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Short communication

Contextual modulation of autonomic pain reactivity

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ABSTRACT

Although modulation of cardiac activity may be influenced by several factors, interaction between autonomic nociceptive responses and the high-level of cortical processes is not clearly understood. Here, we studied in 26 subjects whether empathetic or unempathetic contexts could interact with autonomic pain responses. RR intervals variability was used to approach parasympathetic and sympathetic responses to painful thermal stimulations, according to contexts evoked by experimenters' comments. We observed that unempathetic context increased sympathetic reactivity to comments and to painful stimulations without any parasympathetic change. These results show an interaction between context and nociceptive processes in cardiovascular control.

1. Introduction

Pain is well-known to induce changes in autonomic cardiac controls. RR intervals (RRI) variability analysis, a non-invasive tool for examining cardiac autonomic functions, had showed that this autonomic response is characterized by a decrease in RRI underpinned by sympathetic activation and parasympathetic withdrawal (Koenig et al., 2014). This autonomic reactivity is more important when stimuli are painful than non-painful stimulations (Koenig et al., 2014), is preserved during sleep (Chouchou et al., 2011) and under anesthesia (Martini et al., 2015). Thus, the monitoring of RRI variability was proposed to assess pain perception in clinical settings (Wodey et al., 2003).

However, autonomic reactivity is not specific to pain and a large variety of processes are also accompanied by changes in cardiac activity. Negative emotions (Lane et al., 2009), attentional overload (Ruscio et al., 2017), or mental stress (Wang et al., 2016) are known to induce deep change in autonomic activity, marked by a decrease in parasympathetic and an increase in sympathetic activities as described in response to painful stimulations. Moreover, these cognitive and emotional processes also interact with pain perception and are a source of pain exacerbation or relief (Tracey and Mantyh, 2007). It is now well established in the studies using placebo models that the context surrounding painful experience influences pain perception itself (Carlino et al., 2014). The context integrates diverse external elements, including an important load of interpersonal interaction but also the conditions under which these interactions are conducted (e.g. friendly or unfriendly interactions).

Among the possible contextual modulations of pain perception, witnessing another person's pain is known to enhance pain perception (Godinho et al., 2006) and activates brain network that overlap with those activated by the acute pain perception (Lamm et al., 2011). Recently, we have shown that empathetic/unempathetic contexts were able to modulate both pain perception and cardiac reactivity (Fauchon et al., 2017). Indeed, unempathetic context raised cardiac reactivity, while empathy reduced the pain perception. However, contextual-autonomic changes underpinning this exacerbated cardiac reactivity during a pain test remain unknown. The aim of the present report was to study the interaction between empathetic context and nociceptive processes in autonomic cardiovascular control, not assessed in the previous study. We analyzed our data (Fauchon et al., 2017) using heart rate variability analysis and studied according to empathetic/unempathetic contexts: 1) basal autonomic activity and 2) autonomic pain responses. We hypothesized that unempathetic context induce an increase in 1) basal cardiac activity, and 2) in cardiac reactivity to painful stimulations underpinned by a sympathetic overactivity and parasympathetic withdrawal.

2. Methods

2.1. Experimental task and stimulation

Twenty-six healthy subjects, all right-handed (27.8 ± 6.3 years; 17

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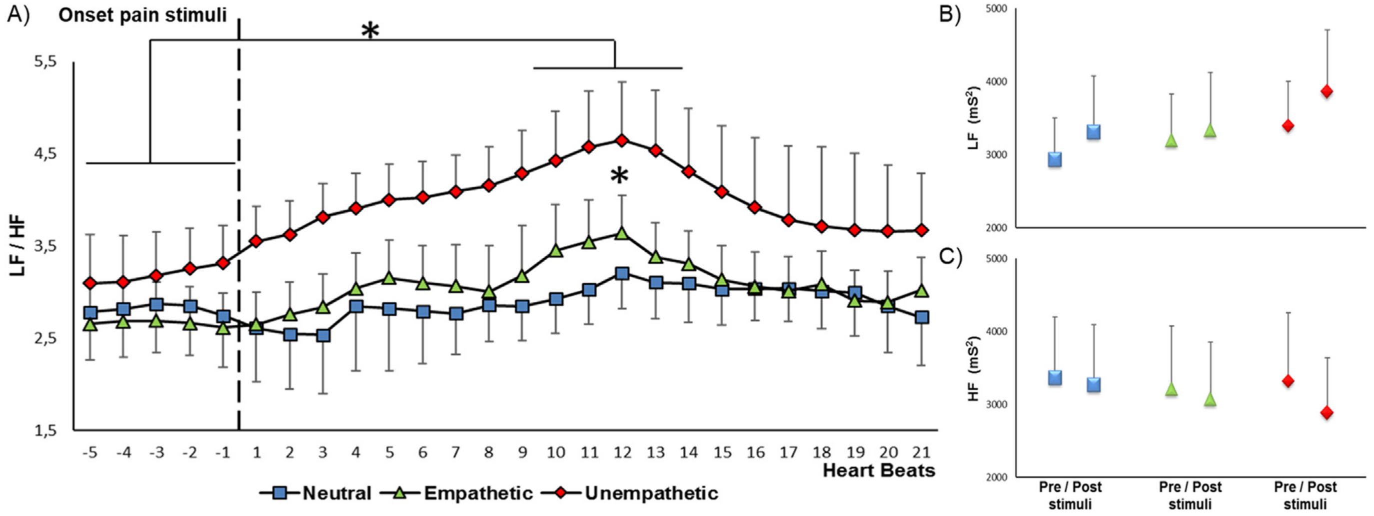

Fig. 1. RR interval variability in response to pain stimuli and its modulation according to the empathetic context. (A) LF/HF ratio, (B) LF (low-frequency) and (C) HF (high-frequency) expressed the difference before and after nociceptive stimulations according to experimental conditions. Nociceptive-induced LF/HF ratio increased which was significantly enhanced during unempathetic condition as compared to the neutral and empathetic condition. *$p < 0.05$, (mean ± SEM).

women) were included, in absence of any known cardiac abnormalities, chronic pain, neurological, psychiatric or mood disorders. The study was approved by the local Ethics Committee (CPP, Sud-Est 1, Saint-Etienne, France) and agreed with the Declaration of Helsinki.

In this experiment, subjects were exposed to heat pain stimulations and they could overhear the discussion of two observers who commented their attitude towards pain. The aim was to create two opposite situations where positive or negative empathetic support were provided to participant through observer's conversation. Audio-scenarios were used to manipulate the degree of empathetic feedback received by the participants. Scenarios included three different sets of comments, labelled ‘Neutral’ (N), ‘Empathetic’ (E) and ‘Unempathetic’ (U) (see Fauchon et al., 2017 for more details).

Two types of stimulations were separately delivered: verbal stimuli (audio comments) and pain stimuli. Between 10 and 15 verbal exchanges were broadcast in each condition (N, E, or U) using high-quality speakers (MSP5 STUDIO®, Yamaha, Japan) and a pseudo-randomized inter-stimulus interval (mean ISI = 67.3 s ± 10.6 s). Three series of 30 heat pain stimuli were delivered through a 30 × 30 mm contact probe (TSA II Neuro-sensory analyser®, Medoc Ltd., Israel) on the back of the left hand at a predefined target temperature for 14 s, including 4 s of ascending and descending ramps. A stable pain perception was rated around 60/100 by participants. The interval between pain stimuli was also pseudo-randomized (mean = 23.6 s ± 11.2 s).

2.2. Autonomic cardiac activity

Three-lead EKG signal were recorded, with four electrodes on the extremity of the hands and feet, using lifescope 6® acquisition system (Nihon Kohden, Tokyo, Japan). The EKG signals were recorded with an electrocardiographic MAC5000® acquisition system (Marquette Medical System, USA) and a multifunction data acquisition unit (National instruments Inc., USA), sampled at 500 Hz.

2.2.1. RR intervals pre-processing

The R waves of the EKG were detected by an automatic algorithm based on wavelet transform, using the free software HRVanalysis (Pichot et al., 2016). Artefacts were corrected with a cubic-spline interpolation and each QRS complex was visually validated before being implemented in the analysis. The signal corresponding to the intervals between consecutive heart beats (R-R intervals, RRI) was computed. To synchronize thermal painful stimuli and EKG, digital triggers were sent to the recording system and stored along with EKG data. For verbal stimuli, the onset of each audio comments on EKG signal was computed from the trigger of pain stimuli and the ISI.

2.2.2. Spectral analysis of RR intervals

RRI variability analysis in response to pain stimulations: wavelet transforms are devoted to study transient modifications in signals (Pichot et al., 1999). This wavelet analysis of the RRI signal enables to follow the time evolution of each frequency contained in the RRI signal, using the mother function *Daubechies* 4. Wavelet analysis was applied on 2.4 Hz re-sampled RRI signal. Fast frequency in RRI signal were gathered in High Frequency power (HF, 0.15 to 0.4 Hz) to assess parasympathetic reactivity, and in Low Frequency power (LF, 0.04 to 0.15 Hz) to assess sympathetic reactivity (Pichot et al., 1999, 2016). Because LF is controlled by both the sympathetic and parasympathetic systems, while HF is only controlled by the parasympathetic system, LF/HF ratio was used to assess relative sympathetic activity (Malliani et al., 1991). Each RRI variability index 20 s before and after stimulations was compared.

RRI variability according to context: The RRI variability indexes obtained from the wavelet transforms also make it possible to study stable states on short periods (Scheer et al., 2010). For this, the average of the RRI variability indexes were averaged over the periods of interest, namely the different periods of audio stimulation (mean verbal stimuli ± SD = 25.4 s ± 16.7) according to experimental conditions.

2.3. Statistical analyses

Statistical analyses were performed with SPSS (SPSS Statistics 20 Inc., Chicago USA). Differences were considered as significant when $p < 0.05$, after appropriate Greenhouse-Geisser (ANOVA) and Bonferroni (post-hoc) corrections. RRI variability indexes in response to pain stimulations were submitted to two-way repeated measure analysis of variance (RM-ANOVA) with time (pre- vs post-stimulus) and conditions (N, E, U) as *within* factor. RRI variability during verbal stimuli were submitted to a one-way RM-ANOVA with experimental conditions (N, E, U) as *within* factor.

3. Results

3.1. RRI variability in response to pain stimulations and its interaction with contexts

Following painful stimulations, HF and LF powers (see Fig. 1) were