LETTER TO THE EDITOR

HEART RATE VARIABILITY AND SENSITIVITY TO EXPERIMENTALLY INDUCED PAIN: A REPLICATION

To the Editor,

The neural systems involved in autonomic control and perception of pain are closely coupled,[1] and extensive interactions between these sets of neural structures can be observed.[2,3] The functional interaction of these systems[4] is an important component of the pain regulatory process.[5] Blood pressure and heart rate are both products of autonomic reactivity, and have been studied to specify the relationship between pain stimuli and autonomic reactions.[6–9] Heart rate variability (HRV), by contrast, attempts to tease out the relative contributions of sympathetic and parasympathetic activity underlying autonomic reactivity, and therefore bears great potential to study autonomic nervous system (re)activity in experimental pain research.[10]

However, while several experimental studies have explored the effect of experimentally induced pain on HRV,[10] only 2 previous studies have treated resting HRV as an independent variable, to investigate interindividual differences in pain sensitivity.[11] Appelhans and Luecken[11] found that HRV was associated with ratings of pain unpleasantness but not pain intensity in subjects receiving painful cold stimulation. In a recent study published in *Pain Practice*, Nahman-Averbuch et al.[12] found that the relationships between parasympathetic function, pain perception, and pain modulation were prominent only in individuals with higher anxiety, where higher parasympathetic arousal was associated with higher ratings of tonic heat pain and a more efficient conditioned pain modulation capacity (ie, a decrease in sensitivity to pain). In this letter, we aimed to replicate previous findings by Appelhans and Luecken[11] to further elucidate the association of pain sensitivity and resting autonomic function.

Data for this analysis was taken from the first session of a previous study investigating the 2-week test-retest reliability of the cold pressor task (CPT).[13] Healthy undergraduate students were recruited at the SRH University Heidelberg from September 2012 through January 2013. Participants provided written informed consent and completed several questionnaires. Self-rated health (S-RH) was measured using the question "How do you rate your current health status?" on a 0 ("very bad") to 6 ("excellent") scale. Only subjects indicating an S-RH of ≥ 3 ("fair") were included in the trial. The sample of participants included in this analysis consisted of 28 female and 6 male, healthy undergraduate students. The age range was 20 to 31 years (mean 22.85 years, SD = 2.46). Each participant was given a day of the week (Monday through Friday) and a time (between 9:00 am and 6:00 pm) when assessments would be made. Date and time of measurements were recorded by a protocol. Before the CPT, HRV was measured. Sociodemographic variables were assessed using a self-developed questionnaire. All participants received class credits or an allowance of 20€ for completion of the study.

Heart rate variability was measured for 5 minutes in a sitting position immediately before hand immersion into cold water. A Polar RS800CX portable device (Polar Electro Inc., Bethpage, NY, U.S.A.) using a transmitter consisting of a stable polyamide case with electrodes attached to an elastic belt fixed to the chest of the subjects was used to record interbeat intervals (IBIs) at a sampling frequency of 1,000 Hz, providing a temporal resolution of 1 millisecond for each R–R interval. Device-specific software (Polar ProTrainer 5) was used to transfer recordings to a PC. IBI data (.txt files) were exported and analyzed using Kubios HRV (Biosignal Analysis and Medical Imaging Group, University Kuopio, Finland, Version 2.0).[14] In line with the previous study,[11] an autoregressive model was fitted to the RR-interval series, and the area under the power spectral density function within the low-frequency (LF; 0.04 to 0.15 Hz) and high-frequency bands (HF; 0.15 to 0.4 Hz) was derived, and underwent natural log transformation. The peak frequency of HRV power within the HF band was used as an estimate of respiratory rate.

Cold pain sensitivity was assessed by immersing the nondominant hand up to the wrist in an acrylic glass tank with circulating water to prevent local warming. Water temperature was controlled constantly at 4°C (mean = 4.32°C; SD = 0.25°C) with a chilling device, and water pump, and measured with 3 digital thermometers at different spots. Subjects were told to keep their hands open rather than closed in a fist while they were immersed in the water. Before the immersion the subject was told to keep his or her hand in the water until the pain became intolerable, with a cutoff time of 4 minutes. The latencies to the first pain sensation (pain threshold) and to the intolerable pain (pain tolerance) were measured with a stopwatch in seconds. The

Table 1. Sample Characteristics

Age, mean years (SD)	22.80 (2.45)
Women, *n* (%)	29 (85.3)
Men, *n* (%)	6 (14.7)
BMI, mean (SD)	23.02 (4.67)
Pain intensity, mean VAS (SD)	5.15 (2.05)
Pain threshold, mean seconds (SD)	18.48 (13.63)
Pain tolerance, mean seconds (SD)	64.26 (73.84)
PSWQ, mean (SD)	37.14 (12.88)
PSS, mean (SD)	16.88 (11.08)
HADS: depression, mean (SD)	2.24 (2.61)
HADS: anxiety, mean (SD)	4.50 (2.94)
HF-HRV, mean log (SD)	7.05 (1.62)
LF-HRV, mean log (SD)	7.45 (1.11)
Respiration, mean Hz (SD)	0.20 (0.08)

BMI, body mass index; VAS, visual analog scale; PSWQ, Penn State Worry Questionnaire; HADS, Hospital Anxiety and Depression Scale; HF-HRV, high-frequency heart rate variability; LF-HRV, low-frequency heart rate variability.

Table 2. Multiple Linear Regression Models on Heart Rate Variability Predicting Pain Sensitivity

	M1			M2			M3		
	β	*t*	*P*	β	*t*	*P*	β	*t*	*P*
Pain threshold									
HF-HRV	−0.082	−0.396	0.695	−0.138	−0.693	0.494	0.137	0.630	0.538
LF-HRV	−0.040	−0.217	0.829	−0.124	−0.704	0.487	0.159	0.717	0.484
Pain tolerance									
HF-HRV	0.205	1.001	0.324	0.176	0.778	0.443	0.065	0.246	0.809
LF-HRV	0.244	1.380	0.177	0.233	1.172	0.251	0.037	0.137	0.893
Pain intensity									
HF-HRV	**−0.571**	**−3.154**	**0.003**	**−0.594**	**−2.982**	**0.006**	**−0.667**	**−2.468**	**0.026**
LF-HRV	**−0.440**	**−2.680**	**0.012**	**−0.461**	**−2.519**	**0.018**	**−0.644**	**−2.269**	**0.038**

M1, controlling for respiration; M2, controlling for respiration, sex, age, and body mass index; M3, controlling for respiration, sex, age, body mass index, Penn State Worry Questionnaire, Perceived Stress Scale, Hospital Anxiety and Depression Scale (HADS)-Depression, and HADS-Anxiety; HF-HRV, high-frequency heart rate variability; LF-HRV, low-frequency heart rate variability. Significant regression models are identified by bolded text.

ambient temperature and humidity of the testing room was recorded. Subjects rated their pain intensity on hand removal on an 11-point visual analog scale (VAS of 0 to 10) derived from the German short form of the McGill Pain Questionnaire (SF-MPQ[15]). Details on the procedure are published elsewhere.[13]

The Penn State Worry Questionnaire (PSWQ)[16] was used to control for a traitlike tendency to worry and the generality, excessiveness, and uncontrollability characteristics of pathological worry (eg, "I am always worrying about something"). High scores on the PSWQ are associated with increased worry and generalized anxiety problems. The reliability and validity of the PSWQ are well established.[17] The Perceived Stress Scale (PSS)[18] was used to evaluate the level of perceived stress. Higher total scores indicate a higher level of perceived stress. We controlled for symptoms of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS).[19] The HADS consists of 14 items: 7 items on depression (HADS-D) and 7 items on anxiety (HADS-A), reported by respondents over the preceding week. Both subscales (HADS-A and HADS-D) were used for analysis.

Multiple linear regression (MLR) analysis was performed to explore the association of the independent (LF- and HF-HRV) and dependent measures (pain threshold, pain tolerance, pain intensity). Three models (M1 through M3) were applied: M1, exploring the association of pain sensitivity and HRV while controlling for respiration; M2, controlling for age, sex, body mass index (BMI), and respiration; and M3, controlling for the aforementioned covariates and scores derived from the PSWQ, PSS, and both subscales of the HADS. Alpha was set at the 0.05 level for all statistical tests. All analyses were performed using SPSS software (version 21; IBM, Chicago, IL, U.S.A.).

Sample characteristics are given in Table 1. MLR models revealed possible determinants of pain sensitivity for ratings of pain intensity on hand removal only (Table 2). HRV did not predict pain threshold or pain tolerance. HRV recordings predicted pain intensity, even when controlling for all covariates within the full model.

Within the present analysis we aimed to replicate previous findings on the association of HRV and pain sensitivity. MLRs revealed that HRV predicts later pain intensity. These findings are somewhat contradictory to those of Appelhans and Luecken,[11] who found that greater LF power was associated with lower ratings of pain unpleasantness but not pain intensity. Furthermore, those researchers found that HF power was unrelated to measures of pain sensitivity. Our results indicate that both LF and HF power obtained before painful stimulation predict later self-reports of pain intensity, indicating that subjects with higher levels of LF- and HF-HRV perceive a standardized pain stimulus as being less intense. However, a critical aspect explaining the different results between studies might be the distinction between pain intensity and unpleasantness. While Appelhans and Luecken[11] informed participants about the distinction between pain intensity and unpleasantness through a standardized script, we derived pain intensity ratings from a questionnaire after painful stimulation.

Furthermore, the present study had 2 major limitations that should be noted and are likely to contribute to the different findings. First, the sample consisted of healthy undergraduate students, and therefore these findings might not be generalizable to other (particularly older) populations. Second, we administered pain to the nondominant hand, and results might be different when administering pain to the dominant hand.[11]

In line with previous findings, we showed that pain sensitivity to cold pain can be predicted by measures of heart rate variability obtained prior to painful stimulation. In particular, we found that pain intensity after stimulation with thermal cold pain is predicted by HF- and LF-HRV even when controlling for potential covariates (eg, worry, depressive, and anxious symptomology), in line with the original study by Appelhans and Luecken.[11] Further research is needed to address if heart rate variability is capable of predicting subjective pain experience and how psychological distress (eg, worry, depression, anxiety, and stress) may interact with heart rate variability and subjective pain experience, given the known relationships between psychophysiological factors and pain perception.

CONFLICT OF INTEREST

The authors state that they don't have any conflict of interest.

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