Psicothema

Effects of temporal contexts and contextual habituation on latent inhibition

Andrés Molero-Chamizo[1] and G. Nathzidy Rivera-Urbina[2]
[1] University of Granada and [2] Autonomous University of Baja California (México)

Abstract

Background: Latent inhibition of conditioned taste aversion (CTA) is sensitive to external and internal cues. Time of day can serve as an internal cue, and latent inhibition may be reduced if the pre-exposure and conditioning stages occur at different times of day. This contextual cue attributed to a change in the time of day may reveal a temporal specificity of latent inhibition. Although the habituation period to spatial contexts is a determinant variable for the spatial specificity of latent inhibition of CTA, the influence of contextual-temporal familiarity (time of day) on latent inhibition of CTA has not been explored through direct comparisons between different periods of habituation to the temporal context. **Method:** Two different periods of contextual habituation (short vs. long) previous to taste pre-exposures were compared in Wistar rats to analyze the influence of these periods on the temporal specificity of latent inhibition of CTA. **Results:** A long period of habituation, in relation to a short period, facilitated the effect of a change of the time of day between pre-exposure and conditioning on the magnitude of taste aversion. **Conclusions:** A long habituation to temporal contexts facilitates the temporal specificity of latent inhibition of CTA.

Keywords: Conditioned taste aversion, contextual habituation, latent inhibition, rats, temporal context.

Resumen

Efectos de contextos temporales y habituación contextual sobre inhibición latente. **Antecedentes:** la inhibición latente del aprendizaje aversivo gustativo (AAG) es sensible a claves externas e internas. La hora del día puede actuar como una clave interna, y la inhibición latente puede ser reducida si pre-exposición y condicionamiento ocurren a diferentes horas del día. Esta clave contextual atribuida a un cambio en la hora del día puede revelar una especificidad temporal de la inhibición latente. Aunque el período de habituación a contextos espaciales es determinante para la especificidad espacial de la inhibición latente del AAG, la influencia de la familiaridad contextual-temporal (hora del día) sobre la inhibición latente del AAG no ha sido explorada mediante comparaciones directas entre diferentes períodos de habituación al contexto temporal. **Método:** en ratas Wistar se compararon dos diferentes períodos de habituación contextual (corto versus largo) previos a pre-exposiciones gustativas para analizar la influencia de éstos sobre la especificidad temporal de la inhibición latente del AAG. **Resultados:** un largo período de habituación, en relación con uno corto, facilitó el efecto de un cambio de la hora del día entre pre-exposición y condicionamiento sobre la magnitud de la aversión gustativa. **Conclusiones:** una larga habituación a contextos temporales facilita la especificidad temporal de la inhibición latente del AAG.

Palabras clave: aprendizaje aversivo gustativo, contexto temporal, habituación contextual, inhibición latente, rata.

Conditioned taste aversion (CTA), that is, an acquired aversion to a taste stimulus (or more than one) after its association with gastrointestinal malaise, is an adaptive learning that facilitates the survival of many species (Bernstein, 1999; Lubow, 2009). It has been shown that previous exposures of the taste stimulus without negative consequences before conditioning reduce the magnitude of the acquired taste aversion (Best, 1975). This reduced conditioned response derived from the effect of pre-exposures is known as latent inhibition, and it seems to be a mechanism that allows organisms to attenuate responses to possibly inconsequential stimuli (De la Casa & Lubow, 1995;

Lubow & Weiner, 2010; Schmajuk, Lam, & Gray, 1996). An animal model used to study both phenomena is the rat (Pearce & Bouton, 2001). Furthermore, in this species external cues may modulate the magnitude of CTA (Boakes, Elliot, Swinbourne, & Westbrook, 1997; Bonardi, Honey, & Hall, 1990; Bouton, 1993; González, García-Burgos, & Hall, 2012; Innis & Mills, 1985) and latent inhibition of CTA (Hall & Channell, 1986). However, knowledge of the role of temporal contexts, such as time of day of conditioning (Manrique, Gámiz, Morón, Ballesteros, & Gallo, 2009; Manrique, Molero, Ballesteros, Morón, Gallo, & Fenton, 2004), and the specific function of the habituation to temporal contexts or familiarity of these contexts (Quintero, Díaz, Vargas, Schmajuk, López, & De la Casa, 2011) on the latent inhibition of CTA is scarce.

The concept of temporal specificity of latent inhibition refers to the fact that the magnitude of latent inhibition can be controlled by the contextual-temporal cues included in the behavioral procedure. It has been described temporal specificity

of the CTA retrieval (Morón, Manrique, Molero, Ballesteros, Gallo, & Fenton, 2002) and temporal specificity of latent inhibition of CTA (Molero, Morón, Ballesteros, Manrique, Fenton, & Gallo, 2005; Molero-Chamizo, 2013), but the direct effect of different periods of contextual habituation on the temporal specificity of latent inhibition of CTA is unknown. More specifically, the differential involvement of long versus short periods of habituation to the time of day of taste exposures in the temporal specificity of latent inhibition of CTA has not been studied consistently.

In order to explore the possible effects of contextual habituation on the temporal specificity of latent inhibition of CTA, two different periods of temporal-contextual habituation were compared. According to the proposed role of contextual familiarity on latent inhibition (De la Casa & Lubow, 2001; Hall & Channell, 1986; Morón et al., 2002; Rudy, Rosenberg, & Sandell, 1977), the effect of a long period of temporal-contextual habituation (nine days) on the temporal specificity of the latent inhibition of CTA was compared with that of a short period (two days). The time of day between taste pre-exposure and conditioning was changed in some animals, which was considered to be different temporal contexts. The effect of this change on the magnitude of taste aversion was compared with the typical latent inhibition of pre-exposed groups without temporal-contextual changes and with non-pre-exposed groups. Under these conditions, the groups in which pre-exposure, conditioning and testing are performed in the same temporal context should have a reduced conditioned taste aversion (ergo, latent inhibition) compared to non-pre-exposed animals. However, temporal specificity of the latent inhibition implies that a different time of day for the conditioning session may interfere with this phenomenon. Given the influence of prolonged periods of habituation to physical contexts on conditioning (Bouton, Westbrook, Corcoran, & Maren, 2006; Escobar, Arcediano, & Miller, 2002; Quintero et al., 2011; Rosas & Bouton, 1997; Todd, Winterbauer, & Bouton, 2012), it is expected that a long period of habituation to temporal contexts may also facilitate the temporal specificity of latent inhibition of CTA.

Method

Participants

Seventy-nine adult male Wistar rats, weighing between 280-300 g, were individually housed in boxes measuring 30 cm × 15 cm × 30 cm. All of the animals were exposed to a daily 12 hours light-dark cycle (lights on from 9:00 to 21:00), and the temperature conditions were kept constant at 23 °C. Food was provided ad libitum, and the availability of fluid was restricted to two daily 15 min sessions, one in the morning (10:00) and one in the evening (20:00). The procedure was approved by the Ethics Committee for Animal Research of the University of Granada and was conducted in accordance with both the NIH Publications (Nº 80-23) of the National Institute of Health Guide (United States) for the Care and Use of Laboratory Animals (2015 revision, Office of Laboratory Animal Welfare, Health Research Extension Act of 1985, Public Law 99-158, November 20, 1985, "Animals in Research") and the European Community Council Directive 2010/63/UE. The National Legislation, in agreement with this Directive, is defined in Royal Decree 53/2013; Law 32/2007.

Procedure

Rats with a long period of contextual habituation were randomly distributed among the following two groups: pre-exposed (PE) and non-pre-exposed (NPE) to the taste. Each of these groups were further divided into two groups according to whether the pre-exposure (if applicable), conditioning and testing were performed at the same ("S") time of day (PE-S and NPE-S) or according to whether the conditioning was performed at different ("D") time of day from the pre-exposure and/or testing (PE-D and NPE-D). Each final group consisted of the following number of subjects: PE-S ($n = 10$); NPE-S ($n = 9$); PE-D ($n = 10$); NPE-D ($n = 10$).

These animals were water restricted and received two 15 min sessions of access to water per day (at 10:00 and 20:00), as described above, over nine days to facilitate the differentiation of the temporal contexts (morning vs. evening) by a long period of habituation. After this period of habituation to fluid restriction in both temporal contexts, all of the rats had access to water in the morning session (15 min) for two days. The non-pre-exposed groups (NPE-S and NPE-D) also received water in the evening session (15 min) of these two days, while the pre-exposed groups (PE-S and PE-D) were exposed to a sodium chloride solution dissolved in water (saline 1%) for 15 min. On the day following the last pre-exposure, conditioning took place in the morning session for all of the "D" groups (PE-D and NPE-D). These animals were exposed to saline for 15 min in the morning, and the amounts ingested were recorded. Twenty minutes later, they received an injection of lithium chloride (LiCl) (0.15 M, 2% of body weight, i.p.). Water was available for 15 min in the evening session. In contrast, all of the "S" groups (PE-S and NPE-S) received conditioning in the evening session and water (15 min) in the morning session. After one day of recovery with water (15 min) in the morning and evening sessions, the response to saline was tested in all of the groups in the evening session by the one-bottle test. Water was available for 15 min in the morning sessions. The water and saline were administered throughout the procedure by calibrated burettes to facilitate recording of the ingested amounts.

Rats with a short period of contextual habituation were also randomly distributed among the following four groups: PE-S ($n = 10$); NPE-S ($n = 10$); PE-D ($n = 10$); NPE-D ($n = 10$). Access to water prior to pre-exposure was restricted to two daily 15 min sessions, as described above, over two days (a short period of habituation). The remainder of the procedure for these animals was unchanged. Figure 1 represents the behavioral procedure.

Data analysis

The saline consumption on the conditioning day was analyzed using a 2 × 2 × 2 factorial design with three between-subjects factors, the first being pre-exposure (*pre-exposure* vs. *non-pre-exposure*), the second factor being context (*same* -"S"- vs. *different* -"D"- *temporal context of conditioning*), and the third factor being contextual habituation (*long habituation* vs. *short habituation*). The saline consumption on the test day was analyzed by the same 2 × 2 × 2 factorial design. In all tests, the critical level of significance for differences was set to $p < 0.05$.

Results

Figures 2 and 3 show the mean consumption by the groups with long and short (respectively) contextual habituation period on the pre-exposure, conditioning and test stages. The results
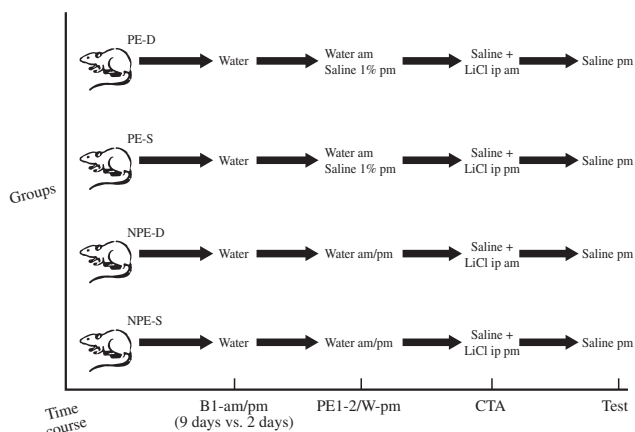
Figure 1. Behavioral procedure. BL (baseline), days 1-9 (long period) or 1-2 (short period) of habituation to restricted (15 min) water consumption in the morning (10:00) and evening (20:00) sessions; PE1-2/W-pm, days 1 and 2 of pre-exposure to saline or water in the evening session; CTA, conditioning day; PE-D, pre-exposed group in the "different -D-" condition (CTA in the morning session); PE-S, pre-exposed group in the "same -S-" condition (CTA in the evening session); NPE-D, non-pre-exposed group in the "different -D-" condition; NPE-S, non-pre-exposed group in the "same -S-" condition. LiCl ip, lithium chloride intraperitoneal. For brevity, the morning consumption after CTA is not represented
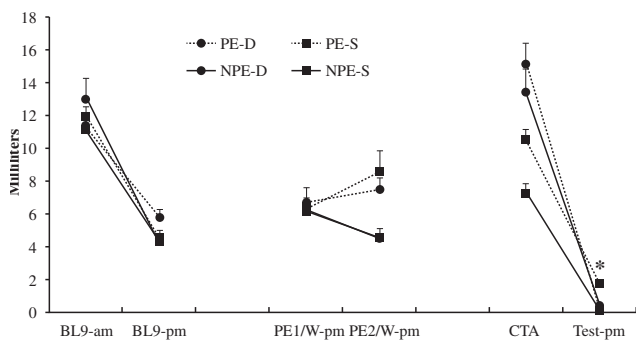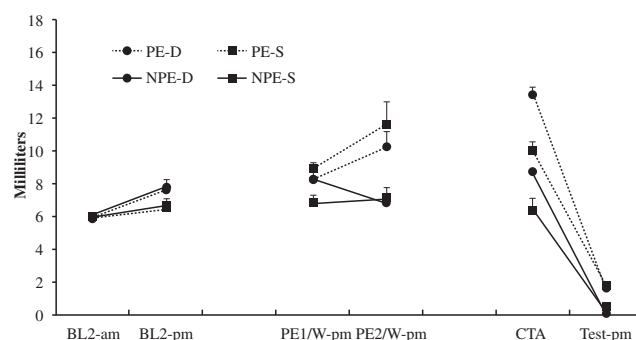

Figure 2. Mean consumption of saline/water by the groups (in milliliters) at different stages of the behavioral procedure (animals with 9 days of temporal-contextual habituation) and standard deviation. BL9 (baseline), ninth day (and last) of habituation to restricted water consumption in the morning (am) and evening (pm) sessions; PE1/W-pm and PE2/W-pm, days 1 and 2 of pre-exposure to saline or water in the evening session; CTA, conditioning day; Test-pm, test day in the evening session; PE-D, pre-exposed group in the "different -D-" context (CTA in the morning session); PE-S, pre-exposed group in the "same -S-" context (CTA in the evening session); NPE-D, non-pre-exposed group in the "different -D-" context; NPE-S, non-pre-exposed group in the "same -S-" context. For brevity, the morning water consumption after CTA is not represented. In the test day, the saline consumption of the PE-S group was significantly higher (1.77 ± 0.26) than those of the NPE-S group (0.08 ± 0.3) and PE-D group (0.46 ± 0.22). There was no significant effect of pre-exposure in the "D" groups (p = 0.87), indicating that the PE-D group did not acquire latent inhibition * $p<0.05$. These results show that, after nine days of temporal-contextual familiarity, the latent inhibition of taste aversion was acquired only in the "S" group and was disrupted in the "D" group, which suggests a temporal specificity of latent inhibition

indicate that a change of the time of day between pre-exposure and conditioning (PE-D group) disrupts the latent inhibition of CTA when animals have a long contextual habituation period. In these conditions, latent inhibition was acquired when the pre-exposures and conditioning were performed at the same time of day (PE-S group). In contrast, a short period of habituation disrupts this temporal specificity of the latent inhibition of CTA compared to a long period. A change of the time of day between pre-exposure and conditioning (PE-D group) has no effect on latent inhibition when the procedure includes two days of habituation to the temporal context. Therefore, a long period of contextual habituation previous to the pre-exposure seems to be suitable for the temporal specificity of the latent inhibition of CTA.

An ANOVA of the mean consumption recorded on the conditioning day showed that there was a significant effect of the pre-exposure factor ($F(1,71) = 20.19$, $p<0.01$). The pre-exposed groups consumed more saline (12.22 ± 1.73) than the non-pre-exposed groups (8.94 ± 2.4). The interactions between pre-exposure and context ($F(1,71) = 1.03$, $p = 0.86$), pre-exposure and habituation ($F(1,71) = 1.19$, $p = 0.27$), context and habituation ($F(1,71) = 2.98$, $p = 0.08$), and pre-exposure, context and habituation ($F(1,71) = 0.71$, $p = 0.4$) were non-significant.

An ANOVA of the mean consumption recorded on the test day indicated a significant effect of the interaction between pre-exposure, context and habituation ($F(1,71) = 4.03$, $p = 0.04$). The analysis of the interaction revealed a significant effect of the pre-exposure factor in the "S" groups with a long temporal-contextual habituation ($F(1,16) = 12.19$, $p<0.01$). The consumption of the PE-S group with a long habituation period was higher (1.77 ± 0.26) than that of the NPE-S group (0.08 ± 0.3). There was no significant effect of the pre-exposure factor in the "D" groups with long habituation ($F(1,17) = 0.12$, $p = 0.87$), indicating that the PE-D group did not acquire latent inhibition. The analysis of the

Figure 3. Mean consumption of saline/water by the groups (in milliliters) at different stages of the behavioral procedure (animals with 2 days of temporal-contextual habituation) and standard deviation. BL2 (baseline), second day (and last) of habituation to restricted water consumption in the morning (am) and evening (pm) sessions; PE1/W-pm and PE2/W-pm, days 1 and 2 of pre-exposure to saline or water in the evening session; CTA, conditioning day; Test pm, test day in the evening session; PE-D, pre-exposed group in the "different -D-" context (CTA in the morning session); PE-S, pre-exposed group in the "same -S-" context (CTA in the evening session); NPE-D, non-pre-exposed group in the "different -D-" context; NPE-S, non-pre-exposed group in the "same -S-" context. For brevity the morning water consumption after CTA is not represented. In the test day, the saline consumptions of the PE-S (1.84 ± 1.6) and PE-D (1.63 ± 1.66) groups were higher than those of the NPE-S (0.49 ± 1.1) and NPE-D (0.07 ± 0.12) groups, respectively, indicating that both groups acquired latent inhibition

interaction also revealed an effect of the context factor in the pre-exposed animals with long habituation ($F(1,18) = 13.18$, $p<0.01$). The consumption of the PE-S group with a long habituation period was higher (1.77 ± 0.26) than that of the PE-D group (0.46 ± 0.22). There was no significant effect of the context factor in the non-pre-exposed animals with long habituation ($F(1,17) = 0.02$, $p = 0.51$). With respect to animals with a short temporal-contextual habituation, there was a significant effect of the pre-exposure factor in the "S" ($F(1,18) = 17.56$, $p<0.01$) and "D" ($F(1,18) = 15.48$, $p<0.01$) groups. The consumptions of the PE-S (1.84 ± 1.6) and PE-D (1.63 ± 1.66) groups with short habituation were higher than those of the NPE-S (0.49 ± 1.1) and NPE-D (0.07 ± 0.12) groups, respectively, indicating that both groups acquired latent inhibition. There was no significant effect of the context factor in the pre-exposed ($F(1,18) = 0.25$, $p = 0.64$) and non-pre-exposed ($F(1,18) = 1.05$, $p = 0.35$) animals with short habituation.

Discussion

The results of the present study suggest that temporal cues are relevant to acquire latent inhibition of CTA only when animals have enough familiarity with temporal contexts. Thus, temporal specificity of the latent inhibition of CTA was only found after nine days of habituation to temporal contexts. Under this familiarity condition, animals that were conditioned at different time of day relative to the pre-exposures (PE-D) did not express latent inhibition compared to animals that were pre-exposed and conditioned at the same time of day (PE-S). However, when a short period of contextual habituation was used (two days), all pre-exposed animals (PE-D and PE-S) showed latent inhibition regardless the time of day of conditioning. The reduction of the taste aversion on the test day (i.e., latent inhibition) in the groups without change of temporal contexts was congruent with the effect of a two-day pre-exposure period (De la Casa & Lubow, 1995, 2001; Lubow, 2009; Lubow & De la Casa, 2005, 2010). Thus, it can be argued that the effect of a change of the time of day between pre-exposure and conditioning on the latent inhibition of CTA seems to depend on the availability of a sufficient period of habituation to the temporal contexts of consumption. Previous studies have shown temporal specificity of latent inhibition of CTA when the procedure includes only five (Manrique et al., 2004) or four (Molero-Chamizo, 2017) days of contextual-temporal habituation, but not if the procedure includes only two days of habituation (Morón et al., 2002). However, a direct comparison between clearly differentiated habituation periods (short versus long periods) has not been previously reported. In the present study, this direct comparison has shown that two days of contextual-temporal habituation is not a sufficient period to observe temporal specificity of latent inhibition of CTA.

Contextual habituation is one of the variables that could explain the spatial specificity of latent inhibition (De la Casa & Lubow, 1995, 2001; Escobar et al., 2002; Hall & Channell, 1986; Katz, Rogers, & Steinmetz, 2002; Quintero et al., 2011; Westbrook, Jones, Bailey, & Harris, 2000). Similarly, we have found that a change in the time of day of conditioning after nine days of habituation also interferes with latent inhibition. Therefore, both external and internal cues could modulate the latent inhibition of CTA through long periods of contextual habituation. Our findings are consistent with previous reports that have shown contextual dependence of latent inhibition of CTA when a novel external context was exposed prior to conditioning and after habituation (Rudy et al., 1977), or when external contexts were changed in the pre-exposure phase (Quintero, Vargas, Díaz, Escarabajal, Carrasco, & López, 2014). Also in CTA, Quintero et al. (2011) found contextual dependence of latent inhibition if the external context that was introduced between pre-exposure and conditioning or between pre-exposure and testing was novel. However, if the context that was introduced between conditioning and testing was physically familiar, then latent inhibition was increased. Unlike these changes in external contexts, in the case of the temporal contexts more complex influences on eating behavior should be considered because both contexts (morning and evening) were always present in the habituation period. Nevertheless, the effect of contextual novelty may still be valid for the temporal specificity of the latent inhibition, as revealed in the present study. When animals are habituated for long periods of time to consume at specific times of the circadian rhythm, the temporal context can acquire value and influence conditioning. In this case, a change in the circadian context (time of day) in the conditioning day enhances the novelty value of the conditioned stimulus and its associative strength, which interferes with the effect of taste pre-exposures. Nevertheless, shorter periods of habituation can hinder the discrimination process of temporal contexts and its effects on learning (Morón et al., 2002).

Temporal specificity of latent inhibition of CTA may be of evolutionarily adaptive significance. For example, contextual cues, including ones of a temporal nature, can influence whether animals decide to consume potentially toxic substances (Gemberling, 1984; von kluge & Brush, 1992). These contextual cues are essentially both physical or spatial and temporal (Gallistel & Gibbon, 2000; Lukoyanov, Pereira, Mesquita, & Andrade, 2002; Ribeiro, Huziwara, Montagnoli, & de Souza, 2012). Thus, a clear discrimination of the temporal-contextual environment might facilitate the temporal specificity of latent inhibition as an adaptive mechanism useful to identify when a pre-exposed food is potentially toxic. Through this contextual familiarity, an organism would have more information to correctly recognize the effects of taste pre-exposures.

An important question concerns how animals discriminate between temporal contexts after long habituation periods. In other words, what is the mechanism that accounts for the relationship between temporal context and latent inhibition of CTA. Several mechanisms can explain the role of the time of day as learning context. On the one hand, the internal state induced by the circadian rhythm of biological functions can be considered itself as contextual cue to learning (Benstaali, Mailloux, Bogdan, Auzeby, & Touitou, 2001; Morin, 2013; Winocur & Hasher, 1999; Yannielli & Harrington, 2001). This is a valid possibility for procedures such as those of the present study, because the experimental sessions were always conducted during the light period. Another possibility is that animals are able to calculate the time between sessions (in our study, between morning and evening) or the time interval between the start of the light cycle (or even the dark cycle, depending on the procedure) and the experimental session. It is known that rodents can use this strategy to handle short time intervals (Gallistel & Gibbon, 2000), but the same strategy could hardly be used when the signal passes cyclically over long periods, something that is common in nature. A final possibility is the fact that rats can learn the appearance order after turning on the light or can learn to alternate their response. Nevertheless, in the present study the time intervals between stimuli were hours,

and it is unlikely that animals were able to discriminate between contexts by calculating the elapsed time. Instead, perhaps it is more likely that animals learn the appearance order after the onset of the light period or an alternation of the response. However, these options have also been questioned by a study in which researchers alternated sessions with different order of appearance and the contextual dependence remained intact (Arvanitogiannis, Sullivan, & Amir, 2000). As mentioned above, a more plausible explanation for the present results is that the circadian rhythm of some physiological functions served as a temporal-contextual variable involved in the modulation of taste aversion. After an appropriate period of temporal-contextual familiarity, the time of day had a different influence on taste aversion depending on the circadian physiological phase in which the conditioned stimulus was exposed. The exposures of the conditioned stimulus had the same circadian cycle in the "S" condition (saline was always exposed at the same time of day), but the conditioned stimulus had different circadian cycle in the "D" condition.

In short, the findings of the present study suggest that in rats the temporal context could be a distinctive cue in the acquisition of taste aversion under sufficient periods of habituation to different contexts. The temporal-contextual control of the latent inhibition of CTA could be an adaptive advantage in situations where it is necessary to correctly discriminate potentially toxic foods.

Some limitations of the study should be considered. It would be important to control the consumption of the groups during the habituation period (for example by restricting the amount of consumption) to reduce the effect that the different consumptions between morning and evening may have on the pre-exposure and conditioning stages. Moreover, adding groups where context change occurs in the morning or in the evening would also strengthen the results. Finally, implementing a control of consumption on the day of conditioning could also reduce a possible influence of the habituation to neophobia phenomenon on the results.

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