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Pre-exposure and retrieval effects on generalization of contextual fear

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ABSTRACT

The degree of generalization from a fearful context to other contexts is determined by precision of the original fear memory. Experiences before and after fear learning affect memory precision. Pre-exposure to a similar context *before* context conditioning results in increased generalization to the similar context. In contrast, exposure to the conditioning context *after* fear learning reduces fear generalization. In the current study we aimed to investigate whether the events before and after fear learning interact. We hypothesized that pre-exposure-induced enhanced generalization could be reduced by a return to the conditioning context. We found that, in contrast to previous findings, pre-exposure did not affect generalization. However, a reminder of the conditioning context reduced generalization to both a similar and a different context. The results stress the dynamic nature of emotional memory.

1. Introduction

Generalization of fear allows a subject to treat a new situation that is similar to a threatening experience as potentially harmful (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). It is no longer adaptive when a situation that only slightly resembles the threatening event evokes fear. To model fear generalization from one situation to another, animals are trained to fear a context by pairing the context with shock (unconditioned stimulus; US). Next, the animals are exposed to a similar context to test the ability to discriminate between the threatening (conditioning context) and a similar but safe context. A detailed memory of the context in which fear learning took place supports discrimination and reduces generalization (Hardt, Nader, & Nadel, 2013; Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Sahay et al., 2011).

Memory has been shown to be far more dynamic than held possible by traditional consolidation views. It is no longer believed that consolidation results in a fixed memory representation but instead, memories are subject to change in interaction with other events (Forcato, Rodríguez, Pedreira, & Maldonado, 2010; Osan, Tort, & Amaral, 2011; Ramirez et al., 2013; Sevenster, Beckers, & Kindt, 2012; Sevenster, Beckers, & Kindt, 2013; Sevenster, Beckers, & Kindt, 2014). More specifically, the ability to discriminate between similar contexts is affected by experiences *before* and *after* fear learning. In the current study we investigated whether experiences before and after context conditioning interact in producing fear generalization.

First, pre-exposure to a context that is similar, but not the same or different, to the conditioning context enhances generalization on test. Crucial for the understanding of this increase in fear generalization is the phenomenon of pattern completion. If a new

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situation is sufficiently similar to or matches the stored representation of the context, pattern completion mechanisms will ensure retrieval of the existing representation (Blumenfeld, Preminger, Sagi, & Tsodyks, 2006; Hunsaker and Kesner, 2013; Leutgeb and Leutgeb, 2007; Osan et al., 2011). Hence, pattern completion will lead to the retrieval of the similar pre-exposure context during conditioning; both the pre-exposure and the conditioning context will become linked to the shock (Bae, Holmes, & Westbrook, 2015; O'Reilly & Rudy, 2001; Rudy and O'Reilly,1999), facilitating generalization to the pre-exposure context. Second, context re-exposure following fear learning can reduce fear generalization. A return to the conditioning context (without presentation of the US) after context conditioning reduces generalization to a similar context (de Oliveira Alvares et al., 2012, 2013; Wiltgen and Silva, 2007; Zhou and Riccio, 1994). It is well-known that the act of recall promotes memory maintenance (Roediger & Karpicke, 2006). Hence, recall stimulates context specificity of the aversive event, resulting in an increased ability to discriminate between similar contexts.

In sum, it is known that pre-exposure to a similar context *before* conditioning can enhance generalization whereas exposure to the conditioning context *after* fear conditioning can reduce generalization. In the current study we aimed to investigate whether experiences before and after fear conditioning interact. We hypothesized that enhanced fear generalization as a result of pre-exposure can be reduced by a reminder of the conditioning context. On day 1 mice were pre-exposed to a context that was similar to the conditioning context (context A), the to-be conditioning context (context B) or a context that was different from the conditioning context (context C). One day later animals were fear conditioned in context B. Half of the animals were tested first in context A (day 3), followed by test in context B (day 4). The other half were tested first in context B (day 3), followed by test in context A (day 4). All animals were tested in the different context C on day 5. We expected that generalization to context A would be enhanced in those animals that were pre-exposed to context A. Furthermore, we expected that this enhanced generalization would be reduced in those animals first tested in the conditioning context B. Finally, we did explorative analyses to investigate pre-exposure and retrieval effects on generalization to a different context (context C).

2. Methods and materials

2.1. Animals

Thirty female C57BL/6J mice 10–12 weeks of age were used. Animals were housed in a temperature and humidity controlled vivarium with a 12 h light – 12 h dark cycle. Food and water were available ad libitum. Experiments were performed during the light phase. All protocols complied with the European Community Council Directive and were approved by Animal Ethics Committees of the University of Leuven.

2.2. Apparatus

Testing occurred in two identical conditioning chambers (Panlab Startle & Fear Combined System, Panlab, S.L., Cornellà, Spain). The animal compartment (25 × 25 × 25 cm) had black methacrylate walls and a transparent front door and was located in a sound-attenuating cubicle. Shocks were delivered through a stainless steel grid floor. The freezing response was assessed as a measure of learned fear. Movement of the animal was tracked with a motion sensitive floor and registered with Panlab Freezing v1.3 software. Movement could range from 0 to 100; If movement on the sensitive floor remained below a 2.5 threshold for at least 1s, behaviour was classified as freezing. The conditioning chamber was adjusted to create a total of three different contexts (Fig. 1A).

2.3. Context manipulation

The conditioning context B was brightly illuminated (fluorescent lamp) and there was ambient noise produced from the ventilation fan (Fig. 1A). For generalization context A, a piece of cardboard was placed diagonally in the compartment to create a triangular chamber. The chamber was dimly illuminated (small cage lamp) and there was ambient noise produced by the ventilation fan. In context C, the grid floor was covered with a white sheet. There was no room illumination and no background noise. An odor cue was provided by placing a tube containing a cotton ball with a drop of mint solution next to the chamber. After every test session, the chamber was cleaned. Contexts A and B were cleaned with alcohol-detergent solution (70% alcohol, 30 percent detergent), while context C was cleaned with water. Thus, contexts A and B shared several features, including the grid floor, background noise and odor but differed in room illumination and shape of the chamber. Context C was designed to have no features in common (expect that the shape of the context was similar to that of context B).

2.4. Procedure

Testing procedures were adapted from Rudy and O'Reilly (1999) (Fig. 1B). Mice were randomly assigned to one of three pre-exposure conditions. On the first day of the experiment, mice were pre-exposed for 5 min to context A (n = 10), context B (n = 10), or context C (n = 10). One day later, context conditioning took place in context B. The mouse was placed in the conditioning chamber and 2 min later the first US was delivered (0.3 mA, 2 s). The second US was administered 2 min after the first US. One minute later the animal was returned to the home cage. Tests for conditioned fear in contexts A and B were counterbalanced and took place on day 3 and day 4. All animals were tested in context C on day 5. Thus, half of the animals were first tested in the similar context A (test order ABC on day 3, 4, 5, respectively), whereas the other half were reminded of the conditioning context before generalization test (test order BAC on day 3, 4, 5, respectively). Test duration in contexts A, B and C was 5 min. During pre-exposure