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Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study

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Abstract

Recall of fear extinction, which is thought to aid in recovery from a psychologically traumatic event, is hypothesized to be deficient in post-traumatic stress disorder (PTSD), but this has not yet been demonstrated in the laboratory, nor has its origin been investigated. To address these two issues, 14 pairs of monozygotic twins discordant for combat exposure, in 7 of which the combat-exposed twin had PTSD, underwent a two-day fear conditioning and extinction procedure. On Day 1, subjects viewed colored light conditioned stimuli, some of which were paired with mild electric shock, followed by extinction of the conditioned responses. On Day 2, recall of Day 1 extinction learning (i.e., extinction retention) was assessed. Skin conductance response (SCR) was the dependent measure. There were no group differences during acquisition or extinction learning. However, a significant PTSD Diagnosis (in the exposed twin) × combat Exposure interaction emerged during extinction recall, with the PTSD combat veterans having larger SCRs than their own co-twins, and than the non-PTSD combat veterans and their co-twins. These results indicate that retention of extinction of conditioned fear is deficient in PTSD. Furthermore, they support the conclusion that this deficit is acquired as a result of combat trauma leading to PTSD, rather than being a predisposing factor to developing PTSD upon the stress of combat.

Keywords: Stress disorders, Post-traumatic; Fear; Conditioning; Classical; Galvanic skin response; Memory; Twins; Monozygotic

1. Introduction

Extinction is the reduction in conditioned responses (CRs) that occurs when the conditioned stimulus (CS) no longer predicts the unconditioned stimulus (US). Post-traumatic stress disorder (PTSD) involves learned fear (Rothbaum and Davis, 2003). Abnormally high psychophysiological conditioned responses to reminders of traumatic events can persist as long as 50 years following its cessation (Orr et al., 1993). These data suggest that a deficit in either extinction learning or retention of that learning may underlie failure to recover from the effects of the traumatic stressor (Rauch et al., 2006; Milad et al., 2006b; Davis et al., 2006; Sotres-Bayon et al., 2004; Maren and Quirk, 2004). Consistent with this view, slower extinction of corrugator electromyogram responses were found to represent a pre-trauma risk factor for PTSD-related symptoms following a traumatic event (Guthrie and Bryant, 2006). Although studies have supported impaired extinction learning in PTSD (Blechert et al., 2007; Orr et al., 2000; Peri et al., 2000), no previous studies have reported deficits in extinction retention.

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If extinction retention is deficient in PTSD, it could represent either an acquired PTSD sign, e.g., result from the traumatic stress that caused the PTSD and/or the stress of having PTSD, or a pre-existing vulnerability factor for developing PTSD upon traumatic exposure. We have been studying monozygotic twin pairs discordant for combat exposure to address the pre-existing vs. acquired origin of biological abnormalities found in PTSD (Pitman et al., 2006). If an abnormality is genetic or due to environmental influences shared by twins during their rearing, i.e., is a "familial" vulnerability factor, then it should be present in the non-trauma-exposed co-twins of trauma-exposed twins with PTSD. Alternatively, if the abnormality results from the traumatic event, then their combat-unexposed co-twins should not share it.

To test the presence and origin of deficient extinction retention in PTSD, we used a two-day fear conditioning and extinction protocol that has been successfully employed in persons without mental disorders (Milad et al., 2005a, 2006a). On the first day, subjects underwent fear conditioning in one virtual context followed by extinction learning in another virtual context. On the second day, extinction recall was tested in the previous extinction context. The conditioned stimuli (CSs) were colored lights that were presented within both contexts. This protocol differed from other studies that examined conditioning and extinction learning in PTSD (for example, Orr et al., 2000) in two ways: (1) conditioning and extinction learning were conducted in two different virtual contexts, and (2) an extinction retention test was conducted 24 h after extinction learning.

2. Materials and methods

2.1. Subjects

Subjects were drawn from a pool of identical twins who had participated in a previous study of physiological responses to loud tones. A description of the recruitment strategy, and characteristics of the participant population has been reported elsewhere (Orr et al., 2003). Fourteen pairs of male monozygotic twins participated. One "exposed" (Ex) twin had served in the Vietnam combat theater, whereas his "unexposed" (Ux) co-twin had not. Of the Ex twins, seven developed combat-related PTSD (P+), and seven did not (P−), as determined by the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995; Weathers et al., 2001) using DSM-IV criteria. Thus, there were four cells of seven subjects each as follows: ExP+: combat-exposed veteran with current, combat-related PTSD, and UxP+: his combat-unexposed co-twin; as well as ExP−: combat-exposed veteran who never had combat-related PTSD, and UxP−: his combat-unexposed co-twin.

2.2. Demographics and psychometrics

Demographic and psychometric means (SDs) were as follows: *Age* (years): ExP+/UxP+ 58.1 (2.8), ExP−/UxP− 59.1 (2.5), $t(12) = 0.7$, $p = 0.50$; *Combat severity score* (Janes et al., 1991) (range 0–18): ExP+ 7.7 (2.4), ExP− 3.4 (2.4), $t(12) = 3.4$, $p = 0.005$; *Total CAPS score* (range 0–136): ExP+ 59.0 (24.1), ExP− 5.1 (9.4), $t(12) = 5.5$, $p < 0.001$. All subjects were also administered the CAPS with regard to their most severe non-combat related event, as well as the Structured Clinical Interview for DSM-IV (SCID) for non-PTSD Axis I mental disorders (First et al., 2002). Current comorbid disorders included one ExP+ subject with both major depressive disorder and non-combat-related PTSD, two ExP+ subjects with dysthymia, and one UxP− subject with dysthymia. No subjects in the ExP−, UxP+, or UxP− groups had non-combat-related PTSD.

2.3. Conditioning procedure

The procedures used in the present study were previously described (Milad et al., 2005a,b; Rauch et al., 2005). Digital photographs of two different rooms constituted the visual contexts. Each room contained a lamp, and two different colors (i.e. blue and red) of the lighted lampshade constituted the CSs. The selection of the CS+ and CS− colors was randomly determined and counterbalanced across participants. Contexts and CSs were displayed on a computer monitor three feet in front of the participants. The US was a 500 ms electric shock delivered through electrodes attached to the second and third fingers of the dominant hand. The intensity of the shock was previously selected by each participant so as to be "highly annoying but not painful" (Orr et al., 2000).

The experimental protocol was administered over two separate days. On Day 1, the Habituation phase consisted of eight trials, in which the to-be CS+ and to-be CS− (four of each) were presented in a counterbalanced manner within either the to-be conditioning context (CX+) or the to-be extinction context (CX−). The Acquisition phase consisted of five CS+ and five CS− trials, all presented within CX+. The shock US occurred immediately following each CS+ offset without delay. The Extinction Learning phase was divided into two sub-phases: early and late, which were separated by an approximately 1-min rest period. Each sub-phase consisted of five CS+ and five CS− trials, all presented within the CX−. On Day 2, the Extinction Recall phase was identical to an Extinction sub-phase from the previous day. Subjects were instructed that at all times (except for the Habituation phase), they may or may not receive the electric shock US. However, although the shock electrodes remained attached to the participant's fingers during the Extinction Learning and Extinction Recall phases, no shocks were delivered.

For each trial during the experiment, the virtual context was presented for 18 s: 6 s alone followed by 12 s in combination with the CS+ or CS−. The mean inter-trial interval was 16 s (range 12–21 s). Skin conductance response (SCR) was scored as previously described (Milad et al., 2005a; Orr et al., 2000; Orr and Lanzetta, 1980; Pitman and Orr, 1986). Specifically, SCR was calculated for each CS trial