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Dynamics of defensive response mobilization during repeated terminations of exposure to increasing interoceptive threat

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ABSTRACT

Resistant avoidance behaviors play a crucial role in the maintenance of anxiety disorders and are therefore central targets of therapeutic interventions. In the present study, the development of avoidance behavior was investigated in 24 healthy participants who repeatedly prematurely terminated the exposure to increasing interoceptive threat, i.e., the feeling of dyspnea induced by increasing inspiratory resistive loads that were followed by the ultimate threat, a short breathing occlusion. Physiological responses and subjective anxiety preceding terminations were compared to matched intervals of a matched control group ($N = 24$) who completed the exposure. Initially, participants terminated during the ultimate threat, i.e., during occlusion. This first termination was preceded by a strong surge in autonomic arousal and reported anxiety. Startle reflex and the P3 component of event-related brain potentials to startle probes were strongly inhibited, indicating preparation for defensive action. With repetitive terminations, individuals successively terminated earlier, avoiding exposure to the occlusion. This avoidant behavior was accompanied by alleviated autonomic arousal as compared to the first termination. In addition, no indication of physiological response preparation was found implying that the avoidance behavior was performed in a rather habitual way. Matched controls did not show any indication of a defensive response surge in the matched intervals. In matched controls, no changes in physiological response patterns were detected while anxiety levels increased with repetitions. The present results shed new light on our understanding of the motivational basis of avoidance behavior and may help to refine etiological models, behavioral analysis and therapeutic strategies in treating anxiety disorders.

1. Introduction

The avoidance of a threat (e.g., pain, suffocation) is an adaptive instrumental defense behavior to protect the individual from life-threatening consequences, thus ensuring the adaptation to changing environmental conditions (Skinner, 1953; Hamm and Weike, 2005; Cain and LeDoux, 2008). However, if avoidance behaviors become too dominant they may impair psychosocial functioning and quality of life (Barlow, 2002; American Psychiatric Association, 2013). In fact, maladaptive changes in behavior that prevent exposure to or terminate confrontation with a perceived threat are one of the core features of a wide spectrum of mental disorders (Craske et al., 2009; American Psychiatric Association, 2013; Krypotos et al., 2015). These maladaptive behaviors (e.g., avoiding eye contact or taking medication) are typically persistent and inflexible in nature, automatically elicited by threat-related cues (e.g., body sensations or phobic objects), and thus performed in a habit-like manner (Dickinson, 1985; Gillan et al., 2016c; LeDoux et al., 2016). Most importantly, avoidance behavior is often not adaptive and consistently performed even though expected negative outcomes and environmental conditions may have changed (Dickinson, 1985; LeDoux et al., 2016). Of clinical importance is that in patients with anxiety disorders persistent avoidance prevents the disconfirmation of central concerns about the consequences (e.g., the mental representation of the unconditioned stimulus) of a specific situation. As such, avoidance plays a key role in preventing extinction of a learned association and maintaining anxiety and irrational fears (Barlow, 2002; Mineka and Zinbarg, 2006; Craske et al., 2008; Helbig-Lang and Petermann, 2010).

In modern exposure-based therapies, the prevention of safety-seeking behaviors including avoidance and escape is a key prerequisite to facilitate extinction (Barlow et al., 2004; Craske et al., 2014; Pittig et al., 2016). Persistent avoidance, therefore, interferes with extinction learning - one central mechanism of exposure based therapies (Powers et al., 2004; Craske et al., 2008; Lovibond et al., 2009; Helbig-Lang and Petermann, 2010). Possibly, resistant avoidance behavior accounts for the relatively high rates of dropouts or refusals, nonresponders and

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relapses in exposure-based therapies (Craske et al., 2006; Gloster et al., 2013; Fernandez et al., 2015). As such, it becomes clear that a comprehensive analysis of human avoidance behavior and its underlying mechanisms and motivational basis is of high relevance and could help to enhance the effectiveness of exposure therapy.

Early animal data, as well as recent findings from humans, suggest that avoidance behaviors can persist following fear extinction (Solomon et al., 1953; Vervliet and Indekeu, 2015) suggesting that fear might initiate instrumental avoidance behavior but might be less important for its maintenance (see LeDoux et al., 2016 for a review). It has been demonstrated that as rodents start to exert behavioral control over a threat (e.g., show instrumental avoidance responses) defensive fear responses (e.g., freezing) elicited by the threat-predicting cues will diminish (see Campese et al., 2016 for a review). Moreover, there is increasing evidence that different neural networks are involved in regulating freezing and defensive action (Amorapanth et al., 2000; Choi et al., 2010; Ramirez et al., 2015). The switch from reactive responses to instrumental defensive action is assumed to be coordinated by the prefrontal cortex (infralimbic prefrontal cortex) that actively inhibits central amygdala mediated expression of conditioned freezing and thus facilitates defensive action (Martinez et al., 2013; Moscarello and LeDoux, 2013). Finally, when avoidance behavior is performed repeatedly, defensive actions may become inflexible, stimulus-triggered and automatic, i.e., become amygdala-independent defensive habits (Campese et al., 2016; LeDoux et al., 2016).

The findings in animals are consistent with recent human brain imaging data suggesting that the amygdala, prefrontal cortex, and striatum are involved in avoidance learning (Schlund et al., 2010; Schlund and Cataldo, 2010; Schlund et al., 2011; Levita et al., 2012; Schlund et al., 2013; Collins et al., 2014; Boeke et al., 2017). Indeed, in addition there is evidence from human research demonstrating that autonomic arousal decreases during avoidance learning (Lovibond et al., 2008; Delgado et al., 2009; Vervliet and Indekeu, 2015; Boeke et al., 2017). While these data are promising, in most studies individuals are instructed or trained specifically to exhibit avoidance behavior. In contrast, although highly clinically relevant, there are almost no data on spontaneously occurring avoidance behavior and its maintenance in humans. The present study therefore aimed at characterizing defensive behaviors, physiological arousal, and reported anxiety associated with spontaneously occurring repeated termination of exposure to a threat.

In the present study, we used an interoceptive threat increasing in intensity because such threat bears high relevance for a variety of anxiety and health problems. For example, bodily symptoms may spiral into panic and may elicit defensive action in persons with panic disorder (Goodwin et al., 2005; Kessler et al., 2006; Pané-Farré et al., 2013; Pané-Farré et al., 2014). In our study, the increasing interoceptive threat was established by evoking increasing feelings of dyspnea using increasing respiratory loads to impede inspiration and a complete breathing occlusion, a model for a suffocation experience that has been shown to be a potent unconditioned internal threat (Nardi et al., 2006; Pappens et al., 2012; Pappens et al., 2014). Participants were provided with a response button that they could press (during the presentation of increasing loads and the occlusion) to terminate the trial. In the present analysis we explored (1) at which threat intensity (increasing loads vs. occlusion) participants terminated the exposure, (2) how the behavioral pattern, (3) reports of anxiety, (4) physiological responses and brain stem reflex measures as well as (5) startle probe evoked brain potentials as an index of selective attention changed with repetitions of premature terminations of the exposure sequences. To control for the possibility that changing response patterns during repeated terminations could be the result of the mere repetitions of exposure to increasing interoceptive threat, defensive responses prior to terminations were compared to responses during matched control intervals of individuals who completed all exposure sequences.

Based on previous findings and clinical observations, we assumed that after the initial defensive action at the ultimate threat level (e.g., during occlusion) successive defensive actions would be initiated increasingly earlier at lower threat levels. We also predicted that repetitive defensive actions would be accompanied by different autonomic response patterns. We expected that the first termination would be motivated by a strong fear response elicited at the highest threat level, characterized by a surge in sympathetic arousal (increased heart rate and skin conductance level) (Richter et al., 2012; Hamm et al., 2016), as would be predicted by Mowrer's two-factor model (Mowrer, 1939). In contrast, no such strong autonomic responses were expected during later premature terminations supporting animal data and initial evidence in humans, that the maintenance of avoidance is not motivated by fear and therefore not accompanied by strong autonomic indices of fear (Lovibond et al., 2008; Delgado et al., 2009; Campese et al., 2016). In matched control persons, we predicted that there would be no increase in autonomic arousal during the first and subsequent matched control intervals. Besides autonomic measures, we also assessed the modulation of the startle response – an additional rather low-level brain stem measure of fear (see Hamm, 2015 for a review) prior to exposure terminations.

There is evidence showing that if individuals have the option to actively avoid exposure to a threat by performing a motor task (button press), startle response magnitudes are inhibited during the acute preparation for action (Löw et al., 2008; Richter et al., 2012; Löw et al., 2015; Wendt et al., 2017). This inhibition of the startle blink magnitudes was associated with a sharp drop of the probe-elicited P3 component of the evoked brain potentials, suggesting that attentional resources are allocated to the visual cue that signals the critical time window for the initiation of the avoidance response, thus reducing the selective attention to the irrelevant secondary acoustic startle probe (see Löw et al., 2015). Based on these results, we expected an inhibition of the startle eyeblink response and a reduction of the P3 component of the ERP to the acoustic probe stimuli prior to initial defensive action as a result of binding of attentional resources in the context of response preparation. In contrast, we expected that repetitive avoidance would be performed rather automatically or in a habit-like manner, thus not requiring allocation of attentional resources to facilitate the preparation and initiation of the behavioral response (Solomon et al., 1953; Lovibond, 2006; Ilango et al., 2014; Krypotos et al., 2015; Gillan et al., 2016c; LeDoux et al., 2016). As such, we assumed that the startle eyeblink responses would no longer be inhibited and the probe-evoked P3-component would no longer be reduced.

2. Methods and materials

2.1. Participants

Participants were recruited from a pool of 400 university students. Exclusion criteria were cardiovascular, respiratory (e.g., asthma, COPD), or neurological (e.g., epileptic or apoplectic seizures, multiple sclerosis) diseases, current or past psychotherapeutic treatment for anxiety problems, hearing impairment, or pregnancy. Overall, 69 participants took part in the laboratory assessment. Twenty-eight participants prematurely terminated the exposure to the restricted breathing at least once as described in the procedures section. The sample included in this analysis consisted of those 24 individuals who *repeatedly* (more than once) terminated the exposure. Verbal reports of anxiety and physiological responses of repeated terminations were compared with matched exposure sequences from 24 control individuals matched for age, sex, and level of suffocation fear who completed all experimental procedures. A description of the group characteristics is presented in Table 1, indicating that the groups did not differ by age, sex, body weight, height, body mass index, trait anxiety, anxiety sensitivity, suffocation fear, agoraphobic cognitions, fear of bodily sensations or the vigilance to body sensations. All participants provided written informed consent prior to the study and either received course credit or