

Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder [☆]

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Abstract

The β -adrenergic blocker propranolol given within hours of a psychologically traumatic event reduces physiologic responses during subsequent mental imagery of the event. Here we tested the effect of propranolol given after the retrieval of memories of past traumatic events. Subjects with chronic post-traumatic stress disorder described their traumatic event during a script preparation session and then received a one-day dose of propranolol ($n = 9$) or placebo ($n = 10$), randomized and double-blind. A week later, they engaged in script-driven mental imagery of their traumatic event while heart rate, skin conductance, and left corrugator electromyogram were measured. Physiologic responses were significantly smaller in the subjects who had received post-reactivation propranolol a week earlier. Propranolol given after reactivation of the memory of a past traumatic event reduces physiologic responding during subsequent mental imagery of the event in a similar manner to propranolol given shortly after the occurrence of a traumatic event.

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1. Objectives

According to a translational model of post-traumatic stress disorder (PTSD) based upon hormonal modulation of Pavlovian conditioning (Pitman, 1989), a terrifying event (unconditioned stimulus, UCS) overstimulates stress

hormones as part of an unconditioned fear response (UCR). These hormones overly strengthen the consolidation of conditioned fear, which is later manifest in durable fear responses (conditioned responses, CRs) to reminders of the event (conditioned stimuli, CSs). Animal and human data indicate that the effects of stress hormones on conditioning can be opposed by the β -adrenergic blocker propranolol (McGaugh, 2004). In a previous study, we found that propranolol administered within six hours of a traumatic event reduced physiologic responses (CRs) during subsequent mental imagery (CS) of the event (Pitman et al., 2002).

In rodents, the period of time during which stress hormones can modulate the consolidation of conditioned learning is typically no more than a few hours. After this, β -blockers are no longer able to attenuate fear conditioning

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(Ji et al., 2003). PTSD cannot be diagnosed in humans until a month after the traumatic event, which presumably is long after this window of opportunity has closed. However, in previously conditioned animals administration of propranolol following re-presentation of the CS reduced subsequent conditioned inhibitory avoidance (Przybylski et al., 1999) and cue-elicited freezing (Debiec and Ledoux, 2004). We wondered whether reactivating PTSD subjects' memories of their traumatic events could re-open the window of opportunity for propranolol to weaken subsequent physiologic responding associated with the traumatic memory.

We employed the psychophysiologic script-driven imagery technique (Pitman et al., 1987) used in the acute, post-trauma psychophysiologic PTSD study cited above (Pitman et al., 2002). Physiologic responses during traumatic imagery have been shown to be larger in PTSD compared to non-PTSD trauma victims (Orr et al., 2002), leading to the inclusion of the PTSD criterion "physiological reactivity on exposure to internal ... cues that symbolize or resemble an aspect of the traumatic event" in the DSM-IV.

Here, 19 subjects described the event that caused their PTSD, which served to reactivate their traumatic memories. Immediately afterwards the subject received either randomized, double-blind, oral 40 mg short-acting propranolol followed two hours later by 60 mg long-acting propranolol ($n = 9$), or look-alike short- and long-acting placebo capsules ($n = 10$). An investigator composed and recorded scripts portraying the event. A week later, in the psychophysiology laboratory, the subject listened to their personal traumatic scripts and imagined the event while physiologic responses were measured. We hypothesized that subjects who received post-reactivation propranolol a week earlier would show smaller physiologic responses than those who received placebo.

2. Materials and methods

Exclusion criteria included (a) systolic blood pressure (SBP) <100 mm Hg; (b) asthma, heart failure, heart block, certain cardiac arrhythmias, or insulin-requiring diabetes; (c) previous adverse reaction to a β -blocker; (d) use of another β -blocker; (e) use of medication that could involve potentially dangerous interactions with propranolol; (f) pregnant or breast feeding; (g) "recovered" memory of traumatic event; or (h) dissociative experiences scale (Bernstein and Putnam, 1986) score >20.

Nineteen individuals with chronic PTSD according to the structured interview for DSM-IV (First et al., 2002) were randomly assigned to propranolol ($n = 9$, 5M/4F) or placebo ($n = 10$, 4M/6F) groups by the study physician (JT), who kept the other investigators and the subjects blind as to his allocation, and who, aside from medication study administration and medical monitoring, did not otherwise participate in the experimental protocol. Respective group means (SDs) included: age 34.8 (10.1) vs. 35.1 (10.5), $t(17) = 0.1$, $p = 0.95$; years elapsed since traumatic event

10.9 (12.5) vs. 10.1 (10.8), $t(17) = 0.2$, $p = 0.88$; impact of event scale-revised (Weiss and Marmar, 1997) 56.3 (10.8) vs. 55.0 (10.7), $t(17) = 0.3$, $p = 0.79$. Etiologic traumatic events included: propranolol group: childhood sexual abuse (3), motor vehicle accident (3), rape, being taken hostage, and witnessing a physical assault; placebo group: rape (2), physical assault (2), childhood sexual abuse (2), being taken hostage, severe death threats, house fire, and witnessing a physical assault. Comorbid mental disorders included: propranolol group: major depressive disorder (MDD, 1), panic disorder (PD) with (1) and without agoraphobia (2), social phobia (1), bulimia (1); placebo group: MDD (1), PD without agoraphobia (2), bulimia (1), generalized anxiety disorder (1). Subjects gave written informed consent after the procedures had been fully explained.

An approximate 20-min script preparation procedure (Pitman et al., 1987) entailed the preparation of two personal traumatic scripts for each subject, each addressing an aspect of the traumatic experience that caused the PTSD. The subject described the experience in writing on a standard script preparation form. The investigator reviewed the descriptions and requested additional details as necessary. Later, the investigator composed and recorded an approximate 30-s "script" portraying each experience. Each subject then received 40 mg short-acting propranolol or placebo. Two hours later, if the subject's SBP had not fallen by 30% or more, or below 100 mmHg, and the short-acting dose was well tolerated, they received 60 mg long-acting propranolol or placebo. All subjects received both the short- and long-acting doses of study medication.

The psychophysiologic script-driven imagery procedure (Pitman et al., 1987) took place one week later. After a 30-s baseline period, the subject listened during the playing of each script and then imagined the event portrayed for 30 s. Heart rate (HR), skin conductance (SC), and left corrugator (facial frowning muscle) electromyogram (EMG) were recorded. Responses (change scores) were calculated by subtracting the preceding baseline period mean for each physiologic measure from the mean for the imagery period that followed it. Responses to the subject's two traumatic scripts were averaged, and the averaged responses were square-root (designated by the exponent^{1/2}) transformed to reduce heteroskedasticity.

Physiologic responses were subjected to multivariate analysis of variance (MANOVA) with $HR^{1/2}$, $SC^{1/2}$, and $EMG^{1/2}$ responses as simultaneous dependent variables, as well as univariate, independent t -tests. The criterion for significance was $p < 0.05$. Additionally, data from 152 individuals with ($n = 79$) or without ($n = 72$) PTSD previously studied using the same script-driven imagery technique employed here were entered into univariate discriminant function analyses in order to determine optimal PTSD cut-offs for $HR^{1/2}$, $SC^{1/2}$, and $EMG^{1/2}$ responses separately (Orr et al., 2002). These cut-offs are shown as dashed lines in Fig. 1.

Additional methodological details appear under [Supplementary Material](#).

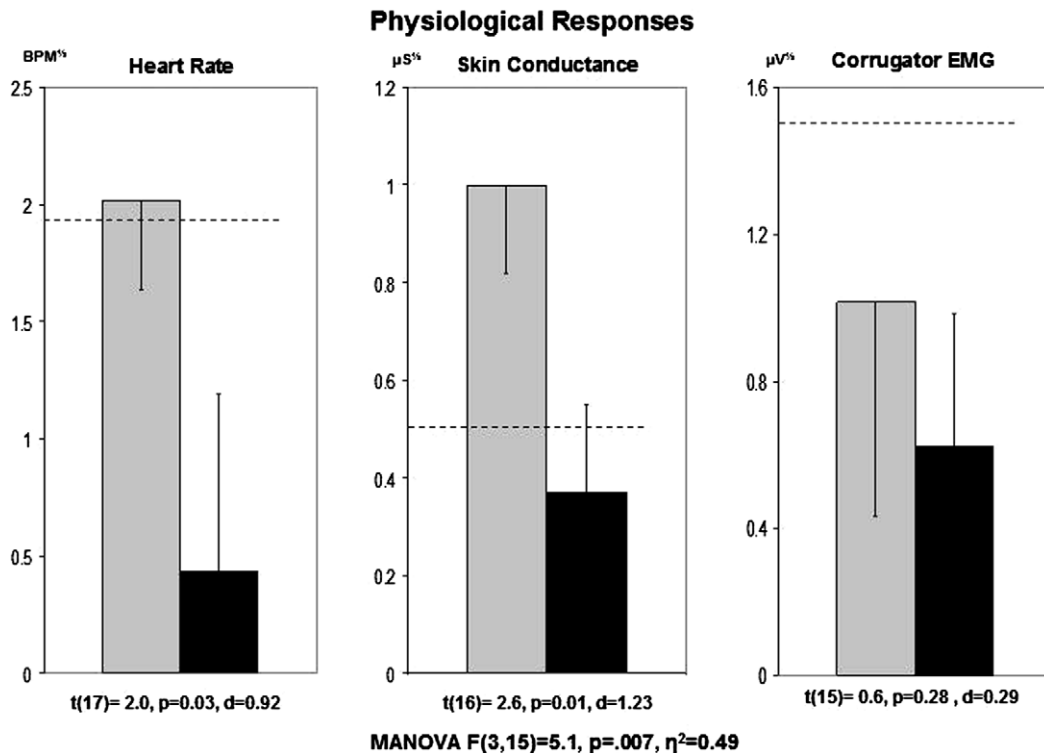


Fig. 1. Physiologic responses of participants with post-traumatic stress disorder (PTSD) during mental imagery of personal traumatic events, measured one week after memory retrieval that was followed by propranolol or placebo. Gray bars (left)-placebo; black bars (right)-propranolol. Error bars represent SEM. Dashed lines represent empirical cut-offs for PTSD based upon prior research. Abbreviations: EMG—electromyogram, BPM—beats per minute, μS — μ Siemens, μV — μ Volts.

3. Results

Overall physiologic responding during mental imagery of the traumatic event was significantly smaller in the PTSD subjects who had received propranolol a week earlier compared to those who had received placebo ($F(3,15) = 5.1$; $p = 0.007$; $\eta^2 = 0.49$). Univariate analyses indicated that HR and SC, but not EMG, responses were significantly smaller in the propranolol compared to the placebo subjects (Fig. 1). The mean HR and SC responses of the placebo subjects were above the normative cut-offs for PTSD, whereas the mean HR and SC responses of the propranolol subjects were below the normative PTSD cut-offs. The mean EMG responses of both groups fell below the normative PTSD cut-off. The observed effect sizes (Cohen's d , shown in Fig. 1) were all in the predicted direction. By conventional standards (Cohen, 1988), these effect sizes were very large for SC, large for HR, but small for EMG.

4. Discussion

A comparison of the results of the present study with those of a previous study in which propranolol was administered acutely post-trauma (Pitman et al., 2002) reveals that propranolol given after the occurrence of a traumatic event and propranolol given after retrieval of the memory of a past traumatic event similarly reduce physiologic

responding during subsequent mental imagery of the event. In the present study, the PTSD subjects who received post-retrieval placebo showed physiologic responses typical of trauma victims with PTSD, whereas the PTSD subjects who received post-retrieval propranolol showed physiologic responses typical of trauma victims without PTSD. Drug condition accounted for 49% of the variance in overall physiologic responding.

A candidate explanation for the reduced physiologic responses observed in the propranolol group is pharmacologic blockade of memory reconsolidation (Nader et al., 2000; Przybylski et al., 1999). However, this explanation is premature without additional controls. The present study did not include a group that received propranolol in the absence of traumatic memory reactivation. To infer blockade of reconsolidation, it should be shown that the physiologic responses of a reactivated propranolol group are smaller than those of a non-reactivated propranolol group, in order to rule out non-specific effects of propranolol (Nader, 2003). It should also be shown in a follow-up study that the reduced physiologic responding during traumatic imagery achieved by post-reactivation propranolol is lasting. Although it might be suggested that the propranolol facilitated extinction of the traumatic CR, animal research indicates that propranolol blocks, rather than enhances, fear extinction (Cain et al., 2004). It is possible that coupling traumatic cues with reduced peripheral sympathetic arousal

(achieved by the propranolol) led to the lower physiologic responding observed during subsequent traumatic imagery.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.jpsychires.2007.05.006](https://doi.org/10.1016/j.jpsychires.2007.05.006).

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