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Research report

Think twice, it's all right: Long lasting effects of disrupted reconsolidation on brain and behavior in human long-term fear

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HIGHLIGHTS

- Exposure to feared cues after memory actvation attenuates phobic fear expression.
- Effect of reconsolidation disruption on long term fears are long lasting.
- Disrupting reconsolidation attentuates amygdala activity over 6 months.
- Disrupting reconsolidation facilitates approach behavior over 6 months.

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ABSTRACT

Memories can be modified when recalled. Experimental fear conditioning studies support that amygdala-localized fear memories are attenuated when reconsolidation is disrupted through extinction training immediately following memory activation. Recently, using functional brain imaging in individuals with lifelong spider fears, we demonstrated that fear memory activation followed by repeated exposure to feared cues after 10 min, thereby disrupting reconsolidation, attenuated activity in the amygdala during later re-exposure, and also facilitated approach behavior to feared cues. In contrast, repeated exposure 6 h after fear memory activation, allowing for reconsolidation, did not attenuate amygdala activity and resulted in less approach behavior as compared to the group that received disrupted reconsolidation. We here evaluated if these effects are stable after 6 months and found that amygdala activity was further reduced in both groups, with a tendency towards greater reductions in the 10 min than the 6 h group. Hence, disrupted reconsolidation results in long lasting attenuation of amygdala activity. The behavioral effect, with more approach towards previously feared cues, in the 10 min than the 6 h group also persisted. Thus, the brain effect of disrupted reconsolidation is stable over 6 months and the behavioral effect also remained. We therefore conclude that disrupted reconsolidation result in a long-lasting diminished fear memory representation in the amygdala which may have clinical importance.

1. Introduction

Experimental fear conditioning studies in rodents [1,2] and humans [2,3] show that extinction training following memory activation can prevent subsequent fear expression. When reconsolidation is disrupted the fear memory trace in the amygdala is updated and permanently altered, both in rodents [1,4] and humans [5,6] (but see also [7]), and plastic processes within the amygdala are held to mediate disruption effects on fear reconsolidation. Since this mechanism does not primarily involve formation of a new inhibitory safety memory, but rather updates the emotional memory representation in the amygdala, it might therefore be a prime candidate mechanism for translation to exposure therapy in the anxiety disorders. There have been demonstrations that disruption of reconsolidation can attenuate long-lasting fears, but in rodents, older memories seem more resistant to reconsolidation disruption [8–13]. In humans with almost life-long fear of spiders we recently demonstrated that disrupting reconsolida-

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tion attenuate amygdala activity in response to feared cues for fear memories that have been present for several decades. After a brief memory activation, shortly followed by repeated exposure to feared cues, diminished neural and behavioral fear expression was observed 24 h later [14]. Typically, in studies investigating the effect of disrupted reconsolidation, the retrieval test is carried out 24–48 h after the experimental manipulation [2], which does not inform on the possible long-term duration of the disruption effect. However, experimental fear conditioning studies employing the post-activation extinction procedures have shown that reduced fear expression is present up to one month in rodents [1,2], and up to 18 months in humans [3,15]. Also, a study investigating pharmacologically disrupted reconsolidation in specific phobia, using post-activation propranolol administration, found lasting effects on approach behavior 12 months after the manipulation [16], but neural effects were not studied. Because the behavioral disruption effect most likely is amygdala-dependent it would be of interest to evaluate if the durability of behavioral effects is parallel to amygdala attenuation.

Originally, Björkstrand et al. [14] investigated short-term effects of disrupted reconsolidation on long-term fear memories using functional magnetic resonance imaging (fMRI) and a fear provocation paradigm in individuals with life-long fear of spiders. Amygdala activity and avoidance behavior was reduced as a function of disruption, and brain activity was coupled to behavior. Here, we investigated long-term stability of these effects by repeating the provocation paradigm 6 months after the manipulation. See Fig. 1 for a design overview. Because we found that disrupted reconsolidation affected a conceptual fear memory representation, rather being cue-specific [14] we here grouped all spiders, both those used for activation and/or exposure with those used to study generalization processes, to evaluate disruption persistence. Based on previous experimental results [1–3,15,16] we hypothesized that both brain and behavioral effects would remain over 6 months.

2. Methods

2.1. Participants

Of the 45 subjects tested day 1 and 2, 39 individuals were available at follow-up on day 180. All subjects initially scored over the 95 percentile for spider fear using a validated fear questionnaire [17,18]. In the 10 min group, 3 subjects were lost. Two subjects had moved, and one had become pregnant and was therefore excluded due to safety concerns regarding magnetic resonance imaging (MRI). In the 6 h group, 3 subjects were lost to follow-up. One subject had moved, and two subjects were unavailable for personal reasons. In addition, one subject in the 6 h group discontinued the re-exposure procedure on day 180 because of a panic attack in the scanner and had to be excluded from the brain imaging analyses. This subject completed the behavioral test and is included in these analyses. Also, one subject in the 10 min group, who had discontinued the behavioral test on day 2, completed it on day 180, and was included in group, but not correlation analyses. Written informed consent was obtained from all participants. For additional information, see original paper [14].

2.2. Stimuli

For the re-exposure procedure, a set of 8 spider pictures obtained from Peira et al. [19] was used, all depicting a spider on a white background. For the behavioral approach test we used 5 additional spider and 5 additional mushroom pictures, also obtained from Peira et al. [19]. For both the re-exposure session and the behavioral test the same pictures as previously shown on day 2, were used. The picture presentations were implemented using E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA).

2.3. Procedure

In our previously published study [14], participants viewed pictures of spiders in an MR-scanner during 2 consecutive days. Day 1, participants first performed a fear memory activation session outside the scanner consisting of exposure to two sets of counterbalanced spider pairs presented for 6 s each. Then, after 10 min, subjects in the 10 min group underwent scanning, whereas the 6 h group had the scanning session 6 h later. During scanning, subjects' heads were lightly fixated with foam cushions, and they viewed pictures through a stereo display. One of the previously activated spider picture pairs was presented 7 times together with 8 presentations of a pair that had not been shown previously. Thus, each trial consisted of 2 previously activated spider slides, and 2 spider slides that had not been activated. The presentation order was randomized within each trial, for a total of 7 trials, with one presentation of the non-activated spider pair added at the end. During the exposure session 30 spider slides were presented, in total. After the exposure session, anatomical reference images were collected, and the participants were dismissed. On day 2, approximately 24 h after the exposure session, subjects were again placed in the scanner and shown 4 different pairs of spiders, one set consisting of the activated and exposed spiders from the previous day, another set consisting of the activated but not exposed spiders, an additional set consisting of the exposed but not activated pair, with a new pair of never presented spiders also added. Thus, each trial consisted of a spider pair from each within-group condition, with the presentation order randomized. The re-exposure session was followed by a behavioral approach-avoidance test described below. On day 180, the stimuli and experimental procedures were identical to the ones used on day 2, consisting of re-exposure to spider pictures in the MR-scanner as well as a behavioral approach-avoidance test. The subjects were placed in the scanner and presented with the same 8 spider pictures shown on day 2, for two trials respectively. The pictures were presented in a randomized order within each trial. For all phases of the experiment, each slide was shown for 6 s with a mean average inter-trial interval of 6 s, varying between 4.5 and 7.5 s.

After the re-exposure session, all subjects completed a behavioral approach test, in which they had to choose to watch either a picture of a spider or a mushroom. Choosing the spider was rewarded with small monetary amounts, whereas the mushroom choice was never rewarded. Subjects were shown a slide with a red and a blue square appearing side-by-side on a white background. They were told that if they chose the blue square a spider picture would appear on the screen after a short delay, whereas if they chose the red square, a picture of a mushroom would follow. Colors were counterbalanced across subjects. Above each square a gray circle was displayed that indicated the amount of money received given that a particular square was chosen. The amount associated with choosing the mushroom was always 0, and the amount for choosing the spider varied between, 0, 0.1, 0.5, 1, 2 and 5 Swedish Krona (SEK), 1 SEK being roughly equal to $0.1. Responses were made by pushing either of two buttons on a hand-held control. The slide during which subjects made their choice was shown for 6 s and the response could be made at any time during this interval. Then, contingent on the response, either a mushroom or a spider slide appeared on the screen for 6 s. Subjects completed 4 trials for each value condition adding up to a total of 24 trials presented in randomized order. Between each trial there was a fixation cross with an average duration of 6 s, varying between 4.5 and 7.5 s. See Fig. 1 for a design-overview.