Genetic influences on human conditionability: A twin study of the conditioned eyeblink response

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Abstract:

Acquisition of the classically conditioned eyeblink response is generally regarded as one of the most basic forms of associative learning. A great deal is known about how the brain encodes this simple form of learning, so that performance of this task may be an indirect indicator of brain functioning. Individual differences in response acquisition have been revealed, but largely ignored, in the research literature. We tested the temporal stability and familial origins of these individual differences using a classic twin study design. Results reveal substantial individual differences in acquisition of the conditioned eyeblink response. These differences are stable across brief retest, and differences in response acquisition exhibit familial aggregation, apparently due, in part, to genetic resemblance.

Keywords: Eyeblink conditioning | associative learning | test–retest stability | individual differences | twin study | heritability

Article:

INTRODUCTION

Acquisition of the classically conditioned eyeblink response is a basic form of learning and the subject of numerous research investigations over many years. The work of Gormezano and his colleagues (1987) has provided considerable information regarding the behavioral parameters of eyeblink conditioning in rabbits and in humans. More recently, eyeblink conditioning has become the focus of neuropsychological studies attempting to identify the neuronal systems underlying the acquisition of the conditioned response (for a review, see Woodruff-Pak *et al.,* 1990a). Given its well-established and replicated research base, the eyeblink conditioning paradigm is ideal for the study of simple associative learning.

The basic paradigm uses a light puff of air directed at the eye as the unconditioned stimulus (US) paired with an auditory conditioned stimulus (CS), such as a tone. The conditioned response (CR) is defined as an eyeblink following the onset of the tone which precedes the onset of the air puff, while an unconditioned response (UR) is an eyeblink following the onset of the air puff. There are several different variants of the basic model, the most common one being the delay paradigm, in which the offset of the CS overlaps briefly with the onset of the US. The interstimulus interval (ISI), defined as the duration of time between the onset of the CS and the onset of the US, can be varied and is an important determinant of conditioning rate. Optimum human performance in delay eyeblink conditioning has been found to occur when the ISI is 500 ms (Prescott *et al.,* 1992).

Despite the seemingly basic nature of eyeblink conditioning, not all subjects achieve the same level of performance. There is considerable evidence from previous studies indicating the existence of individual differences in rates of conditioning, as well as differences in characteristics of the eyeblink CR, such as response latency, amplitude, and topography.

Such differences have been found in clinical studies where the eyeblink conditioning model has been employed as an indirect technique for the exploration of cognitive functioning in human populations. For example, abnormal conditioned response topographies have been found in autistic subjects (Sears *et al.,* 1994), and lower rates of response acquisition have been found in mentally retarded children (Ohlrich and Ross, 1968). Patients with Alzheimer's disease, which is associated with impairment of the hippocampus, also have been examined with conditioning tasks. Deficits in conditioning performance have been shown to be associated with probable Alzheimer's (Woodruff-Pak *et al.,* 1990b) and with Alzheimer-like neuropathology (Woodruff-Pak *et al.,* 1994).

Individual differences also have been reported in developmental studies. Eyeblink conditioning has been used in investigating developmental changes in neural anatomy and functioning. Several studies have found that acquisition of the delay eyeblink CR in older rabbits is slower than in younger rabbits (e.g., Powell *et al.,* 1981). Others report significant differences between older and younger rabbits in trace conditioning, in which the CS and US do not overlap, but not in delay conditioning (Graves and Solomon, 1985). Human subjects over the age of 50 demonstrate significant decrements in CR acquisition using a delay paradigm (Solomon *et al.,* 1989; Durkin *et al.,* 1993), although the magnitude of age differences is affected by the timing of the CS and US onsets (see Woodruff-Pak and Finkbiner, 1995). Similar results were found in a study using trace conditioning with a long ISI (Finkbiner and Woodruff-Pak, 1991).

Individual differences in eyeblink conditioning are evident in previous studies, although these differences have been largely ignored. Most studies report only mean values for acquisition rates, CR latencies, and CR amplitudes. Furthermore, variations in procedures and apparatus between laboratories prohibit the comparison of different studies. However, individual differences can be inferred from several sources. Solomon *et al.* (1989) constructed a figure displaying the relation between age and conditioning as a function of percentage CRs across a training session. Within each age group, substantial variations in conditioning rates were shown. Another indication of differences in performance can be found in articles which categorize subjects as "good" and "bad" conditioners (e.g., Perruchet, 1985).

The "bad" conditioners are defined as those showing lower rates of conditioning or no conditioning. Prescott *et al.* (1992), in a study of eyeblink conditioning as a function of ISI, also reported that while many subjects acquired the conditioned response, others failed to condition, regardless of ISI.

One goal of this investigation was to examine the magnitude and stability of individual differences in conditioning performance within an age-restricted, homogeneous sample. A few studies have reported data on the test-retest stability of conditioning performance. Runquist and Towart (1965) report that, when subjects completed 100 delay conditioning trials per day for 5 consecutive days, there was a decrease in CRs within conditioning sessions but an increase in CRs across sessions. One study, designed to examine trace versus delay eyeblink conditioning in preschool children (Werden and Ross, 1972), found that the distribution of "voluntary responders" (defined as those subjects whose response occurs too rapidly following the CS) remained the same across sessions. There was also evidence that the difference between performance on trace and delay conditioning tasks remained approximately the same for each subject across sessions.

There is some evidence that performance across sessions may be a function of age. A study examining 1-day retention in younger versus older adults reported that retention was poorer in older subjects; acquisition tended to improve across the first session while stabilizing during the second session for both groups (Woodruff-Pak and Finkbiner, 1995). However, using a longer intersession interval (7 days), Durkin *et al.* (1993) found no significant differences in retention across sessions between four age groups: young (19-33), midyoung (35-48), midold (50-63), and old (66-78). They also report that, while the performance of subjects in the young and old groups did not change across the second session, performance in the mid young and midold groups continued to improve during Session 2.

The second goal of this study concerns the origins of individual differences in conditionability. Individual differences in neural functioning, which may be influenced by genetic factors, could mediate these differences in conditionability, and data from several animal studies support this notion. One example is a study by Royce and Covington (1960) examining differences in avoidance conditioning in nine strains of rats. A shuttle box paradigm was used; the US was a shock delivered through the floor of the animal's cage; a buzzer served as the CS. The researchers found significant differences between several of the strains. Katzev and Mills (1974), using a similar type of conditioning procedure on three rat strains, found comparable results.

A basic twin design was used for the investigation of genetic influences in this study. The underlying logic of the twin design rests on the fact that monozygotic (MZ) twins share 100% of their genes, while dizygotic (DZ) twins, on average, share only 50%. When studied in late adolescence/early adulthood, both MZ and DZ twins have shared a lifetime of common experience. So, if differences in the dependent variable are primarily genetic in origin, the performance similarities of MZ cotwins are expected to be twice the similarities observed among DZ cotwins.

METHODS

Subjects

Subjects were ascertained through the Indiana University Twin Registry and were paid for their participation. Zygosity was determined by standard questionnaire screening items completed by each twin independently and by studying facial photographs. For those twins whose zygosity remained uncertain after screening, finger and palmar dermatoglyphics were obtained and compared, and the twins' mothers were interviewed, by telephone, to obtain information on similarity of appearance and development during childhood. A total of 47 pairs of siblings, including 8 male monozygotic (MZ) pairs, 19 female MZ pairs, 3 male dizygotic (DZ) pairs, 7 female DZ pairs, and 7 male-female DZ pairs, was tested. Because we were unable to locate as many DZ twin pairs as MZ pairs, we recruited an additional three pairs of female siblings, requiring sisters in each pair to be less than 18 months apart in age. The nontwin pairs were grouped with the DZ twins for our analyses. All sibling pairs were Caucasian with the exception of one pair of African-American sisters; all were college students, with the exception of one twin pair yet attending high school. The mean age across all subjects was 19.7 years (range, 15-23 years).

Apparatus

Eyelid activity was monitored and recorded via electromyogram (EMG). The active disk electrode, 4 mm in diameter, was placed directly below the outer corner of the subject's right eye, with the reference electrode located approximately 10 mm to the right. The ground lead was positioned on the subject's left earlobe. The raw electrical signal was amplified 1000 times, band-pass filtered between 5 Hz and 1000 KHz, and the signal was electronically rectified and integrated using a Bak EMG Integrator. The resulting DC (direct current) signal was then input to a computer, digitized, and stored and all calculations were made. The resulting eyeblink response measurements (e.g., area) are in arbitrary units ranging from 0 (eye open, no EMG activity) to 17 (eye closed, maximum EMG activity).

The US, an air puff, was delivered through a rubber tube attached to a compressed air tank regulated by a solenoid set at 5 psi. Subjects were fitted with a Velcro headband upon which a padded metal plate, resting against the right side of the head and supporting an air nozzle 4 mm in diameter, was mounted. The nozzle, connected to the rubber tube and adjustable in every direction, was directed from the outside corner of the subject's right eye across the cornea. The CS, a 60-dB, 5-KHz tone, was delivered through a pair of lightweight stereo headphones.

A computer program (Lavond and Steinmetz, 1989) controlled the delivery of all stimuli and collected EMG data at 5-ms intervals for 1800 ms during each stimulus presentation, yielding a total of 360 data points per trial. Only data after the onset of the CS are analyzed, and from those 240 data points the program constructs a response curve for each trial. Area, a measure of response magnitude used here, represents the area under the response curve. The data for each session were stored for later analysis.

Procedure

Subjects were tested independently, such that cosiblings were tested at different times during late morning to early afternoon, often on different days, depending on their individual schedules. Upon arriving at the laboratory, subjects were told that the experiment was an investigation of performance on a simple learning task and were asked to sign a consent form.

Subjects were told that they would be experiencing a series of tones and air puffs which would occasionally occur together and at other times would be separate. They were advised that, although the air puff was harmless, it may be sufficient to make them blink. They were seated in a comfortable chair and were given reading materials (popular news and entertainment magazines) with which to occupy themselves throughout the data collection period. Subjects were told that they were free to read the magazines during the experiment and that they should not focus their attention on the tones and air puffs. Subjects wearing watches removed them during the experiment to prevent them from trying to predict the occurrence of the stimuli.

Subjects received the following sequence of conditioning trials: 20 preacquisition trials (unpaired tones and air puffs), 100 acquisition trials (10 blocks each of 9 CS-US pairs and 1 CS alone), and 20 extinction trials (unpaired tones and air puffs). The intertrial and interstimulus intervals were set at 15-25 s and 600 ms, respectively. The duration of the tone CS was 700 ms, and it coterminated with a 100-ms air puff US. The first 43 individuals who participated in the experiment returned to the lab for a second session with an identical protocol in order to assess stability of conditioning measures. The average length of time interval between the first and the second testing sessions was 11 days.

A conditioned response was defined as muscle activity, recorded by the EMG, that was sufficient to produce an eyeblink with an amplitude of at least 0.5 U beginning 25-600 ms after the presentation of the CS. An unconditioned response was defined as a comparable change occurring 600-1200 ms after the CS presentation (and therefore after the US presentation). The program omitted those trials on which the subject exhibited a spontaneous eyeblink measuring at least 8 U within 100 ms before the CS presentation.

The data collected during the conditioning sessions provided several useful measures of overall conditioning rates, as well as other related characteristics. For the purposes of this study, the main dependent variables were overall measures of conditioning rate. These included the percentage of the 90 paired acquisition trials on which the subject showed a CR (as defined above); the percentage of 10 tone-alone, or CS-alone, trials delivered during the acquisition phase on which the subjects showed a CR; and the percentage of 10 CS-alone trials during extinction on which the subject showed a CR. A "reaction time" measure was obtained by averaging the response time on the 10 US-alone preacquisition trials. Finally, a measure of the average area under the response curve reflected the magnitude of a subject's eyeblink reponse. Both the average area under the unconditioned response curve (during the preacquisition phase) and that under the conditioned reponse curve (during the 90 acquisition trials) were used in the following analyses.

To assess genetic influences on individual differences in performance on the dependent variables, we computed intraclass correlations and compared absolute intrapair differences for MZ and DZ twins. To transform distributions of conditioning data to normality, a square root

transformation was applied to all percentage CR measures and a log(x +1) transformation was applied to CR area prior to conducting the twin analyses. In addition, one extreme outlier (a DZ twin) was eliminated from the twin analyses for UR area.

RESULTS

The data collected in this study were analyzed in two ways. For analyses concerning the magnitude and stability of individual differences, as well as for testing effects of sex and zygosity, subjects were treated as individuals, yielding a total of 94 subjects. Twin and family analyses treated subjects as twin pairs, yielding 47 pairs. For all analyses, except the test-retest correlation, only data from Session 1 were used.

Descriptive data show substantial variability in the measures of conditionability: the mean percentage CRs for the acquisition trials was 37.2% (SD, 32.7%), and means for CS-alone trials during acquisition and extinction were 38.6% (SD, 35.0%) and 26.4% (SD, 29.4%), respectively. Unconditioned response latency showed little variation: mean 64.1 ms (SD, 1.2 ms). Figure 1 presents a histogram showing overall conditioning performance across all conditioning blocks. The figure shows the number of subjects achieving given percentage of CRs of 90 paired acquisition trials. Figure 2 illustrates learning curves separately for all MZ and DZ twins. The average percentage CRs for MZ and DZ twins do not significantly differ for any block of trials.

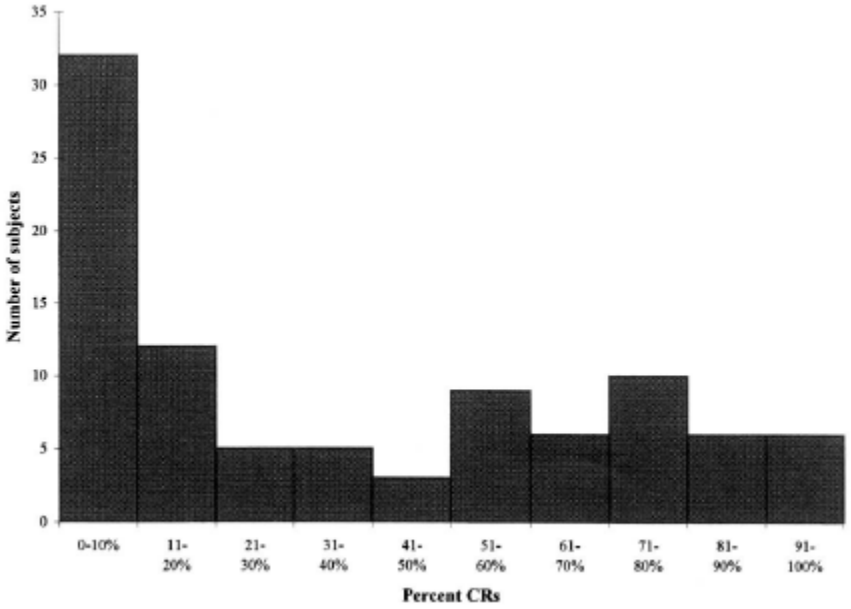

Figure 1. Distribution showing number of subjects achieving a given percentage of conditioned responses in 90 acquisition trials *(n* = 94).

The dependent variables were tested for associations with age, sex, and zygosity using Pearsonian correlations (for age) with adjusted significance tests that account for covariance between cotwins and *t* tests (for sex and zygosity) with adjusted effective sample sizes [see Griffin and Gonzalez (1995) for a description of these procedures]. Mean values for the variables are given in Table I. No significant associations with zygosity or sex were found. Age, which has been found to affect conditioning performance, was controlled by restricting subjects to the

narrow age range of 15 to 23. Within this narrow range, the correlations between age and conditioning were nonsignificant: r = -.06, r = -.03, and r = -.05 for percentage CRs during acquisition, percentage CRs on CS-alone trials during acquisition, and percentage CRs on extinction trials, respectively. Correlations between age and the other dependent variables also were nonsignificant: r = -.03 for CR area, r = -.09 for UR area, and r = .06 for UR latency.

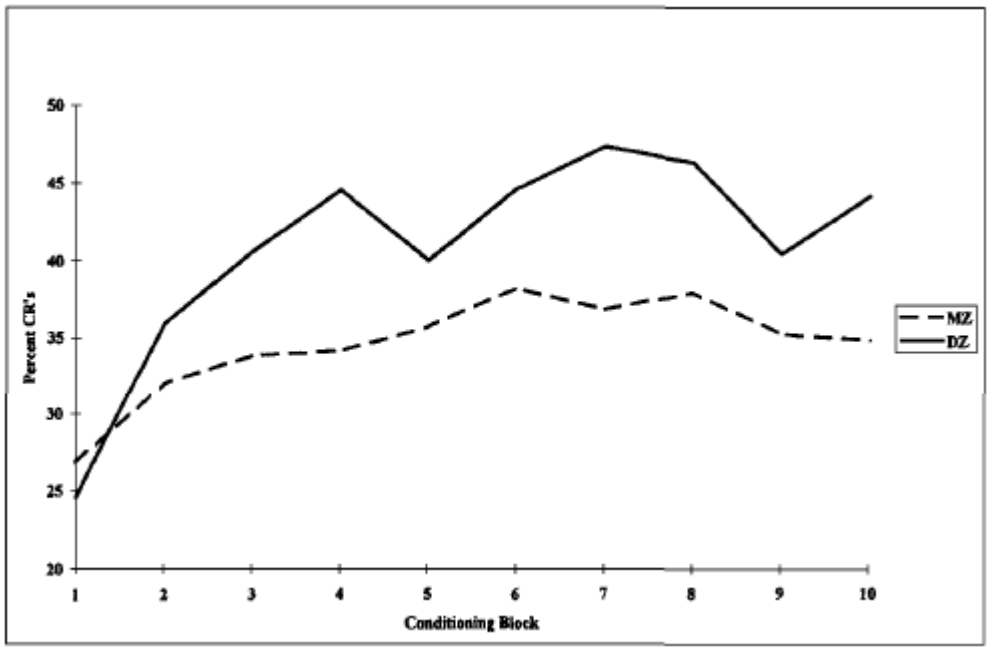

Figure 2. Learning curves for MZ and DZ twins illustrating the mean percentage CRs across 10 blocks of acquisition trials in Session I.

Table I. Mean Dependent Variable Values (and SD) Shown as a Function of Zygosity and Sex[a]

	Zygosity		Sex	
Variable	**MZ (n = 54)**	**DZ (n = 40)**	**Female (n = 65)**	**Male (n = 29)**
UR latency	63.99 (10)	64.19 (16)	64.04 (10)	64.13 (16)
UR area	525.3 (235)	488.9 (249)	533.0 (245)	456.7 (225)
CR %(p)	34.59 (32)	40.78 (33)	38.41 (37)	34.53 (30)
CR %(t-a)	36.53 (33)	41.31 (37)	40.53 (36)	34.16 (32)
CR %(t-e)	23.15 (27)	32.65 (32)	30.78 (32)	19.14 (14)
CR area	35.98 (87)	20.18 (36)	35.58 (80)	15.07 (37)

[a] CR %(p), percentage CRs for paired acquisition trials; CR%(t-a), percentage CRs for tone-alone trials during acquisition; CR%(t-e), percentage CRs for tone-alone trials during extinction.

Pearsonian correlation coefficients were computed between all the dependent variables, using all individuals in the sample. Again, following the procedure described by Griffin and Gonzalez (1995), adjusted Z scores were computed for significance testing. These correlations are given in Table II. As expected, many of the variables were strongly correlated with one another. Highly significant correlations, ranging from r = -.33 to r = -.45, were found between UR latency and the three measures of conditioning performance. The significant, negative correlation between UR latency and conditioning rate, which has not been reported in previous studies, indicates that shorter latencies during preacquisition to the US alone were related to higher overall rates of

conditioning. In addition, higher conditioning rates were found to be associated with larger UR response areas.

Table II. Pearsonian Correlations Between the Dependent Variables, Nontransformed[a]

	UR lat	UR area	CR%(p)	CR%(t-a)	CR%(t-e)	CR area
UR lat	1.00**					
UR area	0.51**	1.00				
CR%(p)	–0.45**	0.56**	1.00			
CR%(t-a)	–0.41**	0.48**	0.91**	1.00		
CR%(t-e)	–0.33**	0.38**	0.79**	0.75**	1.00	
CR area	–0.18	0.43**	0.58**	0.48**	0.57**	1.00

Note. Intercorrelations were repeated for these variables after transformations as described in the text; resulting correlations differed negligibly for all correlations except those with CR area, which were uniformly higher following transformation. $^{**}p < .001$

[a] CR%(p), percentage CRs for paired acquisition trials; CR%(t-a), percentage CRs for tone-alone trials during acquisition; CR% (t-e), percentage CRs for tone-alone trials during extinction.

Stability of the rate of overall conditioning was determined using data from the 43 individual twins who participated in two sessions. As on any learning task, subjects were expected either to improve or at least to maintain their level of performance from Session 1 to Session 2, thereby generating an equal or higher percentage CRs during Session 2. It was predicted, therefore, that a subject's performance would maintain rank order, relative to that of the other subjects. This was tested by computing a Spearman rank-order correlation on the percentage CRs for the 90 acquisition (paired) trials, which yielded a correlation coefficient of 0.658 *(p* <. 04), indicating that a subject's relative level of performance in Session 1 is strongly related to relative performance in Session 2.

Table III. Intraclass Correlation Coefficients and Absolute Intrapair Differences[a]

	Intraclass correlation		Intrapair difference	
Variable	**MZ**	**DZ**	**MZ**	**DZ**
UR latency	0.31	0.32	08.3	12.5
UR area	0.65**	0.39*	165.5	217.1
CR%(p)	0.60**	0.34^{t}	12.0	18.0^{b}
CR%(t-a)	0.52**	0.28	15.4	21.0
CR%(t-e)	0.61**	0.35^{t}	04.1	05.5
CR area	0.65**	0.38*	01.0	01.2

Note. $^{**}p < .01$. $^{*}p < .05$. $^{t}p < .06$.

[a] CR%(p), percentage CRs for paired acquisition trials; CR%(t-a), percentage CRs for tone-alone trials during acquisition; CR% (t-e), percentage CRs for tone-alone trials during extinction.

[b] MZ-DZ differences significant at $p < .05$.

The results of the twin analyses are given in Table III. For the percentage CRs on paired acquisition trials, intraclass correlations were 0.60 *(p* = .00) for MZ twins and 0.34 *(p* = .06) for DZ twins; although suggestive, we note that none of the differences between MZ and DZ intraclass correlations was significant. Absolute intrapair differences in percentage CRs were 12 and 18% for MZ and DZ twins, respectively. These differences were significant *(p* = .05). For percentage CRs on CS-alone trials, similar intraclass correlations were found, and absolute intrapair differences were larger for DZ twins, although the difference was not significant. For the area measures, MZ correlations were 0.65 and DZ correlations were 0.38, again with absolute

intrapair differences nonsignificantly higher in DZ twins. No evidence of heritability was found for the UR latency measure.

Because of the significant correlations found between characteristics of the UR and conditioning performance, it is conceivable that the high twin correlations on the percentage CR measures may reflect similarity in UR response characteristics, not in conditioning performance. A suggestion from an anonymous referee prompted us to reexamine the percent CR variables, after partialing out the UR effects. A linear regression, using UR area and latency to predict percent CRs, produced residuals which were subjected to genetic analyses. The results of these analyses are given in Table IV. As can be seen, the intraclass correlations for DZ twins were essentially unchanged. Intraclass correlations for MZ twins were reduced from about 0.60 to about 0.40, thus reducing the magnitude of the MZ-DZ difference.

Table IV. Intraclass Correlation Coefficients and Absolute Intrapair Differences for Percentage CR Measures After Removing Effects of UR[a]

	Intraclass correlation		Intrapair difference	
Variable	**MZ**	**DZ**	**MZ**	**DZ**
CR%(p)	0.43**	0.26	5.4	7.2
CR%(t-a)	0.39**	0.27	7.5	10.1
CR%(t-e)	0.41**	0.39*	2.4	2.5

Note. ***p*<.01. **p*< .05.

[a] CR%(p), regression residuals, percentage CRs for paired acquisition trials; CR%(t-a), regression residuals, percentage CRs for tone-alone trials during acquisition; CR%(t-e), regression residuals, percentage CRs for tone-alone trials during extinction.

DISCUSSION

Individual differences in acquisition of the conditioned eyeblink response in human subjects are evident in previous literature but have not been examined systematically. This study used a sample of normal, young adult twins in order to address the following four questions of individual differences: (1) How much individual variation in conditioning performance will be found in a homogeneous, age-restricted sample using the delay conditioning paradigm? (2) Are these differences stable across testing sessions? (3) If the individual differences are stable and can be construed as consistent characteristics, what is their origin? Do the differences exhibit familial aggregation? and (4) If so, is some of that familial aggregation heritable?

For the purposes of data analysis, the twin status of the sample was ignored for the first two questions. The latter two questions, concerning familiality and heritability, were addressed through twin/sibling analysis.

Are there individual differences in conditioning and associated parameters? Descriptive data from the current study, as well as several works cited previously, support the fact that, even in a small, homogeneous sample, there is substantial individual variability. Further analysis showed that these differences were not related to subjects' age, sex, or zygosity.

Are the individual differences in conditioning performance temporally stable over brief retest? It was expected that subjects either would improve their overall performance across sessions or, at least, maintain their performance level. Results of this study confirm that a subject's overall

relative performance rate in the first session is strongly related to relative performance in the second session. Our results suggest that conditioning performance is a consistent, trait-like characteristic, but the generalizability of this finding is limited by the relatively brief time interval between sessions (mean number of days between sessions was 11.2).

Do subjects exhibit familial similarity of these stable differences? If so, twin siblings are expected to show significant similarity in conditioning characteristics, regardless of age, zygosity, or sex. Findings from the current study suggest familial similarity. Intraclass correlation coefficients were significant for MZ twin pairs for all dependent variables except UR latency. For DZ twin pairs, correlations for CR area and UR area were significant, and correlations for percentage CRs during acquisition and extinction approached significance.

A final question: Is the familial aggregation, in part, attributable to genetic differences? Evidence from this study is affirmative: a modest genetic influence on the acquisition of the conditioned eyeblink response was evident in the smaller MZ intrapair differences (significantly so only for percentage CRs during acquisition) and higher intraclass correlations for all three measures of conditioning performance. When the effects of UR characteristics were partialed out, MZ twin correlations for percentage CR measures were somewhat reduced but remained higher than the corresponding DZ correlations. Findings were similar for the measures of response magnitude. MZ intrapair differences were smaller, but not significantly smaller, for CR and UR area, and MZ intraclass correlations were higher for both UR area and CR area. However, these conclusions lack power, due to the very small sample of twins used. A larger sample size will be required to estimate confidently genetic influences on conditioning measures. An additional limitation was our inability to recruit an appropriate number of DZ twins relative to the number of MZ twins, thereby resulting in an unbalanced sample.

In conclusion, ours is the first genetic study of individual differences in the human conditioned eyeblink response. Future research is necessary in order to enhance understanding of these preliminary results. First, larger and more representative samples of twins should be tested in order to assess MZ/DZ differences. Second, results from this study may be related to the delay conditioning paradigm and its associated underlying neural circuitry. Individual differences should be studied using other conditioning paradigms, such as the trace paradigm, that are theoretically mediated by different neural circuitry. Third, previous studies have established age-related differences in characteristics of conditioned response acquisition. Because this study focused exclusively on individuals between 15 and 23 years of age, age effects should be examined in the context of individual variation, stability of individual differences, and possible modulation of genetic effects.

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