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Research report

No evidence for blocking the return of fear by disrupting reconsolidation prior to extinction learning

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ABSTRACT

Fear extinction is a central model for the treatment of anxiety disorders. Initial research has reported that the single presentation of a conditioned stimulus prior to extinction learning can permanently block the return of fear. However, only few studies have explored this issue and could not always replicate the findings.

The present study examined human fear extinction using a four-day design. On the first day, two neutral stimuli were paired with electrical stimulation (UCS), while a third stimulus (CS−) was not. Twenty-four hours later, one conditioned stimulus ($CS+_{rem}$) and the CS− were reminded once, 10 min before extinction learning, while the other conditioned stimulus ($CS+_{non\text{-}rem}$) was not presented prior to extinction learning. All stimuli were presented during extinction learning and during two re-extinction sessions (24 h and 6-months after extinction learning) without reinforcement. Blood oxygen level-dependent (BOLD) responses and skin conductance responses (SCRs) to both CS+ and the CS− were explored during acquisition, extinction, and in both re-extinction sessions.

Regarding SCRs, the results showed that a single presentation of a conditioned stimulus did not block the return of fear during re-extinction: Fear recovery during re-extinction (24 h and 6-months after extinction learning) was observed for both CS+ compared with the CS− with no difference between $CS+_{rem}$ and $CS+_{non\text{-}rem}$. Regarding BOLD-responses, no significant differences between $CS+_{rem}$ and $CS+_{non\text{-}rem}$ were found in region of interest (ROI)-analyses (amygdala, ventromedial prefrontal cortex) during extinction learning and both re-extinction sessions. Whole-brain analyses showed increased BOLD-responses to the $CS+_{non\text{-}rem}$ as compared to the $CS+_{rem}$ in several regions (e.g., middle frontal gyrus) during extinction learning and re-extinction (24 h after extinction learning).

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The present findings suggest that the effect of preventing the return of fear by disrupting reconsolidation seems to be a more labile phenomenon than previously assumed. Possible boundary conditions and implications are discussed.

1. Introduction

Fear conditioning and extinction are well-established models for the development, maintenance, and treatment of anxiety disorders (Goode & Maren, 2014; Milad & Quirk, 2012; Milad, Rosenbaum, & Simon, 2014; Vervliet, Craske, & Hermans, 2013). While fear associations can be rapidly acquired and persist over time, the extinction memory is susceptible to disruptions and cannot permanently block the initial fear memory (Myers & Davis, 2007). Consequently, treatments of psychiatric disorders based on extinction learning (e.g., exposure therapy) often produce effective short-term fear reductions, but relapses are not uncommon (Choy, Fyer, & Lipsitz, 2007; Lipsitz, Mannuzza, Klein, Ross, & Fyer, 1999; Sharma, Thennarasu, & Janardhan Reddy, 2014). Therefore, the identification of specific factors that may decrease the return of fear and the number of relapses are of high clinical interest.

Differential fear conditioning paradigms typically consist of different phases (fear acquisition, extinction learning, and re-extinction). During *fear acquisition*, one or two neutral stimuli (CS+) are initially paired with electrical stimulation (UCS), while another stimulus (CS−) is not. After a few trials, the CS+ elicits conditioned responses (CRs) such as increased skin conductance responses (SCRs), startle amplitude, or subjective ratings (Hamm & Weike, 2005; Lang, Davis, & Öhman, 2000). After that, the CS+ and CS− are repeatedly presented without the UCS (*extinction learning*), which finally results in a decrease of CRs in subjective and physiological responses (Milad & Quirk, 2012; Myers & Davis, 2007; Quirk & Mueller, 2008). During this time, the extinction memory is mainly modulated by the amygdala (Quirk & Mueller, 2008). After that, the CS+ and the CS− are again presented without reinforcement (*re-extinction*), e.g., 24 h after extinction learning. The return of fear could be observed under a variety of conditions such as spontaneous recovery, reinstatement, and renewal (Bouton, 2002; Myers & Davis, 2002, 2007). Spontaneous recovery can be described as the reappearance of previously extinguished CRs after a delay following extinction learning without any further learning sessions due to the mere passage of time. Reinstatement refers to the reoccurrence of CRs after extinction learning through the presentation of an unpredictable UCS. Finally, renewal refers to the reactivation of CRs if a subsequent test session is conducted in a different context than the extinction phase. Many methods have been developed to analyze the re-occurrence of CRs of fear during re-extinction. While some studies compared the responses towards the CS+ and the CS− during the first half or the first trial of re-extinction, others authors calculated different "fear-recovery indices" (e.g., first re-extinction trial minus last extinction learning trial; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Schiller et al., 2010).

Recently, animal and human studies have demonstrated that the re-occurrence of conditioned fear during re-extinction can be prevented by different techniques, which presumably alter the initial fear memory (Agren, 2014; Agren, Furmark, Eriksson, & Fredrikson, 2012; Johnson & Casey, 2015; Kindt, Soeter, & Vervliet, 2009; Liu et al., 2014; Nader, Schafe, & Le Doux, 2000; Schiller et al., 2010, 2013; Warren et al., 2014). A frequently used technique in human studies is the presentation of a previously conditioned stimulus ($CS+_{rem}$) 10 min prior to extinction learning without reinforcement, while the other conditioned stimulus ($CS+_{non\text{-}rem}$), also previously paired with the UCS during fear acquisition, is not presented prior to extinction learning (Schiller et al., 2010, 2013). It has been suggested that this single presentation of the $CS+_{rem}$ reactivates the original CS+/UCS memory, which enables a new "CS+/no-UCS" association during extinction learning to be permanently incorporated (Agren, 2014; Schiller et al., 2010). Influential studies have demonstrated successful blocking of the return of fear to the $CS+_{rem}$ as compared to the $CS+_{non\text{-}rem}$ during re-extinction when using this procedure (Schiller et al., 2010, 2013). Regarding the underlying neural correlates, a previous study found increased activity in the ventromedial prefrontal cortex (vmPFC) and altered effective connectivity to the $CS+_{non\text{-}rem}$ compared to the $CS+_{rem}$ during extinction (Schiller et al., 2013). Regarding re-extinction, increased amygdala responses to the $CS+_{non\text{-}rem}$ were found compared to the $CS+_{rem}$, which has been assumed as an indicator for fear responses (Agren, 2014; Schiller et al., 2013).

However, other studies using similar paradigms could not replicate these promising findings (Golkar, Bellander, Olsson, & Ohman, 2012; Kindt & Soeter, 2013; Soeter & Kindt, 2011). They showed a return of fear to both CS+ and could not find any differences between the $CS+_{rem}$ and the $CS+_{non\text{-}rem}$. In a recent review, Agren (2014) hypothesized that these contrary results might be due to specific subgroups in which the blocking is effective. It was argued that the Val^{158}Met-polymorphism in Catechol-O-Methyl-Transferase (COMT) is of special interest, because recent studies have been able to show an association of the COMT Val^{158}Met-polymorphism with fear acquisition and extinction learning (Agren, Furmark et al., 2012; Lonsdorf et al., 2009; Wendt et al., 2014). For instance, Lonsdorf and colleagues showed deficits in extinction learning as well as a poorer treatment outcome in extinction-based therapy in Met/Met individuals (Lonsdorf et al., 2009, 2010, 2011). However, no study has investigated the association between the COMT Val^{158}Met-polymorphism and delayed extinction recall or return of fear.

Based on the above-mentioned findings, the present study aimed to investigate the following: First, we investigated potential SCR differences between $CS+_{rem}$ and $CS+_{non\text{-}rem}$ during