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Startle responding in the context of visceral pain☆

Erik Ceunen [a], Jonas Zaman [a], Natacha Herssens [b], Lukas Van Oudenhove [b], Katleen Bogaerts [a], Huynh Giao Ly [b], Steven J. Coen [b], Jan Tack [b], Johan W.S. Vlaeyen [a], Ilse Van Diest [a,]*

[a] Health Psychology, KU Leuven, Belgium
[b] Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical & Experimental Medicine, KU Leuven, Belgium

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ABSTRACT

This study aimed to investigate affective modulation of eye blink startle by aversive visceral stimulation. Startle blink EMG responses were measured in 31 healthy participants receiving painful, intermittent balloon distentions in the distal esophagus during 4 blocks (positive, negative, neutral or no pictures), and compared with startles during 3 'safe' blocks without esophageal stimulations (positive, negative or neutral emotional pictures). Women showed enhanced startle during blocks with distentions (as compared with 'safe' blocks), both when the balloon was in inflated and deflated states, suggesting that fear and/or expectations may have played a role. Men's startle did not differ between distention and non-distention blocks. In this particular study context affective picture viewing did not further impose any effect on startle eye blink responses. The current results may contribute to a better understanding of emotional reactions to aversive interoceptive stimulation.

1. Introduction

Eye blink startle is modulated by affective background (Vrana et al., 1988). As such, it can be used to distinguish between appetitive, neutral, and aversive emotional states, with decreased magnitudes during the former, and increased magnitudes during the latter. This affective modulation of startle is only evident when the emotional states are sufficiently arousing or intense (Bradley et al., 2001). Such emotional and physiological arousal can be indexed by skin conductance, reflecting sympathetic activation (Dawson et al., 2007). Together, eye blink startle magnitude and skin conductance measures can be used to assess the biphasic aspects of emotion, respectively reflecting motivational direction, and motivational intensity (Bradley and Lang, 2007).

Because affective modulation of startle has been found when using visual (e.g., Jansen and Frijda, 1994; Schupp et al., 1997), auditory (Bradley and Lang, 2000), and olfactory (Ehrlichman et al., 1995) mood stimuli, it has been suggested that such modulation occurs regardless of the sensory modality used for mood induction (Bradley and Lang, 2007). Recent research with interoceptive stimuli seems to contest this notion (Ceunen et al., 2013). For example, during aversive and arousing dyspnea as induced by loaded breathing (a mechanical stimulus creating respiratory resistance similar to breathing through a straw), startle potentiation has not been evidenced (Pappens et al., 2010). Moreover, when fear-inducing dyspnea was elicited by CO_2 inhalation, it led to inhibition of startle, relative to startle measured during room air breathing (Pappens et al., 2012). Also during tonic cold pain and tonic heat pain, which are both interoceptive according to the definition of interoception forwarded by Craig (2002), no startle potentiation has been observed (Deuter et al., 2012; Horn et al., 2012). In contrast, during anxious *anticipation* of respiratory and other interoceptive sensations, the expected startle potentiation has been found (Hubbard et al., 2011; Lang et al., 2011; Melzig et al., 2008; Naliboff et al., 2009; Pappens et al., 2013; Twiss et al., 2009).

Apart from a small number of studies, at present the pattern of startle in response to emotions induced by actual presence, rather than anticipation of interoceptive sensations (including pain), largely remains to be elucidated. Therefore, the major aim of the current study was to unveil the startle response pattern that occurs in a period of time during which there is repeated exposure to an aversive interoceptive stimulus, namely stimulation of the distal esophagus at pain threshold, i.e. first sensation of pain. We hypothesized that startle potentiation would occur during 'unsafe' periods during which painful stimulation occasionally and unpredictably occurred relative to 'safe' periods without such stimulation.

An additional aim was to find out whether in the unsafe periods, startle potentiation is present both during anticipation of and during actual painful stimulation, relative to safe periods. Based on the various findings on startle in response to interoceptive stimuli as discussed earlier, it would be expected that startle in anticipation of visceral stimulation is elevated relative to startle elicited during actual visceral stimulation.

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* Corresponding author at: Research Group Health Psychology, KU Leuven, Tiensestraat 102, Box 3726, 3000 Leuven, Belgium.
E-mail address: Ilse.VanDiest@ppw.kuleuven.be (I. Van Diest).

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Although the study was not purposely set up to study gender differences, findings in the literature suggest that sex differences exist in neurobiological mechanisms involved in the processing of visceral signals (Kano et al., 2013; Kilpatrick et al., 2010; Labus et al., 2013; Pennebaker and Roberts, 1992). Therefore, we included gender in our analyses in an attempt to explore its possible effects. As the literature on startle in response to interoceptive stimuli is on itself already relatively limited, it follows that the literature on gender effects on startle during interoceptive stimulation is nearly non-existent. Therefore we did not make any specific assumptions on how the startle would be different between genders, if at all, even if there are indications for the existence of gender specific differences in the processing of interoceptive stimuli.

The choice for distal esophageal stimulation was in part motivated by the ability to stimulate solely visceral tissue without involving stimulation of any overlying somatic tissue (Aziz et al., 2000), thus being classified as an interoceptive stimulation even by those who define interoception in its strictest sense (e.g., Dworkin, 2007). Opting for the esophagus as the site of stimulation also allows for future research to expand upon the current research findings, for example contrasting purely visceral stimulation (distal esophagus) with purely somatic stimulation (proximal esophagus) (Aziz et al., 2000). We decided to stimulate at first pain threshold for our stimulus to qualify as aversive; pain by definition comprises a component of unpleasant affect according to the International Association for the Study of Pain (Merskey and Bogduk, 1994).

Given the extensive literature of affective modulation of pain (Rhudy and Meagher, 2001; Wiech and Tracey, 2009), we included three different affective backgrounds by means of pictures. These were included in order to explore whether these backgrounds would differently affect the eye blink startles elicited during blocks with esophageal distention compared with those without. An additional argument in favor of the inclusion of the emotional picture series that we had in mind when designing the experiment, was that the inclusion of affective pictures would control for any extraneous confounding factors that might affect mood of participants.

2. Methods

We recruited 31 healthy university students (18 women); they received 50 € for participating in the study. As 7 participants were excluded from analysis (see Data analysis section, subheading Eye blink startle) we only studied the responses of the remaining 24 participants (14 women); they had a mean age of 22 years old (SD = 3). All participants received an informed consent prior to deciding on whether to participate, and reread the consent just prior to signing it. The informed consent was in accordance with the declaration of Helsinki (1997) and stated that participants were free to halt their participation at any point without any negative consequences. This study was approved by the psychological and medical ethical committees of KU Leuven.

At the start of the experiment, a standard pediatric catheter was inserted trans-nasally with the end reaching the distal, autonomously innervated part of the esophagus, 35 cm from the nostril. A deflated medical balloon was firmly attached to the end positioned in the esophagus, while the extraneous part of the catheter was gently attached to the face with tape to prevent it from moving. The remaining end was draped over the ear and connected to an air filled syringe. Although the insertion itself was invariably experienced as unpleasant, once the catheter was in its proper position, we did not continue with the next steps of the procedure, until subjects reported that they became habituated to any sensations due to the presence of the catheter, which never took more than a few minutes. This procedure has been used extensively in previous research (e.g., Aziz et al., 2000; Coen et al., 2009).

After inserting the catheter, the pain threshold of participants was determined by gradually inflating the esophageal balloon thrice, and taking the average of these three volumes of distention (at which subjects indicated that they first felt a sensation that they would call painful) as the best approximation of their actual pain threshold. Additionally, during threshold determination, we assured ourselves that the balloon was in the distal part of the esophagus by asking participants if they could indicate where they felt a sensation: if their answer indicated that they could feel the sensation somewhere around their chest level, but that they could not locate it at a specific site, this was taken to indicate that the balloon was indeed in the autonomously innervated, i.e. visceral part of the esophagus (Aziz et al., 2000). After threshold determination, a 3-minute baseline measure of skin conductance was obtained, and subjects were exposed to 10 startle probes in order to habituate them before proceeding to the actual experiment. There was an interval of 10 s between each of these habituation probes.

The experiment consisted of seven blocks, each lasting 5 min 23 s. In six of the seven blocks, participants viewed a series of 36 mood-inducing pictures of one same valence, selected from the International Affective Picture System (IAPS, Lang et al., 2008). Each picture was presented only once throughout the entire experiment (8 s on, 1 s off). Two picture blocks contained positive pictures, two blocks contained neutral pictures, and two blocks contained negative pictures. Both blocks of each valence had equal mean valence, arousal, and dominance levels according to the normative data collected by Mikels et al. (2005). Furthermore blocks of the same valence were also matched according to the proportion of animals, objects, humans, and overall picture content complexity (see Appendix A for more information of the exact pictures that were selected). A similar blocked presentation of pictures has been used earlier by Smith et al. (2005), and results of their study indicate that affective modulation is maintained and even increased throughout the consecutive presentation of pictures of the same valence.

In the block without pictures, participants were instructed to look at a fixation cross presented on the monitor. The latter block, and 3 of the picture viewing blocks (one for each picture valence) were each accompanied by 10 esophageal balloon distentions. Balloon distentions in those blocks were administered manually at individual pain threshold, started simultaneously with picture onset (in the distention blocks with pictures), and ended after 5 s. Inflations and deflations were performed as instantaneous as physically possible, implying that throughout each distention, the balloon's volume was nearly constant. The available air volume for inflation was limited to the individual threshold to prevent accidentally exceeding the determined volume. The order of the block presentations was semi-randomized, taking into account that blocks of the same pictorial valence or blocks with distentions would never be presented consecutively. The first, third, fifth and seventh blocks were blocks with distentions, whereas the second, fourth and sixth blocks were free of distentions. Participants were informed that blocks with and blocks without distentions would alternate, and were informed that a new block would start only after filling in self-report items. The 10 distentions in each of the four distention blocks occurred with varying intervals between each distention (22–40 s), making the exact onset of each distention unpredictable.

Self-reports of fear, valence and arousal were obtained after each block, respectively on a horizontal VAS ranging from 0 (no fear at all) to 10 (worst fear imaginable), and two 9-point self-assessment manikin (SAM; Bradley and Lang, 1994) scales, one ranging from unpleasant (1) to neutral (5) to pleasant (9), and the other from calm (1) to aroused (9). Furthermore, participants rated pain intensity on vertical bars after each block. Scores ranged from 'no sensation' (0) to 'moderate' (5) to 'most intense I can imagine' (10). Finally, we also assessed to which extent persons had experienced a set of 10 hyperventilation symptoms on a 5 point Likert-scale. The latter self-reports addressed an exploratory research question that goes beyond the scope of the present paper and will not be further discussed here.

Per block, 10 white noise startle probes (50 ms) with a peak dBA of 103 dB were administered binaurally. Although startles were always administered 4 s after picture onset, their occurrence was made