A single brief stressful event time-dependently affects object recognition memory and promotes familiarity preference in marmoset monkeys.

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Abstract

A stressful experience can enhance information storage and impair memory retrieval in the rodent novel object recognition (NOR) task. However, recent conflicting results underscore the need for further investigation. Nonhuman primates may provide a unique, underexplored and more translational means to investigate stress-mediated changes in memory. Therefore, we assessed whether a single brief extrinsic stress event affects information encoding, storage and/or retrieval in adult marmoset monkeys submitted to the NOR task. This consisted of an initial 10 min familiarization period with two identical neutral objects. After a 6 h delay, a 10 min test trial was held where a new and familiar object could be explored. Stress was induced by a 15 min restraint event held before or after the encoding phase, or prior to retrieval. Pre-encoding stress had no effect on task performance, as this group displayed above-chance novelty preference similar to non-stressed controls. Postencoding stress induced memory deficits, with both objects being explored equally. Interestingly, pre-retrieval stress induced an above-chance familiarity preference. A single brief stressful event thus affects recognition memory in a time-dependent manner. Also, negative discrimination ratios can be used as a measure of memory in the NOR task and a change in strategy may not mean memory failure in spontaneous learning paradigms.

Keywords: marmoset; memory; object recognition; restraint stress

1. Introduction

A wide range of stimuli are perceived as actual or even potential threats. This leads to physical tension and/or psychological distress, frustration and anxiety that triggers a stress response comprised of several adaptive changes, including activation of the hypothalamuspituitary-adrenal (HPA) axis and the storage of information for more efficient future reactions (Joëls and Baram, 2009). However, stress-mediated changes on memory function can be highly complex, as impairments or even a lack of effect are also reported (for a review see Cazakoff et al., 2010; Wolf, 2009). Prolonged and/or recurring events seem to have an adverse effect on memory function, while the outcome of a single brief event depends, for example, on the nature, intensity and/or duration of the stressor (Sandi and Pinelo-Nava, 2007), as well as the type of task (Shields et al., 2017) and phase of the memory process (i.e., encoding, storage and retrieval; Roozendaal, 2002).

In animals, while many studies traditionally use emotional learning (e.g., *rodents*: Hui et al., 2004) or spatial working memory tasks (e.g., *rodents*: Diamond et al., 1999; *monkeys*: Abreu et al., 2020), others have more recently begun to assess the effects of stress on the novel object recognition (NOR) task. This is typically a two-trial procedure. After an initial familiarization during the sample trial, the original object is encountered again alongside a novel item on the subsequent test trial. Under normal conditions, the new object is usually explored more than the familiar one as animals demonstrate an innate novelty preference (Ennaceur, 2010). On the NOR task, this implies that information about the familiar object was retained and this item recognized, thereby resulting in the novelty preference. A lack of preference, on the other hand, indicates a NOR memory deficit. This simple trial-unique procedure does not require explicit reward or aversive stimulation and thus generally allows for low levels of stress and arousal during the encoding phase (i.e., minimal increase in stress hormone release; Li et al., 2012). As such, stress-induced changes in performance may, for

the most part, be attributed to an extrinsic (task-unrelated) event. There is now evidence in rodents that a single brief stressful event or stress-hormones can enhance information storage (Cunha et al., 2019; Dornelles et al., 2007; Jurado-Berbel et al., 2010; Morrow et al., 2000; Roozendaal et al., 2008) and impair retrieval in the NOR task (Howland and Cazakoff, 2010; Li et al., 2012; Nelissen et al., 2018), as seen in similar studies with humans (Wolf, 2008). Then again, conflicting results emerging in the human (Shields et al., 2017) and rodent literature underscore the need for further investigation (Guercio et al., 2014; Li et al., 2012; Maroun and Akirav, 2008; Nelissen et al., 2018; Okuda et al., 2004; Roozendaal et al., 2006).

The use of nonhuman primates at this time may provide a unique, underexplored and more translational means to investigate how stress affects recognition memory encoding, storage and/or retrieval. Marmoset monkeys were recently shown to perform well on the NOR task (Kalinichenko et al., 2021a, b; Oliveira et al., 2021) and its variants (de Castro and Girard, 2021; Melamed et al. 2017; Vannuchi et al., 2020). They are also highly responsive to different brief stressful events (i.e., \leq 30 min; Duarte et al., 2018), including restraint stress (Pereira et al., 2019). This is a simple, low-cost, painless and reversible means to trigger stress by restricting the range of movement. It inherently induces HPA axis hyperactivity, decreases motivation and triggers immunosuppression (Buynitsky and Mostofsky, 2009).

Therefore, in this study we exposed adult marmoset monkeys (*Callithrix penicillata*) to a single 15 min restraint stress event either before or after the encoding phase, or prior to the retrieval phase of the NOR task. Based on previous animal studies, we hypothesized that this stressful event would significantly affect task performance, yet due to recent discrepancies did not predict which or how each memory stage would be altered. The data obtained here helps elucidate some of these discrepancies and translate animal data to clinical research.

2. Materials and methods

2.1. Ethics statement

Animal numbers and the procedures herein were approved by the Animal Ethics Committee of the University of Brasilia (no. 114/2017). All procedures were carried out according to the Brazilian regulations for the scientific use of laboratory animals (Lei Arouca 11.794/2008), as well as the CONCEA/Brazil and NIH/USA guidelines for the care and use of laboratory animals.

2.2. Subjects and housing conditions

Twenty-four adult black tufted-ear marmosets were used (*Callithrix penicillata*; 13:11 males:females aged 4.5-8.0 years old), weighing 348 ± 8 g (280-460 g) at the beginning of the study. The phase of the females' estrous cycle was not established, yet none were pregnant or had infants recently prior to or after the study. The marmosets were pair-housed at the Primate Center of the University of Brasilia under natural light, temperature and humidity conditions. The colony room had a central corridor from where 12 home-cages could be accessed on either side. Each home-cage (1 x 2 x 2 m; L x W x H) had a nest-box, ropes, wood perches, a monkey chow dispenser and a tray for fresh food. The latter consisted of pieces of fresh fruits and vegetables, nuts, boiled eggs and live mealworms. Fresh food was provided daily at 07:00 h and unconsumed items were removed at 17:00 h. Water and monkey chow were available ad libitum. The housing and maintenance conditions complied with the regulations of the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA).

2.3. Apparatus and experimental set-up

Behavioral testing was held in a rectangular open-field (OF) arena (130 x 75 x 40 cm; L x W x H) suspended 1 m from the floor. For a full description see Melamed et al. (2017) and Vannuchi et al. (2020). Briefly, it had a wire-mesh floor and three aluminum sides, whereas the fourth side and top were made of transparent glass. The arena was painted white, except for the glass top and side, in order to video-track the animals. A guillotine-type door located centrally on one of the longer aluminum sides provided the subjects with an entry/exit point. The OF was set-up in a test room separate from the housing facility and thus subjects were transported to and from this location in an aluminum transport box (20 x 35 x 20 cm; L x W x H) that attached directly to the arena's access door. A camera mounted above the apparatus and another one placed in front of its glass side were connected to a computer located in an adjacent observation room for remote tracking.

2.4. Novel object recognition (NOR) memory task

This task (Fig. 1) consisted of an initial 10-min sample trial, during which the subject was given access to the OF arena and could freely explore two identical objects placed in different corners. After a 6 h retention interval, the subject was again given access to the OF arena for a 10-min test trial. Here, a novel item with a different shape, color, size and texture replaced one of the previously seen objects. The subject could freely explore the new and familiar item during the 10 min trial. Six objects were used: a brown cupcake-shaped plastic container (10 cm diameter x 9 cm high), a green plastic water bottle cut in half (9 cm diameter x 10 cm high), a dark grey and a white plastic 6-egg storage container (13 x 8 x 7 cm; L x W x H), and a white T-shaped (15 x 6 x 10 cm; L x W x H) and a white U-shaped (15 x 12 x 5 cm; L x W x H) plastic water pipes. These objects had no apparent significance to the marmosets and could not be displaced by them as they were filled with plaster. The items assigned as the familiar/new object and their specific location in the OF arena varied between subjects. Also, between trials, the apparatus and objects were cleaned with a 70% ethanol solution.

2.5. Procedure

The marmosets were initially habituated to an empty OF arena for 10 min (Fig. 1). They were then randomly assigned to one of four groups (n=6/group) and submitted 24 h later to the NOR task described above. Each group/subject was tested only once. The no-stress control group (4 males, 2 females) was only submitted to the NOR task. The other three groups underwent the same stress procedure, yet each at a different moment of the task (Fig. 1). The pre-encoding group (3 males, 3 females) was stressed before the sample trial, the postencoding group (4 males, 2 females) was stressed after the sample trial and the pre-retrieval group (3 males, 3 females) was stressed prior to the test trial. The stress event consisted in placing the marmoset for 15 min in the same box used for transport, thus limiting its space to move. Furthermore, as the box was kept in the OF arena's test room, the subject had no visual or olfactory contact with other animals. The sudden onset, movement restriction and social isolation induced by this procedure causes psychological distress and hyperactivity of the neuroendocrine stress response. We recently showed a two-fold increase in circulating cortisol during this same restraint stress procedure, compared to non-stressed marmosets (Pereira et al., 2019). This cortisol response was reliably detected across all individuals, regardless of sex or history with this type of stressor. This procedure differs significantly from the <1 min interval required only for transport. At the end of the stress event, the subject was released in the OF arena for the sample or test trial (pre-encoding or pre-retrieval groups) or taken back to its home-cage (post-encoding group). The habituation and sample trials were held between 08:00 and 12:00 h, and the test trial was from 14:00 to 17:00 h.

2.6. Behavioral and statistical analyses

For each trial of the NOR task, the time spent in motion within the OF apparatus (i.e., locomotor activity), as well as the time spent exploring the objects were manually recorded by

a single investigator, blind to the experimental group, using the AnyMaze analysis software (Stoelting, USA). Locomotion was used as a control measure for possible behavioral changes induced by the stressor that could affect subsequent exploratory behavior on the NOR task. Stress-induced hyperlocomotion has been previously reported in marmosets (e.g., Duarte et al., 2018). Object exploration was operationally defined as the time spent performing direct gazes (sustained fixed orientation of the head toward the stimulus), head cocks (continuous side-to-side pendular-like head movements) and visual monitoring (continuous sweeping movements of the head directed at the stimulus). NOR memory was established using a discrimination ratio (Ennaceur et al., 1997): time spent exploring the novel object minus the time spent exploring the familiar object, divided by the time spent exploring both objects. A positive score indicates a novelty preference, whereas a negative score indicates a familiarity preference.

Data were normally distributed and with equal variance, as assessed by Shapiro-Wilk and Levene's test, respectively. The discrimination ratios were compared to (zero-value) chance level performance using the one-sample t-test, while a one-way analysis of variance (ANOVA) was used for between-group comparisons. For locomotion and total object exploration, between-trial comparisons were held using a mixed-design two-way ANOVA, with 'group' as the independent factor and 'trial' as the repeated measure variable. Whenever significant effects were obtained, subsequent comparisons with the non-stressed control group were performed using Dunnett's test. The results were considered statistically significant when $p \le 0.05$.

3. Results

On the test trial, the discrimination ratio of the non-stressed marmosets and the preencoding group was significantly above (zero-value) chance level (control: $t_5=4.00$, p=0.01; pre-encoding: t_5 =4.89, p=0.005; Fig. 1). These two groups thus spent more time exploring the new rather than the familiar object. The discrimination ratio of post-encoding group did not differ from chance level, with both objects being explored to the same extent (t_5 =-1.07, p=0.34; Fig. 1). However, the pre-retrieval group demonstrated a familiarity preference as its discrimination ratio was significantly below chance level (t_5 =-3.75, p=0.01; Fig. 1). A one-way ANOVA analysis also revealed a between-group effect ($F_{3,23}$ =15.68, p<0.001; Fig. 1), with both the post-encoding and pre-retrieval groups having a discrimination ratio that was significantly lower (p<0.05) than that of the no-stress controls.

Total object exploration differed significantly between groups ($F_{3,20}$ =4.76, p=0.01; Table 1). The values of the pre-retrieval group were significantly (p<0.05) higher than those of the control group. However, for this same parameter, significant effects were not observed when comparing the sample versus tests trials ($F_{1,20}$ =0.01, p=0.96), nor was there a trial versus group interaction ($F_{3,20}$ =0.28, p=0.84). Furthermore, locomotor activity did not differ between groups or trials (group effect: $F_{3,20}$ =1.23, p=0.33; trial effect: $F_{1,20}$ =0.08, p=0.78; interaction: $F_{3,20}$ =0.51, p=0.68; Table 1).

4. Discussion

In this study we showed that a single brief stressful event affected the recognition memory of monkeys in a time-dependent manner. When the stressor took place right after the encoding phase, performance on the NOR task was significantly impaired given that both objects were explored to the same extent. A recognition deficit leads the individual to incorrectly perceive both objects as new, resulting in a lack of exploratory preference. Postencoding stress or stress-hormone administration have been shown to facilitate NOR memory in rodents (*stress*: Cunha et al., 2019; Maroun and Akirav, 2008; Morrow et al., 2000; *hormones*: Dornelles et al., 2007; Jurado-Berbel et al., 2010; Okuda et al., 2004; Roozendaal et al., 2006, 2008). Nonetheless, under conditions that resemble ours, it also impaired task performance. For example, when learning and stress occurred in distinct spatial contexts, storage of neutral information was inhibited in favor of the emotional content of the stress event (reviewed in Sazma et al., 2019). Prior habituation to the task environment also lowered emotional arousal during encoding, which prevented post-encoding corticosteroids from enhancing NOR memory (Maroun and Akirav, 2008; Nelissen et al., 2018; Okuda et al., 2004; Roozendaal et al., 2006). It should be noted as well that, even after the removal of the object, encoding processes remained briefly active (Akkerman et al., 2015) and that stress hormones can exert rapid nongenomic effects on memory function (e.g., Wolf, 2017). It is thus possible that the memory deficits seen here are due to disruptions in encoding and/or storage.

Performance on the NOR task was not affected by pre-encoding stress. Both the preencoding group and the non-stressed monkeys showed above-chance preference for the novel object. Thus prior exposure to a single brief stressful event does not seem to alter the value or attention paid to neutral objects during encoding, nor does it state-dependently affect the NOR task (Nelissen et al., 2018). As such, monkeys can retain and retrieve information about neutral stimuli after experiencing stress, consistent with reports in rodents (Cunha et al., 2019; Li et al., 2012; Nelissen et al., 2018; Vargas-López et al., 2015). However, depending on stress intensity/duration (Sandi and Pinelo-Nava, 2007) and the delay between the stressor and the encoding phase (Joëls et al., 2011), pre-encoding stress may impair recognition in both rodents (Baker and Kim, 2002; Cunha et al., 2019; Eagle et al., 2013; Kart-Teke et al., 2006; Nava-Mesa et al., 2013; Vargas-López et al., 2015; Wang et al., 2012) and humans (Shields et al., 2017).

Notably, when the stressful event took place prior to retrieval the monkeys explored more the familiar rather than the new object. Although this familiarity preference may be linked to an enhanced emotional arousal brought on by the stressor, this may be a complex issue. Initial exploration of the objects and locomotor activity were not affected by the extrinsic stressor. Overall exploration on the sample and test trials also remained constant, suggesting that motivation to explore the object was not affected as well. Further, although cortisol levels in marmosets vary during the day (Bertani et al., 2010), we believe that this group's distinct response is not due to the specific time of day that the stressor was delivered, but rather to the stress event itself. The same 6-h retention interval assessed in non-stressed controls resulted in a novelty preference, similar to previous reports (Kalinichenko et al., 2021a, b; Oliveira et al., 2021). Why the pre-retrieval group had higher levels of general exploration is still unclear, but it may be inherent to this particular group. Differences in personality traits (Slipogor et al., 2021), potentially related to right/left cerebral hemisphere dominance (Gordon and Rogers, 2015), have been shown to influence exploration-avoidance responses of marmosets to environmental stimuli. Further studies should thus be held to properly assess these aspects in the marmoset NOR task. Nonetheless, a change in strategy like the one seen here does not mean memory failure, given that to consistently explore the familiar object over the new object one must have a memory trace of the familiar item (Ennaceur, 2010). A deficit in this task actually requires a lack of preference (i.e., zero-value discrimination ratio), as was seen in our post-encoding group. Recent studies have reported negative discrimination ratios as a measure of recognition memory in rodents (Contreras et al., 2019; Pereda et al., 2019; Vargas-López et al., 2015), yet others found that pre-retrieval stress did impair memory (Howland and Cazakoff, 2010; Li et al., 2012; Nelissen et al., 2018). Prolonged stress, short retention interval and/or lengthy delays between the stressor and memory retrieval in the latter studies may account for this inconsistency.

Taken together, our results show that the effect of a single brief stressful event on recognition memory depends on when the event took place. While pre-encoding stress had no

effect, post-encoding stress impaired NOR task performance. Interestingly, pre-retrieval stress altered object preference rather than memory. As an adaptive defense strategy, familiarity preference may decrease environmental exposure (Rosellini and Widman, 1989) and enhance/update information about familiar/safety cues (Ennaceur et al., 2009, Ennaceur, 2010). Our results thus provide evidence for the use of negative discrimination ratios as a measure of memory in the NOR task and that changes in strategy may not mean memory failure in spontaneous learning paradigms. This not only sheds new light on the use of additional behavioral indicators for measuring recognition memory, but also corroborates the highly-complex modulatory effect that stress exerts on memory function.

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CRediT authorship contribution statement

Clara S. Costa: Conceptualization, Investigation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. André W. C. Oliveira: Investigation, Methodology, Formal analysis, Writing - review & editing. Alexander Easton: Formal analysis, Writing - review & editing. Marilia Barros: Conceptualization, Supervision, Formal analysis, Funding acquisition, Writing - original draft, Writing - review & editing.

Declaration of competing interest

none

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Figure Legend

Figure 1. *Top*: Schematic representation of the procedure, indicating when the pre-encoding (pre-ENC), post-encoding (post-ENC) and pre-retrieval (pre-RET) groups were submitted to a single 15-min restraint stress Circles and triangle represent the familiar and new objects used during the novel object recognition (NOR) memory task. *Bottom*: Effect of the stress event on the marmosets' NOR memory. Non-stressed controls (CTRL) and the pre-ENC group had similar positive discrimination ratios indicative of NOR memory via novelty preference. The post-ENC group showed no memory, with chance-level performance. The pre-RET group also showed NOR memory, yet via familiarity preference (negative ratio). Data are expressed as mean + SEM; n = 6/group. *p<0.05 vs. zero-value chance level, #p<0.05 vs. the no-stress control group.



Behavioral parameter	Trial	
	Sample	Test
Total exploration		
no stress (control)	16±5	18±7
pre-encoding stress	15±2	17±8
post-encoding stress	22±4	22±8
pre-retrieval stress	46±8*	39±11*
Locomotion		
no stress (control)	51±15	52±14
pre-encoding stress	90±30	93±29
post-encoding stress	101±21	93±17
pre-retrieval stress	79±15	84±19

Table 1. Total object exploration and locomotor activity recorded for each experimental
 group during the sample and test trials of the NOR task, expressed as mean±sem seconds.

* p<0.05 vs. no-stress control group