Different effects of unexpected changes in environmental conditions on prepulse inhibition in rats and humans

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Abstract

The reduction of the startle response to an auditory stimulus caused by the presentation of another stimulus of lower intensity closely preceding it, a phenomenon known as prepulse inhibition (PPI), can be modulated by changes in dopaminergic activity. Schmajuk, Larrauri, De la Casa, and Levin (2009) demonstrated that this dopaminergic modulation of PPI in rats can be influenced by manipulating the experimental context, specifically by introducing changes in the ambient lighting condition that include novel elements. In this paper we analyse the effects of introducing changes in context illumination on PPI in male rats (Experiment 1) and humans (Experiment 2). The results with rats showed a reduction of PPI when the illumination condition switched from dark to light, but not from light to dark. In the experiment with human participants the reduction of PPI occurred for both changes in illumination conditions. The animal experiment results are interpreted in terms of competing exploratory behavior that appear when the context is illuminated after the dark-light transition; while in the case of human participants a perceptual and/or attentional mechanism after both illumination transitions is proposed, which may result in a reduced processing of the prepulse and subsequent lower PPI.

Keywords: Prepulse inhibition; Novelty; Dopamine; Rats; Humans.

1. Introduction.

The startle response includes, among other behaviors, the involuntary contraction of the skeletal muscles and occurs after the presentation of a stimulus of some intensity [1,2]. Typically, the startle response is assessed by quantifying the intensity of muscle contraction after the stimulus presentation. The startle response is susceptible to modulation through various manipulations such as the repeated presentation of the stimulus, which can lead to habituation or sensitization of the response [3,4], the induction of a particular emotional state prior to stimulus presentation [5,6] or to changes in environmental conditions in which the stimulus is presented [7]. Another form of modulation of the startle response that has received much attention from researchers in the field of psychophysiology in the last decades is prepulse inhibition (PPI), a phenomenon that occurs when a stimulus of lower intensity precedes the presentation of a startling stimulus, resulting in the reduction of the response to the latter [8]. The occurrence and intensity of PPI depends on a number of variables such as the time interval between the prepulse and pulse stimuli [9], their intensity [10] or the background noise level in which the stimuli are presented [11].

PPI is believed to reflect sensorimotor gating abilities, i.e., the ability to respond to potentially relevant stimuli, simultaneously inhibiting the processing of other stimuli and/or responses that might hinder the in-depth processing of a stimulus under analysis [12]. According to this point of view, PPI would reflect an effective inhibition of the motor response to the stimulus of greater intensity (pulse), ensuring an in-depth analysis of the prepulse stimulus (which preceded

the pulse presentation), and thus representing a simple example of sensorimotor modulation [13].

The neural circuitry that regulates both the startle response to auditory stimuli as well as PPI has been characterized in detail [8]. The neural systems of both the startle response and PPI are modulated by a number of neurotransmitters such as dopamine, GABA, glutamate and acetylcholine, which regulate the magnitude of the startle response and its inhibition [8]. Zhang et al. [18] studied the effect of indirect dopamine (DA) agonists on PPI in rats, and showed that amphetamine administration resulted in a decrease in the magnitude of PPI. Studies with schizophrenic patients, a disorder characterized among other things by a hyperactivity of the dopaminergic system, support the hypothesis relating elevated dopamine release with PPI attenuation [21].

In addition to pharmacological manipulations, there are environmental changes that can cause changes in dopaminergic activity, such as the exposure to a novel stimulus or context [22,23]. An increase in cortical dopaminergic activity in rats indicates that a novel stimulus is presented to the animal, an effect that is not found with neutral or habituated stimuli [24]. With regards to the subcortical dopamine system, the release of dopamine in the nucleus accumbens is related to the perception of novelty [25].

According to the results presented above, external changes involving the introduction of new elements in the experimental situation, such as a manipulation of the illumination condition in the area where the subject is located, would impact the dopaminergic activity and produce a modulating effect on PPI [26]. Our aim in this paper is to analyze the effect that environmental changes –namely, a variation in the illumination conditions- have

on the startle response and PPI in both rats and humans. Based on the results reported by Schmajuk et al [26] we expect that exposure to novel environmental situations would produce a transient increase in dopamine release in both cortical and subcortical regions [24] and therefore cause a reduction in PPI in both rats and humans. However, it is possible that the effects on PPI may depend on the type of novel stimulus that appears in the experimental situation, since previous results with rats indicate that PPI is reduced after a dark to light transition, but not when the change is from light to dark [26]. It is possible that this lack of symmetry in animals is restricted to the transition from dark to light due to the increase in surrounding visual stimuli that occurs with a sudden illumination increase.

2. Experiment 1

The first experiment is designed to reproduce the results obtained by Schmajuk et al. [26], namely the reduction of the startle response and PPI after a change of illumination in the experimental condition. Some changes to the Schmajuk et al. [26] design were introduced in this experiment: first, a 90 dB SPL prepulse was used instead of a 70 dB SPL stimulus, since in pilot studies in our laboratory no consistent PPI was found with the latter prepulse intensity. A second major change was the use of male rats in our experiment, thus eliminating the source of variability related to the hormonal changes that occur periodically in female rats in estrus function [27], that have been shown to influence PPI [28]. Third, in our experiments Wistar rats were used, instead of the Sprague-Dawley strain tested in Schmajuk et al. [26]. Fourth, in our experiment the animals were maintained under a regular light-dark cycle,

instead under a reversed cycle (thus, in our experiment the animals were tested in their light phase). A final important change in the design was that this experiment used a between-subjects design in which each group of animals received only one of the environmental changes (light to dark [L/D] or dark to light [D/L]) versus the within-subject design used in Schmajuk et al. [26].

Based on the previous results obtained by Schmajuk et al. [26], we expect that the illumination change would produce an attenuation of PPI, but only when the change involves a transition from dark to light.

2.1. Method

2.1.1. Subjects

Sixteen male Wistar rats, experimentally naïve, participated in this experiment. The mean weight at the start of the experiment was 342 gr. (range 297-410). Food and water were available ad libitum throughout the experiment. Rats were individually housed in the colony with a regular light-dark cycle of 12:12 hours. All testing occurred during the 12-h light period (starting at 10:00 AM). Four days before the start of the experimental sessions, each of the animals was handled 5 minutes daily.

2.1.2. Apparatus and stimuli

Four Panlab chambers (model LE 111) designed to detect and record the startle response in rats were used. Each chamber was enclosed in a sound-proof module (model LE 116), and inside each chamber a perspex cylinder of 8 cm in diameter was attached to the floor of the experimental chamber, resting on a platform that registered and recorded each animal's movement. A

loudspeaker was present at the top of each chamber, which produced a constant background white noise of 65 dB SPL. The pulse stimulus was a 20 ms, 120 dB SPL white noise, and the pre-pulse was a 20 ms, 90 dB SPL white noise. The lead interval in the prepulse-pulse trials was 100 ms, and the inter-trial interval was 30 sec (+/- 5). A 24V, 2W key light (light intensity of approximately 180 lx) was located on the left side of the chamber.

Vibrations of the Plexiglas enclosure caused by the whole-body startle response of the animal were converted into analog signals by a piezoelectric unit attached to the platform. These signals were digitized and stored by a computer as a linear parameter. The average startle activity was measured in a 100-ms time window starting at the onset of the sound stimulus, whereas the average baseline activity was measured by selecting the highest response in the interval between trials.

2.1.3. Procedure

For the L/D group (n = 8) the key light inside the experimental chamber was on from the beginning of the experiment, while in the case of the D/L group (n = 8) the key light was off. Once the rats were introduced in the experimental chambers, they went through a 5-minute acclimation period in which the only auditory stimulation presented was the constant 65-dB SPL background noise, which remained throughout the experiment. Following the acclimation period, 4 pulse-alone stimuli were presented with a mean inter-trial interval ITI of 30 sec. After 6.5 additional minutes, 6 pulse-alone and 6 prepulse-pulse trials were randomly presented, with a mean ITI of 30 sec (+/- 5). In prepulse-pulse trials the interval between the prepulse and pulse was 100 ms. Following this

sequence of trials, the change in lighting condition (light to dark or vice versa, depending on the group) was introduced, and the same 6 pulse-alone and 6 prepulse-pulse trial sequence was presented.

2.1.4. Results

A preliminary 4 x 2 ANOVA (Trials x Condition: D/L vs. L/D) conducted on mean startle responses to the 4 pulse-alone trials presented at the beginning of the session revealed no significant main effects or interactions (all ps>.19)

Figure 1 shows startle responses (expressed in arbitrary units) to pulse-alone and prepulse-pulse trials during the experimental phase. It also shows mean response during inter trial intervals (no stimulus trials) computed by collapsing the maximum spontaneous response by contiguous Pulse and Prepulse-pulse ITIs. Panel A presents the startle responses for rats in group L/D, in which the first block of trials took place with the key light on, and the second block with the key light off. Panel B shows the results of rats in group D/L, in which the illumination conditions were reversed. As seen in both panels of Figure 1, during the first block the difference between responses to pulse-alone and prepulse-pulse trials (i.e., PPI) remained constant. However, the introduction of changes in illumination conditions had a differential effect on the startle response in pulse-alone trials: while no change was observed in group L/D (Panel A), PPI disappeared transiently in group D/L during the first trials in the presence of light (immediately after the transition) to gradually recover over the remaining trials (panel B). The responses during the no-stimulus periods remains low and stable across the entire duration of the experiment, thus

discarding any possible floor effect of the startle response on the experimental trials, but showing a general increase after the illumination transition.

Figure 1 about here

These impressions were confirmed by a subsequent statistical analysis. Specifically, a 6 x 2 x 2 x 2 ANOVA test (Trials x Trial type: pulse-alone vs. prepulse-pulse x Position: first block of six trials vs. second block x Group: L/D vs. D/L, with the first three factors being within-subject) on mean startle responses revealed a significant main effect of Trial Type, $F(1,14) = 35.54$; $p < .001$, $\eta^2 = .72$, reflecting the overall PPI effect. A significant Trials x Position interaction was also found, $F(5,70) = 6.77$; $p < .001$, $\eta^2 = .33$**,** due to a general trend of startle amplitude to decrease across trials in the first block of six trials, and to increase in the second block. Finally, the 3-way Trial type x Position x Group interaction was also significant, $F(1,14) = 7.61$; $p < .05$, $\eta^2 = .35$. No additional significant main effects or interactions between factors were found (all ps>.09). In order to identify the source of the 3-way interaction, we conducted separate 2 x 2 ANOVAs (Trial type x Position) for L/D and for D/L groups. The ANOVA for the L/D group revealed only a significant main effect of Trial type, $F(1,7) = 14.05$; $p < .01$, $\eta^2 = .66$**,** due to the general effect of PPI. The ANOVA test on mean startle responses for the D/L group revealed a significant main effect of Trial type, $F(1,7) = 21.95$; $p < .01$, $\eta^2 = .77$**,** due to the PPI effect, and a trend toward a significant Trial type x Block interaction was found, $F(1,7) = 4.84$; $p = .064$, $\eta^2 = .35$. The interaction reflects a trend towards a lower startle responses in pulse-alone trials in the first block of trials (mean = 42.24, SEM =

8.8) when compared to those of the second block (mean = 34.89, SEM = 7.31), an effect that does not appear in prepulse-pulse trials (mean = 13.54, SEM = 3.4, and mean = 14.47, SEM = 2.54, for the first and the second block of trials, respectively).

A 2 x 2 ANOVA (Position: first block of six trials vs. second block x Group: L/D vs. D/L) was conducted on mean activity during the no-stimulus trials (collapsed across trials). The ANOVA test revealed a significant main effect of Position $F(1,14) = 12.48$; $p < .01$, $\eta^2 = .47$ due to a general higher startle response in the second as compared to the first block of trials (mean = 6.65, SEM = .62, and mean = 4.91, SEM = .25, respectively). Neither the main effect of Group nor the interaction between factors was significant (all ps > .08).

These results reveal the differential effect of changes in illumination condition on startle responses to pulse-alone trials, replicating the results reported by Schmajuk et al. [26]. However, in order to get a clearer picture of the results, we conducted additional analyses restricted to the last two trials and the first two trials before and after the illumination change, respectively. The new analysis was restricted to such trials because, as shown in Figure 1, the effect of the illumination change was transient and restricted to the very first trials after such a change. As predicted, a 2 x 2 x 2 x 2 mixed ANOVA (Trials x Trial Type: pulse-alone vs. prepulse-pulse x Position: first block of six trials vs. second block x Group: L/D vs. D/L) revealed a significant main effect of Trial type and a significant Trial type x Position x Group interaction (all remaining ps>.09). The main effect of Trial type, $F(1,14) = 31.44$; $p < .001$, $\eta^2 = .69$**,** reflects the overall effect of PPI. The significant 3-way interaction, $F(1,14) = 6.81$; $p < .05$, $\eta^2 = .33$**,** was explored by independent 2 x 2 ANOVAs (Trials x

Trial type: pulse-alone vs. prepulse-pulse) for D/L and L/D groups. The analysis revealed significant main effects of Trial Type in both groups, $F(1,7) = 24.93$; $p < .01$, $\eta^2 = .78$**,** and $F(1,7) = 8.44$; $p < .05$, $\eta^2 = .55$**,** respectively, due to the general PPI effect. The Trials x Trial type interaction was significant for the D/L, but not for the L/D group, $F(1,7) = 7.24$; $p < .05$, $\eta^2 = .51$**,** and $F(1,7) < 1$, respectively, reflecting the disruptive effect of illumination transition on PPI for the first, but not for the second condition. The ANOVA revealed that neither the main effects nor the interactions were significant (all ps>.08).

In order to identify a possible effect of baseline activity on these results, we conducted a 2 x 2 x 2 mixed ANOVA (Trials x Position: first block of trials vs. second block x Group: L/D vs. D/L) restricted to the two intertrial interval periods that occurred before and after the illumination change (where the effect of the illumination change on the startle response was more evident). The analysis revealed a significant main effect of Position ($F(1,14) = 5.02$; $p < .05$, $\eta^2 = .26$), due to a general higher activity in the second as compared to the first block of two trials (mean = 6.05, SEM = .41, and mean = 5.07, SEM = .31, respectively). The Position x Group interaction was also significant ($F(1,14) = 5.55$; $p < .05$, $\eta^2 = .28$), reflecting an increase in activity after the illumination change for the D/L group (mean = 4.83, SEM = .43, and mean = 6.85, SEM = .65, for the pre- and the post-change periods, respectively) that did not occur in the L/D group (mean = 5.30, SEM = .47, and mean = 5.25, SEM = .37).

3. Experiment 2

The results of Experiment 1 showed a decrease in the intensity of PPI when a change in the illumination condition was introduced in the experimental

context. This change in PPI was caused by a decrease in the startle response in pulse-alone trials immediately after the environmental change from dark to light. However, when the illumination condition was changed from light to dark the response to pulse-alone trials was not affected. This differential effect can be attributed to the triggering of an attentional process caused by environmental novelty that would favor processing of visual stimuli lowering that of auditory cues [26,29]. However, the sudden illumination of the experimental context could trigger in rats (nocturnal animals) the emergence of an emotional response [30] that would have interfered with the novelty effects and altered the results.

The aim of Experiment 2 was to analyze the effect of illumination changes on PPI using a procedure similar to that described in Experiment 1, but with human participants. If a change in the subject's emotional state is the determinant factor of the observed decreases in startle amplitude in pulse-alone trials and PPI after the introduction of light, we would expect that if those reductions were to appear in humans they would occur in the opposite experimental condition, i.e., in the L/D group, since in that condition an intense emotional response is expected to be produced [29]. Conversely, if changes in the startle response were exclusively due to the introduction of novel stimuli, they should occur independently of the nature of the transition (light to dark or dark to light).

3.1. Method

3.1.1. Subjects

Twenty nine volunteers (22 women and 7 men; all students at the University of Seville) were recruited for the study. Their ages ranged between 19 and 29 years. None of the participants reported having any health problems or hearing problems. All participants were informed of the type of stimulation used in the experiment and provided signed informed consent. All testing occurred between 10:00 AM and 15:00 PM.

3.1.2. Apparatus

EMG activity was recorded using a Biopac MP150 Basic Module, with three Ag / AgCl electrodes. After cleaning the skin, conductive gel was applied to the electrodes before placing two of them approximately 1 cm below the eye to record the electromyographic activity of the orbicularis oculi muscle. The third electrode was placed on the forehead to detect the general level of electrical activity in the body. The electromyographic signal was amplified, filtered and integrated by the Biopac system and then converted from analog to digital units (linear parameter) by an external computer.

The different sounds used to produce the startle response and PPI were presented through adjustable headphones (RadioShack). Sound levels were calibrated once a week by using a continuous tone and sound level meter.

On a computer placed in front of the participant (approximately 100 cm from the eyes) 156 neutral pictures were presented. These images were selected from the International Affective Picture System database [31]. The interval between image presentations was 5 seconds. We have repeatedly used this technique in our laboratory to minimize potential distractions in participants, and this procedure also prevented a complete absence of light in the dark

condition, since the experimental room remained dimly lit by the glow of the monitor. During the experiment, image changes did not coincide with the occurrence of auditory (pulse or prepulse) stimuli. A 36 W LED bulb (light intensity of approximately 840 lx) was used as the light source, placed in front of the participants and above their heads (approximately 140 cm) to avoid direct illumination of the eyes. Throughout the experiment, all other lights in the test context were turned off so that the LED bulb was the main illumination source in the room. A light switch placed behind the participant connected to the LED bulb was used to control the contextual illumination condition.

3.1.3. Procedure

The experiment was conducted in an isolated room. After providing signed informed consent, participants sat in a chair facing the computer screen where the above-described images were presented. Once the setup was completed, all instrumentation lights in the test room were turned off. For the 14 participants in the L/D group, the LED bulb remained on at the beginning of the experiment, while for the remaining 15 participants in the D/L group the LED bulb was off. Image presentation on the computer monitor started at the beginning of the test session. For all auditory trials, the ITI was 30 s and the time interval between prepulse and pulse in prepulse-pulse trials was 100 ms. After an 85 s adaptation period in which only the 65-dB SPL background noise was presented, four 95-dB SPL pulses and four 75-dB SPL prepulses were introduced in order to establish the baseline response to the different auditory stimuli. The duration of these stimuli was 50 ms and 20 ms, respectively. Following this adaptation phase the proper test phase began, in which 6 pulse-

alone and 6 prepulse-pulse trials were presented. Immediately after these trials the illumination change was introduced, and an additional 6 pulse-alone and 6 prepulse-pulse trials were presented. The interval between the illumination change and the appearance of the first subsequent auditory (pulse) stimulus was +/- 4 seconds. Finally, 4 pulses and 4 prepulses were presented, like during the pre-test phase. The total duration of the experiment for each participant was 13 minutes.

3.1.4. Results

Prepulse-alone presentations during the pre- or post-test phases did not produce detectable responses in any participant. A mixed 4 x 2 x 2 ANOVA (Trials x Position: pre- vs. post-experimental x Group: L/D vs. D/L, with the two first factors within-subject) on startle responses to pulse-alone trials revealed a significant main effect of Position, $F(1,66) = 26.08$; $p < .001$, $\eta^2 = .54$**,** due to a general higher startle intensity for the pre- as compared to the post-transition block of trials. This difference reflects the expected startle response habituation across auditory stimuli presentations. The Position x Group interaction was also significant, $F(1,66) = 5.18$; $p < .05$, $\eta^2 = .19$. The interaction came from the difference in startle response that appeared for the pre-transition trials (with the startle response in the D/L group being more intense than in the L/D group, Mean = 0.88, SEM = 0.13, and Mean = 0.62, SEM = 0.09, respectively) that vanished for the post-transition trials (Mean = 0.62, SEM = 0.12, and Mean = 0.5, SEM = 0.09, respectively. Probably the interaction is reflecting a floor effect, with the initial difference between D/L and L/D groups diminishing as startle response habituation reached its maximum level. The Trials x Position

interaction was also significant, $F(3,66) = 3.26$; $p < .05$, $\eta^2 = .13$, reflecting the overall decrease of the startle response across trials due to habituation in the pre-transition block that did not appear in the post-transition trials, where the startle response was already habituated. No additional main effects or interactions were found to be significant (all ps>.11).

Figure 2 shows mean startle responses to pulse-alone and prepulse-pulse trials, expressed in arbitrary units. Panel A presents the startle response for group D/L (the first trials in darkness and the last tests in the presence of light), while Panel B shows these responses for group L/D (with the first six trials in the presence of light and the last six in the dark). In both cases, the response pattern was similar, with more intense responses in the first six pulse-alone trials compared to prepulse-pulse trials (reflecting the PPI) and an increase in response to prepulse-pulse trials in the second block of trials, after the introduction of the illumination change (from light to dark or from dark to light).

Figure 2 about here

A mixed 6 x 2 x 2 x 2 ANOVA (Trials x Trial type: pulse-alone vs. prepulse-pulse x Position: first block of six trials vs. second block x Group: L/D vs. D/L, the first three factors being within-subject) revealed significant main effects of Trials and Trial type, $F(5,110) = 8.67$; $p < .001$, $\eta^2 = .29$, and $F(1,22) = 32.44$; $p < .001$, $\eta^2 = .60$, respectively. The main effect of Trials reflects a general decrease of the startle response across trials due to a habituation

process; the main effect of Trial type was due to an overall PPI effect, with higher startle response to pulse-alone than prepulse-pulse trials (mean = 0.56, SD = 0.38, and mean = 0.42, SD = 0.30, respectively). The Trials x Trial type interaction was also significant, $F(5,110) = 2.36$; $p < .05$, $\eta^2 = .10$**,** reflecting a decrease of startle intensity across trials for the Pulse-alone, but not for the Prepulse-Pulse trials. The Trial type x Position was also significant, $F(1,22) = 14.39$; $p = .001$, $\eta^2 = .40$**,** due to the PPI effect obtained in the first block of trials that vanished on the second block. Finally, the Trials x Trial type x Position interaction was significant, $F(5,110) = 4.06$; $p < .01$, $\eta^2 = .16$. An exploration of this 3-way interaction revealed it was due to a decrease across trials of the PPI effect on the first block of trials, and an absence of such PPI effect on the second block of trials. No additional main effects or interactions were found to be significant (all ps>.16)

4. Discussion

The results of both experiments show that the presentation of a novel stimulus, specifically the introduction of a change in ambient illumination conditions, has an important effect on the startle response and PPI. In the first experiment we found that the startle response of rats in pulse-alone trials decreases as a result of novelty –but only after the change was from dark to light-, causing a decrease PPI. In Experiment 2, changes in illumination conditions –regardless of their direction- caused an increase in the startle response on prepulse-pulse trials in humans, and a consequent decrease in PPI. Although yielding a similar outcome in terms of PPI reduction, the results of both experiments are clearly different attending to the way in which changes in

environmental conditions affect the startle response in pulse-alone and prepulse-pulse trials.

The results of animal experiments reproduce exactly those obtained by Schmajuk et al. [26], namely the decrease in startle response in pulse-alone trials. Although our Experiment 1 did not offer any direct neurobiological data, the behavioral data are consistent with the hypothesis that considers the observed startle reduction to the pulse mediated by the release of dopamine in the NAC induced by the introduction of a novel stimulus (the change in ambient illumination). According to this view, the activation of the dopaminergic system would lead to the development of exploratory behaviors that would compete with the generation of startle responses in pulse-alone trials, thus decreasing their amplitude [26]. Several findings support this hypothesis: First, there is experimental evidence showing that increased exploratory behavior is negatively correlated with the intensity of the startle response to intense stimuli [32]; in addition, several studies have revealed that contextual changes involving novelty are positively correlated with increased dopamine release in the NAC [33,34]. Thus, when Sprague-Dawley rats were exposed to an unfamiliar novel environment, an increase of dopamine located in the NAC that persists for about 25 seconds was observed [35] Rebec et al. (1997). Using microdialysis studies, dopamine release in the NAC increased when Long-Evans rats were exposed to an environment containing novel objects [36]. Such phasic dopamine increase seems to be linked to the activity of neurons in Ventral Subiculum (VS), since neurons in this region activate glutamate receptors in the VTA (Ventral Tegmental Area) that results in an increase of dopamine in the NAC to novel stimuli. There is also the possibility that VS direct

glutamatergic projections of neurons to the NAC induce an increase in dopamine to novelty, or that it is related to a circuit involving VS projections to the prefrontal cortex, which in turn involves glutamatergic projections to VTA [36]. In the case of change in the ambient illumination condition from light to dark, it is possible that the exploratory behaviors that compete with the startle response in pulse-alone trials do not appear since the number of visual stimuli available for exploration in this condition decreases. This possibility was confirmed by the analysis of exploratory behavior conducted on two trials before and after the illumination change: an increase in exploratory behavior was observed only in the Dark-to-Light group.

The results of Experiment 2 with human participants exhibit a different pattern from those obtained with animals. First, the PPI reduction effect after the introduction of the illumination change was symmetrical, i.e., it was observed in changes from dark to light as well as from light to dark. A second important difference with the results obtained in the experiment with rats is related to the origin of the observed reduction in PPI. While for rodents PPI decreased as a consequence of a reduction of the startle response in the first pulse-alone trials after the introduction of the environmental illumination change, in humans the reduction was due to an increase in startle responses in the first prepulse-pulse trials following the illumination change. An additional difference between rats and humans results is related to the length of the effect that was restricted to the first two trials in the experiment with rats, but extended across the six post-change trials in the experiment with humans. However, as can be seen in Figure 2, the startle reduction to the Pulse, probably due to habituation, had contributed to the apparent attenuation of PPI.

Therefore, according to the experimental results, the cause of the observed PPI reduction in humans is necessarily different from that observed in rodents, since all changes (not only that induced by the emergence of novel stimuli in the environment introduced in the light condition, but also the change caused by the disappearance of cues when the light was turned off) reduced PPI. An important factor to consider when analyzing these differences is related to the magnitude of the light source used in the experiments with rodents and humans. While in Experiment 1 the stimulus used was a 2 W light, in the case of Experiment 2 a 36 W LED bulb located 100 cm above the head of the participants was employed. It is possible that the illumination provided in the rodent's case could have facilitated the appearance of an orienting response to the novel stimuli, causing the observed reduction in PPI [26], whereas in the human experiment, the more salient light could have launched perceptual and/or attentional processes in addition to the ones exhibited by rodents. Thus, a possible explanation –albeit speculative- for our results, is that the introduction of severe environmental changes in the human experiment may have temporarily changed the detection threshold of auditory stimuli.

Using different preparations to the ones employed in the present experiments (e.g., cross-modal oddball tasks), evidence of the effects of presenting distracting stimuli on the processing of stimuli of different sensory modality with human participants has been reported. Thus, using mainly auditory [37] and tactile [38] stimuli, these researchers showed the existence of what they call "post-novel distraction", a process that reflects the need to redirect attentional resources from a novel to a target stimulus in the experimental situation [39]. Although admittedly speculative, in addition to this

distracting effect, the introduction of changes in ambient illumination conditions in Experiment 2 may trigger a second effect related to the attentional shift caused by the presentation of an unexpected visual stimulus, which would slow the processing of an auditory stimulus appearing immediately afterwards [40-41]. This slowing effect, which results in increased response times in reaction time tasks, appears to be more significant when the stimuli presented are unexpected [42]. In this case, the observed PPI would not indicate a sensorimotor gating effect, but reflect a failure to detect the prepulse.

From a psychophysiological perspective, the dopaminergic activation produced by the presentation of novel stimuli can be found on the basis of different responses given by participants throughout the study. As mentioned above, there is a strong correlation between dopamine release in the nucleus accumbens and the novel effect of the context [33,34]. A dopamine-induced decrease in PPI when subjects are exposed to novel situations could be beneficial in the presence of salient and possible harmful stimuli.

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Figure captions:

Figure 1: Mean startle response to Pulse-alone (P), Prepulse-Pulse (PP), and baseline (No Stimulus) trials for the Light-to-Dark (Panel A) and Dark-to-Light (Panel B) Groups across trials for the experiment with rats (n=8). Error bars represent SEMs.

Figure 2: Mean startle response to Pulse-alone (P) and Prepulse-Pulse (PP) trials for the Light-to-Dark (Panel A) and Dark-to-Light (Panel B) Groups across trials for the experiment with humans (n = 15 for the Dark-to-light condition, and n = 14 for the Light-to-Dark condition. Error bars represent SEMs.

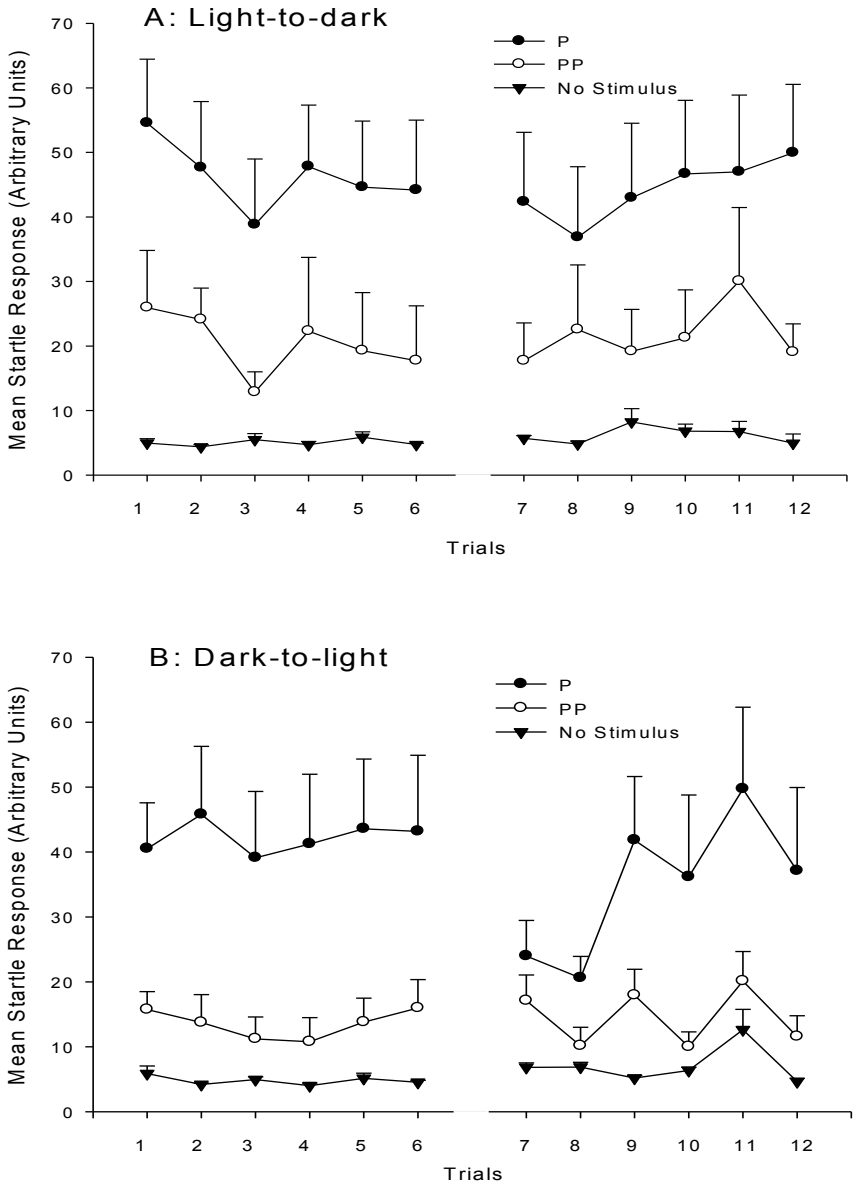
A: Light-to-dark
P
PP
No Stimulus
Mean Startle Response (Arbitrary Units)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
8
9
10
11
12
Trials
B: Dark-to-light
P
PP
No Stimulus
Mean Startle Response (Arbitrary Units)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
8
9
10
11
12
Trials

Figure 1.

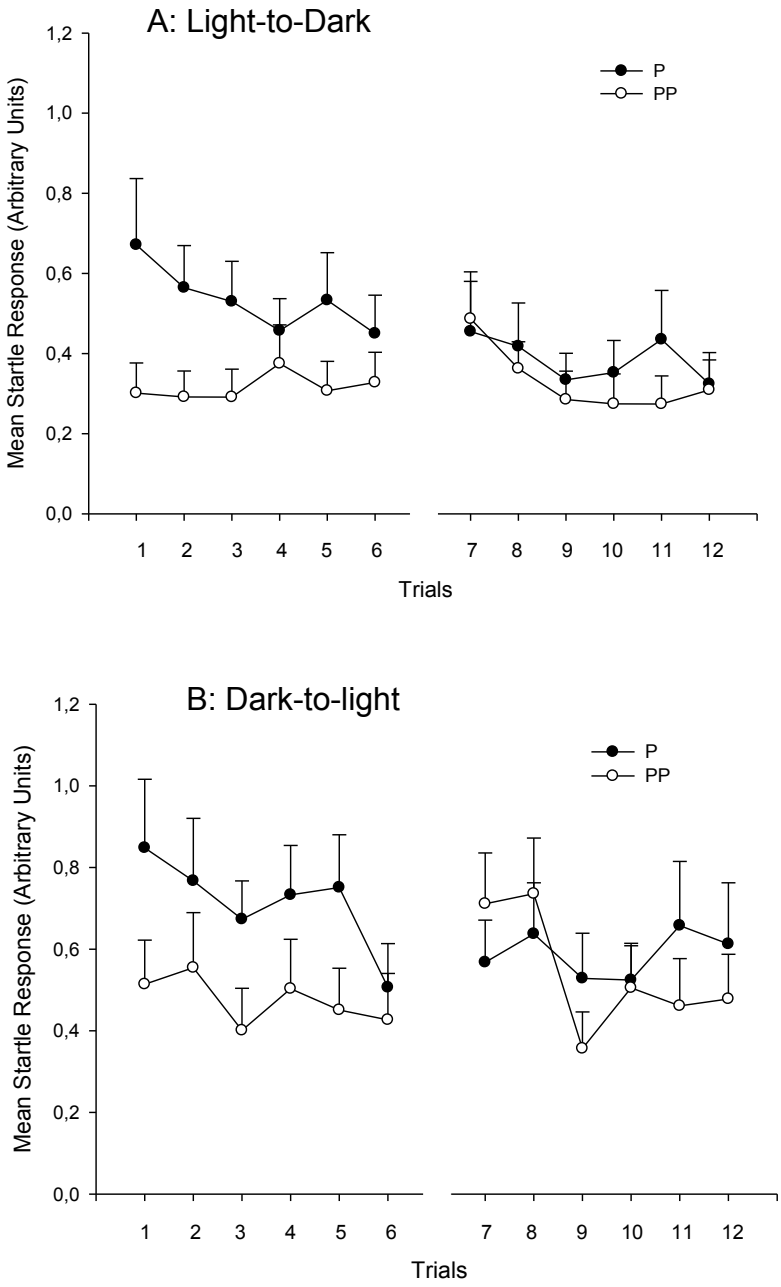
A: Light-to-Dark
Mean Startle Response (Arbitrary Units)
1,2
1,0
0,8
0,6
0,4
0,2
0,0
P
PP
1 2 3 4 5 6 7 8 9 10 11 12
Trials
B: Dark-to-light
Mean Startle Response (Arbitrary Units)
1,2
1,0
0,8
0,6
0,4
0,2
0,0
P
PP
1 2 3 4 5 6 7 8 9 10 11 12
Trials

Figure 2.