



Cue and context conditioning to respiratory threat: Effects of suffocation fear and implications for the etiology of panic disorder



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ABSTRACT

Interoceptive threats play a crucial role in the etiology of panic disorder (PD). While body sensations may become conditioned stimuli (CS) when paired with such interoceptive threats (cue conditioning), the environment in which such interoceptive threats occur may also be learned as a predictor of threat (context conditioning). Suffocation fear (SF) might facilitate these associative learning processes if threats of suffocation become relevant as unconditioned stimuli (US). To investigate whether SF affects associative learning during such respiratory threat, we used mild dyspnea as CS that predicted the occurrence of strong dyspnea (US) in one context (predictable), was not related to the occurrence of the US in another context (unpredictable) or was presented in a different context (safe) in which no US was delivered. Startle eyeblink responses and subjective reports were assessed in 34 participants during learning. Individuals reporting high SF showed a clear potentiation of the startle response during the interoceptive CS predicting the occurrence of interoceptive threat (US). Such startle potentiation was not observed when the CS remained unpaired (safe or unpredictable context). Moreover, high SF persons also showed a significant startle potentiation to the threatening context, when the CS did not predict the onset of the US. No such learning effects were observed for low SF individuals. The data support the view that defensive response mobilization can be triggered by cues but also by contexts that predict the occurrence of interoceptive threats if these threats are relevant for the individuals, supporting learning accounts for the development of PD.

1. Introduction

According to the DSM-5 (American Psychiatric Association, 2013) excessive and persistent fear and anxiety as well as related behavioral disturbances, e.g., avoidance or escape, are the core features of anxiety disorders. Etiological models propose that pathological fear and anxiety are acquired through associative learning processes (Hamm and Weike, 2005; Lissek et al., 2005; Mineka and Zinbarg, 2006; Mineka and Oehlberg, 2008; Craske et al., 2009; Duits et al., 2015). Thus, animal, as well as translational human research, has used fear conditioning studies to elucidate the pathogenesis and maintenance of pathological anxiety and fear as well as its underlying neural networks (LeDoux, 2000; Grillon, 2002; Hamm and Weike, 2005; Davis, 2006; Craske et al., 2009; Tovote et al., 2015). The acquisition of fear to a specific stimulus is typically investigated by repeatedly pairing an affectively neutral stimulus (conditioned stimulus, CS, typically a light, a picture, or a tone) with an emotionally aversive event, i.e., an unconditioned stimulus (US) which is typically a mildly painful stimulus or a loud noise (see Lonsdorf et al., 2017 for a review). As a result of this association,

the previously neutral stimulus is enabled to elicit a fear response. While fear conditioning paradigms using external threat as unconditioned stimuli might provide reliable animal and human analogue models to better understand the development of pathological anxiety and fear (Lissek et al., 2005; Michael et al., 2007; Craske et al., 2009; Duits et al., 2015), there are some mental disorders where fear and anxiety are centered around potential threat coming from inside the body.

Fear of potentially dangerous inexplicable body symptoms (like chest pain; dizziness; dyspnea etc.) is a core symptom in panic disorder (PD) (Bouton et al., 2001; Barlow, 2002) but also in somatic symptom and illness anxiety disorders (American Psychiatric Association, 2013; Newby et al., 2017). Associative learning processes have been discussed as central mechanisms in etiological models of such disorders as well (Bouton et al., 2001; Barlow, 2002; De Peuter et al., 2011; Zaman et al., 2015). Particularly in patients with panic disorder, body sensations or physiological signals linked to risk of suffocation – e.g., dyspnea, breathlessness, or air hunger – elicit anxious apprehension, fear, or even panic (Bouton et al., 2001; Barlow, 2002; Johnson et al., 2014).

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Respiratory restriction or obstruction which ultimately poses the risk of suffocation is known as a stimulus activating the defensive survival circuits in the brain (von Leupoldt et al., 2009; Schmitel et al., 2012; Johnson et al., 2014). Evidence from experimental studies demonstrated that early interoceptive signals of respiratory threat, e.g., dyspnea or breathlessness – either induced pharmacologically or by respiratory challenges – are potent elicitors of defensive mobilization (Schmitel et al., 2012; Johnson et al., 2014).

A number of studies have investigated associative fear learning processes to respiratory threat in humans in more detail. In these studies, severe dyspnea served as a US evoked either by multi-breath CO₂ inhalations, severe inspiratory resistive loads (IRL) or complete breathing occlusions (e.g., Acheson et al., 2007; Pappens et al., 2012b; Pappens et al., 2013). Focusing on intero-interoceptive conditioning, these studies used mild inspiratory resistive loading or brief CO₂ inhalations as CSs preceding the unconditioned interoceptive stimulus. Consequently, a fear response to the previously innocuous body sensations (e.g., mild dyspnea) was acquired when repeatedly paired with the unconditioned strong respiratory threat, e.g., strong dyspnea indicating possible suffocation (Acheson et al., 2007; Acheson et al., 2012; Pappens et al., 2012b; Pappens et al., 2013; Pappens et al., 2014; Pappens et al., 2015; Ceunen et al., 2016).

Cue conditioning, as described above, occurs when cue (CS) and US are paired in close temporal contiguity. However, the associative learning, that is, the association of CS and US, always takes place in a context, that is, a greater set of stable, complex, and multisensory features including diverse internal and external stimuli (Holland and Bouton, 1999; Maren et al., 2013; Urcelay and Miller, 2014). Thus, the US is not only associated with the preceding cue but also to the context. The salience of such context information is enhanced when the US is not preceded by a specific cue and thus is presented unexpectedly or unpredictably at least according to its temporal contiguity (Grillon and Davis, 1997; Grillon et al., 2006; Alvarez et al., 2008; Marschner et al., 2008; Vansteenwegen et al., 2008; Glotzbach-Schoon et al., 2013a; Andreatta et al., 2015; Schroyjen et al., 2016). On a functional level, the context may directly be associated with the CS or the US. Also, the context may become a signal to whether the same CS predicts the occurrence of either an aversive or appetitive US (Asratyan, 1961) or predicts the absence of the US (Rescorla and Wagner, 1972; Holland and Bouton, 1999).

Clinically this latter effect becomes relevant in case of PD where the CS, e.g., a feeling of dyspnea as explained above, may predict a panic attack in one context, e.g., in a shopping mall, but may not predict a panic attack when encountered in another context, e.g., during stair-climbing. Of note, the critical CSs in these situations do not differ and defensive responding to same CS in different contexts is only controlled by the context itself (Kimmel and Ray, 1978; Kimmel and Gardner, 1981; Murrin and Kimmel, 1986; Holland and Bouton, 1999; Maren et al., 2013; Mühlberger et al., 2014). Despite its clinical relevance for the understanding of the development of PD, there are no experimental studies characterizing the acquisition of defensive response mobilization to one interoceptive CS occurring in different contexts that signal whether the same CS is followed by an aversive US or not. Moreover, CS and US (mild dyspnea and panic) may occur independently of each other in a given context and thus the CS may not provide any information *when* the US occurs while the context would be the best predictor. The latter was implicated to lead to the acquisition of context-associated defensive responding (see Pappens et al., 2012b for preliminary evidence). This condition is comparable to the unpredictable condition in the instructed NPU threat test (Schmitz and Grillon, 2012) that was extended and tested for respiratory threat by Schroyjen et al. (2016). It is important to note, however, that in the present study no explicit instructions about the stimulus relations were given. Thus, the current experiment focussed on the associative learning process. We applied an experimentally-controlled within-subject design using the same respiratory CS that was presented

repetitively in three different contexts: (1) In one context (predictable) the respiratory CS predicted *when* the respiratory threat (US) was delivered, (2) a second context (unpredictable) signaled the occurrence of a respiratory threat but the same respiratory CS did not predict when exactly the threat was delivered, or (3) a third context (safe) signaled the absence of the US while the same respiratory CS was presented again. This paradigm is related to previous conditioning tasks using tonic and phasic stimuli in a so-called tansswitching paradigm (Kimmel and Ray, 1978). Also, the design obviously shows some parallels to an un instructed (conditioning) version of the NPU threat test (Grillon et al., 2006).

There is ample evidence that human fear conditioning is modulated by individual trait and temperament factors (like neuroticism or trait anxiety, Eysenck, 1965; Indovina et al., 2011; Glotzbach-Schoon et al., 2013b; Lonsdorf and Merz, 2017 for a recent review). Thus, fear of respiratory sensations might accelerate and strengthen the excitatory conditioning process if aversive respiratory threat is used as an US. In the present study, we, therefore, explored the influence of suffocation fear on the acquisition of fear to cue and anxiety to contextual stimuli that were associated with a maximally tolerable feeling of dyspnea. As a measure of conditioned fear and anxiety, we used the startle eyeblink response – a low-level brain stem reflex – that indexes defensive response preparation (Davis, 2006; Hamm, 2015). It has been demonstrated that the startle eyeblink response is potentiated during cues predicting imminent threat as well as in a context during which a threat could occur at any time (Grillon and Baas, 2003; Hamm and Weike, 2005; Davis et al., 2010).

We predicted that when mild dyspnea was paired with severe dyspnea, cued fear learning would be moderated by suffocation fear. We expected that at the end of the acquisition, startle responses to the CS would be potentiated as compared no-cue intervals in the predictable context (see Pappens et al., 2012b; Pappens et al., 2013; Pappens et al., 2015) in persons reporting high suffocation fear but not in those persons reporting low SF. Moreover, evidence from context conditioning studies in humans demonstrated that persons showed increased context conditioning during unpredictable threat as indexed by increased context associated defensive response mobilization to an unpredictable context as compared to a safe context (Grillon, 2002; Grillon et al., 2006; Alvarez et al., 2008; Marschner et al., 2008; Vansteenwegen et al., 2008; Glotzbach-Schoon et al., 2013a; Andreatta et al., 2015). It has been demonstrated that high anxious individuals including patients with PD who also report high levels of SF (see Hamm et al., 2016) show an exaggerated defensive response mobilization during exposure to unpredictable aversive electro tactile stimuli as compared to non-anxious controls (Grillon et al., 2008). In the present study, we assumed that context-associated anxiety learning would be moderated by suffocation fear. More precisely, we predicted that only persons who report high SF would show increased startle response magnitudes in the unpredictable context as compared to the safe context (see Davis et al., 2010 for a review of studies demonstrating increased context associated defensive responding in patients with anxiety disorders). In accordance with previous evidence (e.g., Pappens et al., 2013; Pappens et al., 2015), we predicted that this conditioning process might be evident in low-level startle reflex modulation but may not be observed in reported valence and arousal.

2. Methods

2.1. Participants

Thirty-four students (19 females, age: $M = 23.06$, $SD = 2.85$) participated in the study. Before study inclusion participants were screened for the following exclusion criteria via telephone interview: cardiovascular, respiratory (e.g., asthma, chronic obstructive pulmonary disease), or neurological (e.g., epileptic or apoplectic seizures, multiple sclerosis) diseases, mental health problems, significant hearing

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