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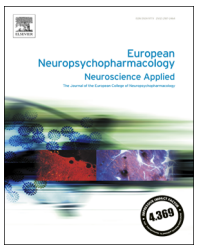

Modeling the development of panic disorder with interoceptive conditioning

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Abstract
Panic disorder is characterized by the paroxysmal occurrence and fear of bodily symptoms. In recent years it has been proposed that patients "learn" to fear cardiorespiratory sensations through interoceptive conditioning. This study sought to model the initial stage of this process in healthy volunteers ($N=44$) using mild cardiac sensations. An additional aim was to explore whether anxiety sensitivity – a known risk factor for panic disorder – modulates such interoceptive learning. Infusions of pentagastrin and saline were used to manipulate the presence versus absence of cardiac sensations, respectively, and served as conditioned stimuli in a differential interoceptive conditioning paradigm. Inhalation of 35% CO_2-enriched air served as the panicogenic, unconditioned stimulus (UCS). In half of the participants ("prepared" condition), cardiac sensations caused by pentagastrin were followed by inhalation of CO_2-enriched air (penta CS+), whereas the absence of such sensations (saline) was followed by room air (saline CS−). The reversed combination ("unprepared" condition) was used in the other half of the participants. Conditioning effects showed up for self-reported UCS-expectancy, but not for skin conductance and anxiety ratings. Only participants from the prepared group learned to expect the UCS, and differential learning was impaired with higher scores on anxiety sensitivity. Expectancy learning was more easily established towards the presence compared to the absence of cardiac sensations, whereas the reverse effect was observed for safety

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learning. Modeling impaired discriminatory learning and the moderating effect of anxiety sensitivity provides new insight in the development of panic disorder.

1. Introduction

Panic disorder (PD) is characterized by the paroxysmal occurrence and fear of bodily symptoms. During panic attacks, patients experience symptoms such as palpitations, dyspnea and chest pain, often associated with the fear of losing control or of dying. As isolated phenomenon, panic attacks are highly frequent: about 22% of the general population experience a panic attack, fulfilling DSM IV criteria, once in their lives (Norton et al., 2008). However, only in a subset of these people this evolves into PD, with frequently occurring panic attacks, both unexpected and linked to certain situations. Genetic factors are estimated to account for about 40% of the risk to develop PD (Hettema et al., 2001). This implies that the majority of the risk is of environmental nature. Human fear conditioning has been proposed to be an important mechanism in the etiology and maintenance of panic disorder as it could explain the transition from relatively isolated panic attacks towards PD (Bouton et al., 2001). In fear conditioning, an initially neutral conditioned stimulus (CS) is paired with an intrinsically aversive stimulus (unconditioned stimulus, UCS) and through associative learning the CS–UCS pairing results in the CS becoming a predictive signal for imminent threat, typically eliciting conditioned fear responses (CR). In recent years, substantial experimental evidence has accrued to support this hypothesis (Grillon, 2002; Lissek et al., 2005, 2009). In most of these studies, environmental stimuli were used as conditioned (CS, e.g. a picture) and unconditioned (UCS, e.g. an electric shock) stimuli. This considerably enhanced insight into the underlying potential learning mechanisms involved in PD. Nevertheless, these studies fall short in modeling the bodily sensations that lead to a panic attack, as panic triggers are often of internal bodily origin (e.g., cardiorespiratory sensations).

To meet this shortcoming, interoceptive fear conditioning (IFC) has been proposed. IFC occurs when a bodily sensation (e.g. palpitations, sweating, heart pounding, minor breathing discomfort) becomes a CS based on the contingency with a UCS (e.g. a panic attack). IFC has been hypothesized to play a key role in the development of PD (Acheson et al., 2011; Bouton et al., 2001; De Cort et al., 2012; Pappens et al., 2012). Specifically, mild interoceptive sensations (for instance, minor heart pounding) that typically emerge in the onset phase of a panic attack are thought to become a CS for a full blown panic attack, thereby reinforcing the learned association and promoting the transition into PD (Pappens et al., 2015).

Previous studies found evidence for IFC in the framework of PD (Acheson et al., 2007; Pappens et al., 2012, 2013, 2014, 2015; Schroijen et al., 2015). Those studies focused on mild respiratory stimuli as conditioned stimuli (CS), and found that fear to a benign respiratory sensation is easily learned when it predicts a more aversive respiratory event (UCS: e.g., an episode of intense dyspnea caused by inhaling CO_2 or being unable to breathe). Interestingly, when the same mild respiratory sensation predicted a "safe" period without aversive respiratory event (UCS), persons still displayed fearful expectations towards the mild respiratory sensation, suggesting that safety learning to interoceptive CSs is hard to establish when they involve the same response system and – therefore – show some resemblance to the initial moments of the UCS (Pappens et al., 2012, 2013; Schroijen et al., 2015). Panic disorder patients show a similar phenomenon, as they typically fear cardiorespiratory sensations that are in essence continuously present and accessible to conscious perception. Such cardiorespiratory sensations are only rarely followed by a panic attack, making them poor predictors thereof. In other words, similar to the experimental findings described above, panic patients seem to remain "blind" for the safety value of mild cardiorespiratory sensations that their body produces continuously, and consequently overestimate the contingency between benign cardiorespiratory sensations and panic attacks.

This is in line with a "preparedness view", positing that evolutionary-prepared, fear relevant stimuli are easier to condition than fear irrelevant, or "unprepared" cues (Mineka and Öhman, 2002). Within a PD framework, previous fear conditioning research has confirmed this using script-based imagery (De Cort et al., 2012; Stegen et al., 1999), or video clips (Forsyth et al., 1996). For example, conditioning is facilitated when using a claustrophobic compared to an emotionally neutral mental image as the CS (Stegen et al., 1999). With the present study, we sought to explore this phenomenon with a truly interoceptive, cardiac sensation as the CS. From a preparedness point of view, it can be hypothesized that anticipatory, panic-related fear is easier established to the presence than to the absence of mild cardiac sensations of arousal. Conversely, safety learning can be expected to be established more easily to the absence than to the presence of such cardiac sensations.

The present study sought to model IFC to the presence/absence of mild cardiac sensations in a group of healthy volunteers without any personal or familial history of panic (to avoid the possibility of inducing actual panic disorder), however taking into account interpersonal differences in vulnerability by measuring participants' anxiety sensitivity (AS). Susceptibility for IFC seems to differ importantly between persons, and only in anxiety sensitive persons this is expected to lead to the subsequent occurrence of panic attacks (Pappens et al., 2014). The construct of AS refers to individual differences in the fear of anxiety related sensations and the expectation that such sensations can have harmful consequences. It has been proposed as a risk factor for the development of PD in particular (Naragon-Gainey, 2010).