Interoceptive fear conditioning and panic disorder: The role of conditioned stimulus–unconditioned stimulus predictability

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Interoceptive fear conditioning is at the core of contemporary behavioral accounts of panic disorder. Yet, to date only one study has attempted to evaluate interoceptive fear conditioning in humans (see Acheson, Forsyth, Prenoveau, & Bouton, 2007). That study used brief (physiologically inert) and longer-duration (panicogenic) inhalations of 20% CO2-enriched air as an interoceptive conditioned (CS) and unconditioned (US) stimulus and evaluated fear learning in three conditions: CS only, CS–US paired, and CS–US unpaired. Results showed fear conditioning in the paired condition, and fearful responding and resistance to extinction in an unpaired condition. The authors speculated that such effects may be due to difficulty discriminating between the CS and the US. The aims of the present study are to (a) replicate and expand this line of work using an improved methodology, and (b) clarify the role of CS–US discrimination difficulties in either potentiating or depotentiating fear learning. Healthy participants (N=104) were randomly assigned to one of four conditions: (a) CS only, (b) contingent CS–US pairings, (c) unpaired CS and US presentations, or (d) an unpaired “discrimination” contingency, which included an exteroceptive discrimination cue concurrently with CS onset. Electrodermal and self-report ratings served as indices of conditioned responding. Consistent with expectation, the paired contingency and unpaired contingencies yielded elevated fearful responding to the CS alone. Moreover, adding a discrimination cue to the unpaired contingency effectively attenuated fearful responding. Overall, findings are consistent with modern learning theory accounts of panic and highlight the role of interoceptive conditioning and unpredictability in the etiology of panic disorder.

Keywords: panic disorder; fear; interoceptive; conditioning; predictability

Fear of benign bodily sensations, including cues or contexts that might occasion them, is a characteristic of panic disorder. How such fears are learned or acquired has been of focal interest within contemporary learning models of panicogenesis (Acheson et al., 2007; Bouton, Mineka, & Barlow, 2001; Forsyth & Eifert, 1996; Mineka & Zinbarg, 2006), with most accounts casting the etiology of panic pathology in classical conditioning terms. Such learning accounts draw heavily on interoceptive conditioning. This term, first introduced to the
Western world by Razran (1961), refers to “classical conditioning in which either the conditioned stimulus [CS] or the unconditioned stimulus [US] or both are delivered directly to the mucosa of a viscus” (p. 81). These notions have not only figured prominently in etiological accounts of panic disorder, but also in recent modifications of exposure-based interventions that now increasingly include both interoceptive and exterceptive exposure exercises (Barlow, Allen, & Choate, 2004).

Drug tolerance research comprises the largest body of work on interoceptive conditioning, and inferences from this line of work have been used to support the role of interoceptive learning in panicogenesis. According to this view, a stimulus repeatedly paired with drug administration becomes a CS producing a conditioned response (CR) opposite the drug’s effect. This CR, in turn, overrides the pharmacologic effect of the drug to create tolerance (Siegel, 1989). For instance, in one of the first studies of its kind, Greely, Le, Poulos, and Cappell (1984) evaluated tolerance in rats using interoceptive CSs in the form of low and high doses of alcohol. In one condition, the low dose preceded the high dose, whereas in a second condition the doses were never paired. Tolerance was lost in the absence of the low dose in rats trained with the low–high combination. In contrast, in rats trained with the high dose alone, tolerance was lost when the low dose was added.

Comparable results showing that associations can be formed between the early and late components of the same event have been reported with morphine tolerance (Cepeda-Benito & Short, 1997). For instance, rats given long-duration exposures to morphine exhibit a CR to a short “probe” injection designed to mimic the onset properties of the longer injection (Kim, Siegel, & Patenall, 1999; see also McDonald & Siegel, 2004; Sokolowska, Siegel, & Kim, 2002), an effect termed “intra-administration association” (Kim et al., 1999; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000; Sokolowska et al., 2002). Thus, interoceptive cues linked with the onset of an event can be associated with later aspects of the event. Collectively, this work is important in showing that an intero-interoceptive relation (Razran, 1961) forms with each drug administration such that animals learn to respond to an early event in anticipation of a later event.

In an analogous fashion, early physiological changes during a panic attack may become signals for more intense and aversive physiological arousal (e.g., a panic attack, or intense fear; Craske, 1991) and thus elicit a panic attack (CR) on their own (Barlow, 2002). For example, a slight rise in heart rate accompanying the beginning stages of a panic attack may become a conditioned stimulus (CS) signaling a larger rise in heart rate characteristic of the later stages of a panicogenic response including other associated sensations (e.g., tachycardia, heart pounding, chest tightness, breathlessness). Such learned relations then alter the function of formerly benign bodily events such that they become significant fear-evoking events in their own right. Under the right conditions and in the context of relevant vulnerabilities (Mineka & Zinbarg, 1996) such learning may contribute to the development of hypervigilance, anxious apprehension, avoidance, and even panic disorder (Barlow, 2002; Bouton et al., 2001; Forsyth & Eifert, 1996).

Though the literature on interoceptive conditioning in a substance abuse context is vast, the same cannot be said for anxiety pathology. One line of research has demonstrated interoceptive conditioning in human subjects employing an olfactory CS and panicogenic US (Devriese et al., 2000; van den Bergh, Kempynck, van de Woestijne, Baeyens, & Eelen, 1995). Here, though, the CS possessed different stimulus properties than the US, and thus the CS could be distinguished from the US. This is important, in part, because relevant preparations for an interoceptive learning model of panic would seem to require that the CS and US share similar stimulus properties that, in turn, make it difficult to predict when similar physiological events signal subsequent increased arousal and panic or not. As it stands, the best evidence of this sort of process comes from basic research on drug tolerance with nonhuman animals (Kim et al., 1999; McDonald & Siegel, 2004; Sokolowska et al., 2002).

In response to such issues, Acheson and colleagues (2007) sought to provide a more direct test of the interoceptive conditioning model of panic in a nonclinical human sample using 20% CO2-enriched air as an interoceptive CS (i.e., physiologically inert 5-s exposures) and US (i.e., physiologically potent 15-s exposures). The study design consisted of three separate conditions: (a) a “CS-only” condition involving only inert, 5-s CO2 exposures; (b) a “paired” condition that included pairing the CS and US in a contingency (i.e., amounting to a 20-s CS–US complex); and (c) an “unpaired” condition, wherein participants received the same amount of CS and US exposures as the paired condition, except that the CS and US occurred randomly and were never paired. The study was divided into three separate phases: a habituation phase consisting of one CS exposure, an acquisition phase consisting of six CS (all conditions) and five US exposures (for participants in the paired or unpaired conditions), and an extinction phase consisting of six CS-only exposures. Electrodermal response magnitude and individual
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