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Neural measures associated with configural threat acquisition

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ABSTRACT

Contextual threat learning reflects two often competing processes: configural and elemental learning. Configural threat learning is a hippocampal-dependent process of forming a conjunctive representation of a context through binding of several multi-modal elements. In contrast, elemental threat-learning is governed by the amygdala and involves forming associative relationships between individual features within the context. Contextual learning tasks in humans however, rarely probe if a learned fear response is truly due to configural learning vs. simple elemental associations. The aim of the current study was to probe both constructs separately to enable a more refined interpretation of configural vs. elemental threat learning performance and mediating circuits. Subjects (n = 25) performed both a novel feature-identical contextual threat conditioning task and a discrete cue threat acquisition task while undergoing functional magnetic resonance imaging. Results demonstrated increased hippocampus activity for the threat configuration compared to the safe configuration. This pattern was not observed in the amygdala. In contrast, elemental threat learning was associated with increased amygdala, but not hippocampus activity. Whole-brain analyses revealed that both configural and elemental threat acquisition share neural circuitry related to fear expression. These results provide support for the importance of the hippocampus specifically in configural threat acquisition and fear expression.

1. Introduction

Learning about and predicting threat is important for adaptive functioning, both in terms of discrete cues associated with threat, and also the surrounding context within which threat occurs (Maren, Phan, & Liberzon, 2013). Context shapes perception and selection of appropriate cognitive, behavioral, and neurobiological responses (Chun & Phelps, 1999). Understanding the neural mechanisms of contextual threat learning may accelerate our capacity to treat psychiatric disorders that have known deficits in contextual threat learning, such as posttraumatic stress disorder (Acheson, Gresack, & Risbrough, 2012; Liberzon & Abelson, 2016).

Animal studies indicate that contextual threat may be learned through two distinct processes: elemental and configural threat learning (Rudy, Huff, & Matus-Amat, 2004). Elemental learning is an amygdala-dependent process which involves forming discrete Pavlovian associations with one or more salient cues in the environment during the aversive event (Davis & Whalen, 2001; LeDoux, 2000; Urcelay & Miller, 2014). These associations are context independent, in that the elemental cue can trigger a fear response in varied environments. Alternatively, configural learning reflects the integration of individual multimodal elements into a single overall representation of the environment or "context" in which the aversive event occurs (Rudy, 2009). The hippocampus supports configural representations via relational and spatial binding of multimodal stimuli (Eichenbaum and Cohen, 2014; Monti et al., 2015). Configural and elemental processes compete over representation of contextual information such that under normal circumstances hippocampal-driven configural learning takes priority by creating a conjunctive representation of the whole context and then is assigned the associative strength, rather than the individual elements (Fanselow, 2000). The hippocampus modulates amygdala-driven learned fear responses via reciprocal connections to the amygdala and cortex (Nees & Pohlack, 2014; Olsen, Moses, Riggs, & Ryan, 2012). However, if there is impaired functioning of the hippocampus then contextual information can be represented, almost solely, through amygdala-driven elemental learning, which increases the likelihood of an individual element from the environment in which the aversive event was experienced to subsequently trigger a fear response (Maren, Aharonov, & Fanselow, 1997; Maren et al., 2013).

The relationship between configural and elemental contextual

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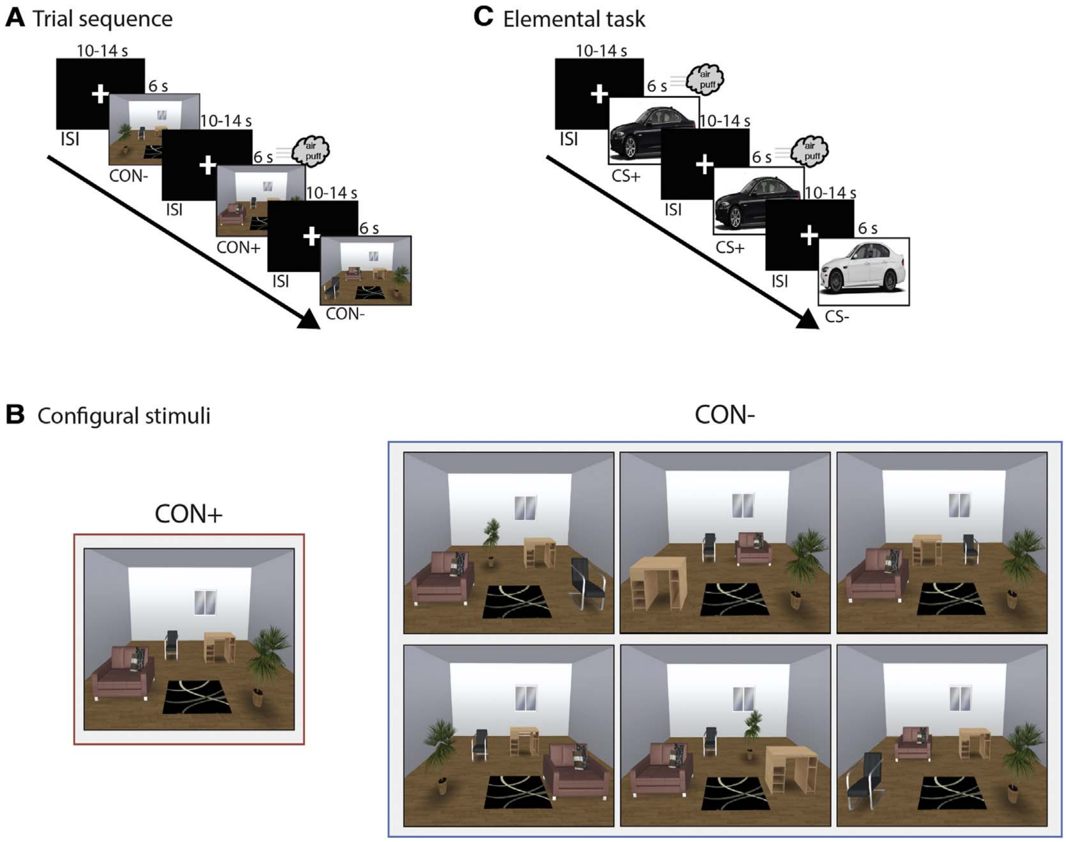

Fig. 1. Configural and elemental threat learning tasks. (A) Trial sequence for the configural threat learning task. CON+ and CON− were presented for 6 s, followed by a 10–14 s ITI. The US co-terminated with CON+ on 83% of trials (see Methods for more details). (B) Examples for the CON+ and the different configurations of CON− trials. For CON− trials, each element was feature-identical to the CON+, but differed only on the arrangement of the furniture. CON− trial types were designed to minimize elemental processing. (C) Trial sequence for the elemental threat learning task. CS+ and CS− trials were presented for 6 s, followed by a 10–14 s ITI. The US co-terminated with the CS+ on 83% of trials.

threat learning has important theoretical implications for the etiology and maintenance of PTSD. Investigators have argued that many PTSD-related re-experiencing and hyperarousal symptoms are associated with a break-down of the hippocampal-configural threat learning process, leading to an overreliance of elemental processing subserved by the amygdala (Acheson et al., 2012; Liberzon & Abelson, 2016). Loss of contextual threat discrimination over time is associated with fear generalization in novel contexts, a key feature of PTSD and anxiety-related disorders (Andreatta, Neueder, Glotzbach-Schoon, Mühlberger, & Pauli, 2017; Lissek, 2012). Thus, there is a great deal of interest in better understanding hippocampus-dependent configural processes of contextual threat conditioning in human populations (Stark, Reagh, Yassa, & Stark, 2017).

Many of the fMRI investigations using unpredictable shock, colored backgrounds, static rooms, or virtual reality contexts generally support the role of the hippocampus and amygdala in contextual threat conditioning (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Barrett & Armony, 2009; Pohlack, Nees, Ruttorf, Schad, & Flor, 2012). These studies utilize experimental designs that manipulate multiple distinct contextual characteristics (US unpredictability, long stimulus duration, multimodal configuration) making it difficult to distinguish between configural or elemental learning (for review see Glenn, Risbrough, Simmons, Acheson, & Stout, 2017). Therefore, before gaining a better understanding of the neural circuitry associated with contextual threat learning, work is needed to delineate how individuals process the multiple cues in the environment. One way of addressing this methodological limitation is to develop feature-identical positive and negative conditioned stimuli that require configural learning of the overall arrangement of contextual elements to accurately predict the likelihood of an aversive event. Baeuchl, Meyer, Hoppstädter, Diener, and Flor (2015) completed the first neuroimaging study of configural threat conditioning to utilize a feature-identical paradigm, with the threat context comprised of several elements, and the safe context comprised of a different configuration of the same elements. Consistent with theoretical models of configural processing, the authors found increased hippocampus activity for the threat configuration relative to safe configuration. However, a limitation of this paradigm is that differentiating threat from safety did not necessitate learning a representation of the entire context, as contextual discrimination could be accomplished based on learning only a pair of elements. Moreover, Baeuchl et al. (2015) did not compare configural threat learning with elemental learning, which limits the conclusions that can be made regarding the neural observations reported.

The current investigation aimed to address the limitations noted above by utilizing a novel feature-identical paradigm to examine the neural measures associated with configural threat acquisition. Here, subjects completed separate configural and elemental threat conditioning tasks (Baeuchl et al., 2015; Glenn et al., 2017) while recording functional magnetic resonance imaging (fMRI) and skin conductance response (SCR). Rather than examining the background context, the configural task was designed to require configural processing of multiple cues in order to discriminate threat from safety, thus we did not measure contextual threat learning as done in other studies (Alvarez et al., 2008; Lang et al., 2009; Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008). Instead, this approach allowed identification and comparison of the neural circuitry associated with configural threat learning versus elemental threat learning. We hypothesized that configural threat learning will be associated with hippocampus and amygdala activity while elemental threat learning would rely on the amygdala but not the hippocampus.