Neurobiology of Learning and Memory 137 (2017) 114–122

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Acquisition and inhibition of conditioned fear is modulated by individual stimulus fear-relevance

Jörg Neubert [a,*], Katja Hillbrandt [a], Mathias Weymar [a,b], Alfons O. Hamm [a], Julia Wendt [a]

[a] Department of Psychology, University of Greifswald, Germany
[b] Department of Psychology, University of Potsdam, Germany

ARTICLE INFO

Article history:
Received 9 August 2016
Revised 21 November 2016
Accepted 25 November 2016
Available online 27 November 2016

Keywords:
Fear learning
Safety learning
Conditioned inhibition
Spiders
Phobia
Startle blink response

ABSTRACT

Inhibitory learning is an important factor for decreasing fear expression. We investigated conditioned inhibition of learned fear responses using conditioned excitors and inhibitors differing in fear-relevance in a sample of 48 healthy female students. To study the effect of stimulus fear-relevance, we used the fear potentiated startle paradigm in an AX+/BX− discrimination learning task with fear-relevant (spider) vs. fear-irrelevant (butterfly) pictures as CS+ (A) and CS− (B), respectively. We found that, during acquisition, participants with elevated fear of spiders showed stronger fear potentiated startle to AX+ compared to BX− when the inhibitor (B) was fear-irrelevant (butterfly) using both median split as well as correlational analyses. In contrast, when the excitor (A) was fear-irrelevant (butterfly), fear potentiated startle to AX+ compared to BX− was reduced for participants with higher fear of spiders. Effects of conditioned inhibition were studied in a summation test, where excitor and inhibitor were presented in compound (AB) and compared to the last four excitor trials during prior acquisition. Conditioned inhibition was stronger for participants with a higher fear of spiders, when the butterfly acted as conditioned inhibitor (B). On the other hand, when the spider served as conditioned inhibitor, effects of conditioned inhibition were weaker for participants with higher fear of spiders. Hence, rather than to a general preparedness our data point to a specific impairment in safety learning for individually fear-relevant stimuli.

1. Introduction

Understanding the mechanisms underlying the acquisition and inhibition of fear responses is essential for improving therapeutic interventions particularly in the context of anxiety disorders (Craske, Liao, & Vervliet, 2012; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). During fear conditioning, a biologically neutral stimulus is repeatedly paired with a harmful or noxious unconditioned stimulus (US) which is capable of eliciting a species-specific defensive unconditioned response (UR). Through this procedure the formerly neutral stimulus becomes a signal for the US, a conditioned stimulus (CS), and will evoke associated species-specific behavioral changes (e.g. freezing, startle potentiation) and physiological adjustments supported by the autonomic nervous system, the conditioned fear response. This associative learning process has been formalized in theories like the Rescorla-Wagner-Model (Rescorla & Wagner, 1972) which predicts that the excitatory strength a conditioned stimulus (CS) gains depends on CS and US salience and the number of pairings between both (number of reinforcements).

During extinction training the CS is no longer followed by the US and as a consequence – after several trials – the elicited fear response declines. However, phenomena such as reinstatement and renewal (Bouton, 2004) falsified the assumption that this response decrement is a consequence of some kind of "unlearning" of formerly acquired excitatory associations between a stimulus and its according response. Instead, the acquisition of new inhibitory associations could explain response decrement after extinction training.

Inhibitory learning has been investigated with various experimental designs, however, for most of them the problem of uncertainty in the separation of extinction and inhibition remains unsolved (cf. Jovanovic et al., 2005). A paradigm that overcomes this limitation is the AX+/BX− discrimination learning paradigm (Jovanovic et al., 2005; Myers & Davis, 2004; Wagner, Logan, Haberlandt, & Price, 1968). Here, the response to a third CS_X depends on the compound presentation with the CS_A or CS_B, because the US follows the presentation of AX but not BX during

* Corresponding author at: Department of Psychology, University of Greifswald, Franz-Mehring-Strasse 47, 17487 Greifswald, Germany.
E-mail address: joerg.neubert@uni-greifswald.de (J. Neubert).

http://dx.doi.org/10.1016/j.nlm.2016.11.015
1074-7427/

acquisition. Thereby, CS_A becomes excitatory and CS_B becomes a pure conditioned inhibitor (also referred to as *safety signal*). The inhibitory potential of CS_B can be determined by a summation test with a combined presentation of CS_A and CS_B (Rescorla, 1971). This test should result in response decrement of AB trials in comparison to AX+ trials (Jovanovic et al., 2005).

1.1. CS fear-relevance as a moderator of conditioning

Traditionally, stimulus salience refers to physical properties of stimuli that "pop out" of their environment and hereby automatically capture attention (Schneider & Shiffrin, 1977; Shiffrin & Schneider, 1977; Yantis, 2005; Öhman, Flykt, & Lundqvist, 2000). Salience of the conditioned stimulus can modulate the acquisition and the extinction of the conditioned response. According to the Rescorla-Wagner-Model, stimuli with higher salience require less conditioning trials to develop their strongest possible conditioned response. Moreover, higher stimulus salience would also result in stronger resistance of extinction of the conditioned association. Salience of conditioned stimuli might, however, not only be modulated by their perceptual features but also by their emotional significance (Sebastiani, Castellani, & D'Alessandro, 2011).

In his preparedness hypothesis Seligman (1971) stated that organisms are prepared by evolution to associate fear more readily with stimuli that are salient for survival threats. Thus, fear-relevant stimuli should be more salient than fear-irrelevant stimuli. Using pictures of snakes and spiders as conditioned stimuli Öhman and coworkers provided substantial empirical evidence that autonomic responses conditioned to these fear-relevant stimuli show stronger resistance to extinction compared to responses conditioned to fear-irrelevant (e.g., pictures of flowers or mushrooms) stimuli (for a review see Öhman & Mineka, 2001). While increased resistance to extinction of fear-relevant conditioned stimuli has been replicated multiple times, evidence for faster acquisition of the conditioned response to these stimuli is less reliable (McNally, 1986) suggesting that fear relevance of conditioned stimuli might be more relevant for conditioned inhibition.

1.2. Effects of fear-relevance on conditioned inhibition

In the present study we investigated the effect of stimulus fear-relevance on fear acquisition and conditioned inhibition using an AX+/BX– paradigm (see Fig. 1). Fear-relevant stimuli (pictures of spiders) served as excitors in one group and inhibitors in another group. Pictures of butterflies were used as fear-irrelevant excitors and inhibitors across groups, respectively. To test for conditioned inhibition we conducted a summation test (AB) after fear acquisition. There is ample evidence that pictures of spiders elicit increased autonomic responses, potentiation of the startle reflex and activate the salience network in the brain in high spider fearful individuals (Fredrikson et al., 1996; Globisch, Hamm, Esteves, & Öhman, 1999; Hamm, 1997; Oosterink, de Jongh, & Hoogstraten, 2009; Wendt, Lotze, Weike, Hosten, & Hamm, 2008). Therefore, we also assessed levels of spider fear using the Spider Phobia Questionaire (Hamm, 2006; Klorman, Weerts, Hastings, Melamed, & Lang, 1974) to investigate whether motivational relevance of the excitor and inhibitor would moderate the fear-relevance effects on conditioned inhibition.

Based on these previous findings we hypothesized that it might be difficult - particularly for individuals with high spider fear - to learn that spider pictures are safety signals. Thus we predicted (1) that learning the AX+/BX– discrimination is impaired with the spider pictures presented as safety signal and the butterfly acting as threat cue particularly in high spider fearful individuals. (2) Since we expected that the spider stimulus is an ineffective safety signal, it should not act as conditioned inhibitor in the summation test (AB), again particularly in the high spider fearful individuals.

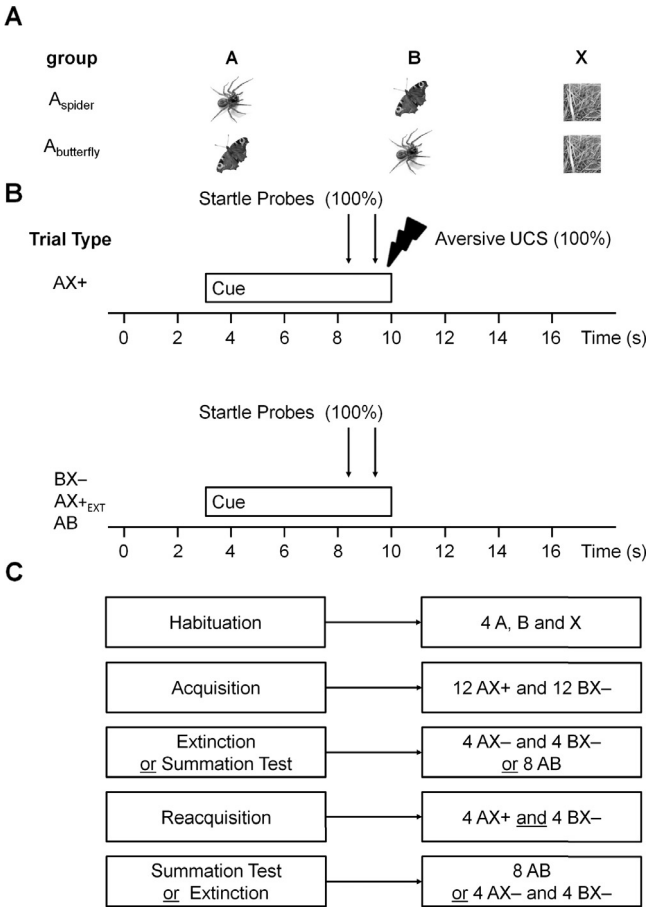

Fig. 1. Experimental Design. A: Assignment of CSs to experimental groups. B: Timing of visual cues, startle probes, and US presentations. Acoustic startle probes followed cue onset by either 5.5 or 6.5 s in 100% of the trials. C: Sequence of the experimental procedure. Half of the participants performed the summation test after the acquisition, while the other half performed it after the reacquisition.

2. Materials and methods

2.1. Participants

Participants were 48 healthy female students of the University of Greifswald. Their age ranged from 18 to 36 years ($M = 22.73$, $SD = 3.41$). All participants completed the German version of the Spider Phobia Questionnaire (SPQ, Hamm, 2006; Klorman et al., 1974; $M = 9.42$; $SD = 6.39$). All participants either received 1.5 h of course credit or 15 Euros for their participation. Participants signed a written informed consent for the study, which was approved by the ethics committee of the University of Greifswald.

2.2. Materials, design and procedure

All participants completed a conditional discrimination paradigm (see Fig. 1) in which a stimulus X was followed by an aversive US when paired with stimulus A, but not when paired with stimulus B. A, B and X were photographs containing a butterfly, a spider and a lump of grass. X was always the lump of grass, while the assignment of the spider and the butterfly to either A or B was balanced across participants. The pictures were presented as visual cues alone (during the habituation phase only) or as compounds