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Research report

Initial and sustained brain responses to contextual conditioned anxiety in humans

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ABSTRACT

Contextual fear conditioning takes place if the occurrence of threat cannot be predicted by specific cues. As a consequence the context becomes the best predictor of the threat and later induces anxiety (sustained fear response). Previous studies suggest that both the amygdala and the hippocampus are crucial for contextual fear conditioning. First, we wanted to further elucidate the neuronal correlates of long-lasting contextual threat within a highly ecologically setting created in virtual reality (VR). Second, we wanted to distinguish between initial and sustained components of the anxiety response to a threatening situation. Twenty-four participants were guided through two virtual offices for 30s each. They received unpredictable electric stimuli (unconditioned stimulus, US) in one office (anxiety context, CXT+), but never in the second office (safety context, CXT−). Successful contextual fear conditioning was indexed by higher anxiety and enhanced US-expectancy ratings for CXT+ versus CXT−. Initial neural activity was assessed by modeling the onsets of both contexts, and sustained neural activity by considering the entire context duration (contrasts: CXT+ > CXT−). Amygdala and hippocampus revealed sustained activity. Initial *and* sustained activities were found in the middle temporal gyrus, and primary motor cortex (M1). Additional initial activity was obvious in orbitofrontal (OFC), dorsomedial (dmPFC), and dorsolateral prefrontal cortex (dlPFC). These results suggest that entering a threatening context initially induces conditioned fear reactions (M1), recall of contingency awareness (dlPFC), and explicit threat appraisal (dmPFC, OFC). While remaining in the threatening context might involve anxiety-like conditioned responses (amygdala, M1) and the generation of a spatial map to predict where and when a threatening event may occur (hippocampus). We conclude that in humans initial versus sustained anxiety responses triggered by a threat associated context are associated with distinguishable brain activation patterns involving a fear network and a "contingency-cognitive" network, respectively.

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1. Introduction

Despite several similarities, fear and anxiety differ in certain key dimensions (Davis, Walker, Miles, & Grillon, 2010). Fear is a phasic and specific response prompted by imminent and real threats, while anxiety is a less specific response alerting the organism towards a potential and distal threat. Fear begins and terminates rapidly, while anxiety is characterized by a long-lasting state of apprehension (sustained fear). From a clinical point of view, panic disorder (PD) or posttraumatic stress disorder (PTSD) are characterized by a sensitivity to unpredictable and uncontrollable threats resulting in enhanced anxiety in very different situations (Grillon et al., 2009). In other words, symptoms of PD and PTSD seem better modeled by sustained fear (Mineka & Oehlberg, 2008).

In the same vein, cued and contextual fear conditioning reflect the essential features of phasic and sustained fear, respectively (Davis et al., 2010). In a cue conditioning paradigm, the conditioned stimulus (CS+, e.g., a geometrical shape) reliably signals an aversive unconditioned stimulus (US, e.g., pain, Pavlov, 1927). Subsequently, individuals show fear responses to this cue, e.g., potentiated startle responses (Alvarez, Johnson, & Grillon, 2007; Andreatta, Mühlberger, Yarali, Gerber, & Pauli, 2010; Glenn, Lieberman, & Hajcak, 2012; Hamm and Weike, 2005) and amygdala activity (Andreatta et al., 2012; Büchel, Morris, Dolan, & Friston, 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; for a recent review see Mechias, Etkin, & Kalisch, 2010). In a context conditioning paradigm, the aversive USs are presented while the individual is within a specific context (CXT+ or anxiety context, e.g., a room), but such aversive USs are not time-bounded with a specific cue and the individual is unable to predict the exact delivery of the USs (Maren, Phan, & Liberzon, 2013; Rudy, 2009). Subsequently, this context elicits anxiety as reflected in startle potentiation (Grillon, Baas, Cornwell, & Johnson, 2006; Tröger, Ewald, Glotzbach, Pauli, & Mühlberger, 2012) and amygdala activation (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Lang et al., 2009; Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008; Pohlack, Nees, Ruttorf, Schad, & Flor, 2012). Importantly, the anxiety triggered by the context differs from the fear elicited by a cue. In fact, the bed nucleus of the stria terminalis (BNST, Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011) and the hippocampus (Alvarez et al., 2011; Marschner et al., 2008; Pohlack et al., 2012) have been found to be crucial brain structures involved in contextual fear learning only (for a recent review see Maren et al., 2013). Specifically, the BNST seems to mediate threat-monitoring and hyper-vigilance (Davis et al., 2010; Somerville, Whalen, & Kelley, 2010), while the hippocampus is important for both spatial and temporal mapping of events and objects within the context (Pohlack et al., 2012; Rudy, 2009). Supportively, lesions of the BNST disrupted freezing and the potentiation of the startle responses in a conditioned context in rats (Luyten, van Kuyck, Vansteenwegen, & Nuttin, 2011), and in humans the BNST was specifically active in a context where the US was unpredictable (Alvarez et al., 2011).

While most animal studies used spatial contexts, e.g., different cages, most previous human studies created contextual stimuli (CXT) by presenting long-lasting cues (Marschner et al., 2008) or by changing the light color in the experimental room (Pohlack et al., 2012). These latter CXT are defined by their temporal characteristics and do not require any spatial representation. However, in real-life a context is defined by both temporal and spatial characteristics. Furthermore, context stimuli are characterized by two kinds of representations (Maren et al., 2013; Rudy, 2009). On the one hand, organisms establish representation of the single features of the context (i.e., elemental associative representation). On the other hand, the single features are bound together in order to experience the context as a particular place or unit (i.e., hierarchical or configural representation).

We use virtual reality (VR) to create ecologically valid contexts meeting these criteria (Glotzbach-Schoon et al., 2013; Tröger et al., 2012). Participants are immersed in these contexts, which they can explore in order to form a spatial representation. In a VR paradigm it is possible to create such enriched and diverse situations in a fully controlled fashion as well as in contingency with observed human responses thus closely imitating real situations (Sanchez-Vives & Slater, 2005). In fact, participants may completely immerse in the virtual world and even forget the real environment, thus they feel present in the virtual world (defined as presence). Given a high level of subjective presence, the individual's responses in the VR are very likely comparable to real-world behavior. For this reason, VR has been proposed as an elegant and innovative tool bridging animal models to real-world human behaviors (Huff et al., 2011; Sanchez-Vives & Slater, 2005).

As mentioned above, the heterogeneous symptomatology of anxiety disorders has been modeled with cue and contextual fear. The anxiety response induced by a threating context after contextual fear conditioning very likely is characterized by both an initial (i.e., at the onset of the context, when entering) and a sustained (i.e., throughout the visit of the context) component. There are only few studies in humans which investigated the neuronal mechanisms underlying contextual fear learning (Alvarez et al., 2008; Maren et al., 2013; Marschner et al., 2008; Pohlack et al., 2012) and even less studies focused on a clear distinction between initial and sustained responses to the threatening context (Alvarez et al., 2011; Somerville et al., 2013). We assume that a better understanding of the brain areas mediating initial versus sustained anxiety induced by contexts would allow a better understanding of the mechanisms behind anxiety disorders like PD and PTSD (Mineka & Oehlberg, 2008). Furthermore, this may allow the development of more efficient therapy for these disorders (Graham & Milad, 2011). Hence, the first goal of this study was to disentangle the initial and the sustained components of the anxiety response to a threatening context by using an ecological valid technique like VR.

Psychological therapies for anxiety disorders focus on exposing the patient to the feared object or the feared situation. Exposure treatment, which can be realized effectively both in-vivo and VR (e.g., Mühlberger, Weik, Pauli, & Wiedemann, 2006; Shiban, Pauli, & Mühlberger, 2013), allows learning a new association between the fear triggering events and safety. This new learning is called extinction learning and has been defined as the decrease of defensive conditioned