to represent the fact that the CS was followed by the US after a short delay. In the
delay procedure, the cerebellum is the essential site of plasticity, and the hippocampus plays a modulatory role affecting the rate of conditioning.

**Insight I: Eyeblink Classical Conditioning as a Preclinical Test of Cognition-Enhancing Drugs**

The hippocampus and septo-hippocampal cholinergic system have proved to be much involved in basic associative learning of the sort represented by eyeblink conditioning in the rabbit (see Berger, Berry, & Thompson, 1986). This provides a point of contact with current interest in the possible role of the forebrain cholinergic system in human memory and in Alzheimer’s disease (Geula & Mesulam, 1994). Neuronal unit activity in the hippocampus increases markedly within trials early in the classical conditioning process. Activity recorded in the CA1 region of the hippocampus forms a predictive “model” of the amplitude time course of the learned behavioral response (Figure 21.2). Neuronal activity to the tone CS and corneal air puff US occurs only under conditions in which the stimuli are presented together in a fixed sequence (CS first followed by the US) and produce behavioral learning (Berger, Alger, & Thompson, 1976). When the CS and US are presented independently in the explicitly unpaired procedure, there is no hippocampal response to the tones or air puffs. The hippocampal modeling of the behavioral CR and UR is generated largely by

![Figure 21.2](image)

**Figure 21.2.** Example of hippocampal cell firing that forms a model of the conditioned nictitating membrane (NM)/eyeblink response in a rabbit: the behavioral response (above) and multiple unit hippocampal recording (below) in the CA1 (cornu ammonis Region 1 pyramidal neurons) layer in a well-trained rabbit responding to the tone conditioned stimulus (CS) that onsets 250 ms before the onset of a corneal air puff conditioned stimulus (US). Both CS and US terminate 100 ms after US onset. This illustration is an average NM response of nine trials with the summation of hippocampal unit responses for all nine trials. The behavioral conditioned response is the initiation of the NM response above baseline before the onset of the US. The behavioral unconditioned response is the NM activity after US onset. Note the resting rate of firing in the CA1 recording that increases significantly just before the beginning of the behavioral NM response.
hippocampal pyramidal neurons in the CA1 and CA3 fields (Berger, Rinaldi, Weisz, & Thompson, 1983; see Figure 21.3). In neuropathological studies of human brains, West, Coleman, Flood, and Troncoso (1994) identified pyramidal cells in the CA1 field of hippocampus as the cells selectively lost in Alzheimer's disease.

It is my working hypothesis that selective loss of hippocampal pyramidal cells and disruption of the septo-hippocampal cholinergic system impair acquisition of eyeblink classical conditioning in Alzheimer's disease beyond the impairment observed in normal aging. I initially based the prediction of severe disruption of eyeblink classical conditioning in patients with the disease on data collected with the rabbit model system. More recently, West and colleagues (1994) reported selective loss of CA1 hippocampal pyramidal cells in Alzheimer's disease. These are the very cells in rabbits that fire just before the behavioral CR and UR are produced.

The marking lesion in the CA1 pyramidal cell layer of the left hippocampus illustrated in Figure 21.3 shows the location of the pyramidal cells that generated a neural model of the conditioned and unconditioned

![Figure 21.3. Photomicrograph of the left hippocampus of a rabbit stained with Nissl to identify cell bodies. The dark bands in the areas labeled CA1 and CA3 (cornu ammonis Region 1 and Region 3) are the pyramidal neuron layers. The hole in the CA1 pyramidal neuron layer is a marking lesion from the electrode implanted there to record hippocampal pyramidal neuron firing shown in Figure 21.2. It is the CA1 pyramidal neuron layer in the hippocampus that is selectively destroyed in humans with Alzheimer's disease.](image)
nictitating membrane (NM) response such as the one illustrated in Figure 21.2. The NM is a third eyelid in rabbits, and it is used to measure the eyeblink response that is correlated almost perfectly with the NM response.

The rabbit model system demonstrated that the hippocampus could play a modulatory role in conditioning (Berger et al., 1986). Although the hippocampus is not essential for acquisition in the delay classical conditioning procedure in rabbits, disruption or facilitation of the hippocampus affects the rate of conditioning. In rabbits, disruption of muscarinic cholinergic receptors with scopolamine injections impairs acquisition of CRs, and this disruption occurs only when the hippocampus is intact (e.g., Solomon, Solomon, Vander Schaaf, & Perry, 1983). Scopolamine injections eliminate hippocampal pyramidal cell activity that would normally occur in conjunction with the CR and UR (Salvatierra & Berry, 1989). Microinjections of scopolamine to the medial septum (Solomon & Gottfried, 1981) or aluminum injections that impair hippocampal acetylcholine release (Meyer, Allen, & Yokel, 1996) slow the rate of acquisition of the classically conditioned eyeblink response in rabbits. Scopolamine also disrupts eyeblink conditioning in humans (e.g., Bahro, Schreurs, Sunderland, & Molchan, 1995). Drugs that reverse the learning and memory impairments resulting from scopolamine have the potential to treat cognitive impairment in Alzheimer’s disease.

The effectiveness of a drug called nefiracetam in reversing the effects of scopolamine in young rabbits was tested in my laboratory (Woodruff-Pak & Hinchcliffe, 1997). Nefiracetam is under development as a cognition enhancer in Alzheimer’s disease. This drug promotes the release of diverse neurotransmitters such as acetylcholine, gamma-aminobutyric acid, and monoamines (Watabe, Yamaguchi, & Ashida, 1993). Scopolamine (1.5 mg/kg) and nefiracetam at several doses were administered to young rabbits tested in the 750-ms delay eyeblink conditioning procedure. Rabbits treated with a 10-mg/kg dose of nefiracetam plus scopolamine acquired CRs significantly faster than rabbits treated with scopolamine alone and at about the same rate as vehicle-only rabbits. Vehicle is the solution in which the drug is dissolved. Thus, nefiracetam reversed the deleterious effects of scopolamine and enabled young rabbits to perform like normal vehicle-treated rabbits.

The site of action of nefiracetam in the eyeblink classical conditioning paradigm appears to be in the hippocampus. Older rabbits administered a dose of 10 mg/kg nefiracetam acquired CRs rapidly like young rabbits. However, when the hippocampus of older rabbits was lesioned bilaterally, a dose of 10 mg/kg nefiracetam was not effective. Hippocampally lesioned older rabbits acquired CRs at a rate similar to vehicle-treated older rabbits (Woodruff-Pak, Li, Hinchcliffe, & Port, 1997). It is likely that cholinergic drugs ameliorate impairments in eyeblink conditioning by means of the hippocampus (rather than the cerebellum) as muscarinic and nicotinic cholinergic receptors are found in high concentrations in the hippocampus.

Nicotinic cholinergic receptor impairment with mecamylamine also slows the rate of conditioning in rabbits (Woodruff-Pak, Li, Kazmi, & Kem, 1994). In Alzheimer’s disease, it is the nicotinic cholinergic receptors that
are significantly reduced in number, in particular the α4β2 nicotinic cholinergic receptor subtype is vulnerable in the disease (Warpman & Nordberg, 1995). A drug in development for cognition enhancement in Alzheimer’s disease, called GTS-21, acts primarily on the α7 nicotinic cholinergic receptor subtype. This drug improves acquisition of CRs in older rabbits so that they learn as well as young rabbits (Woodruff-Pak, Li, & Kem, 1994), and it reverses the effect of mecamylamine in the disruption of learning (Li, Alvarez, & Woodruff-Pak, 1994).

A mechanism of action in the cholinergic system that has been the basis of the currently approved drugs to treat cognitive impairment in Alzheimer’s disease is cholinesterase inhibition. Acetylcholinesterase (AChE) is an enzyme that breaks down acetylcholine in the synaptic cleft as soon as it is released. By inhibiting AChE, a drug makes more acetylcholine available to act postsynaptically. Tacrine and Aricept, two drugs currently available to ameliorate memory loss in the disease, are both cholinesterase inhibitors. As mentioned previously and illustrated in Figure 21.1, Aricept ameliorates learning deficits in older rabbits tested in the eyelink classical conditioning paradigm (Woodruff-Pak, 1998). Although researchers have not demonstrated directly that the site of action of Aricept is the hippocampus, the large body of data available on the neural circuitry involved in eyelink conditioning strongly support this interpretation. Meyer et al. (1996) measured acetylcholine release during eyelink conditioning in young rabbits and found it to increase significantly in the ventral hippocampus during the 2nd and 3rd days of training. Rabbits tested in the explicitly unpaired condition did not show increased release of acetylcholine, indicating that the acetylcholine release was related to the learning.

An abnormally functioning hippocampus impairs acquisition in rabbits. In humans, Alzheimer’s disease appears to profoundly alter hippocampal neuronal function. A major disruption of the brain cholinergic system occurs in the disease, impairing cholinergic innervation of cortical and hippocampal neurons. Data from the animal model led to the prediction that patients with Alzheimer’s disease, having hippocampal dysfunction, should show poorer acquisition of the classically conditioned eyelink response than should normal older adults.

**Insight II: Eyeblink Classical Conditioning in Animals to Better Understand Learning and Memory in Alzheimer’s Disease**

I have focused on the hippocampus in Alzheimer’s disease because there is such widespread agreement that profound hippocampal impairment exists in this disease. The structure essential for eyelink conditioning, the cerebellum, is relatively spared in the disease. In rabbits and humans, the cerebellar cortex is normally activated in eyelink conditioning. Purkinje cells in cerebellar cortex are the central integrating cells for the CS and US input pathways. Loss of Purkinje cells in normal aging correlates highly with slower rates of conditioning (Woodruff-Pak & Trojanowski,
The assumption is that patients with the disease would have Purkinje cell loss that accompanies normal aging and that is associated with a slower rate of conditioning. It is also assumed that patients with Alzheimer’s disease would have abnormal hippocampal neuronal activity associated with cell loss and cholinergic neural dysfunction. Abnormalities in both of the brain structures involved with eyeblink classical conditioning should dramatically impair acquisition of the conditioned eyeblink response. The prediction was that the degree of classical conditioning in patients with probable Alzheimer’s disease would be minimal.

Since it was first proposed that patients with probable Alzheimer’s disease would be impaired on eyeblink classical conditioning based on evidence available from the rabbit eyeblink conditioning model, data have consistently supported that model. With a criterion of producing 25% CRs in a session and combining data from several studies conducted during the last decade in my laboratory, eyeblink conditioning correctly identified 54 of 60 patients with probable Alzheimer’s disease (Figure 21.4). In some cases, eyeblink classical conditioning was effective in differentiating cerebrovascular dementia from probable Alzheimer’s disease (Woodruff-Pak

![Graph showing percentage of conditioned responses (CRs) for patients with probable Alzheimer's disease.](image)

**Figure 21.4.** Percentage of conditioned responses (CRs) of 60 patients diagnosed with probable Alzheimer's disease and tested in the 400-ms delay eyeblink classical conditioning procedure. Using a criterion of 25% CRs, 54 of the 60 patients fell below this level of performance and produced an average of 13% CRs. Age-matched healthy control participants (not shown in this figure) produced an average of 40% CRs.
et al., 1996). In patients with Huntington's disease (Woodruff-Pak & Papka, 1996) and Parkinson's disease (Daum, Schugens, Breitenstein, Topka, & Spieker, 1996), eyeblink conditioning is relatively normal and clearly differentiated from eyeblink classical conditioning in Alzheimer's disease.

In addition to working with probable Alzheimer's disease and other dementing neurological diseases of old age, my colleagues and I extended this work to adults with Down's syndrome who inevitably develop Alzheimer's disease around age 35 (Papka, Simon, & Woodruff-Pak, 1994). Adults older than age 35 with Down's syndrome—Alzheimer's disease perform eyeblink classical conditioning similarly to patients diagnosed with probable Alzheimer's disease, but adults younger than 35 with Down's syndrome perform eyeblink classical conditioning significantly better than patients with probable Alzheimer's disease or Down's syndrome—Alzheimer's disease.

Rabbits with disrupted hippocampal cholinergic systems have delayed acquisition of eyeblink classical conditioning but eventually acquire CRs (Solomon et al., 1983). On this basis, we predicted that if patients with probable Alzheimer's disease and patients with Down's syndrome—Alzheimer's disease were given enough training trials, they would eventually produce CRs. Patients with probable Alzheimer's disease and patients with Down's syndrome—Alzheimer's disease were tested with eyeblink classical conditioning for 5 consecutive days, and most of them eventually attained a learning criterion of eight CRs in 9 consecutive trials (Woodruff-Pak, Romano, & Papka, 1996). Solomon et al. (1995) tested patients with probable Alzheimer's disease in paired tone and corneal airpuff presentations in the 400-ms delay procedure for 4 consecutive 70-trial sessions and reported similar results. The neural substrate supporting eyeblink classical conditioning therefore seems to be impaired by probable Alzheimer's disease and Down's syndrome—Alzheimer's disease beyond the impairment observed in normal aging, but it is not destroyed. Patients with Alzheimer's disease or Down's syndrome—Alzheimer's disease eventually acquire CRs. If these patients can acquire CRs, the essential brain substrate for eyeblink conditioning, the cerebellum, must be relatively intact.

Insight III: Eyeblink Classical Conditioning as a Test Useful in the Early Diagnosis of Alzheimer's Disease

In longitudinal studies of cognitively normal older adults, poor performance on eyeblink classical conditioning predicted subsequent dementia onset. Ferrante and Woodruff-Pak (1995) conducted a 3-year longitudinal study of eyeblink classical conditioning in the healthy control participants tested in one of our studies of patients with Alzheimer's disease. These longitudinal results suggested that eyeblink conditioning has utility in the early detection of dementia. Four of the 8 participants with normal scores on the Information—Memory—Concentration subtest of the Blessed Dementia Rating Scale, a standard clinical measure of disease severity, and scoring at or slightly above the Alzheimer's disease range on eyeblink con-
ditioning (26% CRs or lower) at Time 1 became demented within 3 years. A 5th participant in the group showing poor conditioning died within a year of the initial testing. Of 8 nondemented participants age matched to patients with probable Alzheimer’s disease who scored in the Alzheimer’s range on eyeblink conditioning, only 3 were cognitively normal at the end of a 3-year period. Age-matched nondemented participants producing more than 26% CRs remained cognitively intact during the 3-year period of the longitudinal investigation. Thus, a 3-year longitudinal study of nondemented adults tested on eyeblink conditioning revealed that 63% of the cognitively normal participants who conditioned poorly became demented within 3 years.

Another longitudinal study of eyeblink classical conditioning in my laboratory involved 22 older adults ranging in age from 68 to 96 years (5 diagnosed with probable Alzheimer’s disease, 17 normal control participants) who were tested using the 400-ms delay eyeblink conditioning procedure. All 5 patients with Alzheimer’s disease produced less than 25% CRs. Nine of the 17 healthy control participants were poor conditioners (<25% CRs), and 8 were normal conditioners (>25% CRs). The performance in the poor conditioning group was comparable with the performance of a group of patients with probable Alzheimer’s disease. Longitudinal assessment over a 2-year period of these 17 healthy control participants involved administration of an extensive battery of neuropsychological tests to assess cognitive functioning (Downey-Lamb & Woodruff-Pak, 1999). Neuropsychological assessment included tests of memory, attention, executive function, language, and visuospatial–visuoconstructural abilities, capacities that are known to deteriorate in Alzheimer’s disease. Our aim was to determine if older adults who conditioned poorly had cognitive impairment 2 years later.

Two years after the eyeblink conditioning test, all 8 older adults who produced more than 25% CRs remained cognitively normal. In contrast, those participants who were poor at eyeblink conditioning were impaired in the cognitive domains affected by Alzheimer’s disease: memory, executive function, visuospatial ability, attention, and language. Many of the 9 participants in the poor conditioning group were impaired in several cognitive domains and were at risk for dementia, and 1 participant was actually diagnosed with probable Alzheimer’s disease 6 months after neuropsychological testing for this study. Another participant who had conditioned poorly demonstrated serious deficits but had not been diagnosed with Alzheimer’s disease 3 years after the eyeblink conditioning test. A 3rd participant with a low conditioning score died 5 months after completing the neuropsychological retest component of the longitudinal study.

The results indicate that eyeblink classical conditioning performance of less than 25% CRs identifies older adults who are in the early stages of cognitive decline and who are at risk for dementia. These longitudinal results suggest that eyeblink conditioning has utility for the early detection of people at risk for cognitive decline and dementia. Because my colleagues and I have demonstrated, using participants with various types
of neurological diseases, that eyeblink conditioning is relatively selective for Alzheimer's disease, most individuals who condition poorly and who subsequently become demented likely have Alzheimer's disease.

Eyeblink classical conditioning is a noninvasive behavioral test with results that are reliable over periods up to 3 years. The test is simple to perform and takes less than 30 min. Use of the eyeblink classical conditioning test is relatively inexpensive, and test administration is quite easy for a technician to learn. Eyeblink classical conditioning satisfies many of the criteria for a diagnostic marker for Alzheimer's disease and is a promising diagnostic tool for early detection of the disease.

Conclusion

These results with human patients with a diagnosis of probable Alzheimer's disease parallel the prior observation in rabbits that an abnormally functioning hippocampus impairs acquisition of CRs in the delay eyeblink classical conditioning procedure. There are major difficulties involved in applying an animal model with controlled and experimentally altered brain function to aging humans with a progressive, degenerative disease. In that sense, it is remarkable that predictions from the animal model were so clearly supported in the behavior of patients diagnosed with probable Alzheimer's disease.

The fact that the animal model of a scopolamine- or mecamylamine-injected rabbit predicted severely impaired eyeblink conditioning in patients with Alzheimer's disease gives this animal model utility in preclinical tests of cognition-enhancing drugs. This animal model also has utility in helping researchers to understand mechanisms of learning and memory as they are affected by normal aging. Nevertheless, it must be underscored that there is no animal model of Alzheimer's disease that develops senile plaques, neurofibrillary tangles, and all of the cognitive impairments seen in humans with the disease. My colleagues and I found very little evidence of beta-amyloid plaques even in 8-year-old rabbits (Woodruff-Pak & Trojanowski, 1996). Currently available animal models of Alzheimer's disease simulate one or more aspects of the disease. Rabbits injected with cholinergic antagonists and older rabbits simulate the disrupted cholinergic system in Alzheimer's disease. However, the disease has a much broader range of neuropathologies including (but not limited to) fairly widespread increases in beta-amyloid plaques, increasing presence of neurofibrillary tangles, disruption of many neurotransmitter systems, and severe but regionally selective cell loss. Strains of mutant mice are being developed to simulate a number of these characteristics of the disease, and eyeblink conditioning in these animal models is one promising future method for testing cognition-enhancing drugs and exploring mechanisms of learning and memory in Alzheimer's disease.

It remains to be determined in large samples of adults whether eyeblink classical conditioning detects Alzheimer's disease early and can be implemented as a screening tool for the preclinical identification of the
disease. Data from two longitudinal samples of around 20 healthy older adults are promising, and longitudinal studies with larger samples using eyeblink conditioning and neuropsychological tests are underway in my laboratory. Another means of validating the role of the hippocampus in disrupting the acquisition of CRs in Alzheimer’s disease is to use brain-imaging techniques. We are using anatomical MRI to evaluate hippocampal and cerebellar volume in participants with a wide range of conditioning performance and functional MRI to examine brain activation in hippocampus and cerebellum during eyeblink classical conditioning.

Implementation of eyeblink classical conditioning as a test for the early detection of Alzheimer’s disease resulting in earlier therapeutic treatment has major implications for human psychological health. This link between animal research and human treatment would signify that an observation based on an animal model could contribute to prolonging normal cognitive ability and preventing memory impairment and confusion in thousands of elderly adults at risk for the disease. The 21st century finds tens of millions of adults in the world living to 60 years and older and facing the risk of Alzheimer’s disease. It is critical that researchers use animal models to discover accurate tests to detect this disease early, to ascertain methods to treat it, and to find means to prevent its expression entirely.

References


