Vagally mediated heart rate variability promotes the perception of paradoxical pain

Raymonde Scheuren[a*], Stefan Sütterlin[b,c], Fernand Anton[a],

[a] Institute for Health and Behavior, Integrative Research Unit on Social and Individual Development (INSIDE), University of Luxembourg, Esch-Alzette, Luxembourg;

[b] Section of Psychology, Lillehammer University College, Lillehammer, Norway;

[c] Department of Psychosomatic Medicine, Division of Surgery and Clinical Neuroscience, Oslo University Hospital – Rikshospitalet, Oslo, Norway.

[*]**Corresponding author:**

Raymonde Scheuren, PhD, University of Luxembourg, Campus Belval, Maison des Sciences Humaines, E04, S408, 11, Porte des Sciences, L-4366 Esch/Alzette, Grand-Duchy of Luxembourg, Tel.: +352-466644-6578; Email: raymonde.scheuren@uni.lu

Abstract

Self-regulation mechanisms are governed by prefrontal inhibitory processes and play a crucial role in the modulation of pain. In the present study the thermal grill paradigm was used to investigate the association of vagally mediated resting heart rate variability, a psychophysiological marker of trait self-regulatory capacity, with paradoxical pain sensations induced by non-noxious stimulation. This thermal grill illusion is only perceived by part of the tested individuals. The mechanisms underlying the observed inter-individual differences in paradoxical pain sensitivity are largely unknown. During the experimental task, a temperature combination of 15° C and 41° C was set at the glass tubes of the thermal grill. The fifty-two healthy participants placed their dominant hand on the grill for a duration of one minute. The magnitude of sensory and affective pain sensations perceived during stimulation was assessed with numerical rating scales. Before stimulation, a short-term electrocardiogram was recorded to compute vagally mediated heart rate variability at rest. Logistic regression analyses revealed that participants with higher vagal tone were significantly more likely to perceive the thermal grill illusion than subjects displaying lower resting heart rate variability. Paradoxical pain sensations were primarily predicted by normalized respiratory sinus arrhythmia. Our results confirm that the magnitude of vagally mediated resting heart rate variability is associated with the individual disposition to illusive pain perceptions. Since the latter is considered to be a marker of trait self-regulation ability, the present findings may corroborate and complement previous evidence for an impact of psychological characteristics on paradoxical pain sensitivity.

Keywords

Heart rate variability, paradoxical pain, responder, thermal grill illusion, emotional self-regulation.

Pronounced unpleasantness and negative affect accompany the sensory experience of pain. Both components may be intensified by adverse cognitive and emotional processes like increased attention to pain, expectation of pain, anxiety, or pain catastrophizing (Arntz, Dreessen, & De Jong, 1994; Sullivan et al., 2001; Van Damme, Crombez, & Eccleston, 2002). Rises in blood pressure (BP) and heart rate (HR) often reflect acute pain and associated thoughts or emotions (Loggia, Juneau, & Bushnell, 2011). Alterations in baroreceptor reactivity and concomitant changes in cardiac rhythm and BP related to these processes contribute to the modulation of pain sensitivity (Bruehl & Chung, 2004; Edwards et al., 2003; Guasti et al., 2002; Randich & Maixner, 1984; Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). Self-regulatory ability has been shown to support the flexible control of negative emotional influences and cognitive responses to emotional stimuli during adverse demands (Park & Thayer, 2014; Segerstrom & Solberg Nes, 2007; Solberg Nes, Roach, & Segerstrom, 2009; Thayer & Lane, 2000; Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer et al., 2012). The conceptualization of pain as a homeostatic emotion (Craig, 2003) suggests that regulating actions are also promoted during obtrusive pain states. As a consequence, adaptive behaviour may be guaranteed and the organism's homeostatic drive for an equilibrated body condition (Appelhans & Luecken, 2008; Craig, 2003) may hence be satisfied. In contrast, chronic pain conditions have been related to reduced self-regulation ability and executive functioning (Solberg Nes et al., 2009).

The neural substrates of all homeostatic regulation processes overlap in the prefrontal cortex (PFC; Thayer et al., 2009, 2012). The medial prefrontal cortex (mPFC) plays a particularly important role in ensuring flexible behavioural and autonomic nervous adaptability in response to inner and outer requirements. This higher order regulation system coordinates actions by means of inhibitory processes. The mPFC pathways are linked to the central autonomous network (CAN), a neural system responsible for visceromotor, neuroendocrine, and behavioural homeostatic processes (Benarroch, 1993; Thayer & Lane, 2000) and to brain structures like the amygdala, anterior cingulate cortex (ACC), insula, hypothalamus and diverse brainstem nuclei (Thayer et al., 2009). The CAN is considered as a key feature in reciprocal cortico-cardiac interactions conveying flexible adaptation of the organism to situational demands. Thayer and Lane (2000) included the CAN in their neurovisceral

integration model and suggested that it constitutes a functional unit regulating psychological and physiological control processes via the described neural circuitry and related inhibitory processes.

In recent years, vagally mediated heart rate variability (HRV) measured at rest has been used as an index of prefrontal inhibitory functioning and of cognitive control of responses to emotional stimuli (Appelhans & Luecken, 2006; Park & Thayer, 2014). It has furthermore been specified that vagal tone, as indexed in resting HRV, reflects the individual self-regulation ability predisposition (Appelhans & Luecken, 2006; Segerstrom & Solberg Nes, 2007) and can predict emotional self-regulation capacity in healthy and in clinical samples (Appelhans & Luecken, 2008; Koval et al., 2013; Park, Vasey, Van Bavel, & Thayer, 2014; Solberg Nes et al., 2009; Thayer et al., 2009, 2012). Resting HRV is determined by the quantification of the cardiorespiratory coupling causing systematic fluctuations between heartbeat intervals and the respiratory cycle of inhaling (cardiac deceleration) and exhaling (cardiac acceleration). The resulting respiratory sinus arrhythmia (RSA) is considered a reliable proxy for vagally mediated variations in heart rate and thus for prefrontally modulated vagal activation (Hayano et al., 1990; Grossman & Taylor, 2007).

Higher vagal tone at rest and self-regulation ability has been associated with more adaptive and flexible homeostatic responses, positive emotionality, good health, and psychological recovery (Koval et al., 2013; Solberg Nes et al., 2009; Thayer et al., 2009, 2012). Interestingly, both vagal tone indexed by measures of RSA-related HRV and self-regulation features are considered as individually varying but partially inheritable, stable trait characteristics (Appelhans & Luecken, 2006; Sinnreich, Kark, Friedlander, Sapoznikov, & Luria, 1998; Thayer et al., 2009; Wang, Thayer, Treiber, & Snieder, 2005). Classical pain models based on noxious stimulation established an inverse relationship between resting HRV and pain sensitivity (Appelhans & Luecken, 2008).

The thermal grill paradigm consists in applying interlaced non-noxious warm and cold temperatures to adjacent skin areas and has commonly been used for the induction of the thermal grill illusion of pain (TGI) (Thunberg, 1896), a kind of paradoxical pain sensation often described as painful burning heat (Bouhassira, Kern, Rouaud, Pelle-Lancien, & Morain, 2005; Campero, Baumann, Bostock, & Ochoa, 2009; Craig & Bushnell, 1994; Defrin, Ohry, Blumen, & Urca, 2002). The thermal grill has been used as a valid model for the study of central pain processing (Craig, 2008) and of the

impact of psychological factors like sad mood, depression, and schizophrenia on central pain (Boettger, Schwier, & Bär, 2011; Boettger, Grossmann, & Bär, 2013; Piñerua-Shuhaibar, Villalobos, Delgado, Rubio, & Suarez-Roca, 2011). At this point it is interesting to note that only about one-third to half of the tested individuals experience the painful grill illusion (Boettger et al., 2011, 2013; Bouhassira et al., 2005; Lindstedt, Lonsdorf, Schalling, Kosek, & Ingvar, 2011a). These individuals have been classified as "responders", whereas those who did not perceive the grill illusion have been denoted as "non-responders" The reasons for these inter-individual differences in the perception of the TGI remain largely unknown. In a previous study devoted to the identification of psychological factors that might increase the sensitivity to thermal grill stimulation, we could show that the traits rumination and interceptive accuracy were major predictors of the occurrence of the TGI (Scheuren, Sütterlin, & Anton, 2014).

The extent of HRV respectively of self-regulation capacity may constitute an additional factor engaged in the individual receptiveness to illusive pain sensations. In the literature on noxiously induced pain states, this assumption is supported by a described inverse relationship between vagal tone and pain sensitivity (Appelhans & Luecken, 2008) or between self-regulatory trait features and experimental or clinical pain processing (Appelhans & Luecken, 2006; Koval et al., 2013; Solberg Nes et al., 2009; Treister, Kliger, Zuckerman, Aryeh, & Eisenberg, 2012). Furthermore, imaging studies have revealed that brain structures such as the ACC and the insula that are activated during paradoxical pain processing (Craig, Reiman, Evans, & Bushnell, 1996; Craig, Chen, Bandy, & Reiman, 2000; Lindstedt, Lonsdorf, Schalling, Kosek, & Ingvar, 2011b) are also closely related to the cardiovascular centres of the brain stem (Rau & Elbert, 2001) and to the regulation system attributed to the mPFC (Thayer et al., 2009).

In the present study, we investigated the relationship between the psychophysiological marker HRV measured at rest and paradoxical pain sensitivity. We hypothesized that responders to the thermal grill paradigm would display lower vagal tone as indexed in resting HRV.

Methods

Participants

Sixty-six healthy students and staff members of the University of Luxembourg were recruited. The study was approved by the National Research Ethics Committee and was conform to the ethical guidelines of the International Association for the Study of Pain (IASP; Charlton, 1995). Exclusion criteria were previous or current psychological- (e.g. depression, anxiety disorder), cardiovascular-, neurological-, pain-, and skin-related problems, as well as drug and pain medication intake 24 hours before the experimental session. All health-related items were addressed with a medical history questionnaire. One volunteer had to be excluded during recruitment due to depressive symptoms. Due to an equipment failure, the electrocardiogram (ECG) data of eleven participants could not be used. Two other participants dropped out because of incomplete HRV data. The final total sample hence comprised 52 participants (28 females). The mean age in the sample was 24.1 years (*SD* = 6.1, *range*: 18–51 years). All volunteers signed the informed consent and received financial compensation.

Material and measures

Thermal grill device

A custom-built and water-bath driven thermal grill device (Curio, I., PhD, Medical Electronics, Bonn/Germany) composed of eight alternating cold and warm glass tubes (rectangular surface of 20 x 10 cm; contact area of the skin to the glass tubes of about 71 cm²) was used to elicit the TGI. Two separate thermoelectric recirculating chillers (T255P, ThermoTek, Inc.) regulated the temperatures of the water delivered to the grill tubes. A digital thermometer (PL-120 T2, Voltcraft; visual display of T1-T2 temperatures in °C) allowed a continuous control of the temperatures by the experimenter. The participants were blinded regarding the exact temperatures presented in the different experimental conditions.

During the experimental thermal grill condition (TG; see Figure 1), participants placed the palmar surface of their dominant hand on the interlaced cold and warm bars of the thermal grill. The cold temperature of 15°C was set together with the warm temperature of 41°C. A cuff inflated with a sphygmomanometer was used to induce a weak pressure of 0.7 MPa (0.071 kp/cm²) holding the hand at the grill surface. TG stimulation phases lasted one minute and were repeated two times. In the inter-stimulus-intervals (ISI) of three minutes, the hand was removed from the grill tubes. The TG condition

was followed by two control conditions (CC1 and CC2; see Figure 1). In CC1, the temperature of 15°C was presented in combination with the average baseline skin temperature of 32°C (Kräuchi & Wirtz-Justice, 1994). In CC2, the warm 41°C was paired with the baseline 32°C. The same temporal procedure was used in all conditions.

Psychophysical measures

Participants assessed the intensity and the unpleasantness of paradoxical pain perceived during TG and CC stimulation by means of 100 mm numerical rating scales (NRS; Gracely, 2006; Lindstedt et al., 2011a). They were instructed to refer to a list of verbal descriptors of the various numerical scale increments: 0 = *no sensation*; 10 = *warm/cold*; 20 = *grill pain threshold* (GPT); 30 = *very weak pain/unpleasantness*; 40 = *weak pain/unpleasantness*; 50 = *moderate pain/unpleasantness*; 60 = *slightly strong pain/unpleasantness*; 70 = *strong pain/unpleasantness*; 80 = *very strong pain/unpleasantness*; 90 = *nearly intolerable pain/unpleasantness*; 100 = *intolerable pain/unpleasantness*. Through thorough instructions and confirmation by the participants, we made sure that that values ranging from 0 to 20-NRS were used to rate no- or non-painful warm or cold sensations, whereas values ≥ 20-NRS quantified the intensity and unpleasantness of pain sensations. The magnitude of the sensory-discriminative component of pain was measured before the affective-motivational pain dimension. During each one-minute stimulation trial, the instructor orally invited the participants to rate the perceived perceptions in intervals of 15 seconds.

Psychophysiological recording

We used the BIOPAC MP150 data acquisition system for the continuous measurement of HR. For this purpose a standard precordial lead II electrocardiogram (ECG 100C; 0.5 Hz high pass filtering, R-wave output mode, signal gain 500, 1000 Hz sample rate) was performed via disposable pre-gelled Ag-AgCl electrodes (diameter 35 mm, EL502) placed below the right clavicle and below the left lower rib. A similar Ag-AgCl electrode positioned below the right lower rib served for grounding. The HR data were monitored and analysed using the AcqKnowledge Software package (BIOPAC Systems Inc., USA).

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197 ***Reduction of ECG-related data***

198 Artifact identification, correction, and HRV analysis were performed via ARTiiFACT software (V.
199 2.07; Kaufmann, Sütterlin, Schulz, & Vögele, 2011). R-R intervals (RRI) were extracted from the
200 ECG measurements recorded during the pre-experimental resting condition (last five minutes of the
201 10-min recordings). We included time- and frequency domain measures as well as respiratory sinus
202 arrhythmia normalized for mean RRI (RSAnorm) in our analysis since these parameters have been
203 considered as equally valid indicators of vagally mediated HRV (Grossman & Taylor, 2007; Hayano
204 et al., 1990; Kaufmann, Vögele, Sütterlin, Lukito, & Kübler, 2012; Task Force, 1996). Both time- and
205 frequency domain measures of HRV have been shown to provide high temporal stability, reliability,
206 and reproducibility (Bertsch, Hagemann, Naumann, Schächinger, & Schulz, 2012; Sinnreich et al.,
207 1998; Task Force, 1996). Evidence has also been given for the repeatability and stability over time of
208 the RSAnorm index (Ritz, Thons, & Dahme, 2001; Stein, Rich, Rottman, & Kleiger, 1995), as well as
209 its particularly low confounding with sympathetic (beta-adrenergic) influences (for a discussion see
210 Grossman & Taylor, 2007).

211

212 ***Treatment of vagally mediated HRV indices***

213 Mean heart rate, RMSSD (square root of the mean squared differences of successive NN intervals)
214 and pNN50 (the proportion derived by dividing NN50 by the total number of NN intervals; the NN
215 intervals correspond to elapsed time between subsequent ECG-R-peaks in milliseconds) are reported
216 in the current study as time domain measures (Task Force, 1996). The spectral frequency measures
217 involved high-frequency (HF, 0.15–0.4 Hz) values as expressed in power (ms^2).

218 RSA is a cardiorespiratory phenomenon resulting from the interaction between cardiovascular and
219 respiratory systems and reflecting cardiac vagal tone (Grossman & Taylor, 2007; Task Force, 1996).
220 In the current study, the RSAnorm index (also called Hayano index; Hayano et al., 1990) was used as
221 an indicator of vagal activity and inhibitory capacity. It has been suggested that the normalization of
222 HF (ms^2) with mean interbeat interval allows correcting for the potential influence of sympathetically

induced changes in mean RRI (Grossman & Taylor, 2007; Hayano et al., 1990; Kaufmann et al., 2012).

Experimental Protocol

We informed the participants that the experiment would start with a 10-minute baseline resting condition (BL) that would be followed by the three thermal grill stimulation conditions TG, CC1, and CC2 (see Figure 1). The volunteers were furthermore told that the thermal grill stimulations would generate warm and/or cold sensations, which might be perceived as painful. After familiarization with the pain rating scales, the participants were seated in a reclined test chair (±110°) and the ECG-related electrodes were placed. The participants were instructed to breathe normally and to sit quietly and relax during the resting state HR acquisition. The temperature combination of 15°C and 41°C was then set at the thermal grill and the experimental TG condition was initiated. Each control condition was again preceded by a time interval of about 10–15 minutes (inter-condition-interval, ICI, see Figure 1) to allow the water-bath driven grill temperatures to adjust. At the end of the experimental protocol, the ECG-electrodes were detached and the participants were debriefed and financially compensated. All experimental sessions were run in a temperature-controlled room (22° C) and by the same investigator.

Statistical analyses

The sample was divided in a group of responders and a group of non-responders on the basis of the averaged pain intensity ratings obtained during the TG stimulation condition. We classified participants scoring ≥ 25-NRS as responders (Boettger et al., 2013; Bouhassira et al., 2005). Ratings below the cut-off point of 25-NRS led to the classification as non-responder. The current 25-NRS value may be considered as corresponding to 5/100-NRS on an NRS without a 0–20-NRS pre-pain range (cf. paragraph on 'psychophysical measures') and is in line with the pain rating value of ≥ 6/100-NRS used by Boettger et al. (2013) as a criterion for the responder/non-responder classification. Our cut-off point was moreover situated between pain threshold scores of 20-NRS (GPT) and 30-NRS (very weak pain) to rule out contaminating variability in the near threshold range. The same 25-NRS-

based procedure was used for the identification of responders and non-responders to the affective-motivational component of paradoxical pain.

Mean pain intensity and pain unpleasantness ratings assessed during the TG condition, as well as HR and HRV parameters were analysed for the final total sample and separately for the groups of responders and non-responders. Normality of distribution was verified with the Kolmogorov-Smirnov test (Lilliefors significance correction). The data were log-transformed when the assumption of normality was violated. Pearson's correlation analyses were performed to identify a possible relationship between vagal activation components measured at rest and TG-related pain ratings. Post-hoc comparisons tested potential differences between responder and non-responder values.

The data of the final total sample was included in logistic regression (LR) analyses to examine whether vagal activation indices predicted the probability of the occurrence of the sensory or affective component of the TGI. Separate analyses were run for pain intensity and pain unpleasantness. Thermal grill responder values were coded as 1 and non-responder values as 0. HRV parameter [i.e. RMSSD, pNN50, HF (ms^2) and RSAnorm] values were analysed as absolute and logarithmically transformed values and figured as continuous independent variables in the LR analyses. The pain rating data were used as categorical (dichotomous) dependent variables.

All data were statistically analysed with SPSS, version 21 (IBM, Chicago/IL). The significance level was set at 0.05 (two-tailed testing) in all analyses.

Results

Pain ratings

Mean pain intensity and pain unpleasantness values measured in the TG condition are presented in Table 1. Less than half of the sample (n = 23 responders) perceived the intensity of paradoxical pain when stimulated at the thermal grill, whereas n = 29 did not (non-responders). About one third of the participants (n = 17 responders) rated unpleasant paradoxical pain sensations. Thirty-five participants (n = 35 non-responders) did not perceive unpleasant pain sensations. The proportion of identified responders and non-responders to TG stimulation in terms of pain intensity and pain unpleasantness sensations is shown in Figure 2. The Mann-Whitney U Test revealed a significant difference in the

pain intensity ratings of responders (*Md* = 38.4, *n* = 23) and non-responders (*Md* = 14.2, *n* = 29), *U* = 0.00, *z* = –6.15, *p* < 0.001, *r* = 0.12; see Table 1). Furthermore, a significant difference was observed between the pain unpleasantness ratings of responders (*Md* = 31.7, *n* = 17) and non-responders (*Md* = 10.0, *n* = 35), *U* = 0.00, *z* = –5.81, *p* < 0.001, *r* = 0.11; see Table 1). The ratings collected during the control conditions (CC1 and CC2) were in the non-painful range (0–20-NRS).

The proportion of males (*N* = 24) and females (*N* = 28) was not significantly different in the pain intensity responder (*n* = 10 males, *n* = 13 females) and non-responder group (*n* = 14 males, *n* = 15 females). The *Chi*-square test for independence (with Yates Continuity Correction) did not reveal a significant influence of gender on pain intensity ratings, X^2 (1, *n* = 52) = 0.004, *p* > 0.05, *phi* = 0.05). Both groups did also not significantly differ in age [responders: *M* = 24.04, *SD* = 5.08; non-responders: *M* = 24.21, *SD* = 6.86; *t*(50) = –0.09, *p* > 0.05].

Cardiac activity

HR and HRV values measured at rest are presented in Table 2. Post hoc *t*-tests revealed a significant group effect for resting RSA in the BL condition. Significantly higher resting RSA was measured in responders (*M* = 0.88, *SD* = 0.26) vs. non-responders (*M* = 0.74, *SD* = 0.20; *t* (50) = 2.18, *p* < 0.05, two-tailed) classified according to pain intensity ratings. The magnitude of the difference in the means (mean difference = 0.14, 95% *CI*: 0.01 to 0.27) was moderate (η^2 = 0.09]. The differences in resting HRV values were not significant when considering the pain unpleasantness responders vs. non-responders (all *p* > 0.05). No correlation was found between resting HRV and sensory or affective pain ratings (all *p* > 0.05). In line with previous work, HRV measures were highly inter-correlated (all *p* < 0.05) (Berntson et al., 1997; Berntson, Lozano, & Chen, 2005; Task Force, 1996).

The computation of the predictive power of resting HRV measures on paradoxical pain sensations (sensory component) demonstrated that RSAnorm significantly influenced the LR model (see Table 3). The model [X^2 (1, *N* = 52) = 4.65, *p* < 0.05] explained between 8 % (Cox and Snell R square) and 11% (Cox and Snell R square) of the variation in the TGI responses. 75.9% of the responders and 52.2% of the non-responders were accurately identified (overall percentage: 65.4%). The RSAnorm-related high odds ratio value of 14.58 (CI: 1.12, 190.29) indicated that the probability to experience

306 the illusive pain was 14 times higher in participants with significantly increased resting RSA. The LR
307 analysis of the set of other HRV predictor variables showed that pNN50 and RMSSD contributed
308 significantly to the considered model (see Table 3). The full model [X^2 (4, N = 52) = 8.93, $p < 0.05$]
309 explained between 15% (Cox and Snell R square) and 21% (Cox and Snell R square) of the variation
310 in the sensory pain responses. Overall 65.4% of the participants were accurately categorized either as
311 pain responders (72.4%) or as non-responders (56.5%). The pNN50-related odds ratio was 1.16 (CI:
312 1.03, 1.31). The lower RMSSD-related odds ratio of 0.88 (CI: 0.79, 0.99) pointed to an inverse
313 relationship between RMSSD and paradoxical pain perceptions.
314 In summary, it may be stated that the magnitude of vagal activation measured at rest and mainly as
315 expressed by RSAnorm was significantly higher in the responder than in the non-responder group. The
316 same psychophysiological marker could be identified as strong predictor of the likelihood of
317 paradoxical pain perceptions. Higher values in time domain measures of HRV also added to a higher
318 probability of illusive pain experiences.
319
320 **Discussion**
321 In the present thermal grill paradigm, we investigated vagally mediated HRV at rest to uncover
322 whether resting vagal tone might partly explain the observed inter-individual differences in
323 paradoxical pain sensitivity. We had hypothesized that lower resting HRV, an indicator of lower self-
324 regulation capacity (Segerstrom & Solberg Nes, 2007) and reduced regulation of emotions (Appelhans
325 & Luecken, 2006; Koval et al., 2013; Thayer et al., 2009), would be related to higher paradoxical pain
326 sensitivity. During the resting condition, we observed a predominance of vagal activation in the
327 thermal grill responders. The logistic regression analyses revealed that the probability to feel the TGI
328 was up to 14 times higher in participants displaying higher resting RSA. This result suggests that
329 higher dispositional self-regulation ability makes it much more likely for an individual to respond to
330 TG stimulation and to feel the TGI than lower self-regulatory capacity. Concerning the predictive
331 power of the RMSSD index of HRV, we observed that the low odds ratio result deviated to some
332 extent from the other vagal activation indicator outcomes. It has been claimed that the time component
333 RMSSD is contaminated by sympathetically mediated HRV despite its high but non-linear correlation

with pNN50, HF (ms^2) and RSAnorm (Berntson et al., 2005; Task Force, 1996). No inverse relationship between resting HRV and paradoxical pain could be found. The positive association uncovered between HRV at rest and illusive pain ratings disconfirms our hypothesis and is in contrast with research findings on pain depending on noxious input.

To our knowledge, this is the first study investigating the relationship between the psychophysiological marker HRV and paradoxical pain sensitivity. HRV in healthy and pain-free populations has so far only been studied in association with acute pain states induced by evidently noxious input (Appelhans & Luecken, 2008; Koenig, Jarczok, Ellis, Hillecke, & Thayer, 2014; Treister et al., 2012). The study by Appelhans and Luecken (2008) on the relationship between indices of resting HRV and acute pain sensitivity to noxious cold stimuli is of particular interest in this context In line with our research, the authors used the HRV measures as independent variables to investigate inter-individual differences in pain sensitivity. Their findings however contrast with our results insofar as HF-related HRV measures were not significantly associated with pain sensitivity in their study and HF did not allow predicting pain intensity. Low-frequency HRV was inversely related to pain unpleasantness ratings, but not to pain intensity sensations. Treister et al. (2012) reported a higher HF (ms^2) value measured at rest as compared to the lower HF (ms^2) value recorded during the subsequent painful heat stimulations. In their review, Koenig and colleagues (2014) also described findings on the impact of the magnitude of HRV reactivity on experimentally induced pain and emphasized that lower vagal reactivity was mainly related to higher pain sensitivity. It seems that the attempt to offer explanations for the present findings is hampered by the scarcity of findings and by the fact that in contrast to this previous work, innocuous thermal grill stimuli were used in the current research to investigate the association between vagal tone and the disposition to express pain. It has however been shown that the neurophysiological mechanisms activated during thermal grill stimulation (Craig & Bushnell, 1994) are distinct from those triggered by noxious thermal stimuli (Craig, 2008). This functional neuroanatomical aspect suggests that the autonomic regulatory mechanisms acting during the TGI are not identical to those acting during pain processing induced by noxious input. The higher pain sensitivity in participants displaying increased vagal activation in the resting condition observed

in the present study may hence be attributable to the different neurophysiological substrates underlying “true” and paradoxical pain.

In the framework of dispositional self-regulation ability as indexed by resting HRV (Appelhans & Luecken, 2006; Segerstrom & Solberg Nes, 2007; Thayer et al., 2009, 2012), Solberg Nes and colleagues (2009) also had analysed the relationship between trait self-regulation and pathological pain states. The authors observed that chronic pain patients were characterized by lower self-regulatory ability as compared to healthy individuals. In a number of studies, higher HRV indices have been associated with more effortful and adaptive self-regulation, good impulse control, executive performance, lower affective instability and positive emotionality (Koval et al., 2013; Park et al., 2014; Park & Thayer, 2014). Lower HRV pointed to impaired coping processes, self-regulatory fatigue, stress, affective instability and health-related problems like psychopathological disorders (Segerstrom & Solberg Nes, 2007; Solberg Nes et al., 2009). It has moreover been shown that participants with higher vagal activation react more easily when challenged by external demands (Rottenberg, Salomon, Gross, & Gotlib, 2005). These findings imply that individuals displaying a better trait self-regulation ability recover faster on an emotional level and adapt more efficiently to challenging circumstances. They are also more likely to present enhanced attentiveness to external demands and may hence react with increased sensitivity to thermal grill stimuli. Pain as a warning signal against potential tissue damage and loss of homeostasis provides the drive for immediate protective and regulatory reactions (Craig, 2003). The efficient self-regulation of our thermal grill responders may therefore constitute a healthy reaction allowing them to set their priorities successfully and to react faster and more adequately in the face of potentially threatening stimuli. The flexible adaptability of responders and the inherent efficient control of the emotional and behavioural drive of pain (Craig, 2003) promote their efficacy in reinstalling homeostasis.

In the context of our finding on a positive relationship between HRV-self-regulation and paradoxical pain sensitivity, several studies on emotion regulation ability and interoceptive sensitivity (IS) that may support the previously described coping and adaptation processes of our responders should be pointed out. Füstos, Gramann, Herbert, & Pollatos (2013) and Kever, Pollatos, Vermeulen, & Grynberg (2015) uncovered a positive association between emotion regulation ability and IS and

showed that a more accurate detection of bodily symptoms or changes facilitates emotional regulation in aversive contexts. We had identified IS as a predictor of the occurrence of the TGI in a previous study with higher IS increasing the probability of paradoxical pain perceptions in response to thermal grill stimulation (Scheuren et al., 2014). The finding of a positive relationship between IS and pain sensitivity had also be revealed for pain induced by noxious stimulation (Pollatos, Füstos, & Critchley, 2012). Based on all previous arguments, we would like to propose that higher emotional self-regulation as indexed by higher HRV and previously identified higher IS, may have modulated pain sensitivity in the present thermal grill paradigm.

Conclusion

Previous research from our laboratory (Scheuren et al., 2014) had shown that the personality traits rumination and interoceptive accuracy as well as several interacting psychological characteristics enhance the likelihood of the occurrence of the TGI. The identification of psychophysiological proxies of vagal activation at rest as predictors of paradoxical pain sensitivity in the present study adds to our knowledge about the reasons for the observed inter-individual differences in thermal grill-related pain perceptions. Considering that a higher level of vagally mediated RSA at rest reflects a greater disposition to emotional and cognitive self-regulation ability, it may be stated that the current findings point to an additional psychological characteristic involved in the susceptibility to paradoxical pain. Since thermal grill-related and central neuropathic pain processing share common neural pathways, it could be interesting to study potential effects of the described psychological and psychophysiological factors in clinical samples comprising neuropathic pain and other pain states that are not related to peripheral noxious input. The analysis of vagal reactivity to acute paradoxical pain might be another relevant topic, in particular in the context of a comparison with in literature described relationships between vagal activation and acute pain states depending on noxious input.

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Table 1. Pain intensity and pain unpleasantness ratings in responders and non-responders

	Mean	*SD*	*Minimum*	*Maximum*	*Median*	*U*	*z*	*p*[a]	*r*
All participants:									
(N = 52):									
Pain intensity	24.9	14.2	2.5	63.3	18.7	0.00	–6.1	< 0.01**	0.1
Pain unpleasantness	19.6	14.9	0	64.2	18.6	0.00	–5.8	< 0.01**	0.1
Pain intensity – Responders:									
(n = 23)									
Pain intensity	38.4	9.9	25.4	63.3	35.8				
Pain intensity – Non-Responders:									
(n = 29):									
Pain intensity	14.1	4.2	2.5	24.6	14.6				
Pain unpleasantness – Responders:									
(n = 17):									
Pain unpleasantness	36.1	11.5	25.8	64.2	31.7				
Pain unpleasantness – Non-Responders									
(n = 35):									
Pain unpleasantness	11.6	8.2	0	23.8	10.0				

[a] Significance values of Mann-Whitney *U* tests: *p*-values < 0.01** (two-tailed) were considered highly significant.

Table 2. HR and HRV values measured at rest

	Mean	*SD*	*Minimum*	*Maximum*	*t-test*	*p*[a]	*Mean difference*	*95.0% C.I. of the difference*	*Ej s*
All participants *(N = 52):*									
Mean HR (bpm)	71.9	10.4	50.2	95.3		> 0.05*			
RMSSD[b]	49.7	17.5	22.4	94.0		> 0.05*			
pNN50[c]	23.1	17.2	0	61.7		> 0.05*			
HF (ms^2)[d]	634.4	409.9	88.3	1976.2		> 0.05*			
HF (n.u.)[e]	42.2	19.6	7.9	84.9		> 0.05*			
RSAnorm[f]	0.8	0.2	0.4	1.4	t (50) = 2.2	< 0.05*	0.1	*CI*: 0.01–0.3	η^2
Pain intensity – Responders *(n = 23):*									
Mean HR (bpm)	70.3	8.5	51.0	82.9					
RMSSD	52.7	16.7	23.2	85.3					
pNN50	28.2	16.5	2.2	59.6					
HF (ms^2)	731.4	357.2	88.3	1510.2					
HF (n.u.)	46.5	17.8	14.9	84.9					
RSAnorm	0.9	0.3	0.4	1.4					
Pain intensity – Non-Responders *(n = 29):*									
Mean HR (bpm)	73.2	11.7	50.2	95.3					
RMSSD	47.4	18.1	22.4	94.0					
pNN50	19.1	16.9	0	61.7					
HF (ms^2)	572.1	442.72	129.2	1976.2					
HF (n.u.)	38.8	20.5	7.9	84.1					
RSAnorm	0.7	0.2	0.5	1.2					
Pain unpleasantness Responders *(n = 17):*									
Mean HR (bpm)	69.5	9.2	51.1	82.9					
RMSSD	51.9	18.2	23.2	85.3					
pNN50	26.6	18.5	0	59.6					
HF (ms^2)	595.4	281.4	88.3	1094.8					
HF (n.u.)	46.0	17.6	14.9	84.1					
RSAnorm	0.8	0.2	0.4	1.2					
Pain unpleasantness Non-Responders *(n = 35):*									
Mean HR (bpm)	73.1	10.8	50.2	95.3					
RMSSD	48.7	17.4	22.4	94.1					
pNN50	21.3	16.5	.4	61.7					
HF (ms^2)	649.8	462.7	129.25	1976.2					
HF (n.u.)	40.4	20.4	7.9	84.9					
RSAnorm	0.8	0.3	0.5	1.4					

[a] Significance values of independent *t*-tests comparing HRV scores for responders and non-responders: *p*-values < 0.05 (two-tailed) were considered significant. [b] Square root of the mean squared differences of successive NN intervals; [c] Proportion derived by dividing NN50 by the total number of NN intervals; [d] high-frequency (HF, 0.15–0.4 Hz) values as expressed in power (ms^2) and [e] normalized units (n.u.); [f] Normalized respiratory sinus arrhythmia.

Table 3. Predictors of thermal grill illusion perceptions

	B	*S.E.*	*Wald*	*df*	*p*[a]	*Odds Ratio*	*95.0% C.I. for Odds Ratio*	
Predictors for pain intensity sensations:							*Lower*	*Upper*
RSAnorm[b]	2.68	1.31	4.18	1	0.04*	14.58	1.12	190.29
RMSSD[c]	–0.12	0.06	4.42	2	0.03*	0.88	0.79	0.99
pNN50[d]	0.15	0.06	6.38	2	0.01*	1.16	1.03	1.31

[a] *p*-values < 0.05 (two-tailed tested) were considered significant in the logistic regression analyses. [b] Normalized respiratory sinus arrhythmia; [c] Square root of the mean squared differences of successive NN intervals; [d] Proportion derived by dividing NN50 by the total number of NN intervals.

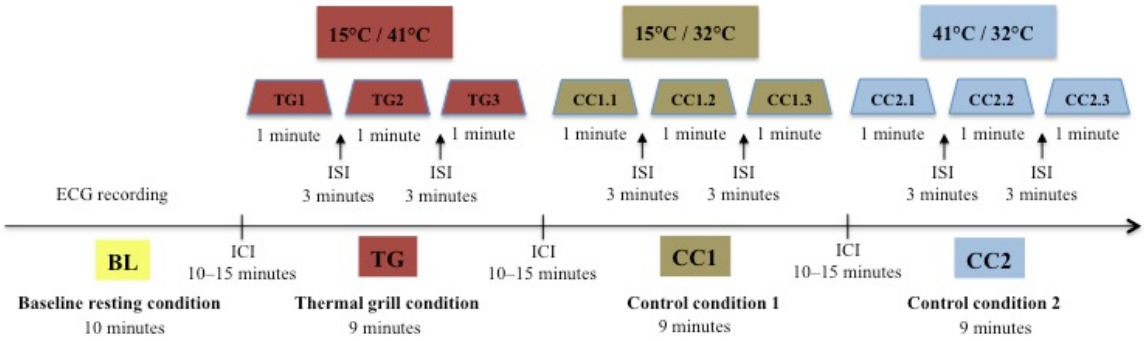
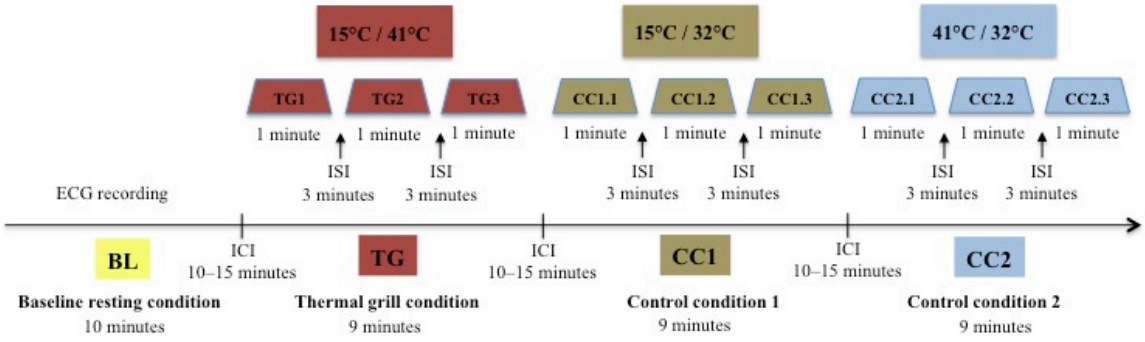


Figure 1. Experimental protocol and thermal grill (TG) stimulation procedure. Three stimulation trials were presented in the TG and control (CC) conditions, each trial lasting one minute. The stimulation trials of each condition were separated by inter-stimulus-intervals (ISI) of three minutes where the participant removed the hand from the grill tubes. Each inter-condition-interval lasted 10–15 minutes to allow for temperature adjustment of the thermal grill-related water-baths.

Figure 2 with legend in JPEG format:



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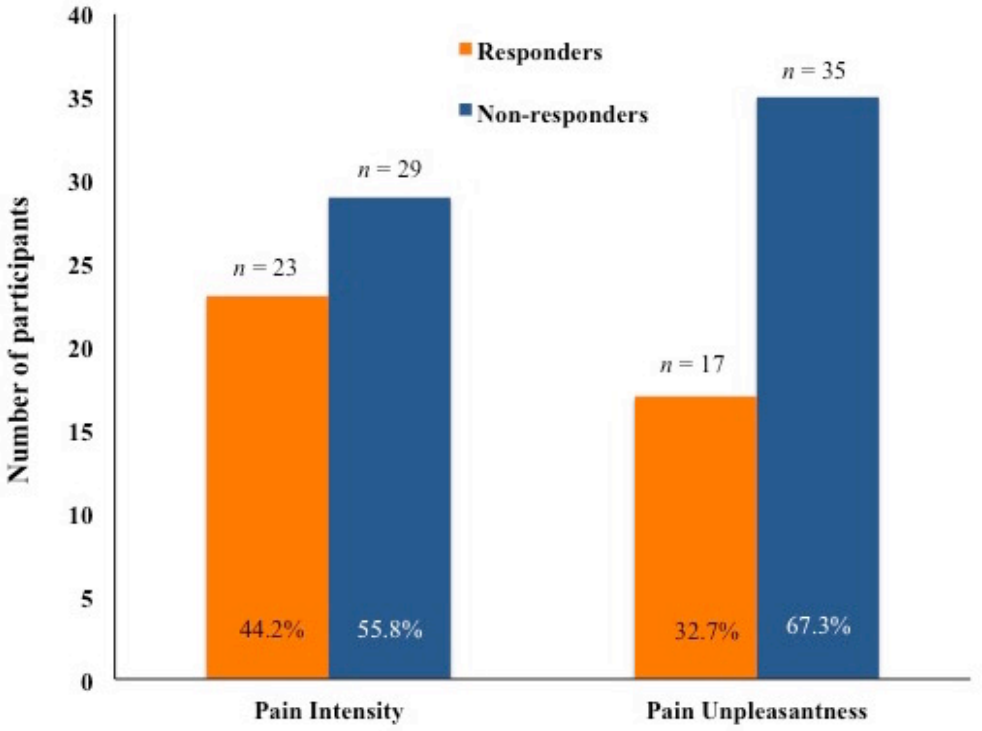

Figure 2. Proportion of responders and non-responders to thermal grill stimulation with respect to pain intensity and pain unpleasantness ratings. Participants displaying pain ratings ≥ to 25 on the NRS were classified as responders. Ratings below this cut-off point of 25-NRS led to the classification as non-responder.