Individual differences in fear-potentiated startle as a function of resting heart rate variability: Implications for panic disorder

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A B S T R A C T

Background: Anticipatory anxiety, which can be indexed by the startle potentiation to a threat of shock, has been implicated in the development of panic disorder. Large individual differences exist in startle potentiation to threat of shock but few differences have been found between panic patients in general and non-anxious controls. The present studies explored resting heart rate variability (HRV) as a source of individual differences in startle potentiation in students at risk for panic disorder and in unmedicated panic patients.

Methods: Participants in Study 1 were 22 students high and 21 students low in anxiety sensitivity (AS). Nine unmedicated panic patients and 15 matched non-anxious controls were included in Study 2. Startle potentiation to the threat of shock was examined as a function of AS (Study 1) and diagnostic category (Study 2) as well as resting HRV.

Results: Whereas no differences in startle potentiation were found as a function of AS or panic disorder diagnosis in general, both studies revealed that low resting HRV was associated with exaggerated startle responses to the threat of shock.

Conclusions: The present results replicate and extend the sparse literature on fear-potentiated startle in panic disorder. Low HRV was associated with more pronounced startle potentiation to both explicit and contextual cues. Thus, low HRV may be a useful endophenotype for at least some anxiety disorders.

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1. Introduction

Panic disorder affects between 3% and 5% of the population and is associated with severe behavioral and economic consequences (Wittchen and Jacobi, 2005). One of the prominent features of panic disorder is anxious apprehension which is the anticipation of potentially threatening events in the future (DSM-IV; American Psychiatric Association, 1994; Grillon, 2002). Moreover, there is an increasing appreciation of the role of anticipatory anxiety in the development of panic disorder (Bouton et al., 2001). Anticipatory anxiety is characterized by strong physiological arousal (increase in heart rate [Deane, 1961, 1969; Deane and Zeaman, 1958], respiratory rate [Masaoka and Homma, 2000, 2001], and skin conductance level [Chattopadhyay et al., 1980]), hypervigilance towards potential threat, excessive worry, uncertainty (Barlow, 2000; Grillon, 2002), and a clear potentiation of the startle reflex (Grillon et al., 1991, 1993; Melzig et al., 2007). The latter finding is particularly important, because the potentiation of the acoustic startle reflex rather specifically indexes the activation of the mammalian defense system (for a review, see Lang et al., 2000). It has repeatedly been shown that the startle eyeblink response elicited by a brief acoustic probe stimulus is augmented during viewing of unpleasant pictures and is even further potentiated during viewing of phobia-relevant stimuli (Bradley, 2000; Hamm et al., 1997). Moreover, this potentiation of the startle reflex by anticipatory anxiety seems to operate on a very fundamental level outside of the participants’ awareness and is mediated by the extended amygdala, a subcortical limbic structure located in the anterior temporal lobe (see Davis, 2000). Although, as explained above, anticipatory anxiety is considered a hallmark of panic disorder, few differences in anxiety-associated startle modulation have been found between panic patients and non-anxious controls when studied using threat of shock paradigms (Chattopadhyay et al., 1980; Grillon et al., 1994; Grillon, 2002; Melzig et al., 2007). However, the data collected in panic patients also indicate that there are large individual differences associated with the quality of emotional functioning, e.g., the severity of depression (Melzig et al., 2007). The present study was designed to explore further possible sources of individual differences in startle potentiation during threat of shock.

One individual difference factor that has recently been shown to influence startle magnitude and emotion-modulated startle is resting heart rate variability (Ruiz-Padial et al., 2003). It was reported that persons with low resting HRV showed potentiated startle responses to neutral
foreground stimuli, which may be interpreted as a constant state of hypervigilance due to anticipation of adverse events in the environment. Thus, individual differences in resting HRV may influence the modulation of startle responses and this may also hold true for startle potentiation during anticipatory anxiety. Interestingly, lowered HRV has been linked to a number of physiological and psychological disorders and emotion regulation ability (see Thayer and Brosschot, 2005 for a review). Furthermore, it has been proposed that HRV reflects the level of inhibitory control of the prefrontal cortex, not only over sympathetic excitatory circuits but also over defensive networks (Thayer and Lane, 2000). Although there is an ongoing discussion that this prefrontal inhibitory control may even be critical for the development of pathological anxiety (Quirk and Gehlert, 2003) as found in panic disorder, to date HRV as a control may even be critical for the development of pathological anxiety.

In the present paper, we report the results of two studies in which we investigated the relationship between startle potentiation during anticipatory anxiety and the resting HRV of the participants. In the first study, persons were selected on the basis of their scores on a measure of anxiety sensitivity, an individual difference variable that has been shown to be associated with the future development of panic disorder (McNally, 2002, Hayward et al., 2000; Schmidt et al., 1997, 1999). In the second study, unmedicated patients with diagnosed panic disorder and matched controls were examined. Consistent with prior research, we expected that the low and high anxiety sensitivity groups as well as the panic disorder patients and matched controls would not differ overall on startle potentiation during threat of shock. However, we expected that independent of anxiety grouping or diagnostic categories, those persons with low resting HRV would show larger startle potentiation compared to those with high resting HRV.

2. Study 1: Anxious apprehension and anxiety sensitivity

2.1. Study 1 — Methods and materials

2.1.1. Study 1 — Participants

Participants were recruited for a study evaluating the influence of anxiety sensitivity on physiological responding to diverse anticipation and symptom provocation tasks. Approximately 250 university students were screened with the Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992). Participants scoring either high or low (at least one standard deviation (9 points) from the mean (20 points)) on the ASI were contacted by telephone and screened for the following exclusion criteria: Participants had to be free of any seizure disorders, cardiovascular or respiratory diseases, and not be in psychological or psychiatric treatment for anxiety problems. Out of 90 eligible participants 43 agreed to take part in a psychophysiological study evaluating the in order (safe condition first) in the second session and vice versa.

2.1.3. Study 1 — Apparatus

The eyeblink component of the startle response was measured by recording the electromyographic activity (EMG) over the left orbicularis oculi muscle beneath the eye, using two electrolyte filled (Marquette, Hellige, Freiburg, Germany) Ag/AgCl miniature electrodes (Sensomedics, Yorba Linda, CA, USA). The raw EMG signal was amplified using a Coulbourn S75-01 amplifier with a 30 Hz highpass filter and a Kemo KEM-00-10 Hz lowpass filter and digitized at 1000 Hz using a 12 bit A/D converter. Digital sampling started 100 ms before and lasted until 400 ms after the onset of the acoustic startle stimulus. To remove eye movement artifacts, a digital 60 Hz highpass filter was applied to the raw EMG data off-line before the scoring procedure started.

The electrocardiogram (ECG) was obtained using an Einthoven lead II setup with two standard, electrolyte filled Ag/AgCl electrodes (Marquette Hellige). The raw signal was 0.1–13 Hz bandpass filtered and amplified using a Coulbourn S 75-01 bioamplifier and continuously digitized with a sampling rate of 100 Hz. Additionally, an online Shimuzu R-wave trigger was applied. The digital trigger channel was stored separately with a sampling rate of 1000 Hz.

2.1.4. Study 1 — Data reduction and analysis

The raw orbicularis oculi EMG was integrated off-line (time constant of 10 ms). Reflex eyeblinks were scored using a computer program (Globisch et al., 1993) that identified the latency of blink onset (in milliseconds) and peak amplitude (in μV). All blinks occurring within a 20–100 ms time interval after startle probe onset and reaching peak amplitude within 150 ms were scored as valid startle response trials. Trials with clear movement artifacts or excessive baseline activity were rejected (2.2%) and treated as missing trials. Trials in which no response could be detected in the defined time window were scored as zero magnitudes.

Inter-beat-intervals (IBI) were derived from the ECG signal using software provided by the VPM data analysis package (Cook et al., 1987).
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