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Effect of a retention interval between pre-exposure and conditioning on latent inhibition in humans using a blink conditioning procedure

Luis Gonzalo De la Casa Rivas, Luis Miguel Traverso Arcos and Raúl Márquez Zamora
Universidad de Sevilla

Latent inhibition, retarded learning after pre-exposure to the to-be-conditioned stimulus, was examined using a blink conditioned procedure in humans. Experiment 1 showed that the procedure is suited to inducing the latent inhibition effect. In Experiment 2, the introduction of a 3-minute interval between pre-exposure and conditioning phases attenuated latent inhibition. These results contribute to identify the mechanisms involved in pre-exposure and subsequent conditioning of a stimulus, which is particularly important if we bear in mind that latent inhibition has been used repeatedly as an instrument to analyze the course of attentional processes in normal and pathological populations.

Efecto de un intervalo de retención entre la preexposición y el condicionamiento sobre la inhibición latente en humanos con un procedimiento de condicionamiento palpebral. El fenómeno de la inhibición latente se refiere al retraso que se observa cuando se presenta repetidamente sin consecuencias un estímulo que va a ser posteriormente condicionado. En este trabajo empleamos un procedimiento de condicionamiento palpebral para analizar la inhibición latente en participantes humanos. El Experimento 1 reveló que el procedimiento empleado era adecuado para reproducir el efecto de inhibición latente. En el Experimento 2, la introducción de un intervalo de tres minutos entre las fases de preexposición y condicionamiento dio lugar a la atenuación de la inhibición latente. Estos resultados contribuyen a la identificación de los mecanismos que participan en la preexposición y posterior condicionamiento de un estímulo, aspectos particularmente importantes si tenemos en cuenta que el fenómeno de la inhibición latente ha sido utilizado repetidamente como un instrumento para analizar el curso del proceso atencional tanto en poblaciones normales como con determinadas psicopatologías.

When a neutral stimulus is presented without consequences and subsequently paired with an Unconditioned Stimulus (US), the Conditioned Response (CR) to the preexposed stimulus is weaker than it is to a novel Conditioned Stimulus (CS) at time of conditioning. This phenomenon, termed Latent Inhibition (LI), seems to be at the basis of efficient stimulus selection, by allowing correct differentiation between relevant and irrelevant stimuli. LI has important implications for the study of attentional, memory, and associative processes, both from psychological and psychophysiological perspectives (e.g., Bouton, 1993; Lubow, 1989; Weiner, 1990), and it has been used as the basis of an animal model of schizophrenia (see, for a review, Lubow, 2005). LI is normally obtained in controlled conditions at the animal learning laboratory by programming two (pre-exposure and conditioning) or three (pre-exposure, conditioning, and testing) stages. In a typical two-stage situation, a pre-exposure phase involves repeated presentations of the to-be-CS without any relevant consequence. At conditioning, the preexposed stimulus is paired with an US and the course of conditioning is compared with learning involving a non-preexposed CS. In the three-stage situation, the CR to the preexposed and conditioned CS is compared with the CR to a CS that was new at the time of conditioning in an additional test stage.

The evidence for LI comes mainly from experiments with non-human participants, while there are relatively few studies conducted with human participants (see Lubow, 1989 for a review). Besides, experiments with non-human animals have usually employed classical conditioning techniques, such as fear conditioning (e.g., Weiner, Lubow, & Feldon, 1988), appetitive conditioning (e.g., Rosas & Bouton, 1997), or conditioned taste aversion (e.g., De la Casa & Lubow, 2000), but almost all experiments with humans have used operant discriminative tasks (e.g., Zalstein-Orda & Lubow, 1995) or rule learning tasks (e.g., Pineño, De la Casa, Lubow, & Miller, 2006). Thus, the differences between the procedures employed in non-human and human experiments make it difficult to assert that the mechanisms governing LI observed in experimental conditions are the same for non-humans and humans (see, for instance, Graham & McLaren, 1998).

In addition to the differences in experimental procedures, several theories have been developed that offer different explanations of LI. One view proposes that LI is the result of an *acquisition failure* at conditioning due to a reduction in the attention or the associability to the CS developed during pre-exposure (e.g., Lubow, 1989; Pearce & Hall, 1980). Conversely, the *retrieval*

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Correspondencia: Luis Gonzalo De la Casa Rivas
Facultad de Psicología
Universidad de Sevilla
41018 Sevilla (Spain)
e-mail: delacasa@us.es

failure view of LI considers that conditioning carries on as normal despite pre-exposure, and that the apparent retardation of the CS-US association is the result of interference between competing memories at testing. From this perspective, LI is seen as the result of a retrieval failure at testing rather than an acquisition failure (e.g., Bouton, 1993; Miller, Kasprow, & Schachtman, 1986).

The main evidence supporting the acquisition failure hypothesis of LI comes from a set of data obtained in experiments with rats when a retention interval is introduced between pre-exposure and conditioning or between conditioning and testing phases in a LI experiment. Specifically, when the delay is inserted between conditioning and testing stages it either attenuates LI (e.g., Aguado, Symonds, & Hall, 1994), or induces a super-LI effect (e.g., De la Casa & Lubow, 2000), depending on *where* the organism spends the delay (Lubow & De la Casa, 2005). From the acquisition failure perspective, the reduced conditioning to the preexposed CS cannot just be attributed to the passing of time, so these results are entirely unexpected and represent a crucial shortcoming for this hypothesis. However, although not explicitly predicted by the retrieval failure perspective, the changes in LI induced by a delay can be accommodated to this perspective if we consider that the retention interval may modulate the CR intensity acquired during the conditioning stage. This may occur, for instance, by way of a change of context between pre-exposure and conditioning, a manipulation that impairs LI, and which is induced by temporal factors (Bouton, 1993).

There are also studies with non-human animals that have varied the delay between pre-exposure and acquisition stages, but the results from such experiments are far from consistent. Specifically, using a conditioned taste aversion procedure, Aguado et al., (1994, Exp. 3) found attenuation of LI after a 12-day delay, but De la Casa and Lubow (2002, Exp. 3) reported intact LI after a 21-day delay. On the other hand, De la Casa & Timberlake (2006, exp. 2), using a maze discrimination task, found disrupted LI after a 21-day delay. Rosas and Bouton (1997), using an appetitive conditioning procedure and a 28-day delay, obtained intact LI in Exp. 1, but attenuated LI in Exp. 2, without any apparent procedural difference between the experiments. Finally, De la Casa & Lubow (2001, exp. 4) reported a loss of LI using a reaction time-based LI procedure with humans when a 15 min delay was introduced between pre-exposure and conditioning stages. However, the fact that the differences came mainly from the non-preexposed groups makes it difficult to reach a clear conclusion over this experiment.

One possible way of breaching the gap between non-human and human LI research is by employing a methodology that reproduces with humans the same processes that appear in classical conditioning experiments with non-human animals. We have selected the Blink Conditioning (BC) procedure because it involves a simple instance of associative learning that allows organisms, including human beings, to learn about the relationship between environmental stimuli (Rescorla, 1988). The BC procedure has a long history in experimental psychology, and has recently been recovered as a very adequate tool for analyzing information processing in healthy and pathological human populations (e.g., Steinmetz, Gluck, & Solomon, 2001).

Unlike other procedures commonly employed in human LI research, BC is not contaminated by motivational or attentional factors and it has already been successfully used to generate LI in humans (e.g., Schnur, & Ksir, 1969). Some additional advantages of this procedure are related to its adaptation to pathological populations (see, for instance, Hofer, Doby, Anderer, & Dantendorfer, 2001), or the detailed knowledge of the neurophysiological basis of BC both in non-human animals (e.g., Thompson, Thompson, Kim, Krupa, & Shinkman, 1998) and in humans (e.g., Thompson & Krupa, 1994).

Therefore, the main objectives of this research were to develop a reliable BC procedure to generate LI in humans, and to evaluate the effect of a retention interval introduced between pre-exposure and conditioning stages on LI intensity. To this end we conducted two experiments. In both of them, the to-be-CS (a tone or a white noise, counterbalanced) was presented without consequences 30 times before proceeding to differential conditioning. The conditioning procedure involved CSA+ and CSB- alternated presentations, with the US being an airpuff directed to the left eye of the participant. For Experiment 1, the interval between the last pre-exposure trial and the first conditioning trial was 10 sec. In Experiment 2 the delay was 10 sec. (No delay condition) or 180 sec. (Delay condition). During the experimental session participants watched a silent movie that acted as a masking task, a condition to obtain LI in humans with the blink conditioning procedure (Lubow & Gewirtz, 1995). The masking task seems to divert controlled from automatic processing in such way that controlled attention to the masking task would allow automatic processing of the preexposed stimulus. Such automatic processing would result in a decline in attention responsible of the low level of processing of the preexposed stimulus at conditioning stage (Lubow & Gewirtz, 1995, but see Escobar et al., 2003).

Experiment 1

Some attempts have been made to reproduce the LI effect in humans with the BC procedure, but with mixed results (see, for instance, Schnur & Ksir, 1969; Pelmutter, 1966). Thus, our first objective was to induce a clear LI effect using the BC procedure. To this end, we employed a differential conditioning procedure that has been shown to support a strong blink conditioning response in previous research (e.g., Smith, Clark, Manns, & Squire, 2005). By introducing a group that received pre-exposure to the to-be-CS prior to conditioning, we expected to obtain retardation in learning compared to a group without experience of the CS prior to conditioning (the non-preexposed group).

Method

Participants

20 students from the University of Seville (Spain) participated in this experiment (4 male and 16 female, age range 18-34). The participants were recruited by advertisements at different faculties. Each subject was paid 5 € for participating in the experiment. All procedures and protocols had been approved by the Seville University Ethical Committee.

Apparatus and procedure

At the reception in the laboratory, each participant was told that the experiment was designed to analyze the effects of distraction on learning and memory, and that they would be distracted by different stimuli as noises or tones while they were seeing a silent film. After signing informed consent, each participant was seated

approximately 0.7 m from a 14" screen and the examiner fitted him/her with the eyeblink apparatus, consisting in an eyewear unit and headphones (San Diego Instruments**,** San Diego, CA). The apparatus included a control unit, which consisted of a PC computer and an EBC chassis containing the stimulus and response modules. The ECB/WIN software (San Diego Instruments**,** San Diego, CA) controlled stimuli presentation and response recording. The experimenter remained in the same room, out of the direct view of the participant. The participants were instructed to view a silent film (*The Kid* by Ch. Chaplin) on the screen during the entire duration of the experiment.

The procedure comprised three stages: Acclimation period, pre-exposure, and conditioning. The acclimation period lasted 2 min and intended to habituate each participant with the eyeblink apparatus employed to present the stimuli and to record the blink responses. The pre-exposure phase consisted for the Preexposed (PE) group in 30 presentations of a tone or a white noise (counterbalanced) without the US. The intertrial interval varied for this and the subsequent stages and was a 10 sec (+/- 5 sec). Those participants in the Non-Preexposed (NPE) group did not receive the to-be-CS presentations, but remained the same time that their counterparts in the experimental situation. The conditioning stage, similar for all participants, consisted of 8 blocks of 8 trials (4 CS+ trials and 4 CS- trials per block), and started 10 sec after the last pre-exposure trial or the equivalent time for the participants in the NPE group. On each block, the CS+ and CS- were presented following an ABBA BAAB sequence. The CS+ and CS- were a 800-ms, 72-db, 1000 cps tone, and a 800-ms, 84-db, 1000 cps white noise, respectively. Both stimuli were counterbalanced within each group and were delivered to the left ear through the headphones. The US was an 80-ms corneal airpuff with an intensity of 9-psi delivered to the inner canthus of the left eye via a specially designed eyewear unit that included an infrared photobeam element for recording eyeblink (San Diego Instruments Systems). Responses were automatically classified as alpha, conditioned or unconditioned responses by the Eyeblink Special Analysis software using standardized response evaluation protocols.

Data analyses

Two ANOVAs were performed on mean percentage of CR at conditioning stage, and on an index of conditioning at test stage (percentage of CR to the CS+ minus percentage of CR to the CS-) in order to detect the effect of preexposure and a possible interaction with block of trials. The SSPS 15.0 version was used for all data analyses.

Results and discussion

Mean percentage of CR to the CS+ collapsed across conditioning trials for the NPE and the PE groups was 78.44% (SD= 12.1), and 23.75 % (SD= 27.05), respectively. The difference was statistically significant, $F(1,18)=34.06$; $p<.001$, revealing the expected LI effect.

In order to identify whether blink conditioning and the predicted LI effect was specific to the conditioned stimulus we computed an index of the difference between CR to the CS+ and CR to the CS- at conditioning (percentage of CR to the CS+ minus percentage of CR to the CS-), that produced 8 blocks of 4 trials each. Figure 1 shows mean percentage of differential CR for each block of 4 trials as a function of pre-exposure. As can be seen in the figure, conditioning was evident across trials for the NPE group, but it was clearly reduced in the PE group (the predicted LI effect).

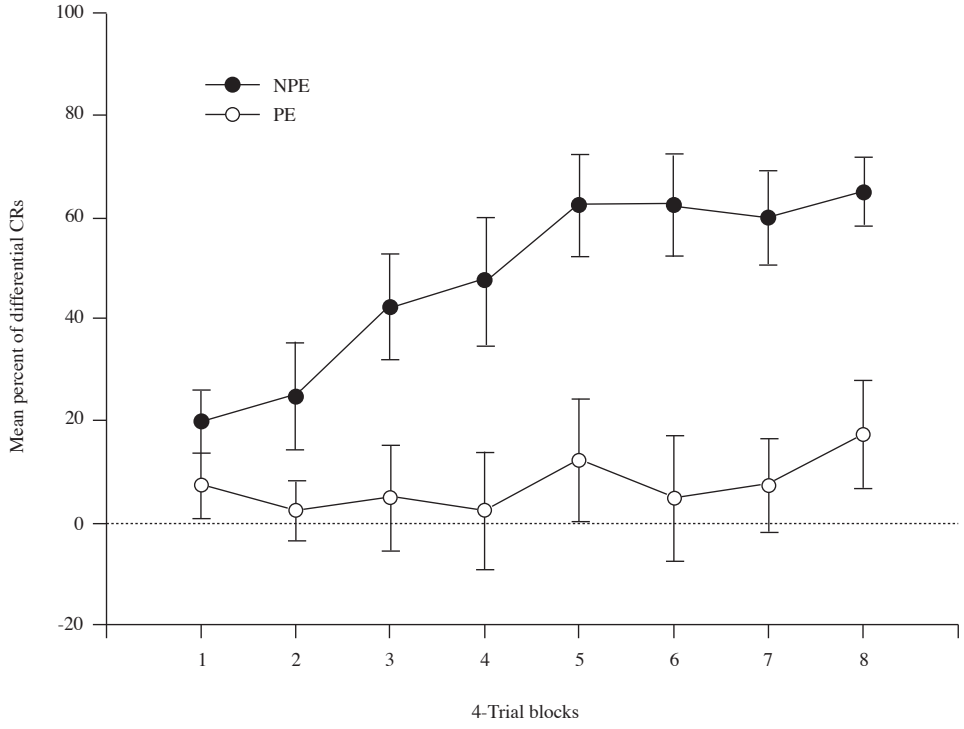

Figure 1: *Mean percentage of differential conditioned responses (percentage of conditioned responses to the CS+ minus percentage of conditioned responses to the CS-) collapsed across 4-trial blocks as a function of Groups. NPE: Non-Preexposed; PE: Preexposed. Error bars represent standard error of the mean*

This impression was confirmed for a 8 × 2 mixed ANOVA (Blocks × Pre-exposure) that showed a significant effect of Blocks, $F(7,126)= 3.23$, $p<.001$, due to the progressive increase in the differential CRs across blocks of trials. The effect of Pre-exposure was also significant, $F(1,18)= 40.57$, $p<.001$. As can be seen in Figure 1, the difference between the NPE and the PE groups emerged from the second trial. Finally, the Blocks x Group interaction was non-significant, $F(7,126)= 1.81$; $p>.09$. In general, the results reveal that the parameters employed in this experiment produced a robust blink conditioning in the NPE group to the reinforced CS, and that exposure to the CS before conditioning resulted in a strong LI effect.

Experiment 2

Experiment 2 evaluated the effect of introducing a retention interval between pre-exposure and conditioning using the blink conditioning procedure described for Experiment 1. This manipulation is theoretically relevant if we look at the different predictions derived from the acquisition failure and the retrieval failure views of LI. Specifically, the acquisition failure hypothesis does not predict any change in LI when a delay is introduced between pre-exposure and conditioning. Conversely, from the retrieval failure perspective, the passing of time can be considered as functionally equivalent to a change of context (Bouton, 1993), a manipulation that consistently disrupts LI (e.g., Hall & Channell, 1986).

In this experiment we used three groups, two of them similar to the PE and NPE groups from Experiment 1 (for which we expected to replicate the LI effect). The third group received the same treatment as the PE group, but a 180 sec. interval was introduced between the last pre-exposure and the first conditioning trial (PE/DEL group). Due to the nature of the procedure for the NPE group, that involved approximately 324 sec without stimulus presentation other than the silent film before conditioning stage, we decided to run only a NPE group similar as that described in Experiment 1 as a valid control for both PE groups, assuming than adding 180 sec to the pre-exposure stage would not alter normal blink conditioning. The 180 sec interval for the PE/DEL group was selected for practical reasons after some pilot experiments revealing that 5 min, 30 min, or 60 min delays did not induced any stronger effect on LI. For this group the predictions are not clear: As far as we know, the evidence of similar manipulations (a retention interval introduced between pre-exposure and conditioning) with humans is limited to one experiment (De la Casa & Lubow, 2001, exp. 4) that used a discriminative trials-to-criterion procedure, and that reported a complete loss of LI due to changes in the NPE group. However, as mentioned in the introduction section, the evidence from non-human animal research is far from consistent, with some experiments producing attenuated LI, while others showed no effect.

Method

Participants

27 students from the University of Seville participated in this experiment (6 male and 21 female, age range 19-27). As described for Experiment 1, the participants were recruited by mean of advertisements and were paid 5 € each for participating in the experiment. All procedures and protocols were approved by the Seville University Ethical Committee.

Apparatus and procedure

The apparatus and procedure were exactly the same as described for Experiment 1, with the following exception: For the PE/DEL group the interval between the end of the pre-exposure and the start of conditioning stage was 180 sec. For groups NPE and PE the treatment was the same received for NPE and PE groups in Experiment 1 (i.e., the interval between Pre-exposure and Conditioning stages was 10 sec). Those participants in the DEL group spent the 180 sec. interval attending to the film, without any additional instruction or stimuli, thus maintaining the same conditions than the groups without the delay.

Data analyses

As in Experiment 1, two ANOVAs were conducted on mean percent of conditioning responses and on an index of conditioning (percentage of CR to the CS+ minus percentage of CR to the CS-) to detect effects of groups and a possible interaction with blocks of trials. To identify differences between groups at testing, *post hoc* analysis (Tukey tests, $p<.05$) were employed. The SSPS 15.0 version was used for all data analyses.

Results and discussion

Mean percentage of conditioned responses to the CS collapsed across conditioning trials for the NPE, PE and PE/DEL groups was 74.31% (SD= 14.72), 34.72% (SD= 32.90), and 62.50% (SD= 21.19), respectively. An ANOVA with Group as the main factor revealed a significant main effect, $F(2,24)= 6.23$; $p<.01$. This effect was explored using *post-hoc* analysis (Tukey tests). The non-reinforced presentations of the to-be-CS were effective in disrupting conditioning (the LI effect) for the PE group, that was significantly different from NPE group, and marginally different from PE/DEL group ($p= .056$). The difference between NPE and PE/DEL was non-significant.

A more exact index of conditioning and LI can be expressed through a differential score computed by subtracting percentage of CR to the CS- to percentage of CR to the CS+. Figure 2 depicts mean percentage of differential CR collapsed across 4-trial blocks for the NPE, PE and PE/DEL groups. As can be seen in the Figure, differential conditioning was evident for the NPE and PE/DEL conditions, but it was less evident for the PE group, revealing that the LI effect was attenuated by the retention interval. An 8 x 3 mixed ANOVA (Blocks × Group) showed a significant main effect of Blocks, $F(7,168)= 6.47$, $p<.001$, due to the progressive increase in the differential CRs across blocks of trials. The effect of Group was also significant, $F(2,24)= 5.25$, $p<.05$. In order to identify the differences between groups, *post hoc* analysis (Tukey tests) were conducted on these data. The results indicated that the LI effect appeared only for the PE group which was significantly different from NPE and PE/DEL groups. There were no significant differences between the NPE and the PE/DEL groups, that indicates that the LI effect was abolished by the 180 sec delay introduced between pre-exposure and conditioning stages. Finally, the Blocks × Group interaction was non-significant, $F(14,148)= 1.14$; $p>.32$.

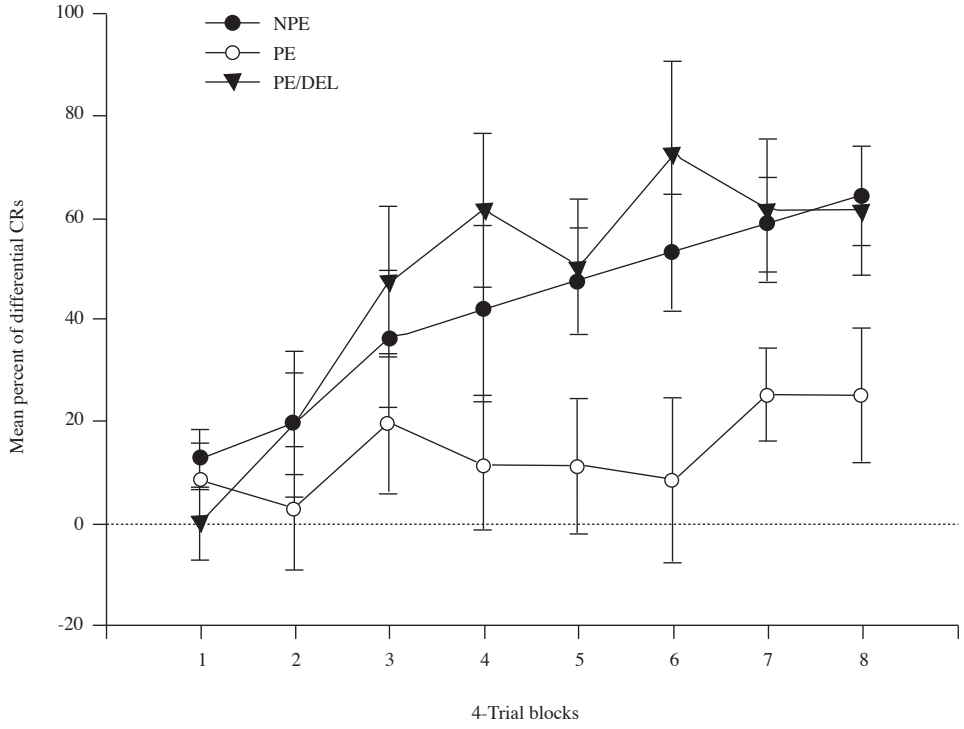

Figure 2: *Mean percentage of differential conditioned responses (percentage of CRs to the CS+ minus percentage of CRs to the CS-) collapsed across 4-trial blocks as a function of Groups. NPE: Non-Preexposed; PE:Preexposed; DEL: Delay. Error bars represent standard error of the mean*

General discussion

The present results revealed that exposure to the to-be-CS retarded blink conditioning (Experiments 1 and 2), but only when pre-exposure and conditioning stages were conducted without any apparent delay. However, when a 180 sec delay was introduced between pre-exposure and conditioning, LI was clearly disrupted. Such a result has been previously observed with human participants (De la Casa & Lubow, 2001), but using a very different procedure which makes it difficult to compare with the results from animal research. Thus, our experimental results add new data to the complex panorama of results from those LI experiments that have introduced a delay between the pre-exposure and conditioning stages.

An additional contribution of this study comes from the similarities between the blink conditioning procedure and those classical conditioning paradigms commonly used in animal research. Conversely, almost all LI experiments in the literature with human participants have used rule learning or operant discrimination tasks. Therefore, the proposal of a reliable classical conditioning procedure for inducing LI in humans is an important contribution in itself.

The results from Experiment 2, in which a 180 sec. interval inserted between the last pre-exposure and first conditioning trials made the LI effect disappear, may be explained from different theoretical perspectives. For example, Escobar, Arcediano and Miller (2003) argue that any type of manipulation allowing participants to differentiate between pre-exposure and conditioning stages (be this the result of instructions, a new task, a time interval or a novel stimulus) will allow them to differentiate between the two experimental stages. This differentiation would encourage the interpretation of the conditioning stage as a new situation and, therefore, the information learnt during pre-exposure would not be applied in the new situation, with the association between CS and US being established as normal. This interpretation is compatible with the assumption that inserting a delay would induce a differentiation between pre-exposure and conditioning contexts, a difference that produces the attenuation of LI (see, for example, Hall & Channell, 1986). This is precisely the view defended by Bouton (1993), whereby the representation of the context would change with the passing of time, so that the insertion of the delay after pre-exposure would explain the differentiation between the pre-exposure and conditioning stages that Escobar et al., (2003) propose to explain LI attenuation.

To determine whether those processes that generate LI in non-human and human experiments are similar is an essential objective bearing in mind the relevance of LI as an animal model for analyzing the antipsychotic action of some drugs (e.g., Weiner, Gaisler, Schiller, Green, Zuckerman, & Joel, 2000), or its role as a tool for evaluating an animal model of schizophrenia (e.g., Kathmann, von Recum, Haag, & Engel, 2000). More specifically, LI has been considered as a tool to analyze attentional process to irrelevant stimuli in both pathological and normal populations (see, for a review, Lubow, 2005).

The interest for identifying the structures and physiological processes responsible of LI developed during the last two decades gave rise to an influential hypothesis according to which the dopaminergic system is essential to regulate the attentional processes underlying LI (see, for example, Weiner & Feldon, 1997). These studies stimulated the interest in the analysis of LI in human populations with dysfunctions affecting to the dopaminergic system, such as in schizophrenic patients (for example, Gray, Hemsley, & Gray, 1992), hyperactive children (Lubow & Josman,

1993) or Parkinson patients (Lubow, Dressler, & Kaplan, 1999). The study of the alterations in the processing of irrelevant stimuli in schizophrenics has led to a psychological model that considers an attentional deficit as responsible of some symptoms of this illness (see, for example, Hemsley, 1987). Those results supporting the dopaminergic hypothesis of LI in schizophrenics have demonstrated the reduction of LI in schizophrenic patients (e.g., Gray, Hemsley & Gray, 1992; Gray, Pilowsky, Gray, & Kerwin, 1995). Of special interest is the research that revealed poorer blink conditioning in medicated schizophrenics as compared to healthy subjects (e.g., Hofer et al., 2001), but better blink conditioning in non-medicated patients (e.g., Sears, Andreasen, & O'Leary, 2000). These results give ground to the use of the blink conditioning procedure as a tool to check the effect of preexposure in schizophrenic patients, and to analyze possible interactions between LI, schizophrenia and medication status (see, for a review, Lubow, 2005).

The research on LI developed with pathological populations has considered a disrupted attentional response to the preexposed stimulus as the source of the retarded learning. Therefore, the implicit assumption has been that LI in humans is the result of an acquisition deficit at conditioning. However, some researchers have tried to integrate the results of the experiments on LI with schizophrenic patients with the hypothesis that considers LI as the result of a retrieval failure at testing (Oberling, Gosselin, & Miller, 1999). Bearing in mind the implications of LI for understanding learning and attentional processes in schizophrenics, we believe that the identification of the mechanisms governing LI in normal humans should become a priority before any other models are developed to explain the dysfunction in the processing of information in schizophrenics.

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