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Impaired Delay Eyeblink Classical Conditioning in Individuals With Anterograde Amnesia Resulting From Anterior Communicating Artery Aneurysm Rupture

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Anterior communicating artery (ACoA) aneurysm rupture can lead to an anterograde amnesia syndrome similar to that observed after damage to the hippocampus and medial temporal lobes (MT). It is currently believed that ACoA amnesia results from basal forebrain damage that disrupts hippocampal processing without direct hippocampal damage. Converging evidence from animal studies and computational modeling suggests that qualitative differences may exist in the pattern of memory impairment after basal forebrain or MT damage. For example, animals with basal forebrain but not hippocampal damage are impaired at delay eyeblink classical conditioning (EBCC). In this study, individuals with ACoA amnesia were shown to be impaired at delay EBCC compared with matched controls; this contrasts with the spared delay EBCC previously observed in MT amnesia. This finding suggests the beginning of a possible dissociation between the memory impairments in MT versus ACoA amnesia.

The anterior communicating artery (ACoA) represents one of the most common sites of cerebral aneurysm and is the most frequent site of cerebral infarct following aneurysm rupture (McCormick, 1984). ACoA aneurysm rupture may result in some degree of damage to the basal forebrain and frontal areas that are vascularized by the ACoA, its collaterals and the anterior cerebral arteries (Carpenter, 1985). Survivors of ACoA aneurysm often present with a constellation of behavioral impairments resulting from infarct to these areas (Alexander & Freedman, 1984; Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; Gade, 1982). ACoA aneurysm survivors often display some degree of anterograde amnesia, a specific deficit in new memory formation, with relative sparing of older memories as well as intelligence and attention. There may also be personality changes and confabulation. These three components—memory dysfunction, personality changes, and confabulation—have been grouped together and referred to as the ACoA syndrome (DeLuca & Diamond, 1995).

The anterograde amnesia demonstrated in some ACoA aneurysm survivors is superficially similar to the amnesia that can result from damage to the medial temporal lobes, including the hippocampus and associated structures (see Squire, 1987). However, ACoA aneurysm typically does not cause any direct medial temporal lobe damage. It appears that the memory deficits associated with ACoA amnesia are instead related to the presence of basal forebrain damage (see DeLuca & Diamond, 1995, for a

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review; Abe, Inokawa, Kashiwagi, & Yanagihara, 1998; Bottger, Prosiegel, Steiger, & Yassouridis, 1998). This would be consistent with prior work in animal models, demonstrating that basal forebrain damage—particularly damage to the medial septum—can cause deficits in learning and memory (e.g., Baxter, Bucci, Gorman, Wiley, & Gallagher, 1995; Berry & Thompson, 1979; see also Kesner, 1988). The precise mechanism whereby basal forebrain lesion may result in human amnesia is unknown, but several researchers have postulated that the basal forebrain normally modulates hippocampal function and that the basal forebrain damage in ACoA amnesia disrupts this modulation, indirectly disrupting hippocampal function (e.g., Damasio et al., 1985; Abe et al., 1998).

Recent data from animal models, pharmacological studies, and computational models suggest that there may be subtle but important differences in the memory impairment following hippocampal lesion versus hippocampal disruption caused by basal forebrain damage.

One important example is delay eyeblink classical conditioning (see Gormezano, Kehoe, & Marshall, 1983; Solomon, Pomerleau, Bennett, James, & Morse, 1989). In this paradigm, a corneal airpuff or paraorbital shock (the unconditioned stimulus, or US) is used to evoke a reflexive, protective eyeblink response (the unconditioned response, or UR). If a previously neutral cue, such as a tone or light (the conditioned stimulus, or CS) is repeatedly presented just before the US, then the CS alone can come to evoke an anticipatory, protective eyeblink response (the conditioned response, or CR). In the delay conditioning paradigm, CS and US overlap and coterminate.

Acquisition of the eyeblink CR in the delay conditioning paradigm has been shown to depend critically on the cerebellum (e.g., Thompson, 1986). Cerebellar damage abolishes the ability to learn new eyeblink responses (Solomon, Lewis, LoTurco, Steinmetz, & Thompson, 1986; Sears & Steinmetz, 1990), whereas animals with frontal lesions can acquire the eyeblink response normally in the delay conditioning paradigm (Kronforst-Collins & Disterhoft, 1998; see also Chachich & Powell, 1998).

Similarly, in humans, there is converging evidence that cerebellar damage impairs or abolishes eyeblink delay classical conditioning (Daum et al., 1993; Solomon, Stowe, & Pendlebury, 1989; Topka, Valls-Sole, Massaquoi, & Hallett, 1993; Woodruff-Pak, Papka, & Ivry, 1996), whereas frontal lobe damage does not disrupt eyeblink conditioning involving a conditional discrimination (Daum, Channon, Polkey, & Gray, 1991).

In animals, lesions of the hippocampus and surrounding areas do not impair acquisition of a conditioned eyeblink in the delay conditioning paradigm (Schmaltz & Theios, 1972; Solomon & Moore, 1975; Solomon, 1977; Akase, Alkon, & Disterhoft, 1989). Recently, several studies have confirmed that humans with amnesia subsequent to medial temporal lobe damage (including the hippocampus) can acquire an eyeblink CR in the delay conditioning paradigm at the same rate as matched controls (Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993; Gabrieli et al., 1995; Clark & Squire, 1998). Other paradigms, such as trace eyeblink conditioning, in which the CS terminates before US can indeed be disrupted in medial temporal amnesia (e.g., McGlinchey-Berroth, Carrillo, Gabrieli, Brawn, & Disterhoft, 1997; Clark & Squire, 1998). However, it appears that the hippocampus is not necessary for acquiring a simple CS–US association in the delay eyeblink conditioning paradigm (see Green & Woodruff-Pak, 2000).

Although the hippocampus may not be strictly needed for delay conditioning, there is good evidence that it normally participates in this learning. In animals, hippocampal neuronal discharge patterns mirror and precede the developing CR (Berger & Thompson, 1977; see also Weiss, Kronforst-Collins, & Disterhoft, 1996; Berger, Rinaldi, Weisz, & Thompson, 1983). Recent neuroimaging (positron emission tomography) studies have found analogous learning-related activity in the human hippocampus during classical conditioning (Blaxton et al., 1996). Further, subseizure electrical stimulation of the hippocampus after each conditioning trial, or throughout the conditioning experiment, disrupts acquisition of eyeblink CRs in the rabbit, although it does not disrupt maintenance of an already-learned eyeblink response (Salafia, Romano, Tynan, & Host, 1977; Salafia, Chiaia, & Ramirez, 1979; Salafia & Allan, 1980). These results suggest that, whereas outright removal of the hippocampus spares delay conditioning, a dysfunctional hippocampus can impair it.

Computational modeling has suggested that the hippocampus may be conceived as a secondary site of conditioned learning, which operates in parallel with the primary sites in the cerebellar and cerebral cortices (e.g., Gluck & Myers, 1993). Under normal conditions, in the intact brain, the hippocampus may provide additional information about the learning situation, such as information about contextual or stimulus–stimulus relationships. In the case of a simple task, like acquisition of an eyeblink response in the delay conditioning paradigm, this additional information may not be strictly necessary—and so hippocampal lesion does not have a deleterious effect on rate of learning. As stimulus contingencies become more complicated, however, hippocampal involvement may be critical, which would explain the common finding that conditioning tasks involving complex timing, stimulus configurations, or contextual manipulations are often disrupted following hippocampal lesion (e.g., Kim, Clark, & Thompson, 1995; Port & Patterson, 1984; Port, Romano, & Patterson, 1986; M. Allen, Myers, & Gluck, in press; Shohamy, Allen, & Gluck, 2000).

The situation should be different for hippocampal disruption. If hippocampal activity is disrupted, then its output will be distorted. Other brain structures that normally make use of this output will receive incorrect or noisy information, and this will retard learning. Learning will be slowed but not abolished; given extensive training, normal asymptotic performance levels should still be reached.

One way to disrupt the hippocampus is by lesion or disruption of the medial septum, a structure within the basal forebrain that sends cholinergic and gamma-aminobutyric acid (GABA)-ergic projections to the hippocampus. Disruption of these projections, by medial septal lesion or pharmacological intervention, might be expected to disrupt hippocampal processing and thus disrupt conditioned learning. In fact, administration of the cholinergic blocker scopolamine into medial septum in rabbit does affect hippocampal neuronal activity (Stumpf, Petsche, & Gogolak, 1962) and also retards delay eyeblink classical conditioning (Solomon & Gottfried, 1981; Salvatierra & Berry, 1989). Systemic scopolamine also impairs delay eyeblink classical conditioning in rabbits (Powell, Hernandez, & Buchanan, 1985; Harvey, Gormezano, & Cool-Hauser, 1983; Solomon, Solomon, Van der Schaaf, & Perry, 1983) and humans (Solomon et al., 1993; Bahro, Schreurs, Sunderland, & Molchan, 1995). Solomon et al. (1983) showed that the disrup-

Table 1
Medical and Surgical Information on the Anterior Communicating Artery (ACoA) Participants

Participant ID no.	Medical and surgical information	Years post
116	ACoA aneurysm rupture; metal clip implanted.	0.7
118	ACoA aneurysm rupture; location confirmed by arteriogram at emergency room admission; metal clip implanted.	1.3
119	ACoA aneurysm; metal clip implanted.	5.1
120	ACoA aneurysm rupture; damage in basal forebrain confirmed by surgical report.	3.0
121	ACoA aneurysm rupture; basal forebrain lesion confirmed by computed tomography.	6.3
122	ACoA aneurysm rupture; basal forebrain lesion and small right frontal-parietal lesion.	1.0

Note. ID = identification; Years post = time in years between surgery to clip aneurysm and eyeblink testing.

tive effects of scopolamine on learning did not occur in animals with hippocampal lesions, suggesting that the critical effects of scopolamine were in disrupting septohippocampal projections.[1] These data are consistent with the idea that septohippocampal projections are critical in normal learning. Solomon has suggested that the age-related decline shown in human delay eyeblink conditioning (e.g., Solomon, Pomerleau, et al., 1989; Durkin, Prescott, Furchtgott, Cantor, & Powell, 1993) may at least partially reflect age-related decreases in brain acetylcholine levels (see Solomon et al., 1993, for discussion).

Arguing from neurophysiological and behavioral evidence, Hasselmo and colleagues suggested that one role of the septohippocampal projections is to modulate hippocampal processing (e.g., Hasselmo & Bower, 1993; Hasselmo & Schnell, 1994; Hasselmo, 1995). Specifically, they suggest that high levels of septohippocampal acetylcholine may increase the rate at which new information is processed and stored by the hippocampus. In subsequent computational modeling, it was shown that this could account for the effects of scopolamine on delay eyeblink conditioning: Specifically, systemic or intraseptal scopolamine slows the onset of delay conditioning but does not affect the rate at which a CR is subsequently acquired nor its eventual asymptotic strength (Myers et al., 1996; Myers, Ermita, Hasselmo, & Gluck, 1998).

If the mechanism by which scopolamine retards learning is through disruption of septohippocampal projections, then it would be expected that lesion of the medial septum ought to disrupt delay conditioning at least as severely. This is consistent with the finding that medial septal lesion does strongly retard the onset of conditioned responding in the rabbit eyeblink preparation (Berry & Thompson, 1979).

In humans, the primary cholinergic projections from the basal forebrain to the hippocampus originate in the medial septum and the diagonal band of Broca, a structure adjacent to and often grouped together with the medial septum (e.g., Swanson, 1977). By analogy with the animal data, lesion to the medial septum–diagonal band complex should impair eyeblink conditioning in humans. As described above, ACoA aneurysm survivors often sustain basal forebrain damage, presumably including damage to the medial septum–diagonal band complex, and this is often associated with dense anterograde amnesia. ACoA aneurysm survivors may also sustain additional damage to other basal forebrain structures and to frontal areas. However, there is little evidence that frontal damage affects delay eyeblink classical conditioning in humans (Daum et al., 1991) or animals (Kronforst-Collins & Disterhoft, 1998; see also Chachich & Powell, 1998) and little evidence that damage to other basal forebrain structures, such as the nucleus basalis, impairs simple learning (e.g., Ginn & Powell, 1992). Thus, it may plausibly be inferred that any disruption in delay eyeblink conditioning observed in individuals with ACoA amnesia can be primarily attributed to damage of the medial septum–diagonal band complex (see also Everitt & Robbins, 1997). In fact, in several case studies, individuals with damage limited to the medial septum–diagonal band complex do show anterograde amnesia, indicating that damage to these structures is sufficient to produce lasting memory impairment (Morris, Bowers, Chatterjee, & Heilman, 1992; Abe et al., 1998).

The purpose of this study was to examine delay eyeblink conditioning in a group of individuals with amnesia following ACoA aneurysm rupture. If, as anticipated, these individuals showed impaired eyeblink conditioning, this would distinguish them from individuals with amnesia resulting from hippocampal–medial temporal lobe damage, because that etiology spares delay eyeblink conditioning.

Method

Participants

Six individuals who survived ACoA aneurysm rupture and repair by craniotomy and aneurysm clipping, and who subsequently demonstrated severe anterograde amnesia, served as the ACoA group (see Table 1).

[1] Although one study has shown that scopolamine injected directly into the dorsal hippocampus does not affect eyeblink conditioning in rabbit (Solomon & Gottfried, 1981), the rabbit does have a ventral septohippocampal cholinergic pathway (Alonso, Sang, & Amaral, 1996; see also Meyer, 1996) that may not have been affected by the dorsal injections. In addition, Woodruff-Pak has noted that whereas scopolamine blocks muscarinic cholinergic receptors, the septohippocampal cholinergic projections target both muscarinic and nicotinic receptors in hippocampus (e.g., Woodruff-Pak, Li, & Kem, 1994). Thus, it is possible that concurrent muscarinic and nicotinic blockade in the hippocampus would elicit impaired learning. Indeed, systemic administration of the nicotinic antagonist mecamylamine disrupts rabbit eyeblink conditioning at least as effectively as systemic scopolamine (Woodruff-Pak, Li, Kazmi, & Kem, 1994).

Available medical records on the presence of the ACoA aneurysm and repair included cerebral angiogram reports, computed tomography (CT) scan, and neurosurgical reports. All were at least 6 months postsurgery and free of confabulation on clinical evaluation. Surgical treatment for the aneurysm involves implantation of a clip; clip artifact on CT scan prevented definite assessment of basal forebrain lesions in 3 participants. This is true of most of the clinical studies examining ACoA individuals. Thus, we refer to "presumed" basal forebrain lesion in the present article, on the basis of extensive reviews of the literature (DeLuca and Diamond, 1995), recent studies of patients who did not have metal clips implanted (thus allowing MRI imaging; e.g., Abe et al., 1998; Bottger et al., 1998), and postmortem analyses (Phillips, Sangalang, & Sterns, 1987), all of which conclude that the basal forebrain is the lesioned structure that is responsible for the amnesia.

A group of 6 healthy individuals, matched for age and education to the ACoA participants, served as the control group; there were no significant differences between groups in age, $t(10) = 0.25$, $p > .5$, or education, $t(19) = 1.58$, $p = .14$. ACoA participants were tested at Kessler Medical Research Rehabilitation and Education Corporation (KMRREC); control participants were tested at Rutgers University. ACoA participants were tested in the course of other ongoing research. Control participants were offered compensation for their participation at a rate of $10 per hour. This study was approved by the institutional review boards at both KMRREC and Rutgers University. Informed consent was obtained from all participants prior to testing.

Neuropsychological Assessment

All ACoA and control participants were given neuropsychological tests to assess premorbid intelligence, attention, memory and frontal-executive function.

Table 2 summarizes the results of the neuropsychological assessment. The North American Adult Reading Test (NAART) was used to estimate premorbid general intellectual ability. The control group scored significantly higher than the ACoA group, $t(10) = 4.51$, $p < .05$, on NAART estimates of Full Scale IQ score (FSIQ; Blair & Spreen, 1989), although all but one participant in the ACoA group (#121) scored within one standard deviation of the FSIQ mean of 100. As a group, the ACoA participants' performance fell within the low-normal (FSIQ = 80–90) to normal (90–110) range. However, it has been suggested that executive dysfunction may result in NAART performance decrement because of unchecked error responses (O'Carroll, Moffoot, Ebmeier, & Goodwin, 1992), thus resulting in underestimates of premorbid IQ scores. The ACoA and control groups did not differ significantly on an index of attention and concentration, the Digit Span subtest from the Wechsler Adult Intelligence Scale—Revised (WAIS–R), $t(10) = 1.60$, $p > .05$.

Participants were also administered tests to assess frontal-executive function. ACoA participants scored significantly worse than control participants on the Controlled Oral Word Association test (COWA), $t(10) = 3.81$, $p < .05$, and also on the Wisconsin Card Sort Test (WCST), achieving fewer categories, $t(10) = 18.46$, $p < .05$ and making more perseverative responses, $t(10) = 5.50$, $p < .05$.

There was also a significant difference between the ACoA and control groups when compared simultaneously on several tests of memory, multivariate $F(6, 3) = 151.98$, $p < .05$, including the California Verbal Learning Test (CVLT). The CVLT is a standardized and well-normed word list learning test entailing recall and recognition procedures. The ACoA group scored well below the control group on all CVLT recall measures, as summarized in Table 2. Total perseverative errors recorded during the CVLT did not differ significantly between groups, and all but 1 participant in the ACoA group (#118) scored within one standard deviation of age- and sex-appropriate means.

Table 2
Demographic and Neuropsychological Data

	ACoA aneurysm survivors								Controls (n = 6)	
Measure	116	118	119	120	121	122	*M*	*SD*	*M*	*SD*
Age (years)	45	61	53	64	29	50	50.33	12.58	48.67	10.69
Education (years)	12	12	12	12	16	18	13.67	2.66	15.83	2.04
NAART-FSIQ	86.5	96.6	106.7	87.0	80.0	91.9	91.45	9.34	113.63	7.59
Digit Span	−1.00	−1.67	−0.67	−0.67	0.00	−0.33	−0.72	0.57	0.06	0.93
COWA	−1.45	−2.70	−1.42	−3.01	−0.86	−1.61	−1.84	0.83	0.25	1.06
WCST pers.	54	113	22	118	82	32	70.17	40.75	6.00	1.67
WCST cat.	3	0	4	0	0	5	2.00	2.28	6.00	0.00
LM-I	−1.30	−1.70	−0.50	2.00[a]	6.50[a]	−1.60	−1.28[b]	0.54[b]	0.43	0.98
LM-II	−1.70	−2.20	−1.90	0.00[a]	2.75[a]	−0.90	−1.68[b]	0.56[b]	0.26	0.87
CVLT										
Total	−4.50	−4.40	−4.20	−4.50	−2.50	−4.00	−4.02	0.77	0.65	1.29
LDF	−5	−4	−4	−4	−3	−4	−4.00	0.63	0.83	1.17
Hits	−4	−4	−3	−1	−2	−3	−2.83	1.17	0.17	0.75
Discriminability	−5	−2	−2	−3	−2	−2	−2.67	1.21	0.33	0.52
Perseverative errors	−1	5	−1	0	0	−1	0.33	2.34	−0.50	0.84
CFT copy	34.0	35.0	35.0	24.5	36.0	35.0	33.25	4.33	35.17	0.98
CFT imm.	8.5	7.0	11.0	6.5	12.0	19.5	10.75	4.80	21.67	5.01

Note. Anterior communicating artery (ACoA) aneurysm survivors are represented by their identification numbers. NAART–FSIQ = North American Adult Reading Test—Full Scale IQ estimates; Digit Span = age-scaled Digit Span z scores from the Wechsler Adult Intelligence Scale—Revised; COWA = Controlled Oral Word Association test sex- and education-scaled z scores; WCST = Wisconsin Card Sort Test raw scores; pers. = perseverative responses; cat. = number of categories attained; LM-I and LM-II = Logical Memory Immediate and Delayed Recall Tests of the Wechsler Memory Scale—Revised, z scores; CVLT = California Verbal Learning Test, z scores; Total = total correct list A Trials 1–5; LDF = long delay free recall; Hits = correct recognition hits; CFT = Rey–Osterrieth Complex Figure Test, maximum score = 36; copy = copy raw score; imm. = immediate recall raw score. [a] Participants 120 and 121 were administered the immediate and delayed portions of the Logical Memory test from the original Wechsler Memory Scales. The scores reported for these 2 participants reflect the average number of conceptual units recalled between the two stories, one story having 23 conceptual units and the other having 24. [b] The means and standard deviations for the standardized z scores of the LM-I and LM-II do not include the raw scores from Participants 120 and 121.

Four participants in the ACoA group and all participants in the control group were administered the Logical Memory Immediate (LM-I) and Delayed (LM-II) Recall tests of the Wechsler Memory Scale—Revised (WMS–R). Two ACoA participants (#120 and #121) were given the immediate and delayed portions of the Logical Memory test from the original WMS. This test involves immediate and 30-min-delayed free recall of two short paragraphs. The ACoA participants showed below-normal immediate recall and minimal recall after the 30-min delay.

Finally, the Rey–Osterrieth Complex Figure Test involves copy and immediate reproduction from memory of a complex drawing. The ACoA group did not differ from the control group on the copy portion but did score significantly worse on the immediate recall portion of the test.[2]

In summary, the ACoA group showed strong impairments relative to the control group on tests indexing both memory and frontal-executive function. The ACoA group was not impaired at a task indexing attention and concentration. Although the ACoA group did score significantly worse than the control group on a test estimating premorbid intelligence, all ACoA participants scored within the low-normal or normal range. All control participants scored within normal ranges on all measures.

Apparatus

The apparatus used to condition the eyeblink response was previously described (Solomon, Pomerleau, et al., 1989). Conditioning took place in a quiet room (ambient noise approximately 60 dB). The participant was seated in a comfortable chair that had stereo speakers placed at head level on either side, approximately 30 cm from the participant's ears. This was used to deliver the CS. The participant was fitted with an adjustable plastic head harness containing a noninvasive transducer. This consisted of a light-emitting diode used to generate an infrared beam that was aimed so it reflected off the participant's right cornea and back into a phototransistor. Interruption of the beam by eyelid closure was transduced into a voltage change and recorded by IBM 360 computer system with analog-to-digital converter (Lavond & Steinmetz, 1989). The amplitude of the eyeblink response was given in arbitrary units on a scale of 0 to 18 (*maximal deflection*) and, for an individual participant, typically ranged from 0 (*eye fully open*) to 2–5 (*eye fully shut*), depending on such variables as the participant's skin color and ambient illumination. An eyeblink response was defined as a deviation of at least 0.5 from baseline deflection level (with eyes open); for each eyeblink response, the computer recorded amplitude (deviation from baseline) and time (in milliseconds) of maximal deflection.

The computer generated both the tone CS and the airpuff US. The airpuff US was directed at the participant's right cornea via a rubber hose attached to the headset.

During conditioning, the participant watched a silent movie (Mel Brooks' *The Silent Movie*) on a monitor located directly in front of the chair. The experimenter and equipment for generating and recording responses were located behind and out of sight of the participant. A video camera trained on the participant's face broadcast this image back to the experimenter, who could then monitor whether the headset remained in place and whether blinking appeared normal.

Eyeblink Conditioning Procedure

Upon entering the laboratory, each participant was told that he or she would be participating in a study to measure eye movements and was asked to sign an informed consent statement. The Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) was administered. The participant was then seated in the conditioning chair, and the experimenter fitted the headset and checked that the participant was comfortable. The experimenter then read the following instructions:

> Please make yourself comfortable and watch the silent film. From time to time, you will hear tones and feel mild puffs of air to your eye. If you feel like blinking, please do so. Just let your natural reactions take over as you watch the film.

The conditioning procedure was adapted from that outlined in Solomon, Pomerleau, et al. (1989). Each participant underwent 70 paired CS–US conditioning trials, divided into seven blocks of 10 trials. The CS was a 500-ms, 1000-Hz tone calibrated to be 72 dB at the approximate location of the participant's ears. The US was a puff of medical-grade oxygen, 6.9 kPa (1 psi) at source, and of approximately 100-ms duration. US onset occurred 400 ms after CS onset, and CS and US coterminated. The intertrial interval ranged from 27 to 33 s, with a mean of 30 s. This procedure deviates from that described in Solomon, Pomerleau, et al. (1989) in that the prior study included one CS-alone test trial per block, as well as presenting a series of US-alone test trials prior to the initiation of CS–US training.

Eyeblink Conditioning Data Analysis

On each trial, the computer recorded changes measured by the headset transducer, including the timing and amplitude of any eyeblink response. A CR was defined as an eyeblink response occurring after CS onset but before US onset. A UR was defined as a response occurring during the US interval (i.e., the last 100 ms of the CS presentation). Trials that had eyeblink responses during the 150 ms prior to CS onset were scored as spontaneous blinks and data from these trials were not analyzed. Additionally, any eyeblink response occurring less than 100 ms after CS onset was scored as an alpha response; it has long been suggested that alpha responses represent orienting responses to the CS rather than true CRs (for review, see Coleman & Webster, 1988), and many human eyeblink conditioning studies have calculated alpha responses separately from CRs (Daum, Channon, & Gray, 1992; Schnur & Ksir, 1969). For each CR and UR, the computer also recorded the latency, defined as time of maximal eyelid closure within the CS period.

For each participant, the "adjusted-total trials" was calculated as the total number of trials scored as including a CR, UR, or alpha response—in other words, excluding trials with a spontaneous blink or no response. Next, for each participant, the "total percentage CRs" was calculated as the percentage of adjusted-total trials on which a CR occurred. The total number of alpha responses was also calculated for each participant.

In addition, to measure overall response strength, the average UR amplitude was recorded for each participant over the first block (10 trials) of training. For each CR trial, the computer also calculated response latency, defined as the time between CS onset and maximal eyelid closure. Note that the airpuff US arrived 400 ms after onset of the tone CS, and so CR latency could range from 100 to 400 ms; latencies less than 100 ms were alpha responses, whereas latencies greater than 400 ms were URs. A longer latency is considered to be more adaptive, because the eyelid reaches maximal closure closer to the time of expected US arrival.

Results

Figure 1A shows the percentage of participants in each group who generated a CR on each of the first 10 training trials. Within this initial 10-trial block, control participants showed an increase in level of responding, whereas ACoA participants showed little improvement over baseline responding.

[2] The Rey–Osterrieth Complex Figure Test also typically involves a delay portion, in which the figure is reproduced after a delay of 15–30 min. These data are not reported here because some ACoA participants received additional organizational procedures as outlined in Diamond, DeLuca, and Kelley (1997) to improve recall.

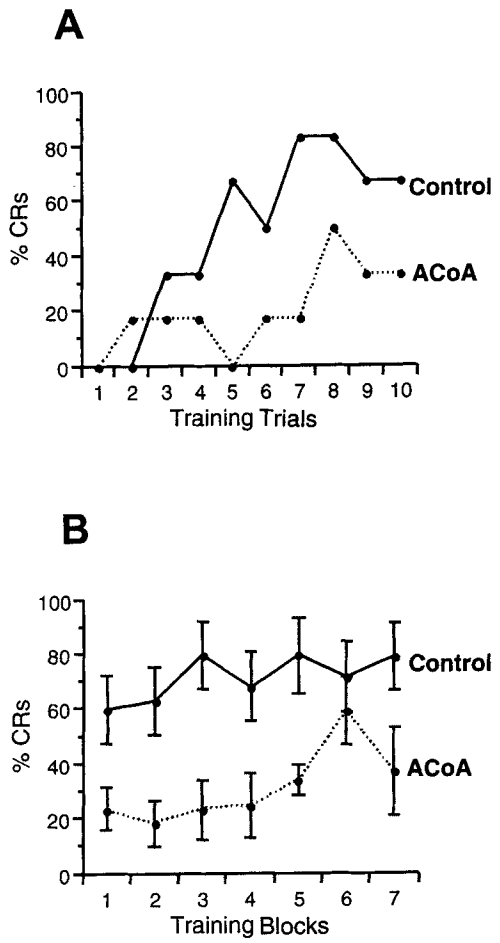

Figure 1. Eyeblink conditioning is impaired in anterior communicating artery (ACoA) amnesia in terms of (A) conditioned responses (CRs) generated during the first block of training and (B) percentage of CRs generated across all seven blocks of training. Error bars represent *SE*.

Across the seven training blocks, the control group averaged a total of 70.9% CRs; the ACoA group averaged a total of only 30.9% CRs. Figure 1B shows the percentage of CRs for each group, broken down across the seven training blocks. A repeated measures analysis of variance (ANOVA) on this measure revealed a significant main effect of group, $F(1, 10) = 7.39$, $p = .022$. There was also a significant effect of block, $F(6, 60) = 4.48$, $p = .001$, and a Block × Group interaction, $F(6, 60) = 2.55$, $p = .029$. Planned comparisons confirmed a significant effect of block in the ACoA group, $F(6, 30) = 4.51$, $p = .002$, but not in the control group, $F(6, 30) = 2.14$, $p > .05$. Thus, responding in the ACoA group improved across training blocks, whereas the control group was responding near asymptote as early as the first block of training.

On several other important measures, there were no significant differences between the control and ACoA groups. First, as shown in Figure 2A, the amplitude of the unconditioned (reflexive) eyeblink response during the first block of training did not differ significantly for control and ACoA groups, $t(10) = 0.77$, $p = .46$. This means that the two groups were equated for blink magnitude and that this could not account for the difference in total CRs between groups.

Second, latency on CR trials in the final block is shown in Figure 2B; again, there was no significant difference between control and ACoA groups, $t(10) = 1.02$, $p = .300$. Third, as shown in Figure 2C, both groups gave similar numbers of alpha responses, defined as eyeblink responses that occurred too soon after CS onset to be considered CRs, $t(10) = 0.41$, $p > .5$. The similarity in latency and alpha responses for the two groups suggests that, on those trials on which CR was generated, the CR was equally well-timed by control and ACoA participants. This in turn suggests that, although the ACoA participants gave fewer CRs overall, the CRs they did generate were as adaptive as control participants' CRs.

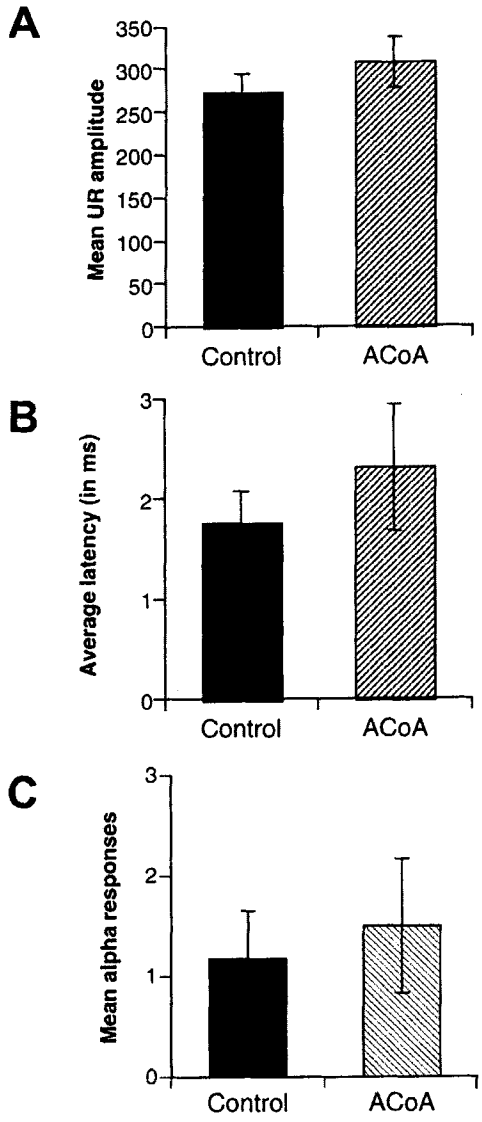

Figure 2. Anterior communicating artery (ACoA) and control groups did not differ on nonassociative measures such as (A) unconditioned response (UR) amplitude on the first airpuff trial, (B) average latency on conditiond response trials, measured in Block 7, or (C) total number of alpha responses. Error bars represent *SE*.

The two groups were also equivalent in terms of excluded trials. The control group averaged 7.33 (SE = 2.64) spontaneous eyeblinks across 70 training trials, whereas the ACoA group averaged 6.33 (SE = 2.54). This was not a significant difference, $t(10) = 0.27$, $p > .5$. There was also no difference between groups in terms of number of trials on which no eyeblink response was measured (control: M = 2.83, SE = 0.48; ACoA: M = 4.33, SE = 1.80), $t(10) = 0.14$, $p = .44$.

A final question involves the possible relationship between frontal-executive dysfunction and eyeblink performance. Figure 3A shows that there was no obvious relationship between frontal–executive function, as indexed by COWA score, and performance on the eyeblink task, as indexed by total percentage of CRs. For example, Participant #120, who received the lowest z score on the COWA, generated only 13% CRs over the course of the experiment; in contrast, Participant #118, who received the second-lowest COWA z score, generated fully 53% CRs within one standard deviation of the performance level shown by the control group on the eyeblink task. The lack of relationship between this neuropsychological measure of frontal-executive dysfunction and performance on the eyeblink task was confirmed by regression analysis (ANOVA), $F(1, 4) = 0.12$, $p > .5$. Similarly, as shown in Figure 3B, there was no obvious relationship between perseverative responding on the WCST and eyeblink performance (ANOVA), $F(1, 4) = 0.12$, $p > .5$.

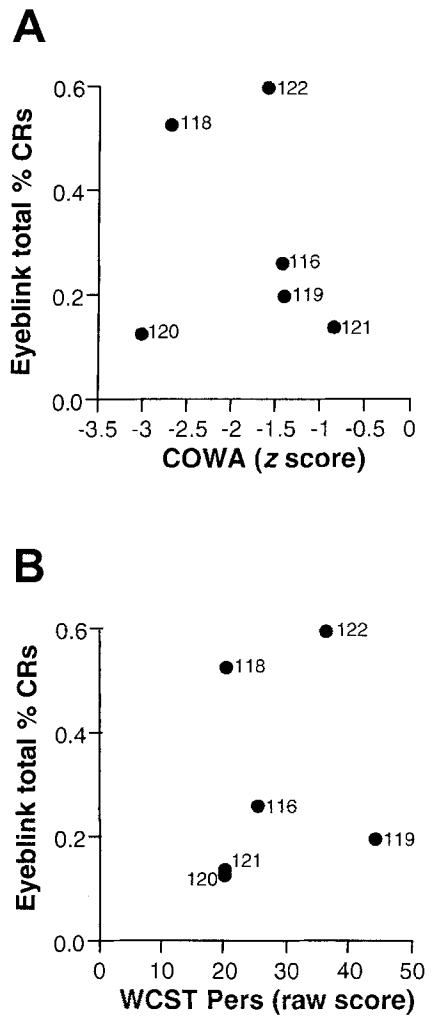

Figure 3. Total percentage of conditioned responses (CRs) among anterior communicating artery participants as a function of (A) Controlled Oral Word Association (COWA) z score and (B) perseverative (Pers) responding on the Wisconsin Card Sorting Test (WCST; raw score). Labels on data points are the participant identification numbers given in Table 1.

Discussion

In summary, these results demonstrate that individuals with amnesia resulting from ACoA aneurysm rupture were significantly slower than control participants in acquiring an eyeblink response in the delay conditioning paradigm. The impaired conditioning in individuals with ACoA amnesia stands in contrast to the well-established finding that individuals with medial temporal (hippocampal) amnesia condition at a normal rate in the delay paradigm (Gabrieli et al., 1995; Woodruff-Pak, 1993). The present study involved a relatively small group of 6 ACoA aneurysm survivors, and clearly one must use caution when generalizing from the results of a small sample to make inferences about the behavior of a larger population. Nevertheless, the results appeared relatively robust within this small group: Whereas control participants generated nearly 60% CRs within the first block of training, and maintained a high rate of responding throughout the rest of the experiment, the ACoA group showed poor conditioning within the 70 training trials.

Because individuals in the ACoA group are presumed to have basal forebrain damage but not medial temporal lobe (including hippocampal) damage, these results suggest that basal forebrain damage in humans, like in animals, may disrupt simple conditioned learning. Although ACoA aneurysm rupture may also result in variable degrees of frontal lobe dysfunction, prior studies have suggested that frontal damage does not disrupt delay eyeblink conditioning (Kronforst-Collins & Disterhoft, 1998). Although we cannot rule out the possibility that combined basal forebrain and frontal damage contributed to the current pattern of results, two neuropsychological tests (COWA and WCST), which are often used to index frontal-executive dysfunction, did not correlate with performance on the delay eyeblink conditioning task (Figure 3).

The impaired delay conditioning in ACoA amnesia is in accord with prior animal and pharmacological studies suggesting that basal forebrain damage—specifically, medial septal damage—does disrupt delay eyeblink conditioning. The presumed mechanism of this disruption is that medial septal damage disrupts septohippocampal projections that normally modulate hippocampal processing; hippocampal disruption in turn impairs delay eyeblink conditioning, even though outright hippocampal lesion does not (Myers et al., 1996, 1998; Solomon et al., 1983). In rabbits, medial septal lesions retard the onset of responding (Berry & Thompson, 1979), so that rabbits take longer to start showing CRs. In contrast, the ACoA group in the present study showed no appreciable learning across the 70 training trials (Figure 1B). It is an open question whether this represents an abolition of conditioned learning or whether the ACoA group would eventually develop CRs with extended training.

This latter hypothesis gains some support from literature on delay eyeblink conditioning in individuals with probable Alzhei-

mer's disease (AD). One component of AD is disruption of the basal forebrain cholinergic system (e.g., Whitehouse et al., 1982), and indeed individuals with AD do show impaired delay eyeblink conditioning compared with age-matched controls (e.g., Solomon, Levine, Bein, & Pendelbury, 1991; Woodruff-Pak, Finkbiner & Sasse, 1990; Woodruff-Pak, Papka, Romano, & Li, 1996). Further, when patients with AD are tested over multiple days, they do eventually acquire the CR (Solomon et al., 1995; Woodruff-Pak, Romano, & Papka, 1996). This is broadly comparable to the findings in animals that disruption of septohippocampal cholinergic pathways retards, but does not abolish, delay eyeblink conditioning (Salvatierra & Berry, 1989; Solomon & Gottfried, 1981). It is therefore plausible that individuals with basal forebrain damage following ACoA aneurysm rupture, given extended training, might likewise reach the same performance level as controls.

It is worth noting that our control participants gave a higher overall response rate than what has often been reported for individuals of that age group in the delay eyeblink conditioning paradigm. For example, whereas our control group had a mean age of about 49 years and a mean response rate of about 71%, an earlier article using similar stimuli found an average response rate of about 80% for individuals aged 40–49 years which dropped to about 50% for individuals aged 50–59 years (Solomon, Pomerleau, et al., 1989). Another study found that individuals aged 40–49 years averaged only about 50-60% CRs (Woodruff-Pak & Thompson, 1988), a considerably lower learning rate than the control group in the present study. However, both these earlier studies included procedural manipulations that are known to retard conditioning in animals. The Solomon, Pomerleau, et al. study intermixed nonreinforced CS-alone trials with CS–US pairings in a 1:9 ratio, whereas Woodruff-Pak and Thompson's study intermixed CS-alone, US-alone, and CS–US pairings in a 1:1:8 ratio. These paradigms thus constitute partial reinforcement schedules. It has long been known that regular omission of expected reinforcement can slow delay eyeblink conditioning in both animals (Prokasy & Gormezano, 1979) and humans (Prokasy & Williams, 1979; Schurr & Runquist, 1973; also C. Allen & Branum, 1971). This may account for the finding of a somewhat lower response rate in the Solomon, Pomerleau, et al. study, relative to our own control group—and for the fact that Woodruff-Pak and Thompson's study, which further reduced the probability that CS was followed by US, showed still lower average response rates.

Although partial reinforcement schedules may have been appropriate for the prior studies, they were not appropriate for the present study. Our a priori hypothesis was that acquisition of an eyeblink CR would be retarded in individuals with ACoA amnesia. Thus, we specifically wished to avoid any paradigmatic manipulations that would be expected to retard overall learning. Because the control group in the current experiment reached criterion within an average of about 40 trials, whereas the ACoA group did not approach criterion performance after 70 blocks of training, it seems that the impairment in the ACoA group was severe and long-lasting.

One question that naturally arises is whether individuals with other kinds of amnesic etiology, such as damage to the diencephalon, are impaired or spared at delay eyeblink conditioning. Diencephalic amnesia often results from Korsakoff's disease, a syndrome often associated with chronic alcohol abuse (Parsons & Nixon, 1993). McGlinchey-Berroth et al. (1995) tested a group of amnesic individuals with Korsakoff's disease in the delay eyeblink conditioning paradigm and found that the patients acquired a CR more slowly than did healthy controls. However, a group of non-amnesic recovered alcoholics showed similarly reduced rates of conditioning. McGlinchey-Berroth et al. (1995) concluded that the impaired conditioning in the recovered alcoholics was most likely due to cerebellar deterioration resulting from years of alcohol abuse. Because the Korsakoff's patients presumably had a similar or greater degree of cerebellar deterioration, this would explain the reduced rate of conditioning. Daum and Ackermann (1994) also studied a woman who became amnesic after a thalamic infarction; neither neuroimaging nor electrophysiological tests (sensory evoked potential, transcranial magnetic stimulation) revealed any lesion or dysfunction beyond the thalamus. This individual showed unimpaired delay eyeblink conditioning. In animals, thalamic lesions may impair delay eyeblink conditioning (Buchanan, 1994) or spare it, at least under conditions of continuous reinforcement (Buchanan, Powell, Beylotte, & Penney, 1998). Thus, at this point, it is an open issue whether diencephalic amnesia impairs or spares delay eyeblink conditioning and, indeed, how diencephalic structures interact with medial temporal and basal forebrain structures in normal learning and memory.

In future work, we plan to compare individuals with ACoA amnesia and medial temporal amnesia on a variety of tasks traditionally considered to be "hippocampal-independent," including skill learning, category learning, and so forth in an attempt to document exactly which tasks are impaired and spared in each group. It is our expectation that delay eyeblink conditioning will not prove to be anomalous in its ability to differentiate between the two amnesic groups. Instead, amnesic etiologies that damage different brain structures are entirely likely to produce a wide range of subtly different impairments within the broader domain of learning and memory. If this is true, then it may be possible to develop a battery of simple learning tests that can be used to discriminate among different amnesic etiologies. This would also have implications for therapy and rehabilitation by allowing development of rehabilitation techniques that are targeted to make use of the particular kinds of learning that are spared in a particular amnesic population.

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