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Stressor controllability modulates fear extinction in humans

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ABSTRACT

Traumatic events are proposed to play a role in the development of anxiety disorders, however not all individuals exposed to extreme stress experience a pathological increase in fear. Recent studies in animal models suggest that the degree to which one is able to control an aversive experience is a critical factor determining its behavioral consequences. In this study, we examined whether stressor controllability modulates subsequent conditioned fear expression in humans. Participants were randomly assigned to an escapable stressor condition, a yoked inescapable stressor condition, or a control condition involving no stress exposure. One week later, all participants underwent fear conditioning, fear extinction, and a test of extinction retrieval the following day. Participants exposed to inescapable stress showed impaired fear extinction learning and increased fear expression the following day. In contrast, escapable stress improved fear extinction and prevented the spontaneous recovery of fear. Consistent with the bidirectional controllability effects previously reported in animal models, these results suggest that one's degree of control over aversive experiences may be an important factor influencing the development of psychological resilience or vulnerability in humans.

1. Introduction

Instrumental control over an aversive experience, or the ability to influence its intensity, duration, onset, or termination, has long been recognized as a critical factor determining its behavioral and physiological impact on an organism (Brady, 1958; Mineka & Hendersen, 1985; Rotter, 1966; Seligman & Maier, 1967). The importance of stressor controllability was initially evidenced by the demonstration that exposure of an animal to inescapable shocks yielded impairment in subsequent avoidance learning that was not observed in animals exposed to identical but escapable shocks (Seligman & Maier, 1967). Subsequent studies revealed that uncontrollable stress exposure results in a host of other behavioral and physiological consequences including neophobia, reduced social interaction, decreased social dominance and aggression, heightened immobility in a forced swim task, decreased food and water consumption, formation of ulcers, and the potentiation of fear conditioning (see Maier & Watkins, 2005 for a review). As many of these behaviors mirror the symptoms of depression and anxiety, it has been proposed that exposure to uncontrollable stress may play an important role in the etiology of these disorders (Maier & Watkins, 2005; Weiss & Simson, 1986). While studies of uncontrollable stress reveal a broad array of deleterious effects, an equally striking result is that controllable stress yields none of these consequences, but in contrast, appears to promote behavioral resilience.

Stressor controllability effects are typically studied using a triadic design. One group of subjects is exposed to aversive reinforcement (such as electric shock) that they are able avoid or escape via the performance of an instrumental avoidance response. A second group is yoked to the first group, receiving reinforcement that is identical in intensity and duration, but that they cannot control through any action of their own. A third control group receives no exposure to the stressor. All three groups then take part in an identical generalization task through which the effects of prior experience are assessed. Importantly, this design enables the distinction between effects of stress exposure and the degree to which controllability modulates these effects. A host of recent studies employing this design have found that subjects exposed to escapable stress exhibit performance in the generalization task

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comparable or even superior to that of unstressed controls (Maier & Watkins, 2010). These findings suggest that the ability to exercise control over a stressor blunts its detrimental effects. Furthermore, several studies report that animals exposed to escapable stress fail to show the typical neurochemical and behavioral consequences of later inescapable stress (Amat, Aleksejev, Paul, Watkins, & Maier, 2010; Amat, Paul, Zarza, Watkins, & Maier, 2006; Williams & Maier, 1977), suggesting that escapable stress yields long-lasting neurobiological changes that immunize an organism to subsequent aversive experiences. Thus, contrary to the conventional notion that stress is physiologically harmful, these studies indicate that stressful experience may actually play a critical role in fostering resilience, provided that it is controllable.

Recent studies in rodents suggest that stressor controllability powerfully influences the expression of conditioned fear (Baratta et al., 2007; Cain & LeDoux, 2007; Rau, DeCola, & Fanselow, 2005). In one such study (Baratta et al., 2007), inescapable stress potentiated and escapable stress mitigated subsequent conditioned fear expression during fear acquisition, fear extinction learning, and a test of extinction retrieval, with respect to unstressed control animals. These findings suggest a mechanism by which individual variation in life experiences may modulate the expression of learned threat and safety associations; however, such effects have not presently been demonstrated in humans. In this study, we explore whether stressor controllability in humans yields the bidirectional effects on conditioned fear expression previously observed in animal models. As dysregulated fear expression is proposed to play a mechanistic role in the etiology of anxiety disorders (Lissek et al., 2005; Milad & Quirk, 2012; Mineka & Zinbarg, 2006), such a finding would implicate stressor controllability as an important experiential mechanism underlying psychological resilience or vulnerability.

2. Materials and methods

2.1. Participants

Participants in both experiments were recruited at New York University. All participants gave their informed consent to take part in the study and were paid for their participation.

Experiment 1: One hundred and two participants (75 female), aged 18–50 (mean age = 22.8) were randomly assigned to one of three experimental conditions, an escapable stress (ES) condition, a yoked inescapable stress (IS) condition, or a control condition. Twenty-five participants in the ES condition who did not learn to perform the necessary avoidance response to criterion were dismissed after the initial session, as the expected effects of control over a stressor would be dependent upon this learning. In addition, 16 participants' data (4 control, 5 ES, and 7 IS participants) were excluded from analysis due to failure to show a measurable increase skin conductance response to the conditioned stimuli during the fear conditioning task (non-responders), preventing the use of this measure as in index of learning. Two yoked IS condition participants were excluded due to their yoked ES counterpart being a non-responder. The remaining 59 participants (41 female), aged 18–43 (mean age = 21.9), are included in the analyses presented here. Of these participants, 20 were in the ES condition, 20 were in the IS condition, and 19 were in the control condition.

Experiment 2: As a large proportion of participants randomly assigned to the ES condition in experiment 1 failed to learn the avoidance response in the stressor task, it is possible any differences in fear conditioning observed in this group could stem from selection bias and not stressor controllability. To address this potential confound, we conducted a follow-up control experiment in which the order to the two tasks was reversed in order to determine whether fear conditioning differed between participants subsequently classified as learners and non-learners in the avoidance task. Forty-one participants (24 female), aged 18–53 (mean age = 23.3) took part in a follow-up control study. Twenty-three of these participants learned the avoidance response in the stressor task (learners) and 18 did not (non-learners). Six participants' data were excluded from analysis due to being non-responders. One additional participant was excluded due to a failure to exhibit any skin conductance response to over one-third of the shock presentations, preventing the use of these measurements for the normalization of the CS-evoked SCRs. The remaining 34 participants (20 female), aged 18–53 (mean age = 23.4) were included in the present analysis, and included 20 learners and 14 non-learners. Due to a technical error, physiological recording terminated early on day 1 for three of these participants (1 non-learner, 2 learners), preventing the measurement of their SCRs at the late extinction timepoint. However acquisition and extinction retrieval measures for these participants are included in the present analysis.

2.2. Experimental paradigms

In experiment 1, participants were assigned to an escapable stress (ES) condition, a yoked inescapable stress (IS) condition, or a control condition. Participants in the ES and IS conditions took part in three experimental sessions: a stressor task, followed seven days later by a two-day fear conditioning paradigm. Participants in the control condition only took part in the fear conditioning sessions and had no exposure to an initial stressor task. E-Prime software (Psychology Software Tools) was used to perform stimulus presentation and response collection in both tasks.

In experiment 2, a separate cohort of participants took part in a follow-up study in which the order of the two tasks in experiment 1 was reversed. Participants completed the two-day fear conditioning task followed two to three days later by the controllable variant of the stressor task. This enabled the assessment of whether fear conditioning and extinction differed between participants subsequently classified as learners and non-learners in the avoidance task, which would suggest that selection of learners for the ES group in experiment 1 might bias the results. In addition, by comparing fear conditioning in learners across both experiments, we can test whether the order in which the tasks were completed appears to influence fear conditioning, a key assumption motivating experiment 1.

Shock administration, skin conductance recording, and the task paradigms were identical across the two studies.

2.2.1. Shock administration

At the start of the initial experimental session, participants determined the level of a mild electric shock (200 ms, 50 pulses/s) via a work-up procedure in which the shock level was gradually increased to a level that the participant deemed to be "uncomfortable, but not painful." This same shock level was used in all subsequent sessions. The maximum shock level administered was 60 mV. Shocks were delivered via a stimulator (Grass Instruments) connected to a bar electrode attached to the wrist of the participant's dominant hand. The stimulator was charged by a stabilized current using magnetically shielded and RF-grounded cable leads.

2.2.2. Skin conductance recording

At the start of each session, shielded Ag–AgCl recording electrodes were filled with a NaCl electrolyte gel and attached to the second and third fingers of the participant's non-dominant hand. Skin conductance data were continuously recorded throughout all three sessions at a rate of 200 samples per second using a Biopac