Fear reactivation prior to exposure therapy: Does it facilitate the effects of VR exposure in a randomized clinical sample?

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ABSTRACT

Background and objectives: The current study is the first to examine whether reactivation of fear memory prior to exposure therapy reduces relapse in a randomized clinical sample.
Methods: In a standardized treatment protocol combining virtual reality and in-vivo exposure, patients underwent a fear reactivation procedure using a virtual spider 10 min prior to a virtual reality (VR) exposure (reactivation group: RG, $n = 15$). A control group (CG, $n = 17$) was exposed to a virtual plant 10 min prior to the VR exposure. Outcome measures were a VR spontaneous recovery test (SRT) and in-vivo a behavioral avoidance test assessed 24 h after VR exposure. One week later an in-vivo exposure session followed. Additionally, a follow-up using psychometric assessment was conducted six months after the first session.
Results: Both groups benefitted significantly and equally from the combined treatment, and importantly, the SRT revealed no return of fear in both groups. Furthermore, follow-up tests showed long-term treatment effects with no group differences.
Limitations: Due to different study components (VR treatment and in-vivo), we were not able to determine which treatment module was mainly responsible for the long-term treatment effect. Furthermore, no direct measure of memory destabilization was possible in this study.
Conclusions: Our treatment package was highly effective in reducing phobic fear up to 6 months following treatment. Explicit fear reactivation prior to exposure was not beneficial in VR exposure treatment, possibly due to a failure to induce a memory destabilization or due to an implicit fear reactivation prior to treatment in both groups.

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1. Introduction

Although there is little doubt about the efficacy of exposure-based treatments for specific phobias, return of fear after successful treatment is still a major problem (Choy, Fyer, & Lipsitz, 2007; Lipsitz, Mannuzza, Klein, Ross, & Fyer, 1999). Several strategies aiming to prevent, or at least, diminish the return of fear have been explored so far. These include exposure in multiple contexts (Shiban, Pauli, & Mühlberger, 2013; Thomas, Vurbic, & Novak, 2009), exposure with a reminder cue of the extinction context (Brooks & Bouton, 1993) or pharmacological interventions, e.g., the administration of Propranolol, a beta-blocker, prior to or directly after fear reactivation in order to disrupt memory reconsolidation (Kindt, Soeter, & Vervliet, 2009).

Reactivation of long-term memory initiates a process similar to memory consolidation, namely memory reconsolidation (Bentz, Michael, de Quervain, & Wilhelm, 2010), which requires de novo protein synthesis to restabilize memory traces. The synthesized proteins for these two processes differ at the gene expression level, e.g., BDNF being expressed in the case of consolidation, and Zif268 for reconsolidation (Barnes, Kirtley, & Thomas, 2012; Lee & Hynds, 2013).

Pharmacological intervention, such as the blockade of beta-adrenergic receptors, shortly before or just after memory reactivation has been used to alter the reconsolidation process. For example Debiec and LeDoux (2004) demonstrated that an intra-

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amygdalar infusion of the beta-blocker Propranolol interferes with memory reconsolidation in rats. Comparable results were also reported in human samples. Propranolol either administered prior to memory reactivation (Kindt et al., 2009; Soeter & Kindt, 2010, 2011) or after memory reactivation (Sevenster, Beckers, & Kindt, 2013; Soeter & Kindt, 2012) reduced conditioned fear responding and prevented the return of fear.

Recent experiments have focused on interfering with the process of memory reconsolidation by a behavioral procedure rather than pharmacologically blocking it. This approach relies on the lability, i.e. the *susceptibility to alteration*, of the memory trace during reconsolidation. The time window for this state of lability is believed to last 6 h after memory reactivation (Nader, Schafe, & Le Doux, 2000). Monfils, Cowansage, Klann, and LeDoux (2009) examined the effect of reactivation in rats and found that only rats which received extinction training within the reconsolidation window (i.e., 10 min or 1 h after memory reactivation) showed significantly reduced freezing in response to the CS at test, while rats who received extinction training outside this window (6 h or 24 h) did not show reduced freezing. Furthermore, extinction effects remained stable even up to one month after the extinction training. These results implicate that extinction training during memory reconsolidation leads to an incorporation of the new valence of the CS into the original fear memory trace (Monfils et al., 2009). However, there are animal studies that do not support this finding (Chan, Leung, Westbrook, & McNally, 2010; Morris, Furlong, & Westbrook, 2005).

Nevertheless Schiller et al. (2010) were able to adapt this procedure to a human sample. In their seminal study, three groups of participants underwent a fear conditioning protocol. In one group, fear was reactivated 10 min prior to the extinction training by exposing the participants to a single presentation of the CS+. In the second group, reactivation took place 6 h prior to the extinction training, and in the third group fear was not reactivated at all. In a spontaneous recovery test 24 h after the extinction training, they found that fear was only eliminated in the first group, as indicated by no return of fear (reflected in mean differential SCRs). This result was stable in a follow-up test one year later. Kindt and Soeter (2013) were unable to replicate the findings of Schiller et al. (2010). Instead, they showed that a single retrieval period prior to extinction did not attenuate spontaneous recovery of extinguished conditioned responses, namely startle potentiating, skin conductance response, and US expectancy ratings. Other studies (Golkar et al., 2012; Soeter & Kindt, 2011) were also not able to replicate Schiller's findings. However, using an auditory fear conditioning paradigm, Oyarzun et al. (2012) were able to replicate Schiller at al. (2010).

As far as we know, these results were not translated to clinical practice yet. Such a translational step could advance exposure therapy substantially if the reactivation of fear memory within the reconsolidation window prior to exposure therapy would erase the fear memory and in turn prevent relapses. Therefore, the aim of our study is to apply the Schiller et al. (2010) reconsolidation protocol to exposure therapy of a clinical sample of spider phobic patients. Based on their results we expect that fear reactivation before exposure reduces spontaneous recovery of fear and improves long-term treatment success.

2. Method

2.1. Design

Participants meeting the entry criteria were randomly (simple randomization 1-1) assigned to two groups (reactivation vs. control). Participants and researcher conducting the analysis were blind to the condition (double blind design) up to the moment of pre-exposure as the researcher could see the presented stimulus on the PC monitor. Data was collected during four sessions within two weeks and a 6-month follow-up questionnaire. G*Power 3.1.7 was used to calculate the sample size.[5] The medical ethic committee at the University of Würzburg, Germany, approved this study. Data collection was carried out from December 2010 to October 2011.

2.2. Participants

Forty-one volunteers with self-reported spider phobia were recruited through advertisements in local newspapers (see trial CONSORT flowchart, Fig. 1). The first screening was conducted via telephone; exclusion criteria were pregnancy, current involvement in psycho- or pharmacotherapy, and cardiovascular or neurological diseases. Forty-one persons were invited to a structured clinical interview (SCID-I, (Wittchen, Zaudig, & Fydrich, 1997) see under 2.3 for details) of which 36 persons fulfilled all DSM-IV criteria for spider phobia (American Psychiatric Association, 2000) and were admitted to the data collection phase. These patients were randomly assigned either to the reactivation group (RG) or to the control group (CG). Four participants were excluded later due to low reactivity to the reactivation cue (virtual spider), i.e. a fear rating of less than five on a scale from 0 to 10 reported 5 s after reactivation. Thus, 32 patients were included in the data analysis, 15 in the reactivation group and 17 in the exposure-only group. All of them were Caucasian, had normal or corrected-to-normal vision, and were aged 18–60 ($M = 31.14$ years, SD $= 10.78$). The study was conducted at a laboratory in the clinical psychology department at the University of Würzburg in Germany.

2.3. Virtual reality scenarios

The immersive virtual reality (VR) environment was generated using the Steam Source engine (Valve Corporation, Bellevue, Washington, USA). Additional 3D elements were designed and compiled with Softimage XSI Modtool 5 and Softimage XSI 6 (Softimage Co.; Montreal, Quebec, Canada). To control the VR environment during the experiment, we used software written in-house called "Cybersession", that ran on a Windows PC (Pentium 4 3.20 Ghz, 1 Gb RAM, Intel 82865G Graphics Controller). The virtual environment was displayed via a Z800 3D Visor head-mounted display (HMD; eMagin, NY, USA). In order to adapt the field of vision to the head movements, the head position was monitored using the Patriot electromagnetic tracking device (Polhemus Corporation, Colchester, Vermont, USA). The tracker was mounted on a headphone (Sennheiser HD 215, Thomann, Erlangen), which was used for the presentation of instructions and information during the experiment.

2.4. Measures

To diagnose spider phobia and comorbid disorders we used the structured clinical interview for DSM-IV (SCID-I, Wittchen et al., 1997). Participants were excluded from the experiment if spider phobia was not the primary diagnosis. The structured interview was conducted either by a graduated psychologist, who had already completed four years of psychotherapy postgraduate training or by a psychology student (almost graduated) who had undergone extensive SCID-I training. All interviews were videotaped, and in

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[5] Sample size of $N = 30$ is based on an expected effect size of .25 similar to a study we conducted where we had a slightly stronger effect size of .33 in the most relevant parameter (Group × Time interaction in the test phase, see Shiban et al., 2013).