

Stimulus similarity decreases spontaneous object recognition regardless of the retention interval in rats

Rocío Angulo^{*1}, Naiara Arriola², and Gumersinda Alonso²

¹*Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile*

²*Universidad del País Vasco, UPV/EHU*

The experiment aimed to test in a spontaneous object recognition (SOR) task the effects of stimulus similarity and the interval between a previous familiarization trial and such a task. 1h or 24 h after the familiarization trial with two identical copies of an object, exploration of one of the objects and another novel object was assessed by recording the number of approaches, as well the time spent close to them. On the test the stimuli could either differ slightly in form (Difficult discrimination condition) or markedly in form and color (Easy condition). Subjects in the Easy but not the Difficult condition preferred to explore the novel object regardless of the retention interval (1h or 24h). After the 24h interval, exploration of the novel stimulus was greater for subjects in the Easy than the Difficult condition but they did not differ in terms of exploring the familiar object. Thus, rats in the Difficult condition might remember the familiar stimuli as well as rats in the Easy condition after 24 h, but were unable to distinguish it from the novel stimulus. The implications of this notion for using the SOR task as a procedure for studying perceptual learning and memory are discussed

It has long been known that animals prefer to explore a novel object over a familiar one when they can choose which stimulus to approach (Berlyne, 1950). Such natural and adaptive behavior has usually been used to assess the memory of these objects over time (e.g. Ennaceur & Delacour, 1988). Clearly, preference for the novel stimulus relative to the familiar one

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will be displayed only if animals remember the object experienced before. The specific type of memory potentially assessed in this way would be recognition memory consisting of the perception of one stimulus as familiar as a consequence of prior experience (e.g., Mackintosh, 1987; Mandler, 1980).

One of the tasks most extensively used to assess recognition memory of objects, particularly in rodents, is the spontaneous object recognition (SOR) task (see for example, Ennaceur, 2010; but see also Ammen-Ali et al., 2015, Blaser & Heyser, 2015, for a review of different variants of the task and their uses). In the simplest version of this task (to be used in the present study) rodents are preexposed to two identical copies of an object. Then, the same object and a further novel one are presented at test, with the spontaneous approaches to both objects being timed. Similar time exploring both objects would indicate an inability to recognize the familiar stimuli whilst a preference for the novel stimulus over the familiar one would imply familiar stimulus recognition. SOR tasks appear to be useful for assessing memory in both normal and pathological aging processes (e.g., Burke et al., 2010, 2011; Eacott et al., 2001), in neurodegenerative disorders (e.g., Álvarez-Ruíz & Carrillo-Mora, 2013; Isono et al., 2013; Santos et al., 2013), or after pharmacological and genetic interventions (e.g., Bertaina-Anglade et al., 2006; Costa et al., 2008). SOR tasks are also useful for deepening the understanding of memory as a basic psychological process, helping to discover its anatomy and physiology as well as the mechanisms involved (e.g., Honey & Good, 2000; Squire, Wixted & Clark, 2007; Tam, Robinson, Jennings, & Bonardi, 2014; Whitt and Robinson, 2013.). This kind of task might also be useful for assessing other basic cognitive processes such as learning (i.e., Anderson, Jablonski & Klimas, 2008). If animals can remember the familiar object, it is because they previously learned something about it. In particular, it is likely that animals learned about the physical features of the stimulus during its non-reinforced presentation in the familiarization trial by a learning process usually termed perceptual learning (see for example, Gibson, 1969; Hall, 2001; Mitchell & Hall, 2014).

Perceptual learning that it thought to occur during exposure to a stimulus has no direct behavioural correlate. Therefore, it is usually inferred from the ability of animals to discriminate between the exposed stimuli after one of them has been conditioned (i.e., Honey & Hall, 1989; Mackintosh, Kaye, & Bennett, 1991; Rodríguez & Alonso, 2011; Wills, Wells, & Mackintosh, 1994). The use of conditioning preparations to measure perceptual learning effects makes it likely that the behaviour of the animals on test will be influenced by motivational variables, which could interact

with what was learned during the stimulus preexposure phase. Thus, the SOR task might offer a good alternative for measuring perceptual learning more directly, without the effect of such motivational variables (because conditioning it is not needed). The SOR task is purely a discrimination task where rodents are required to discriminate between the novel and the familiar object (i.e., Aggleton, et al., 2010). Clearly, only if animals are able to differentiate the stimuli on test, will they tend to approach the novel stimulus and, in this case, the motivation to approach the novel stimulus would be unaffected by a conditioning process.

On the basis of this suggestion, the principal aim of this study was to validate the SOR task as a new procedure for the study of perceptual learning. This new procedure has some important ethical and practical merits in comparison with the standard ones that have been traditionally used to assess perceptual learning. In addition to removing the necessity to induce aversive states in the animals by means of aversive conditioning, it is also unnecessary for the animals to undergo the deprivation regimes that are required by the use of conditioning preparations. Finally, a SOR task can be conducted in a considerably shorter time than standard conditioning preparations.

In order to validate the SOR task as a perceptual learning procedure, the explorative behaviour of non-pathological adult rats was recorded in two experimental situations that differed in terms of the degree of similarity of the novel and the familiar stimulus. The stimuli either differed slightly (Difficult discrimination condition) or more markedly (Easy discrimination condition). We tested in both conditions whether or not the temporal interval between the exposure trial and test might affect performance on the SOR task. Findings regarding the effect of a delay in the SOR task appear to be mixed. And it has been suggested that this is due to the variability of the stimuli employed in the studies, and in particular the fact that the complexity or similarity of the target stimuli do not appear to have been controlled in such studies (see Gamiz & Gallo, 2012). Thus, it might be interesting for further research to establish the effect of a delay with stimuli that are easily reproducible in different laboratories as opposed to the everyday objects employed in previous studies (i.e., Norman & Eacott, 2004; Tam, Jennings, Robinson, & Bonardi, 2014). With this purpose in mind, the stimuli employed here were geometrical figures constructed with Lego bricks, and either a short (1 hr) or long (24 hr) delay was established between preexposure to the familiar object and the recognition test. On the basis of previous findings in the literature, it was expected that the performance on the task will be hindered with the long delay relative to the short one (i.e., Tam, Jennings, Robinson, & Bonardi, 2014). But it has not

yet been clearly established whether or not the effect of delay might vary according to the similarity of the stimuli involved in the in a SOR task in non-pathological adult rats (but see related findings in aged rats in Burke et al. 2010, 2011; Gamiz and Gallo, 2012). The debate regarding the exact nature of the memory process involved in different versions of the object recognition task is becoming increasingly important because of the extensive use of such tasks in studies of memory within the field of behavioural neuroscience (see for example recent reviews by Ameen-Ali & Eacott, 2015; Balsler & Heyser, 2015). A better understanding of interactions between variables such as stimulus similarity and delay might therefore contribute towards elucidating such processes.

METHOD

Subjects, apparatus and stimuli. Thirty-two Wistar naïve and adult healthy male rats were used as subjects (mean 370 g, range: 328-418). Except during the experimental trials, the rats were housed in pairs in their home cages with food and water ad libitum in a colony with a light-dark cycle of 12 hr (starting light at 08:00) and constant temperature (24°C) and humidity (50%).

The SOR task was conducted in a black plexiglass cage of 60 x 50 x 20 cm located in an experimental chamber lightly illuminated and acoustically isolated. The behavior of the rats was recorded with a video camera placed 50 cm above the center of the cage.

The stimuli, called A, A', B and B', were four figures constructed from Lego® game pieces that were easily assembled (2 cubes: 3,2 cm L x 3,2 cm W x 5 or 5,2 H; and two pyramids: 6,4 cm L x 6,4 cm W x 5,2 or 5,4 cm H, see Figure 1). The Stimuli A and B, as well the stimuli A' and B', differed substantially from each other in terms of shape (cube or pyramid, counterbalanced) and color (blue or yellow). Stimuli A and A', as well the stimuli B and B' differed only in terms of a small proportion of their overall shape. In particular, a single Lego® piece was added onto the top of the cube or the pyramid to generate stimuli A' and B'. Therefore, it was assumed that stimuli A and A', or B and B', were more similar (difficult discrimination) than A and B, or A' and B' (easy discrimination).

Procedure. The experimental procedure used in the present study was approved by the Animal Welfare Ethics Committee of the University of the Basque Country (UPV/EHU). The experiment consisted of three distinct trials - habituation to the context, pre-exposure, and testing, the rats being

randomly assigned to four experimental conditions ($n=8$), Difficult-1h, Easy-1h, Difficult-24h and Easy-24h. The conditions differed depending on the stimuli presented during testing (A vs. B, or A' vs. B', counterbalanced for the easy conditions, and A vs. A' or B vs. B', counterbalanced for the difficult conditions), and the retention interval between the exposure trial to the familiar stimulus and the test (1 hour or 24hours, for the groups Difficult-1h and Easy-1h, and the groups Difficult-24h and Easy-24h, respectively).

The experiment began with a single habituation trial to the context, lasting 5 min. During this time the rats were allowed to freely explore a black plexiglass cage. Following this, rats were returned to their home cages for 90 min and brought back for the exposure trial. This trial consisted of the presentation of two identical objects (A, B, A' or B'), counterbalanced in each group), in the same cage for 3 minutes. The objects were placed in the top-left and bottom-right corners of the cage (in relation to the video camera position), and 10 cm away from the walls. Again, the rats were then returned to their home cages and brought back for testing either 1 hour or 24 hours later, according to their experimental conditions. The test trial consisted of the simultaneous presentation of two different objects for 3 minutes. The stimuli presented on test consisted of a copy of the preexposed stimulus and another new one chosen in accord with the experimental conditions. The position of the familiar and novel objects on test was counterbalanced, the familiar stimulus (A, B, A' or B, counterbalanced for each group), being in the top-left corner of the cage for half the rats in each group, and in the bottom-right corner for the remaining subjects.

The video recordings of the behavior of the rats during the test were viewed by two blind observers. The number of approaches were recorded as well as the overall amount of time spent exploring each object. One approach was counted if the rats maintained their nose within 3 cm of the objects and showed vibrissae movement for at least 1 second. For recording the approaches to the objects, a circumference involving the 3 cm perimeter was established around the objects on the screen. Overall time spent exploring the objects was calculated by adding the time spent near the objects in each approach without considering the time the animals spent over or with their backs to the objects.

Data supplied by the two observers were averaged after confirming no significant differences between their observations for any experimental condition ($F_s < 1$). The data obtained for the Easy and Difficult discrimination conditions were then analysed by 2 x 2 ANOVAs conducted

with Stimuli (Novel or Familiar) and Delay (1 h or 24h) as factors, adopting a significance level of $p \leq 0.05$.

RESULTS

During the familiarization trial, the mean amount of time spent exploring the pyramids was 46.50 and 54.5 seconds for A and A' (see Figure 1), respectively, and 37.50 and 51.87 seconds for the cubes B and B', respectively. A 4 x 2 ANOVA conducted on the exploration times with object and position (right or left) as the variables failed to find significant main effects of Object, $F(3, 28) = 0.39$, $p = 0.761$, Position, $F(1, 28) = 0.23$, $p = 0.882$, or an interaction between these factors, $F(3, 28) = 0.263$, $p = 0.851$. The mean number of approaches to the pyramids A and A' were 29.62 and 28.8, respectively, and 27.00 and 29.37, respectively, to the cubes B and B'. A 4 x 2 ANOVA conducted on these data with Object and position (right or left) as the factors also failed to find significant effects of Object, $F(3, 28) = 0.041$, $p = 0.989$, Position, $F(1, 28) = 0.009$, $p = 0.925$, or an interaction between these variables $F(3, 28) = 1.19$, $p = 0.331$.

Figure 2 shows the mean amount of time exploring the novel and familiar objects in the four experimental conditions (upper panel) as well the mean number of approaches to both objects (lower panel). When the test was conducted with the more dissimilar stimuli (Easy Discrimination conditions), rats appeared to spend more time exploring the novel than the familiar object, regardless of whether the test was conducted 1 h or 24 h after the previous presentation of the stimuli. The same pattern was observed for the number of approaches, and delay appeared to have no effect on exploration of either the novel or familiar stimuli. The ANOVAs found a significant main effect of Stimuli, confirming that time exploring the novel stimulus was greater than time exploring the familiar stimulus, $F(1, 14) = 10.08$, $p = 0.007$, and that the number of approaches to the novel stimulus was greater than the number of approaches to the familiar stimulus, $F(1, 14) = 19.47$, $p = 0.001$. The main effect of Delay was not significant for either the exploration time $F(1, 14) = 0.498$, $p = 0.492$, or the number of approaches, $F(1, 14) = 1.36$, $p = 0.262$, and in no cases did the interactions reach statistical significance, $F(1, 14) = 0.005$, $p = 0.944$, and $F(1, 14) = 0.949$, $p = 0.346$, for the exploration time and the number of approaches, respectively.

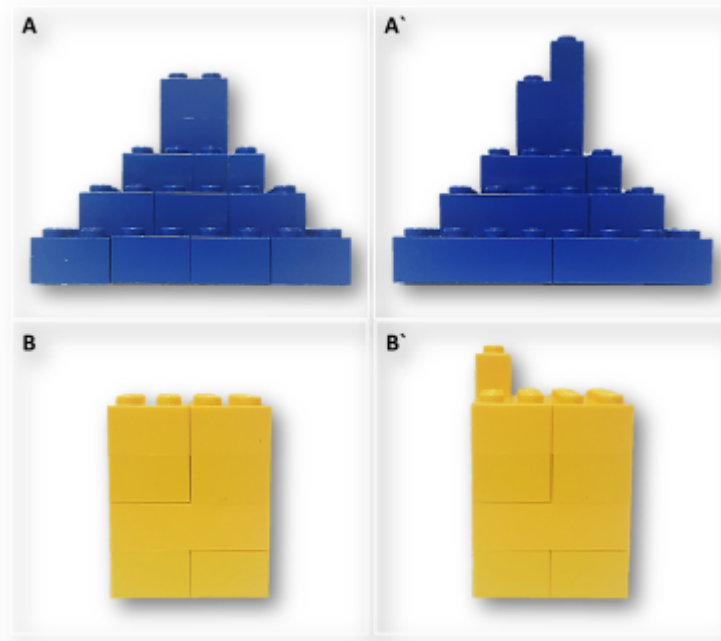


Figure 1. Objects used in the experiment. For the easy conditions the stimuli presented on test were A and B or A' and B' (counterbalanced in each group). For the difficult conditions the stimuli presented on test were A and A' or B and B' (counterbalanced in each group).

When the test was conducted with the more similar stimuli (Difficult Discrimination conditions), however, exploration of the novel objects appeared to be only slightly preferred over the familiar stimulus 1 hour after pre-exposure, with quite the opposite pattern of preference being observed when the test was conducted 24 hours after pre-exposure (more approaches and time spent exploring the familiar stimulus than the novel stimulus). In spite of such observations, an ANOVA conducted on the exploration time data failed to reveal significant effects of Stimulus, $F(1, 14) = 0.11$, $p = 0.739$, Delay, $F(1, 14) = 0.15$, $p = 0.698$, or an interaction between the variables, $F(1, 14) = 1.64$, $p = 0.221$. Similarly, no significant effects were found when analyzing the number of approaches, Stimulus, $F(1, 14) = 0.42$, $p = 0.527$, Delay, $F(1, 14) = 0.001$, $p = 0.978$, Interaction, $F(1, 14) = 2.29$, $p = 0.152$.

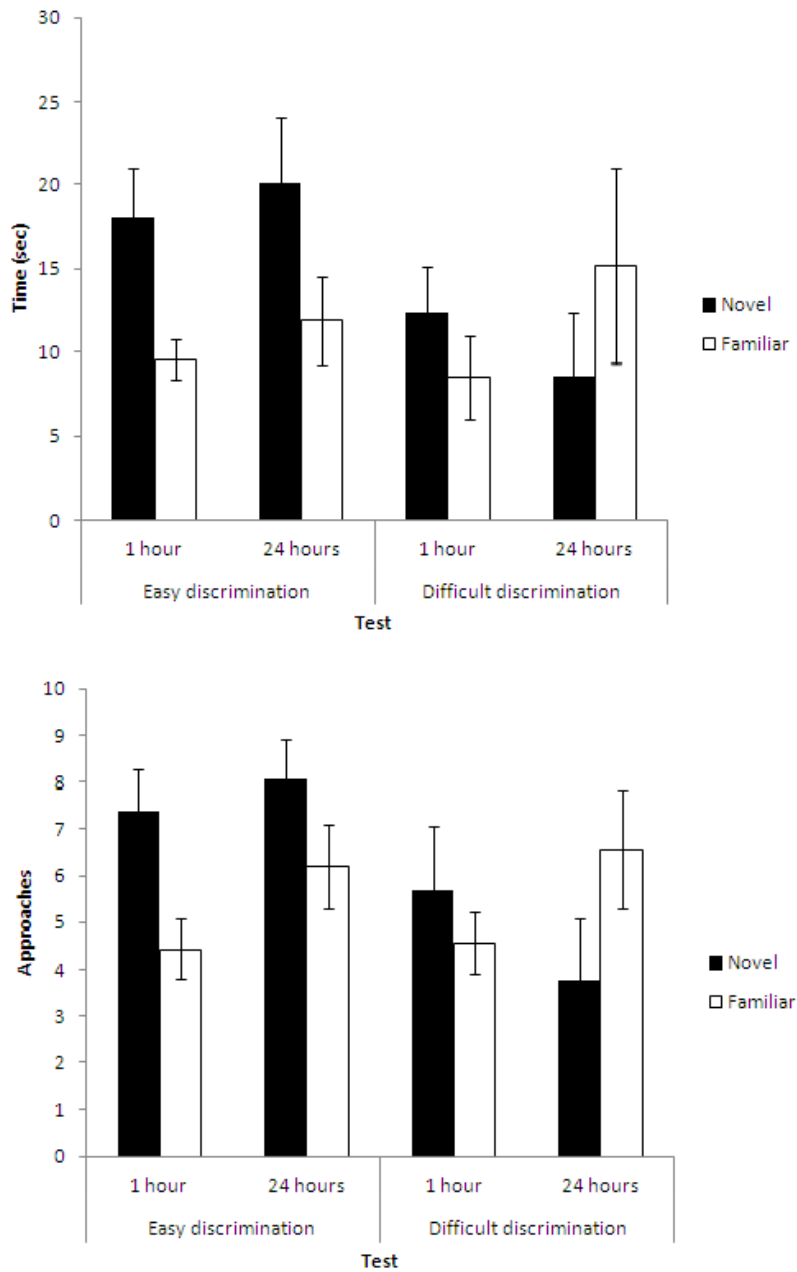


Figure 2. The upper part of Figure shows the time (mean \pm SEM) that the rats in the four experimental conditions spent exploring the novel and familiar objects. The lower part of the figure shows the number of approaches (mean \pm SEM) to the novel and familiar stimuli made by the rats in the four experimental conditions.

Subsequent planned comparisons between the Easy and Difficult Discrimination conditions on the test conducted 24 h after pre-exposure, found no difference in the time exploring the familiar object, $F(1, 14) = 0.260$, $p = 0.618$, or in the number of approaches to such stimuli, $F(1, 14) = 0.057$, $p = 0.814$. However, in the Easy condition, both the exploration time $F(1, 14) = 4.42$, $p = 0.054$, and the number of approaches to the novel stimulus, $F(1, 14) = 7.32$, $p = 0.017$ (although the difference was borderline in the first case), were greater than in the Difficult condition.

Finally, an ANOVA conducted with both the exploration time and the number of approaches to the familiar object during the familiarization trial and the test found that, in general, rats explored the familiar object more extensively during the familiarization trial (when it was novel) than during the test trial: $F(1, 31) = 40.99$, $p < 0.001$, and $F(1, 31) = 64.306$, $p < 0.001$, for exploration time and number of approaches, respectively.

DISCUSSION

This study found that, when the SOR task involved two stimuli that differed markedly in color and form, i.e. discrimination between them was easy, the rats spent more time exploring the novel object than the familiar one, and also made more approaches to the novel one than the familiar, both with the short (1 hr) and long (24 hr) delay intervals. Therefore, as a validation of the SOR task with the parameters and the stimuli employed here, the study established an experimental situation in which a greater exploration of the novel than the familiar stimulus can be observed in adult non-pathological rats both 1 hr and 24 hr after relatively brief exposure to the familiar stimulus. Furthermore, the study established that, using the same procedure but presenting on test two more similar stimuli (differing only in small details), the rats did not display a preference for the novel over the familiar stimulus after either 1 hr or 24 hr. This latter result has usually been interpreted in terms of memory impairments (Ennaceur and Delacour, 1988, Anderson, 2006a, b). If rats do not display a preference for the novel stimulus over the familiar one it is because the memory trace of this latter decayed, and the subjects are not able to recognize the familiar stimulus. However, this seems unlikely to be the case here. The familiar stimuli were in fact the same for both the Easy and Difficult conditions (according to the counterbalancing schedule). Thus, if rats in the Easy condition could remember the familiar stimulus, one might also expect rats in the Difficult condition to remember it. It seems more plausible, however, that if rats in the Difficult condition explored the familiar stimulus and the novel one

similarly, it was not because they forgot the familiar stimulus but because they were unable to differentiate the familiar stimulus from the novel one. If this were the case, the rats would have perceived the novel and familiar stimuli as the same and they would not be exploring them as if both were novel (as would be expected if the memory of the stimuli decayed), but as if they were familiar. This hypothesis is supported by the fact that, in the test conducted 24 hr after the familiarization trial, rats in the Easy and Difficult conditions did not differ in the exploration of the familiar stimulus, but only in the exploration of the novel one. Indeed, rats in the Easy condition seemed to explore the novel stimulus more extensively than those in the Difficult condition. This result is precisely what would be expected if all the rats remembered the familiar stimulus, but only the rats in the Easy condition perceived one of the test stimuli as being novel. Finally, differences in the exploration of the familiar objects between the familiarization and test phases (which are larger in the former than in the latter case) might also be taken to suggest that, in general, the stimuli were treated at test as being familiar and hence they were able to remember the stimuli. This latter finding must be interpreted, however, with the constraint that during the familiarization phase the rats explored two copies of the same object (and thus, two objects in total) and the overall records for these have been compared with the case in which only one object was explored in the SOR task.

According to this analysis, our findings could be taken to indicate that the absence of differences between exploring the novel and familiar stimulus does not always necessarily imply the existence of memory impairments but instead indicates that the animals remember the familiar stimulus (or at least its most general elements) but are unable to differentiate it from other similar but novel stimuli. It has been reported that, while discriminative behavior to very dissimilar stimuli might be maintained for longer intervals between the familiarization trial and test, it disappears for intervals longer than 15 min when the stimuli are more similar (Norman and Eacott, 2004). Our findings are thus consistent with the results of these previous studies and it is possible that shortening the interval between the familiarization trial and test might also allow us to observe discriminative behavior towards very similar stimuli. Further, more extensive exposure to the stimuli during the familiarization phase might improve stimulus differentiation, thereby allowing the subsequent detection of a preference for a similar but novel stimulus when the test stimuli are sufficiently similar.

The principal aim of this preliminary study was to validate a version of the SOR task that could be used for further research on perceptual

learning effects. In this regard, the experiment has been a success. It has been able to establish a situation in which rats can discriminate the stimuli after short exposure and another in which the discrimination is more difficult, this latter protocol being optimal for assessing the effects of preexposure on stimulus differentiation. Moreover, during the familiarization trial the rats did not display a significant preference for any of the objects in particular, or their position in the arena. The more recent reviews about tasks such as the one tested here (i.e., Ammen-Ali et al., 2015, Blaser & Heyser, 2015), have noted that animals usually display preferences for certain objects and spatial locations, and these variables could affect the results found on the test. Thus, an extra advantage of our experimental situation is the control of such potentially confounding variables.

Further, the study represents a potentially important alternative to the standard interpretation of the results of the task. In particular, our findings suggest that the absence of differences exploring the novel and familiar stimuli do not necessarily imply the existence of memory deficits. It is entirely plausible that, results of this sort might also be reflecting perceptual learning deficits due to short or insufficient exposure when the stimuli are very difficult to discriminate. Such learning deficits could be operating instead of or in addition to the memory impairments assumed to occur in normal or pathological aging and other pathological processes (see also Eacott & Heywood, 1995; Norman and Eacott, 2003). These are issues that need to be addressed in further research, since tasks such as the one employed in the present paper provide a potentially useful tool for the study of animal models of memory developed within the field of behavioral neuroscience.

RESUMEN

La similitud entre estímulos reduce el reconocimiento espontáneo de objetos en ratas independientemente del intervalo de retención. El objetivo del experimento fue comprobar en una tarea de reconocimiento espontáneo de objetos el efecto de la similitud de los estímulos y el intervalo de retención entre esta tarea y un ensayo previo de familiarización. 1 hora o 24 horas después de la familiarización con dos copias idénticas del mismo objeto, se midió la exploración de uno de estos objetos y otro nuevo registrando la duración y número de aproximaciones a cada objeto. En la tarea los estímulos difirieron ligeramente en su forma (condición de Discriminación Difícil) o marcadamente en forma y color (Condición de discriminación Fácil). Independientemente del intervalo de retención, la condición Fácil pero no la condición Difícil, prefirió explorar el objeto nuevo. Después del intervalo de 24 horas, la condición Fácil exploró el

objeto nuevo más que la condición Difícil pero no difirieron en la exploración del estímulo familiar. Entonces, las ratas de la condición Difícil podrían haber recordado el estímulo familiar tan bien como las ratas de la condición Fácil pero fueron incapaces de distinguirlo del estímulo nuevo. Se discuten las implicaciones de esta posibilidad en la utilización de tareas de reconocimiento espontáneo de objetos para el estudio del aprendizaje perceptivo y la memoria.

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