

A Comparison of Latent Inhibition and Learned Irrelevance Pre-Exposure Effects in Rabbit and Human Eyeblink Conditioning

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The learning of an association between a CS and a US can be retarded by unreinforced presentations of the CS alone (termed latent inhibition or LI) or by un-correlated presentations of the CS and US (termed learned irrelevance or LIRR). In rabbit eyeblink conditioning, there have been some recent failures to replicate LI. LIRR has been hypothesized as producing a stronger retardation effect than LI based on both empirical studies and computational models. In the work presented here, we examined the relative strength of LI and LIRR in eyeblink conditioning in rabbits and humans. In both species, a number of pre-exposure trials sufficient to produce LIRR failed to produce LI (Experiments 1 & 3). Doubling the number of CS pre-exposures did produce LI in rabbits (Experiment 2), but not in humans (Experiment 4). LI was demonstrated in humans only after manipulations including an increased inter-trial interval or ITI (Experiment 5). Overall, it appears that LIRR is a more easily producible pre-exposure retardation effect than LI for eyeblink conditioning in both rabbits and humans. Several theoretical mechanisms for LI including the conditioned attention theory, stimulus compression, novelty, and the switching theory are discussed as possible explanations for the differences between LIRR and LI. Overall, future work involving testing the neural substrates of pre-exposure effects may benefit from the use of LIRR rather than LI.

IN CLASSICAL conditioning, the rate at which a subject acquires conditioned responses to paired presentations of a CS and US can be affected by prior exposure to those individual stimuli. Many studies have shown that prior exposure to the CS alone can retard the rate at which the CS-US association is subsequently acquired. This phenomenon is known as latent inhibition and has been demonstrated in a wide variety of paradigms and species (for review see Lubow, 1989).

A paradigm that has a long history of testing the neural substrates of latent inhibition is classical eyeblink conditioning. Classical eyeblink conditioning is a preparation that has received extensive study in rabbits, rats, and humans (see Gormezano et al., 1983; Durkin et al., 1990; Steinmetz, 1999). Classical eyeblink conditioning is an associative learning paradigm in which a neutral stimulus such as a tone or light (the conditioned stimulus or

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CS) is paired with a response-evoking stimulus such as a corneal air puff or peri-orbital shock (the unconditioned stimulus or US) (Gormezano et al., 1962). Initially, the CS elicits no behavioral response while the US elicits a reflexive eyeblink response to protect the cornea. By repeatedly pairing the CS followed by the US, the CS alone comes to elicit an anticipatory eyeblink response (the conditioned response or CR).

While there has been a long history of LI work in classical eyeblink conditioning there have been some recent problems in the replication of the LI effect within the eyeblink conditioning literature. In the work presented here, we will review the history of LI in eyeblink conditioning as well as compare LI with a less tested pre-exposure effect, learned irrelevance that may produce stronger retardation of subsequent conditioning than LI.

Learned irrelevance is a pre-exposure effect in which un-correlated presentations of the CS and US retard subsequent conditioning. Some researchers have viewed learned irrelevance as being even more disruptive than either latent inhibition following CS alone pre-exposure or the retardation following US alone pre-exposure (e.g., Mackintosh, 1973; Overmier & Wielkiewicz, 1983; Bennett et al., 1995). Typically, exposure to both the CS and US, un-correlated with each other, retards subsequent CS-US learning more than exposure to the CS or US alone (e.g., Bennet et al., 1995). There have been several theoretical interpretations of this finding. The simplest explanation is that learned irrelevance reflects the sum of CS-exposure and US-exposure effects (e.g., Baker, 1976), and accordingly generates a stronger effect than either CS—alone or US—alone pre-exposure.

However, there is some evidence suggesting that learned irrelevance exceeds the sum of CS—and US-exposure effects alone (Matzel et al., 1988). The lack of correlation between CS and US during the pre-exposure phase may be the variable that further hinders CS-US association during the subsequent training phase (e.g., Baker & Mackintosh, 1979; Matzel et al., 1988; Bennet et al., 1995). Not only does the subject learn that CSs are a phasic non-informational aspect of the conditioning context, but they also learn that USs occur within the conditioning context with no explicit signal.

Another explanation is that learned irrelevance is a special case of latent inhibition (Baker & Mackintosh, 1979; Hall, 1991; Bonardi & Hall, 1996). In many cases, latent inhibition is context-sensitive. That is, CS-US learning is maximally retarded if the conditioning context during training is identical to the conditioning context during CS exposure (e.g., Hall & Channell, 1985). In a learned irrelevance paradigm, the US is present in both the pre-exposure and training phases. Therefore, there may be less of a contextual shift between exposure and training phases in LIRR, maintaining the ability of CS exposure to retard subsequent learning about that CS. It would be of interest to test this hypothesis to see if LIRR is as context sensitive as LI. It may be that the learning during LIRR pre-exposure is not just that the CS is part of the context, but that there is no relationship between the CS and the US and that this non-relationship is generalized to other situations or contexts.

Latent inhibition has been put forth as a hippocampal dependent task in eyeblink conditioning. Non-selective lesions of the hippocampal region disrupted LI in eyeblink conditioning in the rabbit (Solomon & Moore, 1975) and the rat (Schmajuk et al., 1994). Our initial interest was to test the effects of various selective lesions of the hippocampus made with ibotenic acid on pre-exposure effects like LI in rabbit eyeblink conditioning. However, we had some difficulty in producing the LI retardation effect as compared to relative ease for producing LIRR. We eventually were able to produce LI consistently with the manipulation of increasing the number of CS alone pre-exposures. Using this increased number of CS-alone pre-exposures to produce LI, the effects of selective hippocampal and

selective entorhinal lesions on LI have been tested and published (Shohamy, Allen & Gluck, 2000). We have also tested the effects of non-selective cortico-hippocampal region lesions and selective hippocampal and selective entorhinal lesions on LIRR (Allen et al., in press).

In this paper, we will describe the comparisons between LI and LIRR for eyeblink conditioning in both rabbits and humans that led to our lesion work in the hippocampal system of the rabbit. We now turn to a review of LI and LIRR in the classical eyeblink conditioning literature. In reviewing the eyeblink conditioning literature for both rabbit and humans, we have uncovered almost as many failures to observe LI in eyeblink conditioning as successful replications.

LI in Rabbit Eyeblink Conditioning

Latent inhibition has had a long history in rabbit eyeblink conditioning going back to the development of the rabbit eyeblink conditioning paradigm in the 1960s. Many researchers have reported a retardation effect following CS-alone pre-exposure in rabbit eyeblink conditioning (Clarke & Hupka, 1974; Frey et al., 1976; Hernandez et al., 1981; Reiss & Wagner, 1972; Salafia & Allan, 1980; Scavio et al., 1983; Siegel 1969a, 1969b; Siegel, 1970; Siegel & Domjan, 1971; Solomon et al., 1974a, 1974b; Solomon & Moore, 1975; Suboski et al., 1964). These experiments that produced a significant LI effect used between 80 and 1300 pre-exposures with an average of 475 CS-alone pre-exposures.

There have also been several reports of failure to produce LI in rabbit eyeblink conditioning during this same period (Suboski et al., 1964; Plotkin & Oakley, 1975; Prokasy et al., 1978; Hernandez et al., 1981). These early experiments that failed to obtain LI used between 15 and 280 CS pre-exposures. In these cases, the failure to produce LI may have been due to too few CS-alone pre-exposures to be effective in retarding subsequent CR acquisition.

It is of interest to note that compared to the volume of LI work in rabbit eyeblink conditioning that was reported between the 1960s and early 1980s, only a few eyeblink LI studies have been reported in the last decade in rabbits (Robinson et al., 1993; Romano, 1999) and rats (Schmajuk et al., 1994). These successful recent LI experiments used between 300–450 CS pre-exposures.

There have also been more recent reports of failure to produce LI in eyeblink conditioning in rabbits (Miller, 1994; Katz et al., 1995; Allen & Gluck, 1997; Berry et al., 2000; Rogers et al., 2001) as well as in rats (Rush et al., 2001) than reports of success. These failures to observe LI used between 450–700 CS alone pre-exposures. It is likely that there may be other cases of failures to observe LI that have not been reported in the literature. It is interesting to note that both relatively few as well as relatively many pre-exposures have failed to produce LI in eyeblink conditioning. Recent work by Rogers et al. (2001) has identified an interaction within LI between the facilitation effects of context pre-exposure and the inhibitory effects of CS pre-exposure. Therefore, LI may not be the simple CS alone pre-exposure effect that has become the dogma of experimental psychology.

While there have been several successful LI studies, the number of failures to produce LI in rabbit eyeblink conditioning makes the use of LI as a task for the study of the neural substrates of pre-exposure tasks questionable. If CS alone pre-exposure does not reliably produce a retardation effect, the study of the neural substrates of pre-exposure effects would result in experiments in which animals are pre-exposed and trained with electrophysiological recording or lesions, only to fail to produce LI. To provide a possible

stronger retardation effect that would be a better task for studying the neural substrates of pre-exposure, we tested another pre-exposure effect learned irrelevance (LIRR) that results following un-correlated pre-exposures of the CS and US.

In contrast to the long history of LI in rabbit eyeblink conditioning, there have been no complete studies of LIRR in rabbit eyeblink conditioning published to date. A study by Harvey et al. (1983) reported that CS and US pre-exposures retarded acquisition of CRs, but this manipulation was not compared with the proper context pre-exposed control group. Berry et al. (2000) reviewed work done by Borgnis (1993) in which there were reductions in hippocampal theta activity following explicitly unpaired CS and US pre-exposures (LIRR) and CS alone pre-exposures (LI). However, while these pre-exposures altered subsequent hippocampal processing, they did not retard subsequent eyeblink conditioning and therefore did not produce a LIRR retardation effect. Successful retardation following unpaired CS and US pre-exposure has been reported by Rush et al. (2001) in eyeblink conditioning in infant rats.

While there have been many LI studies in rabbit and rat eyeblink conditioning, there has not been a systematic comparison made with LIRR. Therefore, we wanted to test the LIRR effect in rabbit EBC to compare as a possible alternative pre-exposure effect to LI. If LIRR was demonstrated to be a more reliable or more easily producible pre-exposure effect than LI, then LIRR may be a better pre-exposure effect for future studies of the neural substrates of this type of learning.

LI in Human Subjects

Not only is there interest in testing pre-exposure effects in animals, but there is also interest in using these types of tasks to understand the neural substrates of human memory deficits such as medial temporal lobe amnesia and Alzheimer's dementia. In addition, other human pathological conditions such as schizophrenia (Jones et al., 1997) and attention deficit disorder (Oades & Muller, 1997) have been tested with LI. We wanted, therefore, to compare LIRR and LI in eyeblink conditioning in humans.

Few published studies have examined latent inhibition in human eyeblink conditioning. Two early studies (Grant et al., 1948, 1951) found no significant effect of CS exposure on subsequent CS-US learning when using a light CS and only 5–10 pre-exposures. Perlmutter (1966) found marginally poorer CS-US learning after CS exposure; in a follow-up experiment (Perlmutter, 1966) using a differential conditioning procedure, the latent inhibition effect vanished.

Schnur & Ksir (1969) reported a strong LI effect in human eyeblink conditioning using 20 pre-exposures of a tone CS. However, the learning curves reported by Schnur and Ksir were unusually accelerated (i.e., control subjects reached asymptotic responding of 80 percent CRs within 10 trials of acquisition) and may have involved some facilitation that was reduced by the CS pre-exposure. This unusual pattern of learning calls into question this study as a reliable LI effect.

To our knowledge, learned irrelevance has not been reported in human eyeblink conditioning to date. However, one recent study from our laboratory using a computer-based task has shown a related effect in a cognitive analog of conditioning. Un-correlated exposure to two stimuli can retard subsequent learning of an association between them (Myers, Oliver et al., 2000). This effect is disrupted in humans with hippocampal region damage (Myers et al., 2000), which matches the effects of lesions of the hippocampal region in rabbits (Solomon & Moore, 1975; Shohamy et al., 2000). Therefore, the neural substrates

of pre-exposure effects in humans seem to match those in the rabbit.

The purpose of this article is to examine learned irrelevance and latent inhibition in eyeblink conditioning in both rabbits and humans. We compared the effects of un-correlated CS and US pre-exposures to produce LIRR and the effects of CS alone pre-exposures to produce LI in eyeblink conditioning in both rabbits and humans.

In the five experiments presented here, we initially compared LIRR and LI with the same number of pre-exposures in eyeblink conditioning in both rabbits and humans. In both species, the number of pre-exposures that produced LIRR failed to produce LI. We then attempted to produce LI by increasing the number of pre-exposures. This manipulation produced LI in rabbits, but not humans. Finally, altering the interval between trials (ITI) did produce LI in human eyeblink conditioning.

Experiment 1: LIRR and LI in Rabbit Eyeblink Conditioning

In Experiment 1, we tested whether un-correlated pre-exposures of a CS tone and US air puff (i.e., LIRR pre-exposure) would retard subsequent acquisition of CRs in response to paired presentations of the tone and air puff. Performance of LIRR pre-exposed rabbits was compared to that of context pre-exposed controls. We also tested the effects of CS tone alone pre-exposures (i.e., LI pre-exposure) with the same amount of pre-exposure as LIRR. The parameters for LIRR and LI were based on the prior LI experiments of Solomon and Moore (1975) and Romano (1999). The only alteration from Solomon & Moore's (1975) parameters was our use of a 3 psi air puff as a US instead of a peri-orbital shock as a US. However, the use of a 3 psi air puff as a US was successful in producing LI in a recent report (Romano, 1999). Therefore, we were confident that the alteration on the US from a peri-orbital eyeshock to a corneal air puff should not alter LI in rabbit eyeblink conditioning. We hypothesized that this level of pre-exposure would produce both a LI and a LIRR effect with the LIRR effect being more disruptive than the LI effect, based on previous studies comparing these two pre-exposure phenomena.

Method

Subjects. Twenty-two male New Zealand albino rabbits (*Oryctolagus cuniculus*) weighing over 2.0 kg were used in this experiment. The rabbits were purchased from Covance Laboratories (PA). The rabbits were housed in individual cages in the Rutgers University Animal Facility, Newark, NJ. They were given free access to food and water. They were maintained on a 12 hr light/dark cycle with light on at 7:00 am. All testing occurred between 8 am and 6 p.m.

The rabbits were grouped into a learned irrelevance pre-exposure group (LIRR, $n = 5$), a learned irrelevance context pre-exposure group (LIRR context, $n = 5$), a latent inhibition pre-exposure group (LI, $n = 6$) or a latent inhibition context pre-exposure group (LI context, $n = 6$).

Materials. The rabbits were restrained in plexi-glass restraint boxes in individual conditioning chambers. Each chamber contained a speaker, air hose assembly, and an eyeblink detection system.

Presentations of the stimuli and recording of behavioral responses were controlled by a PC computer. The computer housed an interface board (Keithley Metrabyte), which triggered a set of relays that controlled the presentation of the tone CS and air puff US. For information on this software see Chen & Steinmetz (1998).

Eyeblinks were monitored with an opto-electronic sensor that consisted of a light emit-

ting diode (LED) and a phototransistor (for technical details, see Thompson et al., 1994). The LED emitted a beam of infrared light that was reflected off the cornea, and the reflectance of this beam was converted to a DC voltage by a phototransistor. The eyeblink signal was filtered (between .1 Hz and 1 KHz) and amplified (100x) by a differential AC amplifier (A-M Systems, Everett, WA).

When the rabbit closed its eye, the reflectance of the infrared beam changed and was recorded as an eyeblink. Any movement greater than 0.5 mm during the preCS period caused the training trial to be discarded from analysis. A conditioned response (CR) was scored if movement of greater than 0.5 mm was seen in the CS period. Each trial's behavioral record was displayed on the computer screen. The computer analyzed the behavioral data and delivered the data for each block of 50 trials.

Stimuli. The CS was a 450 ms, 95 dB, 1000 Hz tone delivered from a speaker located in front of the rabbit's face. The US was a 50 ms, 3 psi corneal air puff delivered via a rubber hose attached to the eyeblink detector assembly and aimed at the rabbit's cornea.

Design and Procedure

Adaptation. Prior to the pre-exposure phase, all rabbits were adapted to the conditioning chamber and restraint box for two daily sessions. On the first day of adaptation, the rabbit was placed in the restraint box in the conditioning chamber for a half-hour. On the second day of adaptation, the rabbit was placed in the restraint box in the conditioning chamber with the eyeblink detector aimed at its cornea for 45 minutes.

LIRR pre-exposure. Rabbits in the LIRR group were exposed to pseudo-random presentations of the tone CS and air puff US. The exposure trials were 20 sec in length with a 1 sec inter-trial interval. The tone and air puff were pseudo-randomly separated by 5 or 10 sec in either a forward or backward fashion (i.e., on half the trials the tone preceded the air puff and on half it followed the air puff). In this way, the tone had equal probability of occurring either prior to or after the air puff. This separation of the tone and air puff is outside the temporal limit for delay eyeblink conditioning (Gormezano et al., 1983), so no association should be made between the tone and air puff during LIRR pre-exposure. This pattern of forward and backward paired stimulus presentations was used so that there would be no learning of a causal relationship between the tone and air puff during the exposure phase during the LIRR pre-exposure phase.

The LIRR group received 100 daily trials of the random CS and US for four and a half daily sessions for a total of 450 pre-exposures. On the fifth day of pre-exposure, they received 50 pre-exposure LIRR trials followed immediately by 50 acquisition trials of tone-air puff training.

LI pre-exposure. Rabbits in the LI group were pre-exposed to the tone CS. They received 100 daily trials of the tone CS for four and a half daily sessions for a total of 450 exposures. On the fifth day of pre-exposure, they received 50 exposure trials followed immediately by 50 acquisition trials of tone-air puff training.

LIRR and LI Context pre-exposure. The context pre-exposure groups received the same number of exposure trials as the LIRR and LI pre-exposure groups, but these were blank trials with no stimuli presented. In this fashion, the context pre-exposed group received the same amount of pre-exposure to the conditioning context as the pre-exposed group but with no exposure to the stimuli.

Acquisition. Starting with the second half of the fifth day of exposure, all rabbits received forward paired presentations of the tone and air puff that were paired in a standard

delay paradigm. Rabbits received forward paired presentations of a 450 ms, 1000 Hz, 95 dB tone, which coterminated with a 50 ms, 3 psi, corneal air puff. The inter-trial interval (ITI) was on average 30 s and was varied pseudo-randomly between 25 and 35 s. Rabbits received a total of 450 paired trials over four and a half daily training sessions. Training criterion was defined as eight CRs out of nine consecutive trials.

Data Analysis. Conditioned responses were analyzed in blocks of 50 trials. Behavioral results were analyzed with a repeated measures ANOVA with planned pair-wise comparisons between the pre-exposure and context pre-exposure groups.

Results

All rabbits in the LIRR pre-exposure and LI pre-exposure and the two context pre-exposure groups met the training criterion of eight CRs out of nine consecutive trials. The learning curves for these four groups are shown in Figure 1.

All rabbits in the LIRR pre-exposure and LIRR context pre-exposure groups learned to exhibit CRs as training progressed ($F(8, 64) = 59.7, p < .001$). Rabbits in the LIRR pre-exposure group exhibited significantly fewer CRs than those in the context pre-exposure group ($F(1, 8) = 57.056, p < .001$). Overall, rabbits in the LIRR group were slower to acquire conditioned responses as compared to the context pre-exposed group as demonstrated by a group X session interaction ($F(8, 64) = 7.87, p < .001$).

All rabbits in the LI and context pre-exposure groups learned to exhibit CRs as training progressed ($F(8, 80) = 58.5, p < .001$). There were no significant differences in CR production between rabbits in the LI pre-exposure group and the context pre-exposure group ($F(1, 10) = .168, p > .69$).

Discussion

Overall, rabbits who were exposed to un-correlated presentations of the tone CS and air puff US exhibited slower acquisition of CRs as compared to rabbits only pre-exposed to the context. Learned irrelevance pre-exposure did not block the acquisition of the CR, but only retarded its development. We were unable to produce a significant latent inhibition effect with 450 pre-exposures. These findings suggest that learned irrelevance is a more easily producible pre-exposure effect than latent inhibition in rabbit eyeblink conditioning. That is the number of pre-exposures that produced LIRR failed to produce LI.

The failure of 450 CS alone pre-exposures to produce LI is an unexpected result since we had replicated the parameters from Solomon & Moore's (1975) and Romano's (1999) studies of latent inhibition in rabbit eyeblink conditioning. The only difference between our parameters and Solomon & Moore's is that we used an air puff US while they used a peri-orbital eyeshock US. As mentioned earlier, Romano (1999) used the same 3 psi corneal air puff as we did in the current work and successfully produced LI. However, if LI is a simple pre-exposure effect, it shouldn't matter what training follows the pre-exposure as long as the CS is the same and the context has not changed. For example, we should be able to pre-expose the tone and then use it as a CS for eyeblink conditioning with an air puff or an eyeshock, or for any other number of reflexes such as limb flexion, jaw movement, etc., not to mention fear conditioning and other non-motor forms of classical conditioning.

Another difference between the successful LI experiment of Romano (1999) and our

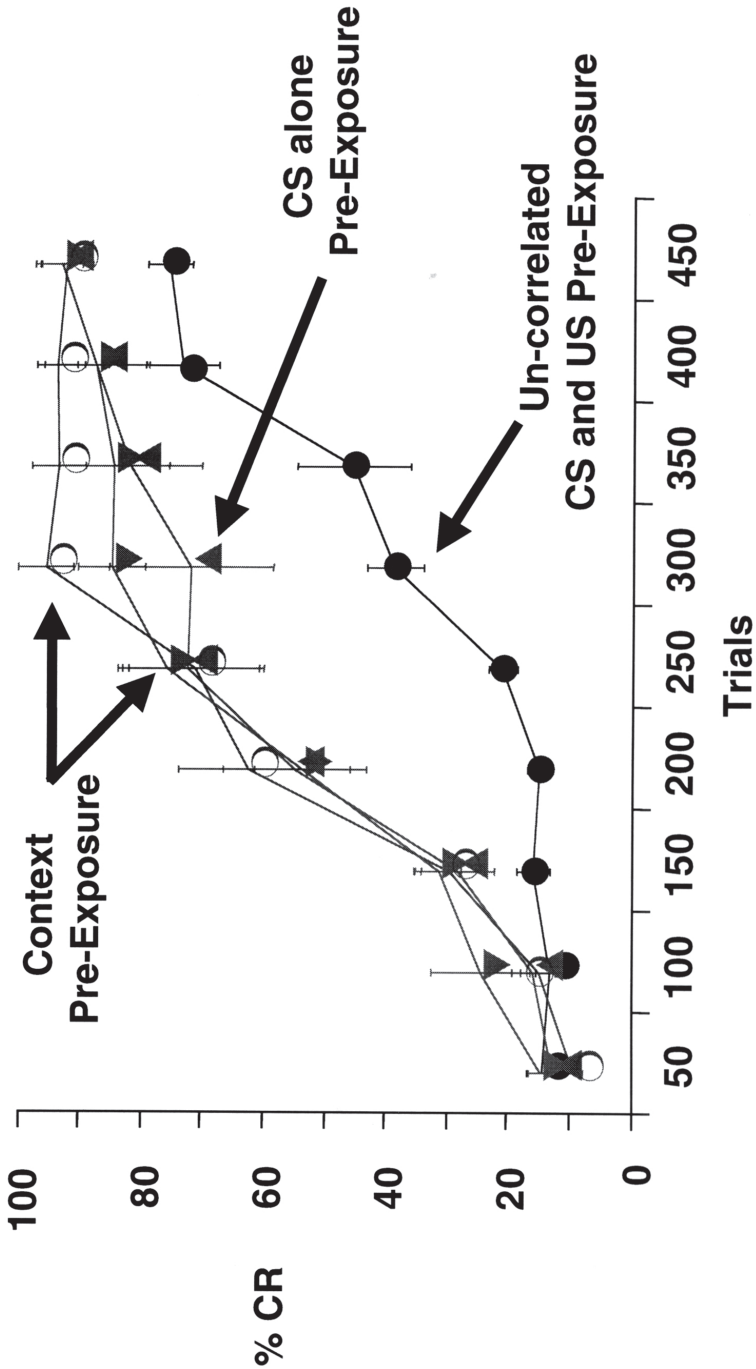


FIG. 1. The behavioral results for learned irrelevance and latent inhibition with 450 pre-exposures in rabbit eyeblink conditioning from Experiment 1. The learning curves (percent CRs) are shown for the LIRR context group (open circles) and the LIRR group (closed circles). Rabbits in the LIRR group (i.e., uncorrelated CS + US pre-exposure) exhibited significantly fewer CRs as compared to rabbits in the LIRR context group (i.e., learned irrelevance). Rabbits in the LI group (upward triangles) and rabbits in the LI context group (downward triangles) conditioned similarly (i.e., no latent inhibition). Error bars represent standard error of the mean (SEM).

failure to produce LI was that Romano (1999) used a longer inter-trial interval (ITI) of around 60 s while our ITI was around 30 s. However, the ITI for Solomon & Moore (1975) was 30 s. Therefore, we did not focus on further testing of LI on this variable.

We decided to test the simplest hypothesis of number of pre-exposure and hold all other variables constant (ISI, ITI, tone intensity, US intensity). Other recent experiments in other laboratories have tested other variables such as US intensity (Rogers et al., 2001). We chose to manipulate the variable that should produce LI, the number of pre-exposures. If LI is a universal phenomenon of classical conditioning, the variables such as how long the CS lasts or trial spacing should not determine whether LI is produced or not.

In the past, a wide range of numbers of pre-exposures have been used to observe LI in rabbit eyeblink conditioning. As mentioned earlier, these prior experiments have included up to 1300 pre-exposures (Siegel, 1969a, 1969b). Therefore, we hypothesized that it may be necessary to simply increase the number of CS pre-exposures to produce a significant retardation effect in rabbit eyeblink conditioning.

Experiment 2: Increased CS Pre-Exposures for LI in Rabbit Eyeblink Conditioning

Since Experiment 1 failed to produce latent inhibition with the same number of pre-exposures as learned irrelevance, it was possible that latent inhibition was a weaker pre-exposure effect. The simplest hypothesis was that while 450 pre-exposures was sufficient to produce LIRR it was not enough to produce a significant LI effect. Therefore, we decided to test whether increasing the number of CS exposures in the pre-exposure phase would produce latent inhibition in rabbit eyeblink conditioning. Other manipulations that could have been tested that might have resulted in LI would have been increasing US salience or changing from corneal air puff to a peri-orbital shock. These other manipulations have been done by Rogers et al. (2001).

Method

Subjects. A total of ten rabbits as described in Experiment 1 were used in this experiment.

Training Procedures. Training procedures were the same as described for latent inhibition in Experiment 1 with the exceptions of a longer pre-exposure phase and a longer training phase.

Long LI pre-exposure. Rabbits now received 850 trials of the CS alone over eight and a half daily sessions.

Long LI context pre-exposure. Rabbits in the Long LI context group received 850 blank trials with no stimuli presented over eight and a half daily sessions, so as to receive equivalent amount of exposure to the conditioning context.

Training phase. On the ninth day of pre-exposure, all rabbits received 50 pre-exposure trials (CS alone or no stimuli) followed immediately by 50 training trials. Training trials were the same as described in Experiment 1 with the exception that 650 trials over six and half daily sessions were trained instead of only 450 as in Experiment 1.

Results

Overall all rabbits learned to give conditioned responses to the tone as training progressed (repeated measures (ANOVA, $F(8, 40) = 6.034, p < .001$). Rabbits in the Long LI group exhibited significantly fewer CRs than did rabbits in the Long LI context group (ANOVA, $F(1, 5) F = 8.072, p < .03$) as shown in Figure 2. There was no significant interaction of group by session ($F(16, 40) F = .990, p > .48$).

Discussion

The results from Experiment 2 demonstrated that 850 presentations of the CS alone produced latent inhibition in rabbit eyeblink conditioning. This finding indicates that the latent inhibition in rabbit eyeblink conditioning is possible with extended pre-exposures of the CS tone, but that it takes more pre-exposure trials to produce latent inhibition than learned irrelevance (Experiment 1).

Our findings from Experiments 1 and 2 were that 850 pre-exposures to the CS tone alone resulted in latent inhibition, while 450 pre-exposures to the CS tone alone did not result in latent inhibition. However, pre-exposure to the CS tone and US air puff for 450 trials did result in learned irrelevance. Taken together, the findings of Experiments 1 and 2 demonstrate that for rabbit eyeblink conditioning, the learned irrelevance effect is a more easily producible pre-exposure phenomenon than latent inhibition (i.e., LIRR can be obtained with less pre-exposure than LI while holding all other training parameters constant).

It is unclear why 450 pre-exposures of the CS alone failed to produce LI when Solomon & Moore (1975) and Romano (1999) were able to observe LI with these parameters. It also of interest to note that Rogers et al. (2001) failed to observe LI following 450 pre-exposures of the CS alone. Further work by Rogers et al. (2001) has tested the effects of altering US intensity and interactions between CS and context pre-exposure effects on LI in rabbit eyeblink conditioning.

However, our manipulation of extending the number of CS alone pre-exposures to 850 has consistently produced LI in our laboratory (Shohamy et al., 2000). We have also continued our investigation of the neural substrates of pre-exposure effects in eyeblink conditioning in the rabbit with selective lesions of components of the hippocampal region for LI (Shohamy et al., 2000) and LIRR (Allen et al., in press).

Experiment 3: LIRR and LI in Human Eyeblink Conditioning

Both the behavioral and neurobiological substrates of eyeblink conditioning appear to be highly similar across species; results obtained in the rabbit generalize well to humans (Thompson et al., 1997). A large number of studies have shown that various stimulus contingencies, brain lesions and pharmacological manipulations in the rabbit (e.g., Solomon & Gottfried, 1981) produce similar behavioral effects in humans (e.g., Solomon et al., 1993).

Therefore, we can replicate the rabbit eyeblink conditioning procedures described in Experiments 1 and 2 in humans with basic parametric changes based on the eyeblink conditioning in humans. These changes entail less overall pre-exposure and training trials and all pre-exposure and training taking place in one session. Human eyeblink conditioning also entails a longer ISI, and a weaker US air puff (i.e., 1 psi rather than 3 psi for the rabbits).

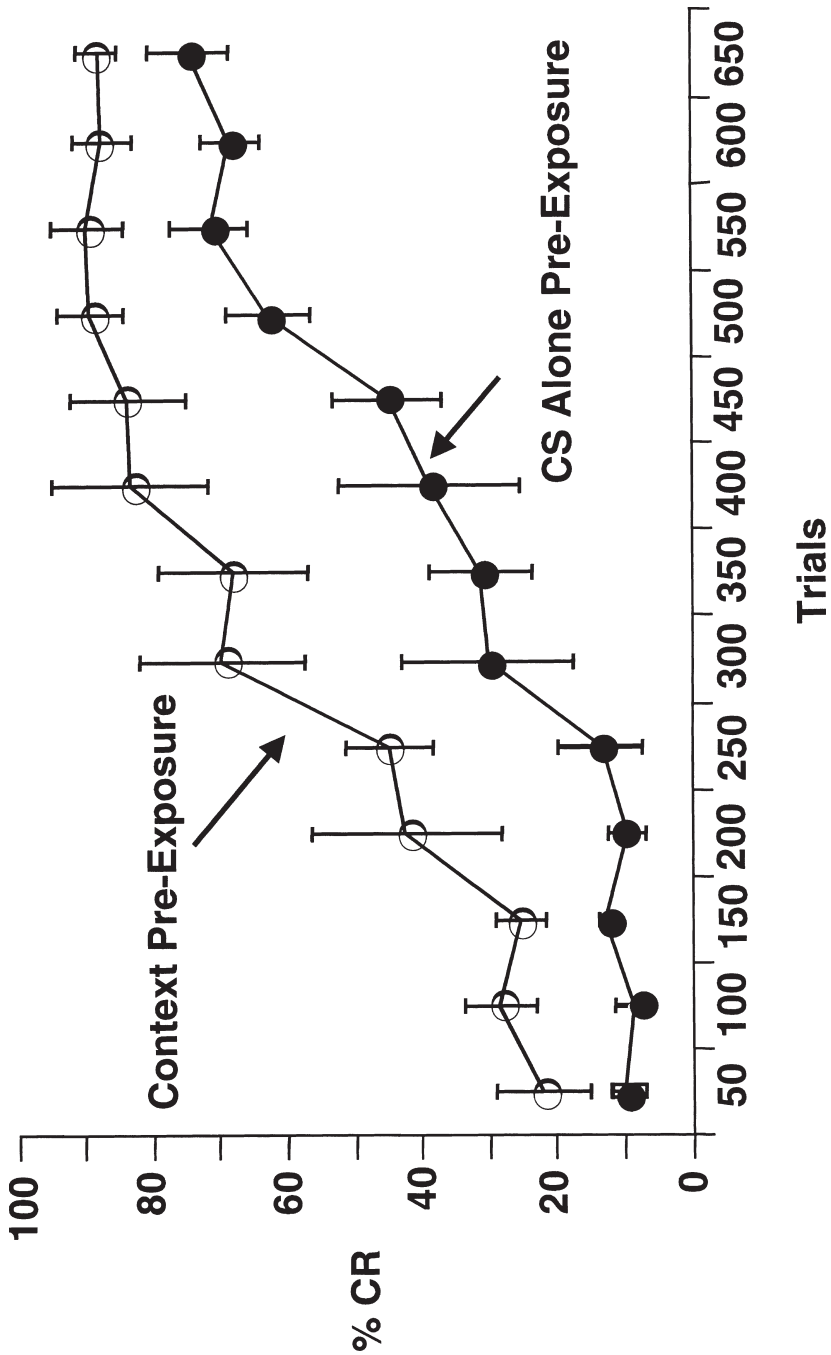


FIG. 2. Behavioral results from latent inhibition with extended pre-exposure in rabbit eyeblink conditioning from Experiment 2. Following 850 pre-exposures of the tone alone, rabbits in the Long LI group (closed circles) were significantly retarded at acquiring CRs as compared to Long context group (open circles). Therefore, 850 pre-exposures of the CS alone produced latent inhibition. Error bars represent standard error of the mean (SEM).

A survey of recent human and rabbit eyeblink conditioning publications indicate that human eyeblink conditioning experiments usually involve less than 100 paired trials presented in one training session (e.g., Gabrieli et al., 1995; Martin & Levey, 1991; Solomon et al., 1989; Clark & Squire, 1999; Tracey et al., 1999) while rabbit eyeblink conditioning experiments involve about 100 trials per daily session with around 4–7 daily conditioning sessions (e.g., Shohamy et al., 2000; Romano, 1999; Chen & Steinmetz, 2000; Kim et al., 1998; Woodruff-Pak & Santos, 2000). The ISIs reported for these human eyeblink conditioning experiments were between 400 and 1250 ms, while the optimal ISI for rabbit eyeblink conditioning is between 200 and 500 ms. For a review of rabbit and human eyeblink conditioning literature work see Woodruff-Pak & Steinmetz (2000a, 2000b). However, while there are some subtle parametric differences between rabbit and human eyeblink conditioning experiments, this work presented here utilized the same CS (tone), same US (corneal air puff), delay paradigm, and same recording of eyeblink movement (infra-red detector).

A previous study by Schnur & Ksir (1969) reported a strong LI effect in human eyeblink conditioning using 20 pre-exposures of a tone CS. However, the learning curves reported by Schnur & Ksir were unusually accelerated (i.e., control subjects reached asymptotic responding of 80 percent CRs within 10 trials of acquisition) and may have involved some facilitation that was reduced by the CS pre-exposure.

Experiment 3 describes an attempt to demonstrate LI and LIRR in human eyeblink conditioning using the same parameters. The number of pre-exposures (40) was chosen in order to be able to present the CS and US in a completely un-correlated fashion as described in the LIRR pre-exposure procedures. Also, we wanted to have about half as many pre-exposure trials (40) as training trials (70) that could be presented in an hour conditioning session. As was the hypothesis in Experiment 1, we expected this level of pre-exposure to produce both LIRR and LI with the retardation of LI being more disruptive than LI.

Methods

Subjects. Sixty Rutgers University undergraduates served as subjects in Experiment 3; they were randomly and evenly distributed into three groups: CS pre-exposure (LI), uncorrelated CS + US pre-exposure (LIRR) and context pre-exposure (context). Each group included 12 females and 8 males. Average age of subjects in the LI group was 18.8 years (S.D. 1.0); in the LIRR group, 18.5 years (S.D. 0.5); and in the context pre-exposed group, 19.1 years (S.D. 1.2). The differences in age between groups did not reach statistical significance (ANOVA, $F(2, 57) = 2.52, p > 0.05$). Subjects who wore glasses or contact lenses to correct vision were required to remove these during testing; any subject who could not see a television at close range without glasses or lenses was excused from testing. For their participation, subjects received credit for an introductory psychology class or were paid at the rate of \$10 for one hour.

Apparatus. The apparatus used to condition the eyeblink response was previously described in Solomon et al. (1989). Conditioning took place in a dedicated testing room (ambient noise approximately 60 dB). The subject was seated in a comfortable chair, which had stereo speakers placed at head level on either side, twelve inches from the subject's ears. This speaker system was used to deliver the conditioned stimulus (CS). During conditioning, the subject watched a videotape played on a 19 inch color television screen located in front of the chair. So that the movie soundtrack would not obscure the CS, the sound was turned off and closed-captioning text was enabled.

The subject was fitted with an adjustable plastic head harness containing a noninvasive photo-electric detector and transducer. This consisted of a light-emitting diode (LED) used to generate an infrared beam that was aimed so it reflected off the subject's right cornea and back into a phototransistor. Interruption of the beam by eyelid closure was transduced into a voltage change and recorded by an IBM 386 computer system with a specialized analog-to-digital converter (for technical details see Lavond & Steinmetz, 1989).

The computer interface generated the CS, a 500 ms, 1 KHz tone, calibrated to be 72 dB. The computer also controlled the delivery of the US, a 100 ms, 1 PSI, puff of medical-grade oxygen, directed at the subject's right cornea.

The experimenter and equipment for generating and recording responses were located behind and out of sight of the subject. A video camera trained on the subject's face broadcast this image back to the experimenter, who could then monitor whether the headset remained in place and whether blinking appeared normal (i.e., subject was neither forcing eyes to remain open nor keeping them shut).

Procedure. Upon entering the laboratory, each subject 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 et al., 1975) was administered. The subject was then seated in the conditioning chair, at a comfortable viewing distance from the television (about 4 feet). The experimenter then fitted the headset on the subject and checked that the subject was comfortable. The experimenter then gave 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.

Each subject then underwent the pre-exposure phase and training phase.

Latent Inhibition (LI) pre-exposure. Subjects in the LI group received 40 CS-alone presentations prior to acquisition trials.

Learned Irrelevance (LIRR) pre-exposure. For subjects in the LIRR group, both CS and US were presented during the exposure phase, but un-correlated with each other. The CS was scheduled to occur once during each of the 40 trials. The US, which lasted 100 ms, was scheduled to occur once each trial. The US occurred with the constraint that the probability of the US occurring during the 500-ms CS period $P(\text{US|CS})$ was exactly the same as the probability of the US occurring in any other 500 ms period during the trial $P(\text{US|}\sim\text{CS})$. To accomplish this, the 20-s trial period was divided into 40 500-ms bins. The US was randomly scheduled to occur once in each bin across the 40 trials; the US always occurred in the last 100 ms of the bin to which it had been assigned. Thus, over the course of the exposure phase as a whole, CS and US appeared together and co-terminated exactly once, and $P(\text{US|CS}) = P(\text{US|}\sim\text{CS}) = 1/40$.

Context pre-exposure. Subjects in the context pre-exposed group received no CS or US presentations during the exposure phase; instead, these subjects simply sat and watched the movie for 13 minutes, the duration of the exposure phase for the other groups. The experiment (phases 1 and 2) lasted approximately 37 minutes.

Training phase. Immediately following the pre-exposure phase, all subjects received 70 paired presentations of the tone and air puff. A 500 ms tone co-terminated with a 100 ms corneal air puff (i.e., a 400 ms interstimulus interval or ISI). The inter-trial interval (ITI) was scheduled to range pseudo-randomly between 18 and 22 s, with a mean of 20 s.

Following the termination of the training phase, the experimenter removed the headset and debriefed the subject.

Data Analysis. For each trial, the computer recorded changes measured by the headset transducer. An eyeblink response was defined as a change of at least 0.5 from a baseline reflectance level of 0.7. For each such event, the computer also recorded time of onset, recorded as latency from the tone onset. An eyeblink occurring with latency greater than 400 ms was defined as an unconditioned response (UR)—a reflexive response to the air puff US.

Any trials for which eyeblink responses of at least 0.5 were recorded during the 150 ms immediately prior to CS onset were scored as spontaneous blink trials; data from these trials were discarded. Eyeblink responses occurring within 50 ms of CS onset were scored as non-adaptive stimulus-evoked alpha responses. An eyeblink occurring with latency between 50 and 400 ms was defined as a conditioned response (CR). Finally, any trials that did not include spontaneous blinks, alpha responses, CRs or USs were scored as no-response trials; no-response trials were also discarded from further analysis as they were presumed to reflect equipment malfunction or slippage of the headset. If more than one no-response trial occurred in sequence, the experimenter paused the experiment to readjust the headset.

Training phase trials were grouped into seven blocks of 10 trials. For each block, the number of “response trials” was defined as the number of trials on which an alpha response, a CR or a UR occurred—discarding any trials in which spontaneous blinks or no-responses occurred. Then, for each subject, a percent-CR measure was calculated for each block of 10 trials and for the training phase as a whole, defined as the percentage of “response trials” on which a CR occurred.

Finally, criterion performance was defined as eight or more CRs out of 10 consecutive response trials (discounting any intervening spontaneous or no-response trials). The trial on which criterion performance was reached was recorded for each subject.

Results

All subjects learned to exhibit CRs in response to the tone as training progressed (repeated measures ANOVA, $F(6, 342) = 13.24, p < 0.001$). Overall, there was a significant difference in the amount of conditioned responses exhibited by the three groups ($F(2, 57) = 12.97, p < 0.001$). There was no significant group-block interaction ($F(12, 342) = 0.48, p > 0.05$).

Planned post-hoc pair-wise comparisons indicated significantly less conditioned responding in the LIRR group as compared to the context group ($F(1, 38) = 16.24, p < 0.001$) as shown in Figure 3.

There was also significantly less conditioned responses exhibited by the between LIRR pre-exposed group as compared to the LI group ($F(1, 38) = 19.73, p < 0.001$). However, there were no significant differences in conditioned responding between the LI group as compared to the context group ($F(1, 38) = 0.25, p > 0.05$).

Discussion

These results indicate that learned irrelevance can be obtained following 40 un-correlated CS + US presentations in human eyeblink conditioning. Subjects receiving prior exposure to un-correlated presentations of the CS and US exhibited a retardation of subse-

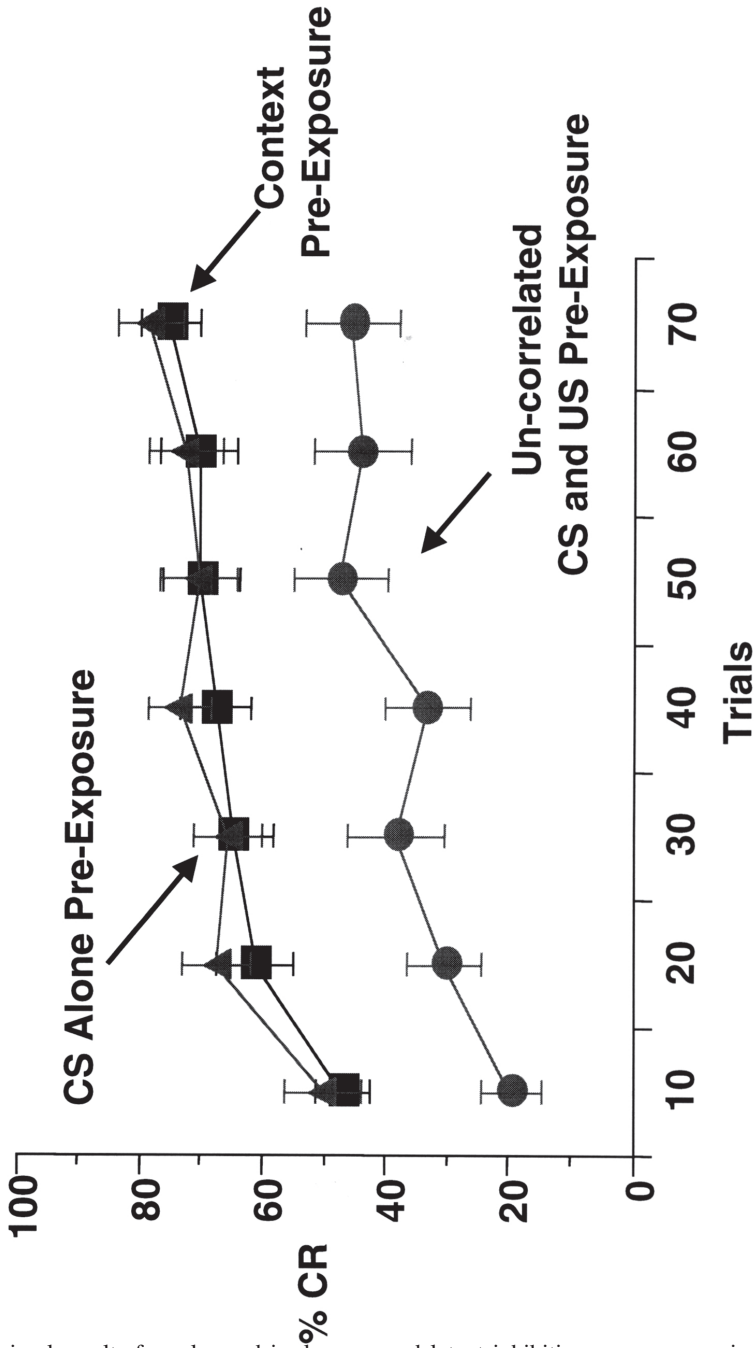


FIG. 3. Behavioral results from learned irrelevance and latent inhibition pre-exposure in human eyeblink conditioning from Experiment 3. Following 40 uncorrelated pre-exposures of the CS + US pre-exposed subjects (circles) exhibited fewer CRs as compared context pre-exposed controls (squares) and thus exhibited learned irrelevance. However, 40 pre-exposures of the CS alone had no effect on subsequent conditioning and failed to produce latent inhibition. There were no significant differences in conditioned responding between the CS pre-exposed subjects (triangles) and the context pre-exposed controls. Error bars represent standard error of the mean (SEM).

quent CS-US learning as compared with a context pre-exposed control group. In contrast to a significant learned irrelevance effect, forty CS alone pre-exposures did not produce latent inhibition.

The learning curve for the LIRR pre-exposed group does not reach the same level of responding as the context pre-exposed controls. This is not that unusual a result in eyeblink LI studies (e.g., Romano, 1999). It is unclear in humans whether LI and LIRR are simply retardation effects in which eventually all subjects will reach the same asymptotic levels of conditioned responding as controls or whether these animals are disrupted in normal conditioned responding and will not ever reach the high levels of conditioned responding. Future work should attempt to over-train subjects following LI and LIRR to see if eventually all pre-exposed subjects achieve the same level of asymptotic responding as controls.

It may well be that learned irrelevance is a more disruptive phenomenon, which is easier to demonstrate under the current experimental parameters. This would be consistent with the results presented in Experiment 1, along with other prior animal studies which suggest that, under a variety of preparations and conditions, learned irrelevance is simply a stronger effect than latent inhibition (e.g., Bennet et al., 1995; Matzel et al., 1988; Rush et al., 2001).

Failure to produce LI may be due to not enough pre-exposures being presented to retard subsequent acquisition. The pattern of results we found in human eyeblink conditioning in Experiment 3 was the same as that previously observed in Experiment 1 with rabbit eyeblink conditioning. That is, the same number of pre-exposures that resulted in a significant LIRR retardation effect failed to produce a significant LI retardation effect. Therefore, we hypothesized, as we did in Experiment 2, that the LI effect may not have been observed because not enough pre-exposures had been presented to result in observed LI.

Experiment 4: Increased CS Pre-exposures for LI in Human Eyeblink Conditioning

We hypothesized that an increase in the number of CS pre-exposures should result in a LI retardation effect. This hypothesis was consistent with early human eyeblink conditioning studies. Grant et al. (1948, 1951) used only 5–10 pre-exposures to a light CS. Perhaps a limited amount of CS exposure is not sufficient to produce a latent inhibition effect in humans. Accordingly, to test this manipulation in human eyeblink conditioning, we doubled the number of CS exposures (from 40 in Experiment 3 to 80 in Experiment 4), to determine whether this extended exposure of the CS tone alone would produce LI in eyeblink conditioning in humans.

Methods

Subjects. Forty Rutgers undergraduates served as subjects in Experiment 4; they were randomly and evenly distributed into two groups: (1) Long-CS pre-exposure and (2) Long-context pre-exposure (control). The Long-CS pre-exposure group had seven males and 13 females with an average age of 21.4 years (S.D. 4.8); the Long-context pre-exposure group had 11 males and nine females with an average age of 24.5 years (S.D. 8.2). The difference in age between groups did not reach statistical significance (t -test, $t(38) = 1.57$, $P > 0.05$). For their participation, subjects received credit for an introductory psychology class or were paid at the rate of \$10 for one hour.

Apparatus, Procedure and Data Collection. The apparatus and data collection were as

those described in Experiment 3. The conditioning procedure was the same as described in Experiment 3 except that the LI pre-exposure phase was doubled to 80 pre-exposures of the CS alone. Subjects in the Long-context group spent an equivalent amount of time in the experimental chair watching the movie. Following the exposure phase, the training phase continued as described in Experiment 3.

Results

Conditioned responding for each 10-trial block is shown for the Long context group and Long LI groups in Figure 4. All subjects learned to exhibit conditioned responses to the tone as training progressed (repeated measures ANOVA, $F(6, 228) = 16.68, p < 0.001$). There were no significant differences in conditioned responding between the Long CS pre-exposure group and the long context pre-exposure group ($F(1, 38) = 0.20, p > 0.05$). There was also no interaction ($F(6, 228) = 1.16, p > 0.05$).

Discussion

There were no significant differences in the acquisition of CRs between subjects in the Long-context pre-exposed and Long-CS pre-exposed groups. Doubling the number of CS alone pre-exposures did not affect subsequent acquisition of CRs and failed to produce a LI retardation effect. Experiment 3 demonstrated that, with experimental parameters sufficient to evoke learned irrelevance, no latent inhibition was shown. In Experiment 4, extending the exposure phase still did not produce latent inhibition.

It may be that other experimental parameters, such as inter-stimulus interval, are also critical for LI. It is already well established that trial spacing can have a strong effect on eyeblink conditioning (e.g., Brelsford & Theios, 1965; Salafia et al., 1973). The inter-trial interval (ITI) of the preceding experiments was fairly short, allowing only on average 20 seconds between CS presentations. In addition, a recent report of successful LI in rabbit eyeblink by Romano (1999) used a very long ITI of 60 seconds. This is an interesting difference since all the other parameters were similar to those used by us in Experiment 1 that failed to result in LI. It may be that the longer interval between trials allows for more learning of the tone as a redundant contextual cue.

It may also be for humans that this short ITI encourages subjects to count down (consciously or subconsciously) to the next stimulus event. Particularly during the exposure phase, it is possible that if stimulus events are too regular and predictable, they are processed in a different way that disrupts latent inhibition. A longer ITI might make the stimulus events less easy to anticipate, and may facilitate latent inhibition.

Experiment 5: Expanded ITI for LI in Human Eyeblink Conditioning

In Experiment 5, we used a longer ITI, averaging 30 s between trials. To keep the overall duration of the exposure phase similar across experiments, we included 30 CS exposures during this phase, so that the total exposure phase took approximately 15 minutes, just slightly longer than in Experiments 3 and 4.

We also considered an additional control group, No-Exposure, which received no phase 1 exposure but proceeded immediately to phase 2 CS-US training. The purpose of this control group was to consider whether context pre-exposure itself somehow slowed overall phase 2 learning, obscuring possible latent inhibition in the subjects given CS alone pre-exposure.

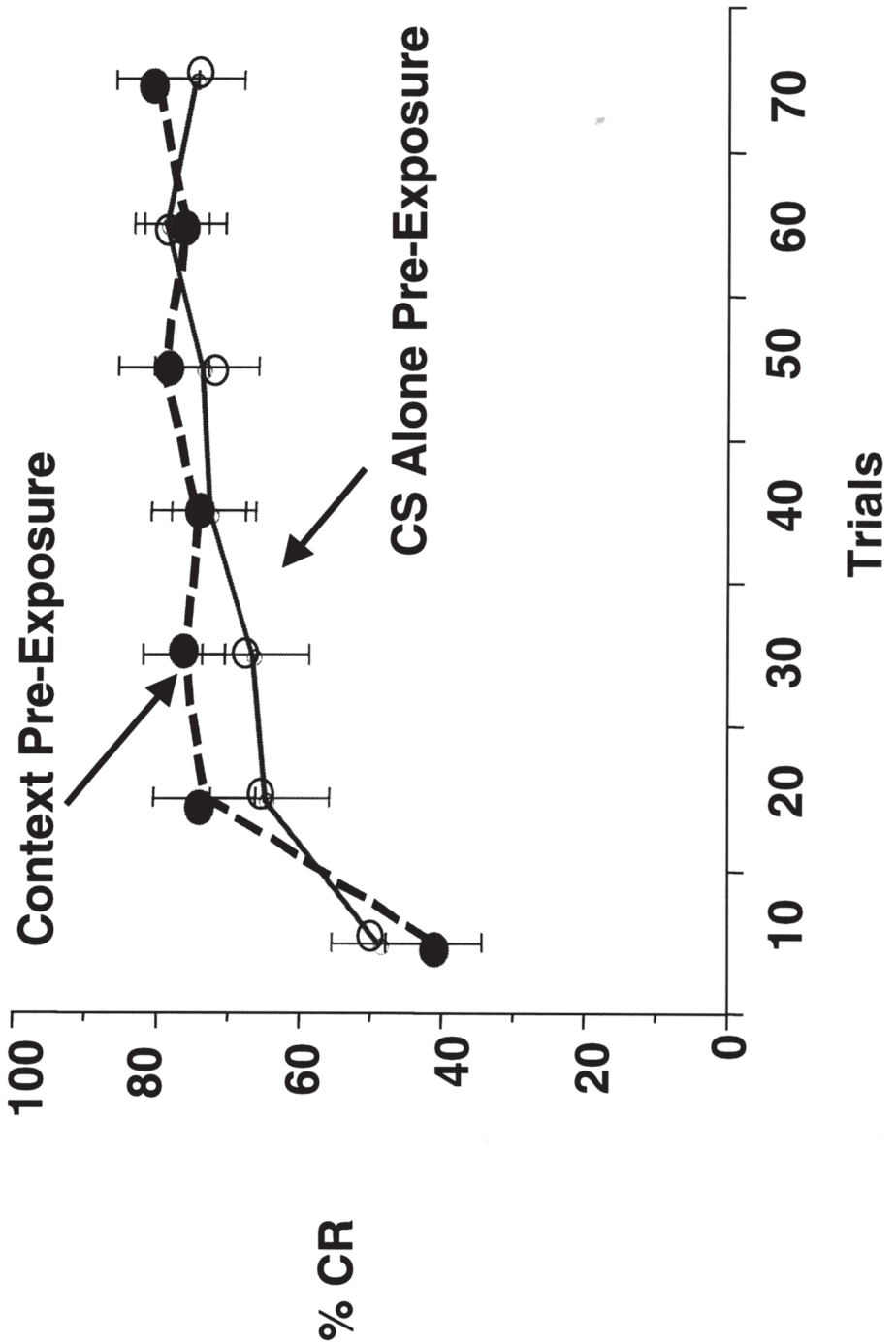


FIG. 4. Behavioral results from latent inhibition pre-exposures in human eyeblink with 80 pre-exposures of the CS tone. There were no significant differences in conditioned responding between the CS pre-exposed subjects (open circles) and the context pre-exposed controls (closed circles). Once again this was a failure to produce latent inhibition. Error bars represent standard error of the mean (SEM).

Methods

Subjects. Sixty Rutgers undergraduates served as subjects in the experiment; they were randomly and evenly distributed into three groups: CS pre-exposure, Context pre-exposure, and No-Exposure. The CS pre-exposure group had seven females and 13 males, with an average age of 19.4 years (S.D. 1.8). The context pre-exposure group had 10 females and nine males, with an average age of 19.7 years (S.D. 1.3). The No-pre-exposure group had 12 females and eight males, with an average age of 20.0 years (S.D. 2.0). The difference in age between groups did not reach statistical significance (ANOVA, $F(2, 57) = 0.72$, $P > 0.05$). For their participation, subjects received credit for an introductory psychology class or were paid at the rate of \$10 for one hour.

Apparatus, Procedure and Data Collection. The apparatus and data collection were the same as those described in Experiment 3. The experimental procedure was the same as in Experiment 3, with the following exceptions. In both phases, the inter-trial interval (ITI) was lengthened from a mean of 20 s to a mean of 30 s (range 27–33 s).

For subjects in the LI group, phase 1 exposure consisted of 30 CS-alone trials. These were identical to the subsequent training trials, except the US was not presented. For subjects in the context group, the exposure phase consisted of a 15-minute period in the experimental apparatus without any CS or US presentation. As an additional control condition, subjects in the no-pre-exposure group did not receive any phase 1 but proceeded directly to phase 2 training.

For all groups, tone-air puff training was shortened to 40 trials, since the previous experiments had demonstrated that most subjects who reached criterion performance did so by this point. Thus, phase 2 lasted approximately 20 minutes, and the overall duration of the experiment (pre-exposure and training phases) was approximately 35 minutes for subjects in the context pre-exposure and LI groups, and approximately 20 minutes for subjects in the no-exposure group (training phase only).

Results

No differences were observed between the Context pre-exposed group and the No-pre-exposure group in terms of either percent CRs (repeated-measures ANOVA, $F(1, 38) = 0.09$, $p > 0.05$) or rate at which criterion was reached (ANOVA, $F(1, 25) = 0.26$, $p > 0.05$). Accordingly, data from these two groups were combined into a single control group.

Conditioned responding for each 10-trial block for subjects in the LI group and combined control groups are shown in Figure 5. All subjects acquired conditioned responses to the tone as training progressed (repeated-measures ANOVA, $F(3, 174) = 27.15$, $P < 0.001$). Subjects in the CS-pre-exposed group exhibited significantly fewer conditioned responses as compared to subjects in the combined Context pre-exposed and No-pre-exposed group ($F(1, 58) = 4.41$, $p < 0.05$). There was no significant group by block interaction ($F(3, 174) = 1.22$, $p > 0.05$).

Discussion

In summary, while there was no difference between subjects in the Context pre-exposure group and No-Exposure group, acquisition of CRs was significantly retarded in the LI group. Thus, latent inhibition was demonstrated.

The results of Experiment 5 were in contrast to Experiments 3 and 4, in which no latent

inhibition effect was obtained. Experiment 5 was constructed to include a longer ITI, which may have reduced the ability of subjects to anticipate upcoming CS (and US) events. Additionally, Experiment 5 involved a shorter CS pre-exposure phase than the earlier experiments. Either or both of these manipulations may have contributed to the observed latent inhibition effect.

General Discussion

Experiment 1 demonstrated a strong learned irrelevance effect in rabbit eyeblink conditioning while Experiment 3 demonstrated a strong learned irrelevance effect in human eyeblink conditioning. In both cases, prior exposure to un-correlated presentations of the CS and US retarded subsequent acquisition of CRs relative to a context pre-exposed control. No latent inhibition effect was observed for either rabbits (Experiment 1) or human (Experiment 3) following the same number of pre-exposures that had produced learned irrelevance. Increasing the number of CS exposures did result in a demonstration of latent inhibition for rabbit eyeblink conditioning (Experiment 2), but not for human eyeblink conditioning (Experiment 4). However, increasing the ITI with the same number of CS pre-exposures as in Experiment 5 did produce latent inhibition in human eyeblink conditioning.

In both the learned irrelevance results of Experiment 1 and 3 and the latent inhibition results of Experiment 2 and 5, the effect of exposure was to retard learning throughout phase 2; in neither case did the exposed group ever reach the same asymptotic performance as the control groups. While this does not necessarily imply that, given extended training, subjects would never have learned the CS-US association, it does imply that the effects of stimulus exposure can be relatively long lasting in this preparation.

A review of prior eyeblink conditioning studies of LI in the rabbit indicates that LI does sometimes result in a lower asymptotic responding (e.g., Romano, 1999; Rogers et al., 2001). However, a previous study of LI from our laboratory did not result in such a deficit (Shohamy et al., 2000). It should be noted that the series of studies by Solomon with LI in rabbit eyeblink conditioning only presented measures of total CRs and did not include learning curves across training sessions (Solomon & Moore, 1975; Solomon, Lohr & Moore, 1974; Solomon, Brennan & Moore, 1974). Therefore the dynamics of CR acquisition across training sessions is unknown for this data set.

LI in rat eyeblink conditioning (Schmajuk et al., 1994) did not report any learning within 500 training trials following the CS in intact rats receiving LI pre-exposure. In this case, LI seems to have completely disrupted the acquisition of CRs, at least within 500 trials.

On a related note, a recent LIRR study in rat eyeblink conditioning also indicates that pre-exposed rats showed lower asymptotic levels of responding (Rush et al., 2001). Therefore in some cases, LI or LIRR produces not only an early retardation of learning, but this deficit in CRs continues until the end of the training session as evidenced by lower levels of asymptotic responding. In the Gluck and Myers (1993) model, this is the indication of LI or LIRR. Not a slower initial learning of the CR, but lower asymptotic responding later on in training. Learning curves in human eyeblink conditioning are much more variable than those observed in rabbit eyeblink conditioning, both in their starting point and in their asymptotes. Tracey et al. (1999) found learning curves that range from about 40–60 percent CR with asymptotic levels of 60–80 percent CR. Solomon (1989) found learning curves starting at about 60 percent CR with asymptotic levels of 90 percent CR. Gabrieli et

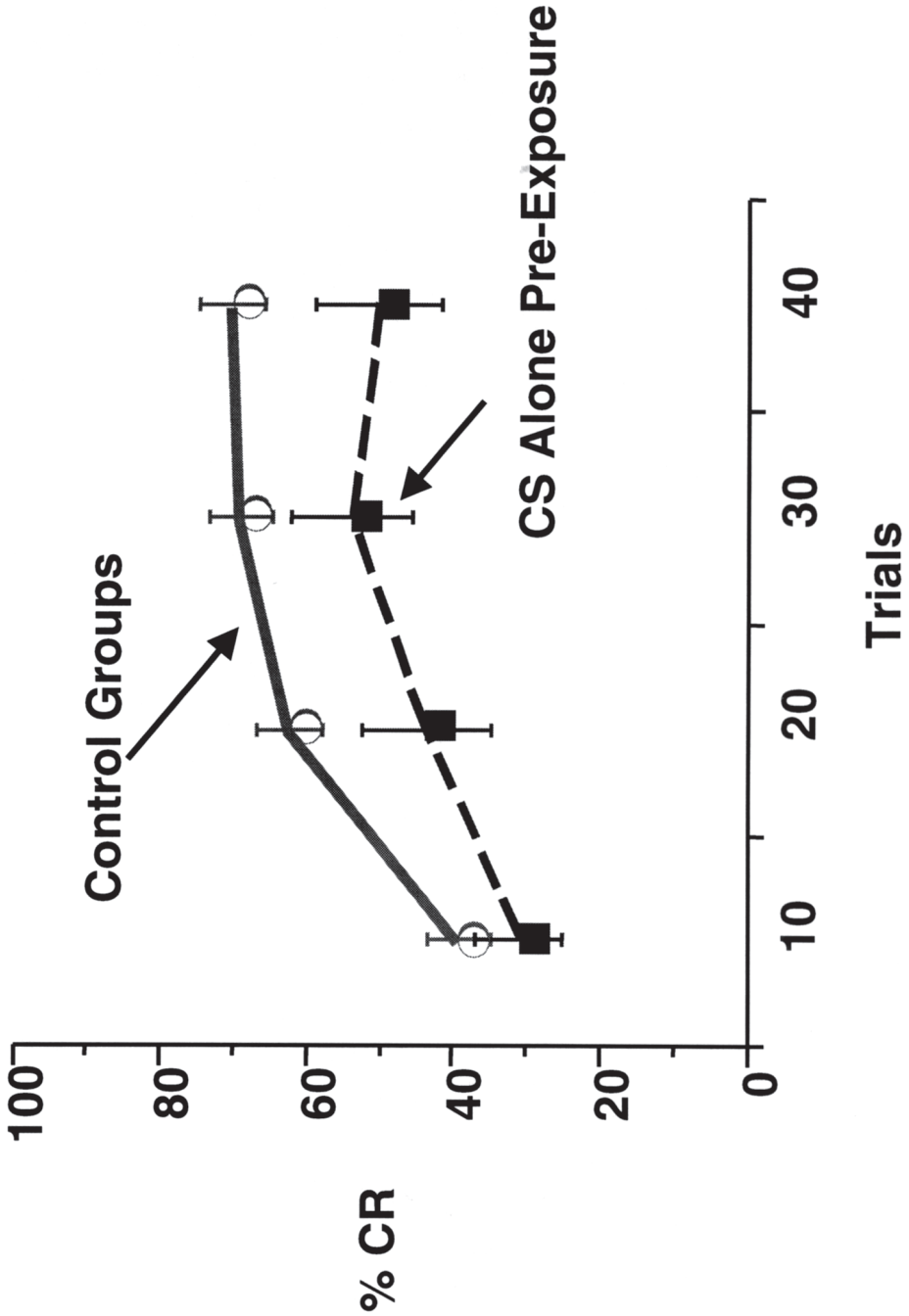


FIG. 5. Behavioral results from latent inhibition with forty CS alone pre-exposures with an extended inter-trial interval (ITI). Subjects pre-exposed to the CS alone (closed circles) exhibited significantly fewer CRs than did context pre-exposed and non-pre-exposed controls (open circles). This pattern of pre-exposure produced latent inhibition in human eyeblink conditioning. Error bars represent standard error of the mean (SEM).

al. (1995) found learning curves starting at 30–40 percent CR and asymptoting at 40 percent CR. Therefore, human eyeblink conditioning overall may result in varied learning curves based on the limited range of percent CRs higher baseline levels of responding and lower and more variable asymptotic levels of conditioned responding overall. The variability and differences in asymptotic learning may not be simply an effect of LI or LIRR pre-exposure effects. Future work should over-train human subjects to see if pre-exposed individuals eventually reach the same levels of responding as controls.

Theorized Mechanisms For Pre-Exposure Effects Support LIRR > LI

Several theories and computational models have been put forth to explain the mechanisms that underlie pre-exposure tasks like LI. Using these established and accepted theories, we are able to interpret our finding that unpaired CS and US pre-exposures (i.e., LIRR) produce a stronger and more disruptive retardation effect than simple CS alone pre-exposures (i.e., LI).

Conditioned attention theory (CAT) put forth by Lubow (1989) states that non-reinforced exposures to a stimulus retard subsequent acquisition of CRs to that stimulus due to the animal learning to not attend to the unreinforced CS. Conditioned attention theory also can account for our finding that CS and US pre-exposure in LIRR results in a more disruptive retardation effect than LI following CS alone pre-exposure. Lubow (1989) says that CAT would predict more profound decremental effect from a non-contingent pre-exposure of the CS and US as compared to that observed following CS alone (LI) pre-exposures. He also explains this through a mechanism based on cue salience. Schnur and Lubow (1976) found that more retardation was found with stronger CSs than with weaker CSs. Lubow (1989), therefore, predicts that the presentation of the more intense and aversive US during un-reinforced pre-exposure with the CS (as in LIRR) would also result in a greater retardation than LI following CS alone presentations.

Gluck and Myers (1993) put forth a computational model that proposes a neural mechanism for LI that can account for the differences between LIRR and LI. Gluck and Myers (1993) proposed a hippocampal region mechanism that can account for the LIRR and LI pre-exposure effects as well as the robustness of LIRR as compared to LI. The Gluck and Myers (1993) model proposes that the hippocampus forms stimulus representations during learning. One mechanism that is used in forming stimulus representations is termed redundancy compression in which a single representation for two stimuli is formed when the two stimuli either co-occur or predict the same behavioral outcome.

In the case of LI pre-exposure, the CS and context co-occur with no behavioral outcome. Therefore, the CS and context are compressed into a single representation. Later in training, when the CS must be differentiated from the context as the predictor for the US, this compression must be uncompressed. Therefore, animals that had undergone CS pre-exposure are slower to learn the CS predicts the US than context pre-exposed controls.

In the case of LIRR, the CS and the US both co-occur with the context but not in temporal proximity to each other. Therefore, during LIRR pre-exposure the CS and the context are compressed and the US and context are compressed, but the CS and US are not compressed together. If the CS and US were compressed during LIRR pre-exposure, then one would expect LIRR pre-exposure to result in a facilitation of CS-US learning since the association was formed prior to training. Therefore, to overcome the effects of LIRR pre-exposure, both the CS and the US must be uncompressed from the context in order to form the CS-US association. It is interesting to note in the simulations of LIRR and LI from the

Gluck and Myers model that LIRR pre-exposure produces a larger retardation effect than LI because learning following pre-exposures to the CS and the US requires more de-compression than pre-exposure to the CS alone.

A hippocampal model put forth by Schmajuk et al. (1996) and Buhusi et al. (1998) proposed that pre-exposure effects like LI are due to a different mechanism based on novelty. Novelty in their models is much like the idea of error correction in the Rescorla-Wagner model (i.e., the difference between the expected US and the actual presentation of the US). In their model, the fastest learning occurs when novelty is high, and slower learning occurs when novelty is low. Therefore, when the CS is not novel (i.e., following CS pre-exposure) CS-US learning is slower.

If this idea of novelty is applied to LIRR and LI, it predicts that LIRR will be more disruptive than LI. Following context pre-exposure, both the CS and US are novel but the context is not novel at the start of the training phase. Therefore, learning should be rapid. Following CS-pre-exposure, only the US is novel at the start of the training phase (i.e., subjects already experienced the CS and context in pre-exposure). Therefore learning should be slower as compared to context-pre-exposed controls. However, following un-correlated CS and US pre-exposures, subjects have been pre-exposed to the context, the CS, and the US, and the only novelty at the start of training is the pairing of the CS and the US. Therefore, LIRR results in less novelty and slower training as compared to both context-pre-exposed and CS pre-exposed subjects.

A related theory based in part on the mechanism of Schmajuk and Moore's (1988) attentional-associative model is the switching theory of Weiner and Feldon (1997). This model proposes that LI effects are based on mechanisms and interactions between the hippocampal system and the nucleus accumbens (NAcc). The switching theory proposes that retardation following CS alone pre-exposures occurs because there is a conflict between the non-reinforced presentations of the CS during pre-exposure and the same cue being reinforced in training. In pre-exposure the animal learns that the CS predicts no event, but in training must learn that the US is predicted by the CS. We can interpret the switching model as fitting with our finding that LIRR is more disruptive than LI. This is due to the fact that there would be less associability between the CS and the US following LIRR since the animal has explicitly learned that the CS and US occur separately. The animal would learn that the CS signals no event and that the US occurs with no signal. This would lead to a lower associability than that due to learning that the CS signals no event.

Overall, we can support our interpretation that LIRR following un-correlated CS and US pre-exposures is a more disruptive retardation effect than LI with a variety of established mechanisms of LI. These mechanisms include the conditioned attention theory (Lubow, 1989), compression of stimulus representations (Gluck & Myers, 1993), novelty (Schmajuk et al., 1996) or the switching model (Weiner & Feldon, 1997).

Recent studies with a computer-based version of latent inhibition and learned irrelevance have found similar retardation effects in humans. The computer-based version of learned irrelevance in which the CS and US are pre-exposed produced a strong pre-exposure effect (Myers, Oliver et al., 2000), the exact same task with only the CS pre-exposure fails to produce a latent inhibition effect (Myers, Ermita et al., 1996). This finding fits perfectly with the rabbit and human eyeblink conditioning results reported in this paper. However, these computer-based versions may not be directly comparable to classical conditioning paradigms, since they involve voluntary responding and a "reward," which is not a reflex-evoking unconditioned stimulus like the air puff US in eyeblink

conditioning. Therefore, it would be important to relate animal and human studies using the same behavioral paradigm, and eyeblink conditioning is a good candidate.

Overall, it appears that for eyeblink conditioning in both rabbits and humans, learned irrelevance following CS and US pre-exposures is a more disruptive and producible retardation effect than latent inhibition in which only the CS alone is pre-exposed. This interpretation of LIRR being more disruptive than LI is supported by various established theories and models that have accounted for the basic phenomenon of LI. It may be more beneficial in future studies of pre-exposure tasks and the effects of lesions in animals and brain pathologies in humans to use the learned irrelevance paradigm over the more commonly used but less reliable paradigm of latent inhibition. Future work should study the differences in LI and LIRR based on context and other manipulations of trial parameters.

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