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Heart rate pattern and resting heart rate variability mediate individual differences in contextual anxiety and conditioned responses

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ABSTRACT

Cardiac activity provides possible markers for the identification of those at risk for the development of anxiety disorders. Cardiac deceleration has been linked to impaired fear conditioning while low heart rate variability (HRV) has been associated with elevated contextual anxiety and enhanced startle potentiation to affective stimuli. In the current study we examined individual differences in conditioned responses as a function of cardiac activity. In addition to classifying participants as decelerators and accelerators, we examined baseline fear responding and conditioned responses in participants with low and high resting state heart rate variability. We complemented well-established physiological measures (startle response and skin conductance) and online distress and retrospective expectancy ratings of fear conditioning with measures of heart rate (HR). In contrast to accelerators, decelerators did not show any sign of startle fear conditioning, but demonstrated increased differential conditioning of online distress. Only marginal differences in contextual anxiety and conditioned fear responding were observed for low and high HRV individuals. These results may contribute to the identification of individuals who are at risk for the development of anxiety disorders.

1. Introduction

Fear conditioning provides an excellent tool to study general principles of fear learning and enables the investigation of individual differences involved in the transition from adaptive to pathological fear. During Pavlovian fear conditioning a biologically neutral conditioned stimulus (CS+) is paired with an aversive consequence, the often noxious unconditioned stimulus (US). As a result of these associations the CS alone comes to elicit a fear response (e.g. potentiation of protective reflexes like the startle response). In a differential fear conditioning paradigm a second cue is introduced that is explicitly not paired with the US (CS−). Patients as well as high anxious individuals demonstrate reduced discrimination between the reinforced threat stimulus and the safety cue. Both groups do not show exaggerated startle fear responding to an explicit threat cue, but elevated startle responding to the safety cue, which may reflect deficient safety learning (Gazendam et al., 2013; Grillon and Morgan, 1999; Grillon, 2002; Lissek et al., 2009; Orr et al., 2000; Peri et al., 2000; Grillon and Ameli, 1998; Morgan et al., 1995; but see Kindt and Soeter, 2014).

Cued fear conditioning effectively models how an individual learns to fear a threat cue that reliably predicts danger. It does, however, not capture the hypervigilance that is typical for anxiety. Since anxiety is future-oriented and not restricted to an explicit cue, it may best be investigated by learned adjustments to the conditioning environment. For example, startle response magnitudes are substantially augmented during baseline prior to a conditioning experiment in which electrical stimulation is used, compared to no aversive stimulus (Böcker et al., 2001). This context-specific elevation of baseline startle responding preceding aversive conditioning is more pronounced in patients suffering from anxiety disorders (Grillon et al., 1994; Grillon and Ameli, 1998; Morgan et al., 1995).

Individual differences in physiological measures of conditioning might serve as markers for maladaptive fear learning and contribute to the identification of individuals prone to the development of anxiety. Beyond trait measures based on verbal report questionnaire data, the use of heart rate (HR) derivatives might be another fruitful variable to test individual differences in fear leaning. First, individuals who showed strong heart deceleration in response to the CS+ did not exhibit the same amount of differential startle conditioning as those individuals who responded with an acceleration of their heart rate during late acquisition (Hamm and Vaitl, 1996). Thus, cardiac deceleration might indicate a different behavioural adjustment to the threat. Interestingly, while the defensive startle reflex differed between accelerators and

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decelerators, conditioning of the skin conductance response (SCR) was observed in both groups. SCR conditioning has been shown to occur irrespective of the valence of the US (e.g. unpleasant electrical stimulation or a reaction time task) (Hamm and Vaitl, 1996; Lipp et al., 1994) and cannot be observed in the absence of US-expectancy (Dawson and Biferno, 1973; Dawson and Furedy, 1976; Hamm and Vaitl, 1996; Hamm and Weike, 2005; Lovibond and Shanks, 2002; Purkis and Lipp, 2001; Sevenster et al., 2014; Weike et al., 2007; but see Bechara et al., 1995; Esteves et al., 1994; Knight et al., 2003, 2006; Schultz and Helmstetter, 2010). SCR conditioning is therefore considered a non-specific measure of arousal/anticipation. Thus, the data by Hamm and Vaitl (1996) suggest that the defensive response was activated in accelerators during cued fear conditioning, while decelerators only learned to associate the CS with the US without a concomitant defensive response. If cardiac deceleration is specifically related to difficulties in activation of the fear network, these individuals might demonstrate elevated baseline startle responding and conditioning of online distress but not US-expectancy.

Second, classifying participants according to their resting state heart rate variability (HRV) is a relatively new method to reveal individual differences in emotional responding. Heart rate variability reflects the heart's beat-to-beat variation as a result of the interplay of sympathetic and parasympathetic activity. In this interaction vagal input from the brainstem to the heart as part of the parasympathetic branch is considered a vital feedback mechanism. Thus, HRV may index the ability to regulate emotion, with higher HRV reflecting greater flexibility and the ability to adapt to environmental changes (Thayer et al., 2012; Thayer and Lane, 2000). In contrast, low HRV is associated with impaired recovery of cardiovascular, endocrine, and immune markers after stress (Weber et al., 2010). Indeed, a role for HRV in modulation of startle potentiation has been demonstrated with different paradigms. In picture- and film clip viewing tasks, participants with high HRV showed startle potentiation in response to negative stimuli relative to neutral (Bos et al., 2013; Ruiz-Padial et al., 2003). This emotion-modulated startle effect was not observed in participants with low HRV. In the study by Ruiz-Padial et al. (2003) this effect was ascribed to enhanced startle potentiation to the neutral stimuli in the low HRV group, while in the study by Bos et al. (2013) HRV correlated with startle potentiation to the negative stimuli. A second paradigm investigated resting HRV as a source of variation in startle potentiation under threat of shock (Melzig et al., 2009). Low HRV individuals showed potentiated startle, irrespective of whether threat of shock was implicit (no cues were given that could indicate US occurrence) or explicit. In sum, low resting HRV is related to impaired emotion modulation of the startle response and increased startle potentiation under conditions in which shock can occur. While these studies convincingly show that low resting HRV is related to emotional dysregulation, the role of resting HRV in differential conditioning, in which cues are explicitly paired (CS+) or not paired with the shock (CS−), remains to be investigated. Normal potentiation to negative stimuli but increased potentiation to neutral stimuli in low HRV participants (Ruiz-Padial et al., 2003) suggests that differential conditioning will be reduced due to increased startle responding to the safe stimulus (CS−) in these participants. However, another study showed decreased startle responding to negative stimuli but no effect on neutral stimuli in low HRV individuals (Bos et al., 2013), suggesting decreased responding to the CS+ in a differential conditioning paradigm. Also, startle responses were potentiated under threat of shock conditions but not under safe conditions (no threat of shock) (Melzig et al., 2009). This would suggest elevated startle responses to the feared stimulus (CS+) but not the safe stimulus (CS−). Therefore, while we would hypothesize that low baseline HRV is related to impaired fear conditioning, it is difficult to predict how these impairments will be manifested. Given that we cannot formulate strong a priori hypotheses, analyses are exploratory. Finally, since HRV is associated with adaptive emotion regulation we hypothesize that the beneficial effects of high resting HRV will be reflected across measures of both defensive reflexes and non-specific arousal.

Previous findings on the relation between resting HRV and contextual anxiety were inconclusive. Baseline startle responding was inversely related to resting HRV in one study (Ruiz-Padial et al., 2003), but was not related to resting HRV in another study (Melzig et al., 2009). It is worth noting that in the former study (Ruiz-Padial et al., 2003) only women participated, while in the latter both men and women participated even though sex differences were not explored (Melzig et al., 2009). Although it has been shown that women have higher resting HRV (Evans et al., 2001; Koskinen et al., 2009; Snieder et al., 2007; but see Bonnemeier et al., 2003; Li et al., 2009; Umetani et al., 1998), little is known about sex differences in HRV in the modulation of emotional learning. This study will include exploratory analyses of the interaction between gender and resting HRV in the modulation of fear learning.

The current study aimed to investigate heart rate derivatives as a source of individual differences in cued fear conditioning and contextual anxiety. First, we aimed to replicate and extend the finding that defensive responses but not non-specific anticipatory arousal are impaired in individuals showing cardiac deceleration (Hamm and Vaitl, 1996). Additionally, we investigated whether defensive responding during baseline is elevated in decelerators. Second, participants were classified as having low and high resting-state heart rate variability (HRV). We aimed to investigate whether low resting HRV is related to difficulties in contextual anxiety and cued fear learning. Finally, we performed explorative analyses to investigate sex differences.

2. Materials and methods

2.1. Participants

Thirty-nine (25 females; 14 males) healthy undergraduate students were included in the current study, ranging in age between 18 and 30 years, with a mean age of 20.54 years (SD = 2.23). All participants were screened for good hearing, and the absence of psychological and physical disorders. Participants received either partial course credit or a small amount of money (€ 35,–) for their participation. All participants gave informed consent and were notified that they could withdraw from participation at any time. The study had full ethical approval of the Ethics Review Board of the University of Amsterdam.

2.2. Apparatus

2.2.1. Stimuli

The testing session started with ten startle habituation trials to stabilize baseline startle reactivity. Conditioned stimuli consisted of different images depicting a spider (IAPS, 1200; 1201). One of the spider pictures (CS+) was paired with a mild shock to the wrist (US, determined individually to be 'uncomfortable though not painful') on 75% of the trials, whereas the other spider picture was never paired with a shock (CS−). Assignment of the pictures as CS+ or CS− was counterbalanced across participants. Both CSs were presented 8 times for 8 s. Startle probe was delivered 7 s after CS onset, followed by the US 500 ms later. The US consisted of an electrical stimulus (2 ms). In addition to the CS presentations 8 startle probes alone (Noise Alone; NA) were presented during the experimental phase. Intertrial intervals (ITI) varied from 15 s to 25 s with an average of 20 s.

2.2.2. Fear potentiated startle

Startle response was measured through electromyography (EMG) of the right orbicularis oculi muscle. Two 5-mm Ag/AgCl electrodes filled with a conductive gel (Signa, Parker) were positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus, respectively; a ground electrode was placed on the forehead, 1 cm below hairline (Blumenthal et al., 2005). Acoustic stimuli were presented binaurally through headphones (Sennheiser, model HD 25-1 II). The EMG signal was sampled at 1000 Hz and amplified in two stages. The input stage