

# Impaired Trace Eyeblink Conditioning in Bilateral, Medial-Temporal Lobe Amnesia

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Trace eyeblink classical conditioning was assessed in patients with bilateral medial-temporal amnesia and matched control participants who had previously shown equivalent delay eyeblink conditioning (J. D. E. Gabrieli et al., 1995). The silent trace interval varied for durations of 500, 750, or 1,000 ms in successive sessions separated by at least 2 weeks; extinction trials followed each session. Patients with amnesia produced significantly fewer conditioned responses (CRs) than did control participants at all trace intervals. Both groups produced fewer CRs as the trace interval lengthened. Thus, the temporal lobe memory system in humans makes an essential contribution to normal acquisition in trace, but not delay, classical eyeblink conditioning.

Delineating the neural underpinnings of simple associative learning with classical eyeblink conditioning as a model system has an extensive history in the animal literature. A great deal of this work has been carried out through investigations of the rabbit nictitating membrane conditioned response (CR), in part because this learned response is so well characterized behaviorally (e.g., Gormezano, Kehoe, & Marshall, 1983) and because the response can be generalized to other mammalian species. The success of this

work has sparked a great deal of interest in unveiling the neural substrates of associative learning in humans.

Animal studies have shown that the cerebellum and its associated circuitry are both necessary and sufficient for eyeblink classical conditioning (R. F. Thompson, 1986, 1988). In particular, the interpositus nucleus ipsilateral to the trained eye is essential for acquisition and retention (Clark, McCormick, Lavond, & Thompson, 1984; Lavond, Hembree, & Thompson, 1985; Lavond, Lincoln, McCormick, & Thompson, 1984; Lincoln, McCormick, & Thompson, 1982; McCormick & Thompson, 1984a; Steinmetz, Lavond, Ivkovich, Logan, & Thompson, 1992; R. F. Thompson et al., 1983; Woodruff-Pak, Lavond, & Thompson, 1985; Yeo, Hardiman, & Glickstein, 1985), whereas the cerebellar cortex appears to be critical for the temporal components of the CR (Perrett, Ruiz, & Mauk, 1993). In addition, electrophysiological evidence indicates that neural activity in the cerebellar cortex and the lateral interpositus nucleus develops patterned changes in discharge frequency that parallel the development of behavioral learning (McCormick & Thompson, 1984b). Finally, several studies with humans have now documented impaired acquisition in cases of cerebellar lesions (Daum, Ackermann, Lutzenberger, Dichgan, & Dirbaumer, 1993; Lye, O'Boyle, Ramsden, & Schady, 1988; Solomon, Stowe, & Pendlebury, 1989; Woodruff-Pak, Papka, & Ivry, 1996) and cerebellar degeneration (McGlinchey-Berroth et al., 1995; Topka, Valls-Sole, Massaquoi, & Hallett, 1992; Woodruff-Pak et al., 1996).

The hippocampus is also actively related to classical eyeblink conditioning. Electrophysiological studies have shown conditioning-specific changes in the pyramidal cells in the CA1 region of the rabbit that correlate with the

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development of CRs (Akase, Deyo, & Disterhoft, 1988; Berger, Rinaldi, Weisz, & Thompson, 1983; Berger & Thompson, 1978a; Berger & Weisz, 1987; Disterhoft, Coulter, & Alkon, 1986; Weiss, Kronforst-Collins, & Disterhoft, 1996). In humans, positron emission tomography studies have also imaged hippocampal activation in conjunction with acquisition (Blaxton et al., 1996; Logan & Grafton, 1995).

Whether or not the hippocampus is essential for learning seems to depend on the associative demands of the conditioning paradigm. The delay conditioning task is perhaps the most simple associative learning paradigm because there is temporal overlap between the conditioned stimulus (CS) and the unconditioned stimulus (US) and both stimuli terminate simultaneously. Given these parameters, the hippocampus does not appear to be essential because rabbits are unimpaired in delay eyeblink conditioning following hippocampal lesions (Akase, Alkon, & Disterhoft, 1989; Berger & Orr, 1983; Schmaltz & Theios, 1972; Solomon & Moore, 1975). Delay conditioning does not appear to depend on the hippocampus in humans either because amnesic patients with bilateral medial-temporal damage show intact (Gabrieli et al., 1995) or relatively preserved conditioning (Daum, Channon, & Canavan, 1989; Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993).

The trace conditioning paradigm is a more complex and demanding associative task because there is temporal separation between the CS and US necessitating the formation of an abstract link or a conjoined representation between the two stimuli in order for learning to occur. Although there are fewer studies investigating trace conditioning following hippocampal removal or damage, the majority of evidence available from animal studies suggests that the hippocampus is essential when two stimuli are temporally dissociated. For example, Solomon and his colleagues (Solomon, Vander Schaaf, Thompson, & Weisz, 1986) reported that lesions of the hippocampus disrupted acquisition of the trace, but not the delay, nictitating membrane CR. Extending this finding, Moyer, Deyo, and Disterhoft (1990) demonstrated that acquisition was eliminated with a 500-ms trace interval in rabbits that had undergone more complete hippocampectomies than were reported by Solomon et al. They also reported that on the few trials in which a CR did occur, most were short latency and nonadaptive. Of note, however, these animals were not impaired with a 300-ms trace interval, suggesting that compensatory strategies may be effective if the trace interval does not exceed some threshold. Moyer et al. suggested that the hippocampus encodes a temporal association between the CS and the US, and that this representation is essential for trace conditioning to occur. This representation remains hippocampally dependent for some time following learning, as was demonstrated by Kim, Clark, and Thompson (1995), who showed that learning was eliminated in rabbits that received bilateral hippocampal aspiration lesions 1 day following training but remained intact in rabbits that were lesioned 1 month following training. Thus, the role of the hippocampus in trace eyeblink conditioning may extend beyond temporal processing and include processes involved in the consolidation of the memory trace. This latter possibility has received electro-

physiological support (Moyer, Thompson, & Disterhoft, 1996; L. T. Thompson, Moyer, & Disterhoft, 1996a).

In the only trace conditioning study conducted to date with amnesic patients, Woodruff-Pak (1993) found that the amnesic patient H. M. and a second amnesic encephalitic patient reached a criterion level of CRs in a trace paradigm in which the CS was presented for 400 ms followed by a 500-ms trace interval. However, acquisition in both amnesic patients was impaired: H. M. and the encephalitic patient required 91 and 16 more conditioning trials, respectively, to reach criterion compared with the normal control participants. Woodruff-Pak (1993) concluded that because acquisition was eventually reached in the amnesic patients, "the hippocampus is not essential for classical conditioning in the trace paradigm" (p. 922). If one defines *essential* as being required for any conditioning to occur, then Woodruff-Pak's conclusion is correct because both amnesic patients showed trace conditioning. However, if one defines *essential* as being required for normal performance, then her conclusion is questionable because both amnesic patients were impaired on trace acquisition. By this latter interpretation, the hippocampus is essential for trace conditioning like it is essential for declarative tasks of recall and recognition.

In this study, therefore, we examined the ability of amnesic patients with bilateral, medial-temporal lobe damage and matched control participants to acquire and extinguish CRs at three different trace intervals: 500, 750, and 1,000 ms. A 500-ms trace interval was used as the starting point because it has been found to produce optimal conditioning in both young and old adults (Carrillo, Fitzpatrick, & Disterhoft, 1995). The within-subject manipulation of trace interval allowed for a systematic examination of the role of medial-temporal lobe structures in trace conditioning.

## Method

### *Participants*

*Amnesic participants.* Seven amnesic patients were tested with the 500-ms trace interval and 6 were tested with the 750- and 1,000-ms trace intervals. One of the patients tested in the 500-ms trace interval was not available for additional testing because of travel difficulties. Four of the patients became amnesic as the result of an anoxic episode, 2 became amnesic from encephalitis, and 1 became amnesic from status epilepticus. Bilateral damage to the hippocampal formation was confirmed by computerized tomography or magnetic resonance imaging in 5 of the 7 cases. One of the remaining 2 cases had enlarged ventricles and diffuse cortical atrophy, and the remaining case had moderate central and cortical atrophy (both were anoxic patients).

The demographic and neuropsychological characteristics of the amnesic participants are presented in Table 1. All of the patients were severely impaired, as indicated by their poor recall performance on the Wechsler Memory Scale—Revised (WMS-R; Wechsler, 1987) and their poor recognition performance for verbal and nonverbal material on the Warrington Recognition Test (Warrington, 1984). The amnesic participants had preserved intellectual and attentional function, however, as indicated by their performance on the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981) and the WMS-R.

*Normal control participants.* Seven control participants were selected from a larger group of volunteers and were screened to be

Table 1  
Patient Demographic and Neuropsychological Characteristics

Patient	Age (years)	Education (years)	WAIS-R full-scale IQ	WMS-R			Warrington	
				General memory	Attention	Delay	Faces	Words
1	55	16	108	76	92	51	41	35
2	58	20	105	65	89	61	34	30
3	45	16	111	81	107	69	32	31
4	37	14	90	90	115	<50	29	33
5	37	12	110	88	108	71	41	40
6	67	18	130	102	114	<50	32	35
7 <sup>a</sup>	31	16	106	96	128	<50	40	35
<i>M</i>	46	15.29	108.57	85.43	107.57	57.43	35.57	34.14

Note. The Wechsler Adult Intelligence Scale—Revised (WAIS-R) and the Wechsler Memory Scale—Revised (WMS-R) scaled scores yield a normalized, age-adjusted mean of 100. The WMS-R does not provide scores below 50. On the Warrington Recognition Test, 1 point is scored for each of 50 items.

<sup>a</sup>Patient participated only in the 500-ms trace interval study.

free of any neurological disease or illness. The control participants were matched to the amnesic patients with regards to age ( $M = 47.14$ ,  $SD = 13.20$ ), education ( $M = 16$ ,  $SD = 6.67$ ), and verbal intelligence as measured by the WAIS-R ( $M = 108.43$ ,  $SD = 9.38$ ). The means of these variables did not differ significantly from the amnesic patients ( $ps > .41$ ). The control participant who was matched to the amnesic patient unavailable for testing in the 750- and 1,000-ms trace intervals was also excluded in the 750- and 1,000-ms interval studies.

The amnesic patients and control participants had all been previously trained in a delay conditioning task (5 of the amnesic patients and 5 of the control participants were reported in Gabrieli et al., 1995). Each participant had received exactly 60 delay conditioning trials and 30 extinction trials.

### Apparatus

The apparatus used was a modified version of that used for eyeblink conditioning in the rabbit (Akase, Thompson, & Disterhoft, 1994; L. T. Thompson, Moyer, Akase, & Disterhoft, 1994). The CS was an 85-dB, 1-kHz tone that was delivered binaurally over earphones for a period of 100 ms and was clearly audible to all participants. This tone CS has been effective in previous trace conditioning studies in rabbits and humans with young and older subjects (Carrillo et al., 1995; L. T. Thompson, Moyer, & Disterhoft, 1996b). The US was a 100-ms, corneal airpuff delivered to the right eye. The magnitude of the airpuff averaged 3 psi. Eyeblink movements were monitored with an infrared diode/phototransistor aimed at the right eye. This device monitors and amplifies light reflectance from the cornea in a 0–5-V DC range, which is then digitized and stored by the computer. Eyeblink amplitude is an inverse function of the amount of reflected light contacting the phototransistor aimed at the cornea. The detector was adjusted so that the baseline or null setting when the eye was open was near 1 V and the highest amplitude possible, when the eye was fully closed, was less than 5 V. The detector and the airpuff delivery nozzle were attached to an adjustable arm that was mounted on a head piece worn by the participants.

### Procedure

After providing informed consent, participants were seated in a upright chair and fitted with the eyeblink apparatus. The experimenter then read the following instructions:

Please make yourself comfortable and watch the silent movie. You will experience different stimuli from time to time

including some tones through the headphones and a mild puff of air in your right eye. If you feel like blinking, please do so; just let your natural reflexes take over and concentrate on the movie you are watching.

The experimenter was seated in the same room, out of the direct view of the participant, and answered questions as they arose. The Charlie Chaplin film "The Goldrush" was shown throughout the testing session.

Each participant took part in three conditioning sessions that were spaced at least 2 weeks apart. Trace interval was varied across sessions and was 500, 750, or 1,000 ms in duration, in that order, across sessions. Each conditioning session consisted of 60 conditioning trials and 30 extinction trials. The conditioning trials were composed of a 750-ms baseline recording period followed by the tone for 100 ms. A silent trace interval then preceded a 100-ms corneal airpuff. In total, eye movements were monitored for 3,000 ms. During extinction trials, the corneal airpuff was withheld. The intertrial interval during conditioning and extinction averaged 10 s but varied randomly from 8 to 12 s (Carrillo, Thompson, Gabrieli, & Disterhoft, 1997).

### Operational Definitions

In defining a CR in this study, we had to consider the fact that longer trace intervals increase the possibility that random blinks may occur during the CS–US interval and be included as CRs. This is a potential source of error in comparing short versus long intervals. Lipkin and Moore (1966) suggested a correction method that computes the number of random blinks occurring in the baseline period and then subtracts that number from the total CRs. More recent eyeblink conditioning studies have used a method reported by Spence and Ross (1959), who suggested that most true CRs occur within 300–400 ms before US onset (Finkbiner & Woodruff-Pak, 1991; Solomon, Blanchard, Livine, Velazquez, & Groccia-Ellison, 1991). We adapted this second method and recorded blinks occurring 400 ms before US onset as CRs. This method corrected for both voluntary and random blinks that could occur as a result of the longer 750- and 1,000-ms trace intervals. Furthermore, an eyeblink was only scored as a CR if it was three standard deviations greater than the mean baseline response amplitude. Finally, eyeblinks with a latency less than 200 ms following CS onset (or 100 ms after CS offset) were recorded as alpha responses and not considered CRs (Gormezano, 1966) for all trace intervals.

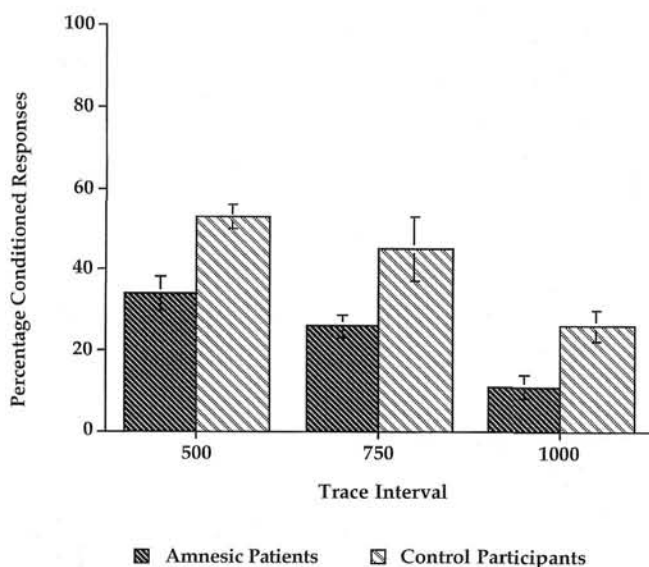
## Results

Conditioning trials were collapsed into six blocks and extinction trials were collapsed into three blocks of 10 trials. The mean percentage of CRs for the amnesic and control participants for conditioning in the 500-, 750-, and 1,000-ms trace intervals are presented in Figure 1. The mean percentage and standard error for these intervals for conditioning and extinction are presented in Table 2.

### Conditioning

**Percentage of CRs.** The primary analysis compared trace eyeblink acquisition of amnesic patients and control participants across the three trace intervals. This was accomplished in a mixed analysis of variance (ANOVA) examining the between-subjects effect of group (amnesic vs. control) and the within-subjects effect of trace interval (500, 750, and 1,000 ms) on the percentage of CRs acquired. As depicted in Figure 1, the amnesic patients had significantly fewer CRs than did the control participants,  $F(1, 12) = 9.16$ ,  $p < .01$ , confirming the amnesic patients' impairment in trace eyeblink conditioning. There was also a highly significant effect of trace interval,  $F(2, 20) = 25.59$ ,  $p < .001$ . Means comparisons of this main effect collapsed across group indicated that the percentage of CRs was marginally greater ( $p < .07$ ) in the 500-ms trace interval ( $M = 43.33$ ,  $SE = 3.51$ ) compared with the 750-ms trace interval ( $M = 35.97$ ,  $SE = 5.08$ ) and significantly greater ( $p < .001$ ) in the 750-ms trace interval than in the 1,000-ms interval ( $M = 18.61$ ,  $SE = 3.24$ ).

To examine acquisition, we compared the mean percentage of CRs for the final three blocks of conditioning trials in this study with the mean percentage of CRs obtained during pseudoconditioning obtained in our earlier study (Gabrieli et



**Figure 1.** Mean percentage of conditioned responses for amnesic patients and control participants as a function of trace interval. Note the impairment in the amnesic patients at each trace interval.

al., 1995) with a series of one sample  $t$  tests. During pseudoconditioning, participants were presented with blocks of randomized, never paired, tone or airpuff presentations. The amnesic patients' mean percentage during pseudoconditioning ( $M = 17$ ) differed significantly in the 500-ms trace interval,  $t(6) = 4.88$ ,  $p < .01$ , and the 750-ms trace interval,  $t(5) = 3.26$ ,  $p < .05$ , indicating some acquisition at each of these trace intervals. Amnesic patients did not show evidence of acquisition in the 1,000-ms trace interval ( $p > .1$ ). The control participants produced significantly greater CRs in the 500-ms trace interval,  $t(6) = 7.62$ ,  $p < .001$ ; the 750-ms trace interval,  $t(5) = 4.17$ ,  $p < .01$ ; and the 1,000-ms trace interval,  $t(5) = 2.59$ ,  $p < .05$ , than they did during pseudoconditioning ( $M = 14$ ).

**CR onset and peak latency.** Figure 2 displays CR onset latency and CR peak latency as a function of trace interval. With regard to onset latency, there was no effect of group but there was a significant effect of trace interval,  $F(2, 20) = 247.25$ ,  $p < .001$ , suggesting that when the amnesics did produce a CR, they initiated it at approximately the same time as control participants. Means comparisons revealed that the CR latency for the 500-ms trace interval ( $M = 402.04$ ,  $SE = 17.32$ ) was significantly shorter ( $p < .001$ ) than for the 750-ms trace interval ( $M = 625.93$ ,  $SE = 14.72$ ), which in turn was significantly shorter ( $p < .001$ ) than the latency for the 1,000-ms trace interval ( $M = 856.23$ ,  $SE = 13.14$ ). With regard to the CR peak latency, however, there was a main effect of group,  $F(1, 12) = 5.29$ ,  $p < .05$ . On average, amnesic patients' peak latency was approximately 50 ms shorter than control participants' latency. There was also a significant effect of trace interval,  $F(2, 20) = 199.67$ ,  $p < .001$ , that followed the same pattern as the CR onset latency measure.

**CR amplitude.** The Group  $\times$  Trace Interval ANOVA did not reveal any significant effects on CR amplitude. As can be seen in Table 3, amnesic patients produced somewhat smaller blinks compared with control participants, but this difference was not significant ( $p > .1$ ). This difference, however, may help account for the significant difference between the two groups in CR peak latency. That is, the slightly weaker blinks reached their peak sooner than the stronger, more robust blinks.

**Unconditioned response amplitude.** The amplitude of unconditioned responses (URs) was also examined in a Group  $\times$  Trace Interval ANOVA. This analysis indicated that amnesic patients' URs tended to be lower in amplitude compared with control participants' URs,  $F(1, 12) = 4.05$ ,  $p < .07$ , and that this tendency was somewhat different across the three trace intervals,  $F(2, 20) = 2.66$ ,  $p < .10$ . To be conservative, we performed means comparisons on the marginally significant interaction and found that, compared with control participants, the amnesic patients' URs were significantly reduced for the 500-ms trace interval ( $p < .001$ ). The URs were not significantly different in the 750- and 1,000-ms trace interval conditions.

The difference observed in the UR amplitude between amnesic and control participants for the 500-ms trace interval, while based on a statistically marginal interaction, could suggest a possible explanation for the learning impair-

Table 2  
Mean Percentage of Conditioned Responses for Three Trace Intervals

Interval (ms)	Amnesic patients				Control participants			
	Conditioning		Extinction		Conditioning		Extinction	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
500	34.05	3.98	20.95	6.2	52.62	2.95	21.43	8.06
750	26.11	3.38	15.56	4.28	45.83	7.96	14.44	4.19
1,000	11.39	2.77	9.44	3.03	25.83	4.21	5.56	0.70

ment of the amnesic patients. That is, perhaps the airpuff was not aversive enough to the amnesic patients to elicit URs of a sufficient magnitude to require adaptive learning. We thus recomputed the Group  $\times$  Trace Interval ANOVA using the percentage of CRs as the dependent measure and covaried the effects of UR amplitude. We found that the pattern of significance was not changed when UR amplitude was held constant: group,  $F(1, 9) = 7.76, p < .05$ ; trace interval,  $F(2, 19) = 24.26, p < .001$ . This pattern of results eliminated any concern regarding differences in the UR amplitude. If it was the case that the amnesic patients' impairment was determined by their reduced URs, the effect of group would not have been significant in the analysis of covariance. As the group effect was maintained, we are confident that the impairment is a true effect. This result is consistent with the fact that the amnesic patients were also impaired at the 750- and 1,000-ms trace intervals when there was no UR difference.

#### Spontaneous Blinks, Alpha Responses, and Short-Latency Voluntary Responses

Spontaneous blinks were measured during the 750-ms baseline period before the CS onset on each trial. These data are presented in Table 4. A Group  $\times$  Trace Interval ANOVA revealed a significant interaction between these two vari-

ables in spontaneous blink rate,  $F(2, 20) = 3.80, p < .05$ . This interaction was due to the amnesic patient's higher rate during the 500-ms and the 1,000-ms trace intervals. Because of this difference, we again adopted a conservative approach and reanalyzed the CR data, this time covarying spontaneous blink rate. As was the case with the UR amplitude, the data were unchanged: There was still a significant effect of group,  $F(1, 8) = 5.31, p < .05$ , and a significant effect of trace interval,  $F(2, 17) = 10.63, p < .001$  (1 control participant did not produce any spontaneous blinks in the 750-ms trace condition).

Alpha or short latency responses are also presented in Table 4. A Group  $\times$  Trace Interval ANOVA indicated that trace interval was the only significant variable affecting alpha responses,  $F(2, 20) = 3.96, p < .05$ . Means comparisons revealed that there was significantly more ( $p < .05$ ) alpha responses during the 500-ms trace interval ( $M = 6.57, SE = 1.15$ ) than during the 1,000-ms trace interval ( $M = 3.17, SE = 0.29$ ). The difference in the number of alpha responses in the 750-ms trace interval ( $M = 5.50, SE = 1.21$ ) and the 1,000-ms trace interval approached significance ( $p < .07$ ).

Voluntary or short-latency eyeblinks were assessed in the 750-ms and the 1,000-ms intervals. Not surprisingly, there was a significant effect of interval,  $F(1, 10) = 23.97, p < .001$ , such that there were more voluntary blinks during the 1,000-ms ( $M = 35.27, SE = 5.53$ ) compared with the 750-ms ( $M = 17.64, SE = 3.78$ ) trace interval. In addition, there was a marginal Group  $\times$  Trace Interval interaction,  $F(1, 10) = 4.46, p < .06$ . Means comparisons indicated that the control participants generated significantly more voluntary, short-latency responses than did the amnesic patients in the 1,000-ms trace interval ( $p < .05$ ). Also, control participants generated more voluntary, short-latency responses during the 1,000-ms compared with the 750-ms interval ( $p < .001$ ). There was a tendency for amnesic patients to produce more voluntary blinks in the 1,000-ms trace interval than during the 750-ms trace interval ( $p < .08$ ).

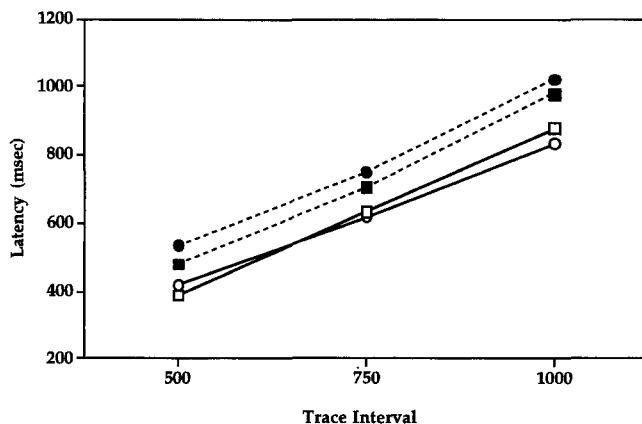


Figure 2. Mean conditioned response (CR) onset and peak latency for amnesic patients and control participants as a function of trace interval. Data from the amnesic patients are depicted with squares, control participants are depicted with circles. Unfilled data points are the CR onset latency, and filled data points are the CR peak latency.

#### Extinction

The percentage of CRs during tone-alone trials following each testing session was also examined. These data are presented in Table 2. An ANOVA examining the effects of group and trace interval on the percentage of CRs revealed a significant effect of trace interval,  $F(2, 20) = 4.58, p < .05$ . As the trace interval was extended, there were significantly fewer CRs produced by both amnesic patients and control

Table 3  
*Mean CR Onset Latency, CR Peak Latency, CR Amplitude, and UR Amplitude  
 as a Function of Trace Intervals*

Participants	Trace interval					
	500 ms		750 ms		1,000 ms	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
<b>Amnesic</b>						
CR latency (ms)	388.31	19.96	631.78	19.30	877.22	16.14
CR peak latency (ms)	476.88	19.44	703.16	22.17	977.80	20.92
CR amplitude (V)	1,116.52	322.12	1,201.77	347.45	949.21	136.50
UR amplitude (V)	1,827.54	237.33	2,101.83	401.61	2,003.60	193.03
<b>Control</b>						
CR latency (ms)	415.78	28.96	620.07	23.82	835.24	17.98
CR peak latency (ms)	533.50	16.45	749.81	39.85	1,021.44	21.17
CR amplitude (V)	1,649.83	404.63	1,665.54	240.65	1,606.64	251.24
UR amplitude (V)	2,806.45	122.02	2,423.52	191.36	2,608.89	112.42

*Note.* Eyeblink amplitude is an inverse function of the amount of reflected light contacting the phototransistor aimed at the cornea. The detector was adjusted so that the baseline or null setting when the eye was open was near 1 V and the highest amplitude possible, when the eye was fully closed, was less than 5 V. CR = conditioned response; UR = unconditioned response.

participants during extinction testing. Thus, the percentage of CRs in the 500-ms trace interval ( $M = 21.19$ ,  $SE = 4.89$ ) was significantly greater than in the 750-ms trace interval ( $M = 15.00$ ,  $SE = 2.86$ ), which was also greater than was produced in the 1,000-ms trace interval ( $M = 7.50$ ,  $SE = 1.60$ ).

Extinction per se was assessed in a series of ANOVAs that examined group differences as a function of trial type (the mean CRs for the final three blocks of conditioning trials vs. the mean CRs that occurred during the three extinction blocks). For both the 500-ms and the 750-ms trace intervals, there was only a significant main effect of trial type: 500 ms,  $F(1, 12) = 16.57$ ,  $p < .01$ ; 750 ms,  $F(1, 10) = 18.31$ ,  $p < 0.05$ . There was no main effect of group and no interaction between group and trial type. As is evident in Figure 3, extinction occurred for both the amnesic patients and control participants. For the 1,000-ms trace interval, there was a

significant effect of trial type,  $F(1, 10) = 20$ ,  $p < .01$ , and a Group  $\times$  Trial Type interaction. The interaction was attributable to significant extinction only for the control participants ( $p < .001$ ), which was not surprising given that the amnesic patients did not demonstrate significant acquisition for the 1,000-ms trace interval.

#### *Learning Curves*

We conducted a final series of ANOVAs to examine group differences in acquisition across trial blocks (1–6). This was done for each trace interval separately. For the 500-ms trace interval, there was a significant effect of group,  $F(1, 12) = 17.41$ ,  $p < .001$ , and a significant effect of block,  $F(5, 60) = 2.82$ ,  $p < .05$ . The interaction was not significant. As is evident in Figure 3a, these data indicate that the amnesic patients remained impaired when compared with the control

Table 4  
*Mean Spontaneous Blinks, Alpha Responses, and Voluntary Blinks  
 as a Function of Trace Interval*

Participants	Trace interval					
	500 ms		750 ms		1,000 ms	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
<b>Amnesic</b>						
Spontaneous blinks	23.14	5.31	20.67	5.39	27.50	5.49
Alpha responses	6.43	1.12	4.67	1.91	2.83	0.31
Short latency, voluntary blinks			17.78	5.27	27.78	4.25
<b>Control</b>						
Spontaneous blinks	16.29	3.49	17.17	3.78	12.33	2.81
Alpha responses	6.71	2.06	6.33	1.59	3.50	0.50
Short latency, voluntary blinks			17.50	5.91	42.78	9.69

*Note.* Mean number of conditioning trials (of a total of 60 trials) on which at least one spontaneous blink occurred during the 750-ms pretrial baseline period; mean number of conditioning trials on which an alpha response was observed during the 200-ms period following tone onset; and the mean number of short latency, voluntary eyeblinks that occurred on conditioning trials during the time interval between 200 ms following tone onset and 400 ms prior to US onset during the 750-ms and 1,000-ms trace intervals.

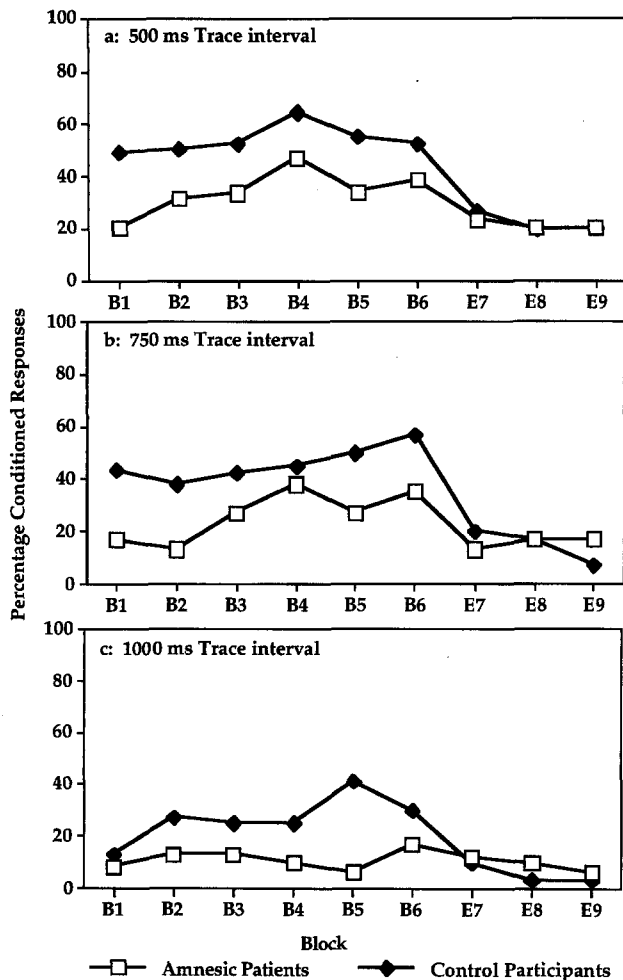


Figure 3. Learning curves of the mean percentage of conditioned responses as a function of trial block for amnesic patients and control participants. B1 through B6 displays the mean for Trace Conditioning Blocks 1 through 6, and E1 through E3 displays the mean for Extinction Blocks 1 through 3. Each conditioning and extinction block represents the mean of 10 trials.

participants at all trial blocks. In the 750-ms interval (Figure 3b), the ANOVA revealed only a main effect of group,  $F(1, 10) = 5.21, p < .05$ , again confirming the amnesic patients' impairment across trial blocks. Lastly, this pattern was repeated in the 1,000-ms trace interval (Figure 3c), in which patients were again performing significantly worse compared with control participants overall,  $F(1, 10) = 8.49, p < .01$ .

### Discussion

This study found that patients with amnesia due to bilateral, medial-temporal lobe lesions are significantly impaired in the trace eyeblink conditioning paradigm. This impairment was manifested in both the percentage of CRs that are produced overall and in their learning curves. These results are consistent with other studies reporting impaired trace conditioning in amnesic patients with bilateral, medial-

temporal lobe lesions (Disterhoft, Carrillo, Hopkins, Gabrieli, & Kesner, 1996; Woodruff-Pak, 1993). In conjunction with the earlier study by Gabrieli et al. (1995), we conclude that, in humans, normal learning in the trace eyeblink conditioning task requires the medial-temporal lobe memory system, whereas delay conditioning does not require this system. The involvement of the medial-temporal region in mediating trace but not delay conditioning is consistent with animal studies (Akase et al., 1989; Berger & Thompson, 1978b; Moyer et al., 1990; Solomon, 1980; Solomon et al., 1986).

Although the amnesic patients were impaired in trace eyeblink conditioning, they did acquire CRs beyond a baseline level in the 500-ms and 750-ms trace intervals. There are at least two explanations for this residual learning. First, it may reflect residual medial-temporal memory function. The patients' hippocampal lesions are not as extensive as the lesions in the rabbits made by Moyer et al. (1990) that eliminated trace conditioning entirely. The incomplete lesions in our patients, like incomplete lesions in the Solomon et al. (Solomon et al., 1986) rabbit study, may have left residual medial temporal tissue that could support partial acquisition. The even more limited lesions in the animals studied by James, Hardiman, and Yeo (1987) and Port, Romano, Steinmetz, Mikhail, and Patterson (1986) that produced only a CR onset latency change in trace eyeblink conditioning are consistent with this account.

Alternatively, what trace conditioning could be learned by the amnesic patients could have been mediated by another memory system that underlied their normal performance in delay eyeblink conditioning. Support for the notion that the limited number of CRs produced by amnesic patients were nonhippocampally based comes from the impressive retention of H. M. in the Woodruff-Pak (1993) study. In that study, H. M. attained criterial learning 2 years following initial acquisition in a fraction of the trials that it took for his initial learning, despite his complete lack of recollection regarding having participated in an eyeblink conditioning study. This finding suggests that even though acquisition is impaired in trace conditioning, retention may be intact.

In this study, we observed a change in peak CR latency of patients with amnesia—a measure of their ability to adaptively time the CR. On average, the amnesic patients' peak latency occurred 50 ms earlier compared with control participants, but it did increase as the trace interval was extended. It is possible that the timing impairment is related to a more reflexive response by the patients compared with the control participants. However, this account is difficult to reconcile with the fact that control participants actually produced more voluntary, short-latency responses than did the amnesic patients. In addition, both groups produced approximately the same number of alpha responses. A tendency to have short-latency CRs in amnesic patients would be consistent with previous lesion studies in the rabbit, even when lesions are not complete (James et al., 1987; Moyer et al., 1990; Port et al., 1986; Solomon et al., 1986).

The fact that we did not find any difference in the number of alpha responses is consistent with Woodruff-Pak (1993),

who also reported fewer alpha responses in H. M. than in his control participant, but contrasts with studies conducted with hippocampectomized rabbits that have a high incidence of short-latency, inappropriately timed alpha responses (Moyer et al., 1990; Port et al., 1986; Solomon et al., 1986). The short-latency CRs mentioned earlier may be the only manifestation of the tendency to produce inappropriately timed alpha responses in these temporal-lobe lesioned patients.

The present human findings also diverge from past reports that have demonstrated an impairment in hippocampectomized rabbits to extinguish CRs in a trace eyeblink paradigm (Moyer et al., 1990). The amnesic patients in the present report successfully extinguished CRs in the 500- and 750-ms trace intervals, the only two intervals in which we observed significant learning.

The successful application of animal eyeblink conditioning paradigms to studies of human memory processing has now been demonstrated in many studies with neuropsychological patients using the delay and trace conditioning paradigms. Despite some specific divergences between animals and humans, the convergent evidence is striking. First, the cerebellum is critical for delay conditioning (e.g., Clark et al., 1984; Daum et al., 1993; Lavond et al., 1985; Lye et al., 1988; Solomon et al., 1989; Woodruff-Pak et al., 1985; Woodruff-Pak et al., 1996; Yeo et al., 1985). Second, the medial-temporal lobe area is active during delay, but its role is not essential (Berger et al., 1983; Berger & Thompson, 1978a; Berger & Weisz, 1987; Blaxton et al., 1996; Disterhoft et al., 1986; Logan & Grafton, 1995; Weiss et al., 1996). Third, the medial-temporal area is critical for trace conditioning (Disterhoft et al., 1996; Woodruff-Pak, 1993), discrimination reversal (Carrillo et al., 1997), and conditional discrimination (Daum, Channon, & Gray, 1992; Daum, Channon, Polkey, & Gray, 1991). A number of additional paradigms would also yield important data regarding the correspondence of findings between species and provide additional insights for the refinement of more global theories of learning and memory. For example, latent inhibition (Solomon & Moore, 1975) and blocking (Solomon, 1977) have also been found to depend on the hippocampus in rabbits. This approach should provide a promising basis for theoretically driven hypotheses to be tested in humans developed from carefully controlled lesion studies in animals.

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