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Active avoidance and attentive freezing in the face of approaching threat

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ABSTRACT

Defensive behaviors in animals and humans vary dynamically with increasing proximity of a threat and depending upon the behavioral repertoire at hand. The current study investigated physiological and behavioral adjustments and associated brain activation when participants were exposed to dynamically approaching threat that was either inevitable or could be avoided by motor action. When the approaching threat was inevitable, attentive freezing was observed as indicated by fear bradycardia, startle potentiation, and a dynamic increase in activation of the anterior insula and the periaqueductal grey. In preparation for active avoidance a switch in defensive behavior was observed characterized by startle inhibition and heart rate acceleration along with potentiated activation of the amygdala and the periaqueductal grey. Importantly, the modulation of defensive behavior according to threat imminence and the behavioral option at hand was associated with activity changes in the ventromedial prefrontal cortex. These findings improve our understanding of brain mechanisms guiding human behavior during approaching threat depending on available resources.

1. Introduction

It is critical for the survival of an organism to effectively respond with appropriate defensive behavior in the face of threat. Research with animals and humans has demonstrated that the pattern of defensive behaviors changes systematically with increasing threat proximity and the behavioral repertoire at hand, as outlined in the threat imminence or defense cascade model (Fanselow, 1994; Lang et al., 1997). If the organism is in a context where an aversive event has been experienced before but has not been detected yet (*pre-encounter mode*), preemptive behavior is engaged including increased threat-unspecific vigilance (Michalowski et al., 2015; Weymar et al., 2014). Once the threat-signaling cue is detected (*post-encounter* mode), response output is characterized by attentive freezing, accompanied by "fear" bradycardia (Campbell et al., 1997) and potentiation of the startle reflex (Hamm and Weike, 2005; Lang et al., 2000). When the threat is most imminent, defensive behavior switches into the *circa-strike mode* in which heart rate acceleration and a general sympathetic dominance facilitate fight or flight responses (Lang et al., 1997).

1.1. Neural control of post-encounter and circa-strike defensive behavior

The neural circuits underlying *post-encounter defense* have been revealed both in animal and human research using Pavlovian aversive conditioning as an experimental model (Büchel and Dolan, 2000; Davis, 2000; LeDoux, 2012). After pairing a neutral stimulus repetitively with an aversive event, the now conditioned stimulus activates neurons in the lateral amygdala, which propagate neural activity to the central nucleus of the amygdala (CeA). Efferents from the CeA to the ventrolateral part of the periaqueductal grey (PAG) then interrupt ongoing behavior, promoting attentive freezing and potentiation of the startle reflex (Gross and Canteras, 2012) as well as hypotension and bradycardia (Bandler and Depaulis, 1991; Bandler et al., 2000).

During the *circa-strike mode* defensive behavior switches from passive attentive freezing to active behavioral defense if possible (e.g. fight, flight or active avoidance) mediated by the dorsolateral section of the PAG (Fanselow, 1994; Kim et al., 2013). Lesions of the dorsolateral PAG increase freezing (De Oca et al., 1998), while damage of the ventrolateral PAG disrupts freezing (Fanselow and Poulos, 2005) suggesting that attentive freezing might obstruct active avoidance and vice versa (Benarroch, 2012). Supporting this intriguing assumption, Moscarello and LeDoux (2013) showed that active avoidance training in rats recruits

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the infralimbic prefrontal cortex (ilPFC) to inhibit central amygdala-mediated expression of conditioned freezing. Pre-training lesions of the ilPFC increased conditioned freezing and at the same time caused a decrease in active avoidance.

1.2. Active avoidance versus attentive freezing: the role of coping strategies for neural control of defensive behavior

In humans, the neural circuits related to different defensive states have rarely been compared within one study. To date, most studies either investigated active avoidance using paradigms in which a dynamically approaching threat can be avoided by a behavioral response or assessed attentive freezing using static Pavlovian fear conditioning paradigms that do not entail any behavioral options. Using an active avoidance paradigm, Mobbs and colleagues found that brain activity shifted from prefrontal brain areas to the amygdala and the PAG when a virtual predator comes closer (Mobbs et al., 2007, 2009). Furthermore, the anterior insula was found to be activated during active coping with threat compared to a motor control task (Collins et al., 2014). Dynamic changes in brain activity during approaching threat without the behavioral option for active avoidance were not investigated in these studies.

In Pavlovian fear conditioning paradigms, however, in which the threat is inevitable, the conditioned stimulus elicits an attentive freezing response in humans, characterized by a robust startle potentiation, after successful fear acquisition training (Lonsdorf et al., 2017). There is ample evidence from human fear conditioning studies that the presentation of conditioned threat cues is associated with increased anterior insula (AI) cortex and decreased ventromedial prefrontal cortex (vmPFC) activity (Fullana et al., 2015; Lindner et al., 2015; Milad and Quirk, 2012) when there is no behavioral option to avoid the threat. The heavily interconnected AI might serve a role in generating an integrated awareness of cognitive threat appraisals and the physical state under threat (Fullana et al., 2015; Wendt et al., 2008). Based on evidence for direct projections of the vmPFC to inhibitory areas of the amygdala (Milad and Quirk, 2012) and increased vmPFC activity during safe compared to threat cues (Brosschot et al., 2017), it was suggested that the amygdala is normally under tonic inhibition of the vmPFC. According to this hypothesis, the inhibitory influence of the vmPFC is reduced under threat to allow for appropriate defensive behavior (Brosschot et al., 2017; Milad and Quirk, 2012). Following these interpretations, activity changes of both the AI and the vmPFC during threat processing should be largely independent of the behavioral option to avoid the threat.

Moreover, about half of the studies employing Pavlovian fear conditioning and neural imaging found bilateral or unilateral transient activation of the amygdala particularly during early conditioning (Sehlmeyer et al., 2009). These findings support animal data suggesting a critical role for the amygdala in association formation during fear conditioning (Maren, 2001). Because of the necessary behavioral constraints in the experimental setting human Pavlovian fear conditioning paradigms, however, do not allow for observing the dynamics of brain activation and response mobilization during approaching threat. Thus, the current study was designed to investigate the dynamics of brain activation and defensive responses during approaching threat from which active avoidance was either possible or not.

Using a novel experimental approach, Löw and coworkers (Löw et al., 2015) demonstrated that humans – like rodents – showed increased attentive freezing characterized by fear bradycardia, linear increase in skin conductance, increasing potentiation of the startle reflex and the N1-component of the event-related potentials to acoustic probe stimuli during the approach of an uncontrollable threat. In contrast, when participants could actively avoid the aversive stimulus, cardiac acceleration and a sharp increase in skin conductance immediately prior to the initiation of the motor response was observed accompanied by an inhibition of the startle reflex, a pattern of defensive responding that is remarkably consistent with findings from animal research (Fanselow, 1991; Walker et al., 1997).

1.3. Hypotheses on brain dynamics during active avoidance and attentive freezing

The current study was designed to extend these findings by investigating the dynamic changes of brain activation along with the behavioral adjustments during approaching threat that could either be actively avoided or not. Following the paradigm developed by Löw et al., 2015, different cues signaled if participants had to expect an upcoming aversive event (threat conditions) or not (safe conditions) as well as the proximity of the threat and whether the threat could be actively avoided or not. We measured physiological changes like heart rate and electrodermal activity as well as the blink component of the startle reflex during fMRI scanning to obtain a comprehensive read-out of the evoked defensive response pattern.

We expected to replicate defensive response patterns that have been previously observed using this paradigm outside the scanner environment (Löw et al., 2015). We also expected dynamic changes in neural network activation with increasing threat imminence modulated by the behavioral options at hand. For both the PAG and the anterior insula we expected increased activity during attentive freezing and active avoidance (Benarroch, 2012; Fullana et al., 2015), which for the dorsolateral section of the PAG should be particularly pronounced during active avoidance in circa-strike mode (Mobbs et al., 2007, 2009). We expected decreasing activity in the vmPFC with increasing threat (Lindner et al., 2015; Milad and Quirk, 2012). Finally, we expected the amygdala activity to play a key role in modulating defensive behavior both during early post-encounter (Sehlmeyer et al., 2009) as well as during active avoidance in circa-strike mode (Mobbs et al., 2007, 2009).

2. Material and method

2.1. Participants

Twenty-four right-handed university students (12 men; mean age = 23.9 years, SD = 2.8) participated in the study. Participants were selected if they reported no history of neurological or mental disorders, no color-blindness and no loss of hearing and did not meet any of the general MRI exclusion criteria. All participants provided written informed consent for the study approved by the ethics committee of the German Psychological Society.

2.2. Design and stimulus materials

In this instructed fear paradigm, a colored frame (blue or yellow) signaled whether participants had the option to actively avoid a possible threat with a fast button press or not (active vs. passive mode). Subsequently, a grey geometric symbol indicated whether an aversive event was likely to occur or not (threat vs. safe condition). This cue (a circle indicating threat and a star indicating safety or vice versa) increased in size in five stages to signal the increasing imminence of the aversive stimulus (see Fig. 1). One trial consisted of five stages each lasting for 3 s (1000 ms frame, 2000 ms frame with figure), thus, each trial had a total duration of 15 s. Each of the four trial types (passive threat, passive safe, active threat, active safe) was repeated 12 times resulting in a total of 48 trials in the experiment. Trials were presented in a pseudo-randomized order and were separated by inter-trial-intervals varying between 11 and 15 s.

In each *passive threat* trial the probability of an aversive stimulus was set to 50% in a time window either 1, 1.5 or 2 s after offset of the fifth cue in the sequence. Participants were instructed that they had no influence on the occurrence of the aversive stimulus. In *active threat* trials, participants could actively avoid the aversive stimulus with a fast button press immediately after offset of the fifth cue. The initial time window for a response that would prevent the aversive stimulus was set to 240 ms. The time window was then adjusted for each trial according to the participant's performance to keep the number of aversive events to about 50%