Impaired fear inhibition learning predicts the persistence of symptoms of posttraumatic stress disorder (PTSD)

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ARTICLE INFO

ABSTRACT

Recent cross-sectional studies have shown that the inability to suppress fear under safe conditions is a key problem in people with posttraumatic stress disorder (PTSD). The current longitudinal study examined whether individual differences in fear inhibition predict the persistence of PTSD symptoms. Approximately 2 months after deployment to Afghanistan, 144 trauma-exposed Dutch soldiers were administered a conditional discrimination task (AX+/BX−). In this paradigm, A, B, and X are neutral stimuli. X combined with A is paired with a shock (AX+ trials); X combined with B is not (BX− trials). Fear inhibition was measured (AB trials). Startle electromyogram responses and shock expectancy ratings were recorded. PTSD symptoms were measured at 2 months and at 9 months after deployment.

Results showed that greater startle responses during AB trials in individuals who discriminated between danger (AX+) and safety (BX−) during conditioning, predicted higher PTSD symptoms at 2 months and 9 months post-deployment. The predictive effect at 9 months remained significant after controlling for critical incidents during previous deployments and PTSD symptoms at 2 months. Responses to AX+ or BX− trials, or discrimination learning (AX+ minus BX−) did not predict PTSD symptoms. It is concluded that impaired fear inhibition learning seems to be involved in the persistence of PTSD symptoms.

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1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by re-experiencing of the trauma, avoidance of its reminders, and hyperarousal (American Psychiatric Association, 1994). Early after trauma, PTSD symptoms are relatively common (Shalev et al., 1996), but, generally, only about 9% of trauma-exposed individuals develop PTSD (Breslau et al., 1998).

Fear conditioning models may explain why PTSD symptoms persist (Engelhard et al., 2009; Pitman et al., 1993). According to contemporary conditioning models (see Engelhard et al., 2009) the traumatic event (unconditioned stimulus; US) triggers an unconditioned response, characterized by strong arousal and fear.

Previously neutral (conditioned) stimuli (CSs), like sights, sounds, and smells present at the time, become associated with the US. As a result of this CS–US pairing, CSs may later activate the representation of the US in absence of the actual US, leading to a conditioned fear response such as re-experiencing and hyperarousal symptoms. Usually, when the CS is no longer followed by the US, acquired fear extinguishes (the individual learns that the CS no longer predicts the US). A breakthrough in the understanding of persistent fear is that extinction involves inhibitory learning (Bouton, 2002; Myers et al., 2006) which results in two acquired meanings of the CS: the originally-learned excitatory meaning (CS–US) and the new inhibitory meaning (CS - no US). In trauma-exposed individuals with persisting PTSD symptoms, no or incomplete inhibitory learning may occur.

It has been proposed that the failure to inhibit the fear response in the presence of safety signals plays a prominent role in PTSD's development and persistence (Davis et al., 2000). Essentially, the inability to suppress fear responses in the presence of safety may be due to (a) the inability to discriminate between danger and safety

signals and (b) the inability to inhibit the fear response to safety signals. The first notion suggests that during acquisition, people with PTSD may mistake the safety signal for the danger signal. In most conditioning paradigms, these stimuli share many stimulus properties (e.g., both are colored shapes; Lissek et al., 2005). Support for such stimulus-generalization is given in fear-conditioning studies reporting more pronounced psychophysiological responses during safety signals (but not during danger signals) in PTSD-patients than in trauma-exposed controls, including electrodermal responses (Peri et al., 2000) and fear-potentiated startle (Grillon and Morgan, 1999). In the latter study, this lack of differential responding was not attributable to a failure to learn the CS– US contingency on a cognitive level (Grillon and Morgan, 1999).

The second notion has received much less research attention. Thus, it is unclear whether individuals with PTSD are less able to inhibit the fear response in the presence of safety cues, even if they have learned to discriminate between danger and safety cues. Critically testing this requires an experimental paradigm that allows the independent assessment of excitatory and inhibitory associations and transfer of inhibition, e.g., the conditional discrimination paradigm called "AX+/BX–" (Jovanovic et al., 2005), originally developed for animal research (Myers and Davis, 2004). In this paradigm, neutral stimulus X is paired with a US (i.e., airblast to the throat) when X is presented with stimulus A (AX+), and not when X is presented with B (BX–). Thus, after AX+ and BX– trials, A has become excitatory, and B is inhibitory. In subsequent crucial AB trials, reduced fear to A is expected, because B transfers its inhibitory properties to A (Jovanovic et al., 2005). A recent study using this paradigm found that individuals with high PTSD symptom-levels showed (a) no significant difference in discrimination between danger and safety (AX+ vs. BX– trials), and (b) did not show reduced fear potentiated startle to AB trials (Jovanovic et al., 2009a). The second finding may directly follow from the first: if no discrimination learning occurs, no inhibitory learning can take place. Similar results were found in another study that compared trauma-exposed individuals with PTSD to trauma-exposed individuals with no disorder or with major depression (Jovanovic et al., 2010a). Results of both studies indicate that individuals with PTSD show a lack of discrimination between danger and safety cues, and do not show fear inhibition under safe conditions. Although the lack of fear inhibition in PTSD may be secondary to failed discrimination learning, the effect size for impaired inhibition learning in the second study (Jovanovic et al., 2010a) was twice as large as the effect size for impaired discrimination learning. This suggests that at least some individuals with PTSD show impaired transfer of inhibition after successful safety cue learning or, alternatively, that impaired transfer of inhibition is a more robust measure of reduced fear inhibition (cf. Jovanovic et al., 2010a). To elucidate whether deficient fear inhibition learning is implicated in the development of PTSD, analyses should focus on participants who showed successful discrimination between the danger and the safety cue.

An important question is whether impaired discrimination learning and impaired fear inhibition learning predict the development of persistent PTSD symptoms. Since previous studies were cross-sectional (Jovanovic et al., 2009b, 2010a), studies using longitudinal designs in individuals at risk for PTSD symptoms are needed to elucidate whether abnormalities in fear conditioning are vulnerability factors or epiphenomena of disease processes.

The current study examined whether reduced fear inhibition learning predicts the persistence of PTSD symptoms using a longitudinal design in a sample of recently trauma-exposed soldiers deployed to Afghanistan. More specifically, we tested whether the persistence of PTSD is predicted by (a) a failure to discriminate between danger and safety (i.e., smaller differences between fear responses during AX+ trials relative to BX– trials) or by (b) a failure to inhibit the fear response in the presence of safety (i.e., stronger fear responses during AB trials).

2. Method

2.1. Participants and procedure

Participants were Dutch Royal Army soldiers ($N = 144$) deployed to Afghanistan from November 2009 to March 2010 and participating in a larger project (Lommen et al., 2013). About 2 months post-deployment, every two out of three soldiers participating in the larger project were approached for participation in the current study. Assessments at pre-deployment (baseline characteristics), 2 months post-deployment (conditional inhibition paradigm, PTSD-diagnosis and PTSD-questionnaire) and 9 months post-deployment (PTSD-questionnaire) took place at the military bases in the Netherlands. They were performed by trained clinical psychologists.

Participants gave oral and written informed consent. The study was approved by the Institutional Review Board of the University Hospital Maastricht.

2.2. Experimental procedure

The AX+/BX– conditional discrimination paradigm (cf. Jovanovic et al., 2005; Jovanovic et al., 2009a) was presented using the software 'Presentation' (Neurobehavioral Systems Inc, www.neurobs.com). Each session consisted of a startle habituation phase followed by three conditioning blocks and a fear inhibition block without any breaks. Conditioned stimuli (CSs) were a compound of two different shapes presented on a computer screen. AX+ trials consisted of cue 'A' paired with a common cue 'X', BX– trials consisted of cue 'B' paired with cue 'X'. The fear inhibition test stimulus was a compound of the previously conditioned A and B cues and was used to determine transfer of inhibition of B to the fear response to A. Cues A, B, and X were blue, black or purple shapes (star, triangle or square; counterbalanced across CSs) and any given pair of cues involved two different colors and shapes. For each compound stimulus, the cues were presented simultaneously with a plus sign between the shapes to facilitate elemental processing (Jovanovic et al., 2010a, 2010b). The aversive stimulus (US) was a mild electric shock (500 ms, .2–4.0 mA) delivered to two fingers of the non-dominant hand. Before the task it was individually set at a 'highly annoying but not painful' level using a work-up procedure (cf. Orr et al., 2000).

The habituation phase consisted of six startle probes presented alone (noise-alone trials, NA). The conditioning phase consisted of three blocks. Each block included 12 trials: four AX+ trials, four BX– trials and four NA trials, in random order. Each trial included a startle probe. Immediately after the conditioning phase, a block of three AB trials was presented. AX+ trials were always followed by the US (reinforced stimulus), whereas the BX– and AB trials were not (non-reinforced stimulus). In the AX+ trials, shape A and X were presented on the computer screen during 6040 ms. The 40 ms startle probe was presented at the end of the first 5 s, and was followed after 500 ms by the US (duration: 500 ms). The shapes remained on the screen for an additional 250 ms, such that both shapes were visible during the startle probe and the US. During the BX– trials, B and X were presented simultaneously during 5040 ms, and the startle probes were presented at 5 s from the start of the trial. The AB trials were similar to the BX– trials. In all trials, visual analog scales (VASs) for measuring US-expectancy were presented at the bottom of the screen during the first 5 s, after which they disappeared. Inter-trial intervals were of randomized duration (range: 9–22 s).