REVIEW ARTICLE

Heart rate variability and experimentally induced pain in healthy adults: A systematic review

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Abstract

Background: Reactivity of the autonomic nervous system to experimental pain stimuli has been extensively studied using measures of heart rate and blood pressure. Heart rate variability (HRV) attempts to tease out the relative contributions of sympathetic and parasympathetic activity in the autonomic control of the heart and may therefore be more appropriate to investigate autonomic response to short-term nociceptive stimulation in detail. The current evidence on HRV and experimentally induced pain has not yet been synthesized within a systematic review.

Method: English articles indexed in PubMed, EMBASE, Psyndex, PsycINFO, CINAHL and the Cochrane Library were reviewed for eligibility under pre-specified inclusion criteria. Studies were included when they reported empirical work on autonomic response (specifically, HRV) to experimentally induced pain in healthy adults. The method of pain induction, the methodological features of HRV analysis (time domain and frequency domain measures), as well as pain and HRV-related findings were derived from the studies.

Results: The search revealed a total of 20 publications eligible for inclusion. Key results demonstrate an increase in sympathetic-baroreflex activity and a decrease in vagal-parasympathetic activity as reflected by changes in frequency domain measures of HRV.

Conclusion: HRV has several advantages compared to other measures of autonomic reactivity in studies investigating physiological response to nociceptive stimulation. Future studies should focus on comparisons between different methods of pain induction, interindividual variability in pain sensitivity by baseline autonomic activity, and the implications of both on the use of HRV within routine clinical evaluations.

1. Introduction

Experimental methods to induce acute pain are widely used to study pain sensitivity in humans and animals. The experience of pain itself is characterized by tremendous interindividual variability (Fillingim, 2005), driven by biological (e.g., sex and genetics), psychological (e.g., mood and attention) and social (e.g., marital status) factors. Non-pathologic acute pain is a complex sensory and emotional experience (Fernandez and Turk, 1992) that signals the organism to somatic damage, leading to an appropriate motor response of protection (Loeser and Melzack, 1999). Because pain is a stressor and environmental challenge (which in turn requires that organism to respond), it has been discussed as a specific emotion that reflects homeostatic behavioural drive, similar to temperature, itch, hunger and thirst (Craig, 2003).

Databases
- This review uses a systematic approach, according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)' statement. The search was performed using the PubMed, EMBASE, Psyndex, PsycINFO, CINAHL and the Cochrane Library database.

What does this study add?
- This review summarizes the current use and evidence on measures of HRV to study autonomic reaction towards nociceptive stimulation.

A comprehensive framework to investigate the way in which organisms function and adapt to diverse types of stressor such as pain is the *model of neurovisceral integration* (Thayer and Lane, 2000, 2007), which posits flexibility in the face of changing physiological and environmental demands as a hallmark of successful adaptation. The authors proposed that a core set of neural structures provides an organism with the ability to continuously assess the environment for signs of threat and safety and to prepare the organism for appropriate action. Heart rate variability (HRV) has been proposed to serve as index of the degree to which this system provides flexible, adaptive regulation (Thayer et al., 2012).

The systems controlling cardiovascular function are closely coupled to systems modulating the perception of pain (Randich and Maixner, 1984) and extensive interactions between the neural structures involved in pain sensation and autonomic control can be observed (Benarroch, 2001; Benarroch, 2006). The functional interaction of these systems (Zamir and Maixner, 1986) seems to be an important component of the pain regulatory process (Bruehl and Chung, 2004). In particular, characterizing the relationship between baroreflex arcs (spontaneous baroreflex sensitivity) and elevated resting blood pressure (BP; Guasti et al., 2002; Chung et al., 2008), and their ability to dampen pain sensitivity (i.e., hypertension-related hypoalgesia; Rau et al., 1994) are promising findings from experimental studies (Droste et al., 1994; Edwards et al., 2003) with clinical impact.

BP (Bruehl and Chung, 2004) and heart rate (HR) are products of autonomic reactivity, and have been extensively studied to specify the relationship between pain stimuli and autonomic reactions (Möltner et al., 1990; Tousignant-Laflamme et al., 2005; Colloca et al., 2006; Loggia et al., 2011). HRV, by contrast, attempts to tease out the relative contributions of sympathetic and parasympathetic activity underlying autonomic reactivity and furthermore serves as an index of baroreflex activity (Casadei et al., 1995; Moak et al., 2009; Goldstein et al., 2011), and may therefore be more appropriate to investigate autonomic nervous system (ANS) reactivity to nociceptive stimulation. However, the current evidence on measures of HRV has not been summarized within a systematic review. We attempt to summarize trends in the use of HRV measures in studies using nociceptive stimuli in healthy adults and the current evidence regarding the interconnections of HRV and experimentally induced pain.
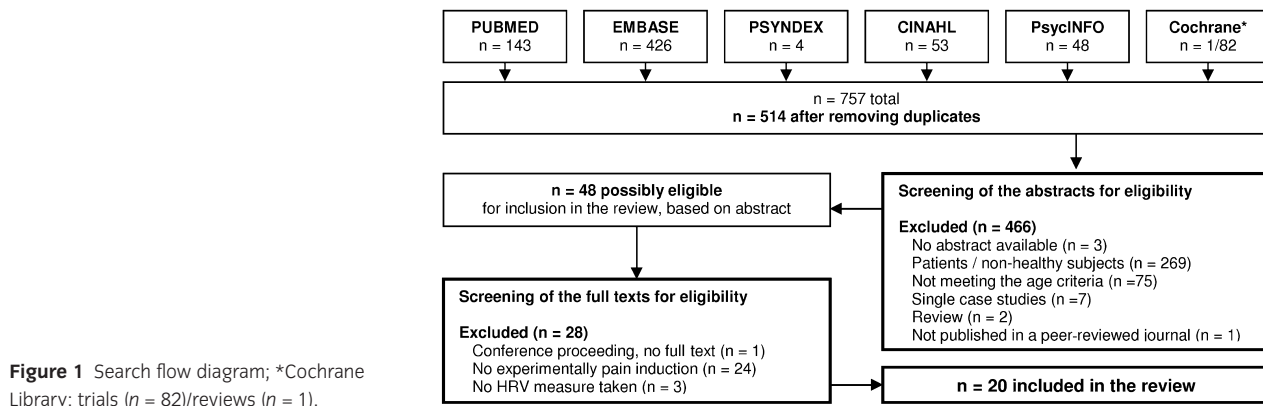
2. Methods

2.1 Search strategy

This review uses a systematic approach according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)' statement (Moher et al., 2009) to identify studies using nociceptive stimuli and measures of HRV, to synthesize research on the relationships between HRV and acute pain within healthy adult populations. The following computerized databases were searched from 1 January 1996 to 31 December 2012: PubMed, Psyndex, PsycINFO, CINAHL, EMBASE and the Cochrane Review Library. The search was restricted to publications published within that time frame since the first guidelines on standards of measurements, physiological interpretation and clinical use of HRV were published in 1996 [Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (hereafter referred to as Task Force) 1996]. Additional online-only material (Supporting Information Table S1) shows the selected databases and reports details on the search strategies applied.

Articles were considered for inclusion if they had a focus on pain (search term keyword: '*pain*') and measured HRV (search term keyword: '*heart rate variability*'). The abstracts of the manuscripts were screened for eligibility based on the following criteria: (1) empirical investigation in (2) healthy (3) human (4) adults, (5) published in a peer-reviewed journal in (6) English. If possible, the (7) full text of the included abstracts was retrieved and screened for eligibility based on the following criteria: (8) use of a nociceptive, non-interventional (e.g., acupuncture) stimuli, and (9) HRV measure taken. The reference list of all included studies was screened for additional study citations.

2.2 Data extraction

Study information on author, country, study population, sample size, gender ratio, age of participants, study design and main study focus was extracted from the papers retrieved in full text. Furthermore, details regarding the

Figure 1 Search flow diagram; *Cochrane Library: trials (*n* = 82)/reviews (*n* = 1).

method of pain induction, further pain assessments, the method of HRV recording, available data length for analysis and HRV measures obtained from data sets were extracted and summarized within a comprehensive table. Findings and strength of reported effects were derived from the papers retrieved in full text.

3. Results

3.1 Eligibility and inclusion of studies

Details were recorded regarding the number of studies found, number of studies meeting the specified inclusion criteria, number of studies excluded and reasons for exclusion (Fig. 1). The search in the selected databases revealed a total of 514 papers (after removing duplicates) from which the abstracts were retrieved. Two reviews, 109 publications that clearly did not relate to the topic and 7 single case studies, were excluded (1); 269 papers with non-healthy participants were excluded (2). If studies compared healthy participants versus patients with recurrent or chronic pain, they were excluded. Seventy-five papers not meeting the age criteria (e.g., newborns or infants) were excluded (4); one paper was excluded because it was not published in a peer-reviewed journal (5). A total of 48 abstracts were considered possibly eligible for inclusion. The full text of 47 papers was retrieved (7). Twenty-four papers were excluded for not using nociceptive stimuli (8) and three papers were excluded that did not report HRV measures (9). This leaves a total of 20 papers for inclusion in the review.

3.2 Nature of the included studies

In addition to studies comparing pain induction to a placebo condition (Ghione et al., 2004), studies frequently investigated differences in the autonomic

physiological response indexed by HRV to pain stimulation by varying specific experimental conditions or investigating differences based on specific characteristics of the participants. The impact of experimenter gender on the physiological response was addressed within a randomized-controlled design (Aslaksen et al., 2007). Furthermore, the modulation of autonomic function and pain perception by distracting stressors such as the paced auditory serial addition task (PASAT) or cold pressor task (CPT) in comparison to control conditions (e.g., attention to the stimulus or listening to relaxing music) was investigated in several studies (Terkelsen et al., 2004, 2005; Bendixen et al., 2012). Other studies compared different intensities or methods of nociceptive stimulation. Among these, one study compared deep versus superficial induced pain (Burton et al., 2009), one compared different categories of pain intensity (Treister et al., 2012), and another study compared hot versus cold thermal pain (Streff et al., 2010). Furthermore, some studies investigated interindividual differences in autonomic reactivity towards pain stimulation. Interindividual differences were investigated addressing the degree of interoceptive sensitivity (IS; Pollatos et al., 2012), differences in personality (Paine et al., 2009) or differences in the susceptibility to hypnosis (Balocchi et al., 2005; Santarcangelo et al., 2008).

In addition to these psychological factors, another group of studies investigated contributing factors that might be categorized as underlying physiological states or mechanisms. These studies addressed the impact of different sleep stages (Chouchou et al., 2011), different stages of the menstrual cycle (Tousignant-Laflamme and Marchand, 2009), the degree of muscle sympathetic nerve activity (MSNA; Fazalbhoy et al., 2012) or baseline HRV (Appelhans and Luecken, 2008) on interindividual variability in pain sensitivity. Additionally, a group of studies investigated interventions to alter the

pain experience such as placebo capsules (Aslaksen et al., 2007), breathing manipulations (Chalaye et al., 2009; Martin et al., 2012) or listening to a CD with relaxation instructions (Olsson and von Schéele, 2011), and used HRV to monitor the outcome or differential effects of the interventions.

3.3 Methods of pain induction and pain assessment used

Cutaneous or deep pain in the experimental setting can be induced by a broad variety of methods (Procacci et al., 1979). Most prominent methods use either pain-inducing substances (e.g., hypertonic saline) or physical agents (e.g., temperature, pressure). Within an experimental setting, several measures regarding the participants' experiences of the painful stimuli are of interest. Most prominent are *pain threshold*, determined by the point or stimulus intensity at which the subject first reports noticeable pain (Edens and Gil, 1995), and *pain tolerance*, determined by the upper limit for endurance or stimulus intensity of noxious stimulation to the point subjects report that they can no longer endure the stimulation. Furthermore, ratings of pain intensity or unpleasantness are derived from numeric rating scale (NRS) or visual analogue scale (VAS). In addition, several questionnaires using qualitative descriptors to characterize the pain experience can be used.

Several studies included within this review used thermal pain as the method of induction. Studies either used heat (Aslaksen et al., 2007; Aslaksen and Flaten, 2008; Chalaye et al., 2009; Streff et al., 2010; Chouchou et al., 2011; Treister et al., 2012) or cold (Appelhans and Luecken, 2008; Tousignant-Laflamme and Marchand, 2009; Streff et al., 2010) pain stimuli. Besides thermal pain, electrical stimulation of the sural nerve (Terkelsen et al., 2004, 2005; Martin et al., 2012) or a pressure pain stimulus (Balocchi et al., 2005; Santarcangelo et al., 2008; Pollatos et al., 2012) was used. Three studies used hypertonic saline infusion to induce muscle pain (Burton et al., 2009; Bendixen et al., 2012; Fazalbhoy et al., 2012). Hypertonic saline was either used in a 5% (Burton et al., 2009; Bendixen et al., 2012) or 7% (Fazalbhoy et al., 2012) concentration and was applied to the belly of the ipsilateral tibialis anterior muscle (Burton et al., 2009; Fazalbhoy et al., 2012) or masseter muscle (Bendixen et al., 2012). Other methods of pain induction used included exposure of the head to a 37 Hz electromagnetic field (Ghione et al., 2004), oesophageal balloon distension (Paine et al., 2009) or lying on a bed of nails (Olsson and von Schéele, 2011).

In terms of pain intensity ratings, a NRS was used most frequently with a large variety of formats (e.g., 9-point, 101-point, 11-point). Several studies used VAS or VAS applied within a potentiometer or a computer-presented scale to assess pain intensity. Besides ratings of pain intensity, equivalent methods to rate the participants' unpleasantness towards the pain stimulus were frequently used. In addition, pain threshold and pain tolerance were assessed by several studies. Besides these pain-related measures, only one study used an additional questionnaire (McGill Pain Questionnaire; Melzack, 1975) to assess pain-related measures (Santarcangelo et al., 2008). Table 1 summarizes the included studies by their participants, the applied methods of pain induction and assessment, and the main study focus.

3.4 Methods and measures of HRV measurement used

Like many organs in the body, the heart is dually innervated. Although a wide range of physiologic factors determine cardiac functions such as HR, the ANS is the most prominent (Thayer et al., 2012). Chronotropic (i.e., the timing of heartbeats) control of the heart is achieved via the complex interplay of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) branches of the ANS. More importantly, the HR is under tonic inhibitory control by the PNS influences (Jose and Collison, 1970).

The basic data for the calculation of all the measures of HRV are the sequence of time intervals between adjacent heartbeats – the inter-beat interval (IBI). Relative increases in SNS activity are associated with HR increases and relative increases in PNS activity are associated with HR decreases. While SNS effects are slow on the timescale of seconds, PNS effects are faster on the timescale of milliseconds (Levy, 1997). Therefore, the PNS influences are the only ones capable of producing rapid changes in the beat-to-beat timing of the heart (Uijtdehaage and Thayer, 2000).

Despite several methods to record the IBI sequence, electrocardiography (ECG) is the most prominent. Different software solutions are available for the analysis of pre-recorded IBI sequences. In the present survey, most studies utilized ECG recordings to derive IBI data for HRV analysis. Data lengths for analysis varied considerably between the studies. Sequences of 1 min (Paine et al., 2009; Streff et al., 2010; Treister et al., 2012), 2 min (Balocchi et al., 2005; Aslaksen et al., 2007; Aslaksen and Flaten, 2008; Santarcangelo et al., 2008; Burton et al., 2009; Fazalbhoy et al.,

Table 1 Included studies by participant, method of pain induction and main study focus.

Authors (year)	Country	n (F/M)	Age in years, mean (SD), range	Method of pain induction	Pain assessment	Main study focus
Appelhans and Luecken (2008)	United States	59 (37/22)	19.74 (1.83), nr	Thermal cold pain (cold plate)	PI and PU on a 101-point NRS; PTh for noticeable and moderate pain	Interlink between interindividual variability in pain sensitivity and HRV
Aslaksen et al. (2007)	Norway	64 (32/32)	F: 23.61 (3.99), 19–40; M: 23.3 (2.49), 19–35	Heat pain induced through a contact thermode	PI and PU on a 100 mm VAS	Effect of experimenter gender on autonomic and subjective responses to pain stimuli
Aslaksen and Flaten (2008)	Norway	63[c] (32/31)	F: 23.1 (4.7), 18–40; M: 25.4 (5.4), 19–39	Heat pain induced through a contact thermode	PI and PU on a 100 mm VAS	Physiological responses to heat pain stimulation with placebo capsules (analgesic effect) or without administration of capsules
Balocchi et al. (2005)	Italy	21	22 (1.3), nr	2-min pressure applied at the second costochondral junction (deep pressure algometer)	PI (0–10)	HRV in subjects with different hypnotic susceptibility, nociceptive stimulation versus suggestions of analgesia
Bendixen et al. (2012)	Denmark	16 (16/0)	22.9 (2.4), nr	Hypertonic saline (5%) induced masseter muscle pain	PI on a 0–10 NRS	Modulation of hypertonic saline induced muscle pain and autonomic function by stressors (CPT and PASAT)
Burton et al. (2009)	Australia	26 (13/13)	28 (nr), nr	Hypertonic saline (5%) into the belly (deep) of tibialis anterior and under the overlying skin (superficial)	PI: potentiometer expressed on a 0–10 VAS	Deep versus superficial experimentally induced acute pain
Chalaye et al. (2009)	Canada	20 (9/11)	25.1 (5.6), nr	Heat pain thermode	PTh and thermal PTo	Respiratory effects on experimental heat pain and cardiac activity
Chouchou et al. (2011)	France	14 (4/10)	32.8 (7.3), nr	Nociceptive radiant heat stimuli were delivered with a Nd:YAP laser	– (subjects a sleep)	Autonomic reactivity to nociceptive stimuli during all-night sleep
Fazalbhoy et al. (2012)	Australia	12 (1/11)	18–48 (nr), nr	Hypertonic saline (7%) into the belly of the ipsilateral tibialis anterior muscle	Potentiometer VAS, 0–10, McGill Pain Questionnaire	Individual differences in the cardiovascular responses and MSNA to tonic muscle pain
Ghione et al. (2004)	Italy	13[a] (0/13)	41 (7), nr	Exposure of head to a 37 Hz electromagnetic field	PTh and PTo	PTh and PTo by exposure of head to a 37 Hz electromagnetic field versus sham
Martin et al. (2012)	Untied States	30 (20/10)	21(5.5), nr	Suprathreshold electric pain stimulations delivered to the sural nerve	PI: computer-presented scale: 0–100	Investigate the mechanisms responsible for respiration-induced hypoalgesia
Olsson and von Schéele (2011)	Sweden	32 (20/12)	39.7 (8.6), nr	Lying on a bed of nails	Pain ratings: NRS from 0 to 10	Effects of lying on a bed of nails on HRV, silence versus CD with relaxation instructions
Paine et al. (2009)	United Kingdom	19 (11/8)	n. r. (nr), 22–54	Oesophageal balloon distension	PI: VAS ranging from 0 to 10	How personality differences affect brainstem autonomic responses to visceral pain
Pollatos et al. (2012)	Germany[b]	60 (30/30)	24.4 (3.2), nr	Ascending pressure pain stimulus	PI and PU: 9-point NRS PTh and PTo: pressure algometer	Modulation of cutaneous perception of a ascending pressure pain stimulus by IS
Santarcangelo et al. (2008)	Italy	19 (19/0)	HI: 21 (2.3), nr SLH: 21 (1.9), nr	Moderate pain (>5 in a scale ranging from 1 to 10) induced by pressure algometer applied at the second costochondral junction	Interview after each nociceptive stimulation about pain perception (range: 1 = no pain to 10 = unbearable pain)	Pain-related modulation of HRV, HI versus SLH
Streff et al. (2010)	Luxembourg	35 (18/17)	24[d] (nr), 19–57	Tonic thermal pain, immersing the hand to cold (CPT: 3–4 °C) or hot (HIT: 47–48 °C) water	PI: verbally anchored scale (0–100); PU: 10 cm VAS; Qualitative aspects: pain sensation scale (SES)	Different physiological effects during hand immersion in hot (HIT) or ice water (CPT)

Table 1 (continued)

Authors (year)	Country	n (F/M)	Age in years, mean (SD), range	Method of pain induction	Pain assessment	Main study focus
Terkelsen et al. (2004)	Denmark	26 (0/26)	24 (nr), 21–31	Electric sural nerve stimulation	NRS of 10 levels; PTh: three series of increasing and decreasing electric stimulation	How distraction or attention affects pain and HRV during sural nerve stimulation
Terkelsen et al. (2005)	Denmark	26 (0/26)	24 (nr), 21–31	Electric sural nerve stimulation	see Terkelsen et al. 2004	HRV responses in acutely stress subjects exposed to a painful stressor
Tousignant-Laflamme and Marchand (2009)	Canada	32 (32/0)	34.3 (7.5), nr	CPT (12 °C) for 2 min	0–100 NRS	Autonomic reactivity to cold pressor pain throughout the menstrual cycle
Treister et al. (2012)	Israel	55 (21/34)	25.9 (4.1), 20–37	Heat pain: TSA thermode (low pain, medium pain and high pain)	0–100 NRS	Ability of autonomic parameters to differentiate among four categories of heat PI

F, female subjects; M, male subjects; HI, Hypnotizable individuals; SLH, subjects with low susceptibility to hypnosis; PI, pain intensity; PU, pain unpleasantness; PTh, pain threshold; PTo, pain tolerance; MSNA, muscle sympathetic nerve activity; IS, interoceptive sensitivity; TSA, thermal sensory analyser.
[a]Three subjects were excused due to vasovagal reaction on insertion of an intravenous cannula.
[b]Unclear where participants were recruited, country was taken out the affiliation of the first author.
[c]Three subjects had to be excluded from analysis.
[d]Median age is reported.

2012), 3 min (Terkelsen et al., 2004, 2005; Balocchi et al., 2005; Aslaksen and Flaten, 2008), 5 min (Appelhans and Luecken, 2008; Santarcangelo et al., 2008; Tousignant-Laflamme and Marchand, 2009; Bendixen et al., 2012), 6 min (Martin et al., 2012), 10 min (Pollatos et al., 2012), 15 min (Ghione et al., 2004) and 20 min (Olsson and von Schéele, 2011) were used. Furthermore, an even shorter sequence of pain induction and HRV measurement with a length of 12 s is reported (Aslaksen et al., 2007).

Numerous methods of operationalizing HRV exist but fall broadly into three classes of measures: time domain, frequency domain and non-linear. The most commonly used measures are summarized and provided as additional online-only material (Supporting Information Table S2). Time domain measures range from short term (e.g., the standard deviation of IBIs or the root mean square successive differences in an IBI series within a 5-min window) to long term (e.g., the standard deviation of all IBIs in a 24-h window). Frequency domain measures submit an IBI time series to spectral analysis and quantify power spectral density within pre-specified frequency bands. The power spectrum of short-term (~5 min) time series contains two major components, a high- (0.15–0.40 Hz) and low- (0.01–0.15 Hz) frequency component reflecting cardiac vagal (i.e., parasympathetic) tone and a mixture of vagal and sympathetic influences, respectively. Respiratory sinus arrhythmia (RSA), the square root of the mean squared difference of successive NNs (RMSSD) and the high-frequency component of the power spectrum (HF power) are

closely related, and are strongly associated with cardiac vagal influence. Of particular interest with respect to studies on acute pain is low-frequency HRV (LF-HRV), which (contrary to conventional wisdom) reflects baroreflex activity rather than sympathetic activity (Casadei et al., 1995; Moak et al., 2009; Goldstein et al., 2011). Acute increases in BP stimulate arterial baroreceptors (Rau and Elbert, 2001); in response, the nucleus tractus solitarius stimulates increased PNS activity and inhibits SNS activity (the so-called baroreflex arc) to restore BP to normal levels (France and Ditto, 1996). Baroreflex sensitivity therefore plays a major role in hypertension-related hypoalgesia (Rau et al., 1994; Guasti et al., 2002; Chung et al., 2008), which can be indexed by LF-HRV. More details on the measurement of HRV are published elsewhere (Thayer et al., 2008).

Among the time domain measures of HRV reported within the included studies are mean normal-to-normal (NN), NN50 count, standard deviation of all NN intervals (SDNN) and RMSSD (Table 2). In the present survey, most studies report frequency domain measures as HF, or HF and LF, or the LF/HF ratio (Table 2). Very low frequency (VLF) is only reported by one study (Pollatos et al., 2012). Most studies implemented the frequency band cut-offs recommended by the Task Force guidelines (Task Force, 1996 , Supporting Information Table S2). Only Ghione et al. (2004) used a LF band from 0.03 to 0.15 Hz. In addition to regular LF and HF bands, one study (Balocchi et al., 2005) reports a mLF band (0.04–0.08 Hz) supposed to represent a pure sympathetic

Table 2 Methods of HRV measurement and HRV and pain-related findings.

Authors (year)	Condition at recording, data length for analysis	Derived HRV measures	HRV and pain-related finding
Appelhans and Luecken (2008)	Resting ECG, 5 min BL in the supine position before pain stimulation	HF (0.15–0.40 Hz), LF (0.04–0.15 Hz)	PI not predicted by LF or HF; LF inversely associated with PU; ↑ LF associated with ↑ PTh (noticeable pain) and predicted ↑ PTh (moderate pain); HF not associated with PTh (noticeable or moderate pain)
Aslaksen et al. (2007)	Placed in a comfortable chair; recording started prior to onset of pain stimuli (pre-test) and was obtained during experimental procedures (about 35 min); pain stimulus intervals (12 s) versus inter-stimulus intervals (2 min)	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz)	↑ LF and ↑ LF/HF ration on pain induction; not affected by presence of experimenters or experimenter gender and subject gender interaction; no correlation of HRV and PI and PU
Aslaksen and Flaten (2008)	On 2 separate days (placebo vs. natural history), recording 3 min BL and during 5 pain stimulations (each lasting 4 min); epoch size for analysis: 120/180 s	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), LF/HF ratio	No significant condition effect on HRV; ↓ LF/HF ratio after administration of the capsules
Balocchi et al. (2005)	BL (3 min), nociceptive stimulation (2 min), BL (3 min), nociceptive stimulation with instructions of analgesia (2 min), BL (3 min)	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), mLF (0.04–0.08 Hz), mean NN, SDNN, RMSSD	↑ HF during pain induction only in low hypnotizable subjects
Bendixen et al. (2012)	Supine position in a quiet room, three experimental sessions on separate days (7 days between sessions), ECG recorded throughout each session (90 min), baseline versus HS infusion (5 min)	HF, LF, CCV-HF, CCV-LF, mean NN, SDNN, RMSSD	CPT: ↓ RMSSD, ↓ HF power ↓ CCV-HF; no results on pain ratings and HRV
Burton et al. (2009)	Resting in a semi-reclined position, 2 min prior to the injection, 2 min following the injection (when HR had stabilized)	HF, LF, LF/HF ratio	↑ LF/HF ratio transiently following intramuscular and subcutaneous injection; LF/HF not differentially affected (deep vs. cutaneous)
Chalaye et al. (2009)	Seated in a comfortable chair, natural breathing (baseline), slow deep breathing, rapid breathing, distraction, HR biofeedback, stimuli induction once the target breathing frequency was reached and maintained	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), mean NN, SDNN	No results on the interlink of HRV and thermal PTh or PTo are reported
Chouchou et al. (2011)	Continuously between 11:00 p.m. and 7:00 a.m. while participants were sleeping	HF^{WV}, LF^{WV}, LF/HF^{WV}, mean NN	↑ LF^{WV} after the stimuli; ↑ LF/HF^{WV} after the stimuli; ↓ mean NN after the stimuli
Fazalbhoy et al. (2012)	Were seated in a semi-reclined posture in a comfortable chair, with the legs supported in the extended position; BL (5 min) prior to infusion, during hypertonic saline infusion (45 min) and 15 min after infusion stopped; calculated over 5 min periods	HF, LF	↑ MSNA during tonic muscle pain, associated with ↑ LF power, ↓ HF power and ↑ LF/HF ratio at rest and during tonic pain; ↓ RMSSD in participants with ↑ MSNA; no results on the interlink of HRV and PI ratings reported
Ghione et al. (2004)	ECG recording throughout the entire length of the experiment (sitting position), averaged over intervals of 15 min	HF (0.15–0.40 Hz), LF (0.03–0.15 Hz)	↑ HF and ↑ HF power progressively increased only during sham exposure; no results on HRV and ratings of PTh and PTo reported
Martin et al. (2012)	Participants sat comfortably in a reclining chair with the footrest extended, ECG was continuously recorded during 6 trials (6 min each)	RMSSD	RMSSD not significantly related to pain outcomes; ↑ RMSSD and lower pain ratings during slow breathing were not significantly associated
Olsson and von Schéele (2011)	Lying on different types of beds, throughout the procedure (4 × 20 min)	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), SDNN	No results on the interlink of HRV and pain ratings are reported
Paine et al. (2009)	1-min epochs (20 s pre-stimulus and 40 s post-stimulus); inter-stimulus interval (1 min)	CVC_{NA}, CSI	↑ CSI during pain, while CVC_{NA} did not change during pain
Pollatos et al. (2012)	During BL (10 min) and pain assessment (9–11 min); analysis of autonomic responses was performed over an average length of 10 min	HF (0.15–0.40 Hz), o LF (0.04–0.15 Hz), VLF (<0.04 Hz)	↓ HF n.u., ↑ LF n.u. and ↑ LF/HF ratio during pain assessment; group differences related to IS; no correlation of LF/HF ratio and PTh and PTo

Table 2 (continued)

Authors (year)	Condition at recording, data length for analysis	Derived HRV measures	HRV and pain-related finding
Santarcangelo et al. (2008)	5 conditions (BL 1: 5 min, pain: 2 min, BL 2: 5 min, instruction of analgesia: 2 min, BL 3: 5 min)	LF/HF ratio, mean NN, SDNN, CSI	NN mean shorter during pain and pain with instruction of analgesia; SDNN significantly larger during B2 and B3 then during instruction of analgesia; no significant condition effect for LF/HF ratio and CSI
Streff et al. (2010)	Continuously monitored (75 min), 5-min resting BL, 10-min rest period between the two tests (hot vs. cold) in alternated order; calculated separately for both test periods and relativized to mean BL (1-min recording 2 min before the pain induction)	LF/HF ratio	↑ LF/HF ratio relative to baseline, significant differences between tests; greater increase in CPT then HIT
Terkelsen et al. (2004)	Lying supine during the experiment with arms and legs in semi-flexed position; 4 × 3 min ECG segments (BL, condition 1, BL, condition 2)	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), CCV-LF, CCV-HF, mean NN, SDNN	↓ HF power, ↓ CCV-HF and ↓ total power PASAT and attention; ↓ LF power PASAT; no results on the correlation of pain ratings and HRV
Terkelsen et al. (2005)	4 × 3 min ECG segments (rest, attention/PASAT, rest, attention/PASAT)	HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), CCV-LF, CCV-HF, mean NN, SDNN	↑ LF power and ↑ CCV-LF painful stimulation; none of the HRV parameters were affected by pain during stress condition
Tousignant-Laflamme and Marchand (2009)	Seated, BL 5 min before procedure and during CPT	HF (0.15–0.40 Hz), LF (0.04–0.15 Hz), LF/HF ratio, NN50	No significant effects
Treister et al. (2012)	Lying in the supine position; recording over 4 stimuli (60 s each), intervals of 10–15 min between stimuli	HF	HF differentiated in 4 of 6 tests, but failed to discriminate between medium versus low and high versus medium pain

PI, pain intensity; PU, pain unpleasantness; PTh, pain threshold; PTo, pain tolerance; MSNA, muscle sympathetic nerve activity; IS, interoceptive sensitivity; BL, baseline; CPT, cold pressor task.

component. Despite these prominently used measures (Supporting Information Table S2), several authors report alternative measures such as the coefficient of HF component variance (CCV-HF; Terkelsen et al., 2004, 2005; Bendixen et al., 2012), the coefficient of LF component variance (CCV-LF; Terkelsen et al., 2004; Terkelsen et al., 2005; Bendixen et al., 2012), the index of cardiac vagal control from nucleus ambiguus (CVC$_{NA}$; Paine et al., 2009) or the cardiac sympathetic index (CSI; Santarcangelo et al., 2008; Paine et al., 2009). CCV-HF and CCV-LF are estimated as the square root of LF or HF power, respectively, divided by mean-NN (Hayano et al., 1991). The CVC$_{NA}$ – which actually represents HF-HRV – is derived from a software called MXedit that first converts the R–R series to time-based data by resampling, then applies a moving polynomial filter producing a smoothed template series and subsequently subtracts this from the original series producing a residual time series before applying a digital bandpass filter to extract variance in the frequency band of 12–40 Hz, and finally natural logarithm transforms this to quantify RSA (Paine et al., 2009). CSI is a novel measure (a ratio of R–R intervals with no unit) and is obtained by software

called CMet. Furthermore, Chouchou et al. (2011) report *wavelet coefficients* (HF^{WV}, LF^{WV} and LF/HF^{WV}), which represent the evolution of the correlation between the signal and the chosen wavelet at different levels along the signal. Table 2 summarizes the details on the methods of HRV measurement and HRV measures reported by the studies included in the review.

3.5 Sympathetic-baroreflex activity

A common finding among the included studies is an increase in sympathetic-baroreflex activity indexed by an increase in LF. For example, in the study by Aslaksen et al. (2007), painful stimulation increased LF and LF/HF ratio compared to inter-stimulus intervals. The authors provide evidence that LF is not affected by the presence of the experimenters or the interaction of experimenter gender and subject gender. However, no correlations of HRV and ratings of pain intensity or pain unpleasantness were found. Within another study, the same authors investigated if the administration of placebo capsules (i.e., supposed to have an analgesic effect) had an impact on pain ratings and/or autonomic response to nociceptive stimulation (Aslaksen and

Flaten, 2008). Pain intensity reports were significantly lower when administrating the capsules. Although a trend for lower LF/HF ratio in the capsules condition was reported, no significant effect of the condition on HRV was observed. However, contrast analysis revealed a decrease in LF/HF ratio after capsule administration, as shown by the difference between the pre-test and the post-test after the second and during the third phase of pain stimulation. The authors did not report results on the relationship between pain ratings and HRV within this study.

An increase in LF/HF ratio transiently following intramuscular injection and subcutaneous injection was observed by Burton et al. (2009). These findings suggest that the LF/HF ratio may not be differentially affected by pain originating in different tissues (deep vs. cutaneous) for the same pattern of response occurs regardless of the source of pain. While another study (Ghione et al., 2004) observed a progressive increase in LF in both conditions (exposure to electromagnetic field and sham) over time, HF progressively increased during sham exposure while remaining constant during exposure to a 37 Hz electromagnetic field. Exposure to the magnetic field also produced an increase in pain sensitivity. However, due to the nature of the study no results on the relationship of HRV and ratings of pain threshold or pain tolerance are reported by the authors. Consistent with these findings, Paine et al. (2009) observed an increase in CSI during pain compared with baseline while CVC_{NA} did not change.

Further studies that addressed the contribution of cofounding variables support the findings on an increase in sympathetic-baroreflex activity. Fazalbhoy et al. (2012) demonstrated that participants who showed an increase in MSNA during tonic muscle pain showed significantly higher LF power, lower HF power and higher LF/HF ratio at rest and during tonic pain than participants who showed a decrease in MSNA. Within their study, RMSSD was lower in the increasing MSNA group but no significant changes during tonic muscle pain on this particular measure were observed. Although the authors report no results on the relationship of HRV and pain intensity ratings of the participants, their findings suggest that resting cardiac sympathetic outflow is higher and cardiac vagal outflow is lower in individuals who respond to tonic muscle pain by an increase in MSNA. Furthermore, the study points to a decrease in vagal-parasympathetic activity indexed by a decrease in HF after painful stimulation.

An increase in LF/HF ratio is also reported by Streff et al. (2010) who immersed the participant's hand into hot or ice water. Significant differences between the test conditions are reported with a greater increase during the cold (CPT) than the heat [hot water immersion trial (HIT)] condition. Contradicting results are reported by other authors which revealed an increase in LF^{WV} contributing to an increase in LF/HF^{WV} after the pain stimuli as compared to pre-stimuli periods (Chouchou et al., 2011). Within this study, mean-NN decreased after the stimuli as compared to pre-stimuli periods. Furthermore, LF^{WV} was significantly modified by states of vigilance. HF^{WV} showed no significant changes at all. Tousignant-Laflamme and Marchand (2009) found no statistically significant differences in LF, HF, LF/HF ratio or NN50 count comparing the baseline and CPT periods.

3.6 Vagal-parasympathetic activity

Another common finding among the included studies is a decrease in vagal-parasympathetic activity indexed by a decrease in HF. In the study by Pollatos et al. (2012), mean HF – expressed as normalized units (n.u.) – significantly decreased during pain assessment compared to baseline, and this decrease was more distinct in the high IS group in comparison with the low IS group. The opposite pattern was observed for LF n.u. Consistent with the findings mentioned earlier, LF/HF ratio significantly increased during pain assessment but was more pronounced in the high IS group as compared to the low IS group. The groups differed significantly in LF/HF ratio during pain assessment, but no significant correlation between the change in LF/HF ratio and pain threshold or pain tolerance was observed. The authors conclude that IS significantly contributes to differences in HRV changes to pain induction. Santarcangelo et al. (2008) explored interpersonal differences related to the participants' susceptibility to hypnosis. The authors observed no significant group differences (hypnotizable subjects vs. subjects with low susceptibility to hypnosis) and no condition effect (nociceptive stimulation with or without instruction of analgesia) on LF/HF ratio and/or CSI. However, no results on the relation of HRV measures and ratings of pain intensity are reported. The other study on susceptibility to hypnosis (Balocchi et al., 2005) reports a significant increase in HF during pain induction only in low hypnotizable subjects.

In the study by Bendixen et al. (2012), both additional stressors (CPT and PASAT) produced a significant and equivalent reduction of evoked muscle pain. The authors observed a decrease in RMSSD (also indexing vagal-parasympathetic activity) during the

CPT sessions. Furthermore, HF power and the CCV-HF were decreased compared to the control condition. The other study using the PASAT as an additional stressor (Terkelsen et al., 2004) consistently reports that HF power, CCV-HF and total power decreased during the PASAT and attention condition while LF power only decreased during the PASAT condition. Both studies report no results on the distinct relationship between pain ratings and HRV.

In the other study by the same authors (Terkelsen et al., 2005), PASAT during painless stimulation reduced SDNN as compared with resting sessions. During attention to non-painful stimulation, no change in SDNN, LF power, CCV-LF, HF power, CCV-HF or total power was observed. LF power and CCV-LF increased during painful sural nerve stimulation during rest. These findings furthermore support the aforementioned evidence on an increase in sympathetic-baroreflex activity. HF power, CCV-HF and total power were not affected by acute pain stimulation during resting sessions. During attention to pain, only CCV-LF increased while LF power, SDNN, HF power, CCV-HF and total power were not affected by painful stimulation. During PASAT, the painful stimulus was scored significantly lower than during rest. None of the HRV parameters were affected by pain during the stress condition.

Martin et al. (2012) found RMSSD not to be significantly related to pain outcomes in their study. The significant increase in RMSSD and the lower pain ratings during slow breathing manipulation were not significantly associated. The other study that investigated the effects of breathing manipulation on autonomic reactivity towards nociceptive stimulation (Chalaye et al., 2009) reports that test conditions significantly affected time domain and frequency domain measures of HRV. No results on the relationship of HRV measures and pain threshold or pain tolerance are reported. In contrast to the consistent findings on a decrease in HF due to painful stimulation, Olsson and von Schéele (2011) report that HF increased when participants were lying on a bed of nails. However, the authors report no results on the relationship of HRV and pain ratings.

3.7 Further studies

Two studies on the relationship of HRV on experimentally induced pain included within this review stood out from the others. The study by Appelhans and Luecken (2008) was the only one addressing baseline HRV as potential source of interindividual variance in the experience of painful stimulation. The authors

found that ratings of 4 °C pain intensity were not significantly predicted by LF or HF, but LF was inversely associated with 4 °C pain unpleasantness. Greater LF was associated with higher pain thresholds for noticeable pain and predicted higher thresholds for the onset of moderate pain, while HF was not significantly associated with thresholds for noticeable or moderate pain. The study by Treister et al. (2012) investigated the ability of autonomic parameters to differentiate among different categories of heat pain (low, medium, high pain). They demonstrated that a linear combination of different parameters [HR, skin conductance level (SCL), number of skin conduction fluctuations (NSCF), changes in photoplethysmography amplitude (PPGA), HF] significantly differentiated between pain and no pain, and between all pain categories. Most sensitive were PPGA and SCL, followed by NSCF, HF-HRV and HR. HF differentiated in four of six tests, but failed to discriminate between the medium versus low, and the high versus medium pain categories.

4. Discussion

Within this systematic review, we attempted to summarize the current use of measurements of HRV in studies on experimentally induced pain in healthy adults. Throughout an extensive search of the literature, publications were reviewed for eligibility under pre-specified inclusion criteria. Compared to the large amount of studies on HRV in patients with chronic or recurrent pain conditions (Fig. 1), studies on HRV and nociceptive stimulation in healthy adults are rare.

BP (Bruehl and Chung, 2004) and mean HR (Möltner et al., 1990; Tousignant-Laflamme et al., 2005; Colloca et al., 2006; Loggia et al., 2011) have been extensively utilized to index how the ANS responds to nociceptive stimuli (Randich and Maixner, 1984; Zamir and Maixner, 1986; Benarroch, 2001, 2006; Bruehl and Chung, 2004). Although mean HR has some predictive power (Kannel et al., 1987) – particularly in predicting morbidity and mortality – HRV, rather than mean HR, has a number of experimental and theoretical advantages: It is a physiologically grounded (Levy, 1997), theoretically explicated (Thayer and Lane, 2000), empirically supported (Task Force, 1996 ; Thayer and Lane, 2007) and computationally tractable (Berntson et al., 1997) measure of autonomic function. Because HR is a product of the complex interplay of the two divisions of the ANS – the SNS and the PNS – changes in mean HR (e.g., pre-stimulus, post-stimulus) are illuminating only to a degree (Porges, 1992; Thayer and Lane, 2000). HRV,

by contrast, attempts to tease out the relative contributions of SNS and PNS activity and may therefore be more appropriate to investigate underlying autonomic reactions to nociceptive stimulation. HRV has also been discussed from a dynamic systems perspective, indexing the degree to which the organism successfully adapts to environmental challenges (e.g., Thayer et al., 2012).

Several experimental studies have explored the effect of experimentally induced pain on HRV either as a primary or a secondary outcome measure. Only two studies took HRV as an independent variable to explain interindividual differences in pain sensitivity (Appelhans and Luecken, 2008) or to investigate measures of HRV compared to other physiological measures in their ability to differentiate among different categories of pain intensity (Treister et al., 2012). In most cases, HRV is quantified as a marker of physiological response to a painful stimulus while controlling for confounds (e.g., experimenter gender, personality, hypnotizability), additional stressors (e.g., CPT, PASAT) or interventions (e.g., placebo capsules, respiratory techniques). Several studies that assessed measures of HRV during, before or after experimental pain induction did not report results on the correlation of pain measures and HRV (Terkelsen et al., 2004; Aslaksen and Flaten, 2008; Santarcangelo et al., 2008; Chalaye et al., 2009; Olsson and von Schéele, 2011; Bendixen et al., 2012; Fazalbhoy et al., 2012).

Except for one study (Tousignant-Laflamme and Marchand, 2009), all included papers report a significant change in HRV following pain induction. Three papers reported a decrease in HRV measures such as HF n.u. (Pollatos et al., 2012), HF power (Bendixen et al., 2012) CCV-HF (Bendixen et al., 2012), mean NN (Chouchou et al., 2011), and RMSSD (Bendixen et al., 2012), following nociceptive stimulation. All other studies reported an increase in HRV related to the induction of a painful stimuli: increase in LF n.u. (Pollatos et al., 2012), increase in the LF/HF ratio (Aslaksen and Flaten, 2008; Burton et al., 2009; Streff et al., 2010; Pollatos et al., 2012), increase in LF power (Terkelsen et al., 2005), increase in HF (Ghione et al., 2004; Balocchi et al., 2005), increase in CCV-LF (Terkelsen et al., 2005), increase in CSI (Paine et al., 2009), increase in LF^{WV} (Chouchou et al., 2011) and increase in LF/HF^{WV} (Chouchou et al., 2011). Since all measures that reflect a modulation of cardiac autonomic outflows by baroreflexes (Casadei et al., 1995; Moak et al., 2009; Goldstein et al., 2011) show an increase (cf. Table 2; LF n.u., LF/HF ratio, LF power, CCV-LF, CSI, LF^{WV} and LF/HF^{WV}), and the measures that reflect a primarily vagally mediated influence (cf.

Supporting Information Table S2; HF n.u., HF power, CCV-HF and RMSSD) show a decrease, a best evidence synthesis is an increase in baroreflex activity and a decrease in parasympathetic activity to acute pain induction. The only findings contradicting this synthesis are those who reported an increase in HF or HF-related measures (Ghione et al., 2004; Balocchi et al., 2005).

The increase in LF/HF ratio seems not to be differentially affected by pain originating in different tissues (Burton et al., 2009), indicating a stimuli independent response. An increase in baroreflex activity mirrored by LF-HRV can therefore be considered a general adaption of the organism to induced pain. However, since changes in LF power to acute manipulations – like nociceptive stimulation – relate to cardiac autonomic outflows by baroreflexes (Casadei et al., 1995; Moak et al., 2009; Goldstein et al., 2011), possible underlying mechanisms remain to be addressed. While an acute increase in BP and the baroreflex arc (France and Ditto, 1996) are possible underlying mechanisms of an increased LF, future studies need to assess BP, baroreflex and HRV to more fully clarify their relationship and common contribution to autonomic reactivity in subjects receiving painful stimulation. Since the position (e.g., resting supine) may contribute to the amount that baroreflex mechanisms account for LF power of HRV (Moak et al., 2009), studies addressing repeated HRV measures under different conditions (Table 2) in a within-subject design are needed. For example, Terkelsen et al. (2005) showed that acute pain induced pure efferent cardiac sympathetic activation during rest and during attention to pain while acute stress (PASAT) changed the HRV responses to nociceptive simulation. Evidence that activation of baroreflex arcs can dampen pain sensitivity (Rau et al., 1994), and findings on the relationship of elevated resting BP, spontaneous baroreflex sensitivity and their association with hypertension-related hypoalgesia to acute pain (Guasti et al., 2002; Chung et al., 2008) underline the possible contribution of baroreflex mechanisms. HRV has the potential to contribute to a detailed discussion on possible mechanisms and their clinical implications.

Individual differences in autonomic response to pain induction are reported in several studies. Pollatos et al. (2012) report that HRV reactivity to pain induction is correlated with subjects' interoceptive awareness. Terkelsen et al. (2005) suggest that the effect of pain induction on HRV is partly affected by the participants' attention to the stimuli, since only CCV-LF increased during painful stimulation regardless of

whether participants paid attention or were distracted. Bendixen et al. (2012) did not report results on the association of HRV and pain measures but found that distraction by two different stressors (CPT and PASAT) produced a significant and equivalent reduction of evoked pain. This finding is also in agreement with Terkelsen et al. (2005) who found that the painful stimulus was rated significantly lower during the PASAT than during the rest condition. Interestingly, HRV was not affected by pain induction during the stress condition. Furthermore, changes in HRV seem to be affected by other physiological parameters such as MSNA, since participants who showed an increase in MSNA during tonic muscle pain induction showed significantly higher LF power, lower HF power, and higher LF/HF ratio at rest and during tonic pain compared to participants who showed a decrease in MSNA. In addition, RMSSD was lower in the increasing MSNA group (Fazalbhoy et al., 2012). On the other hand, studies on intraindividual differences in pain responses explained by autonomic activity are rare (Appelhans and Luecken, 2008).

Studies using measurements of HRV to assess autonomic reactivity to painful stimulation might help gain further insights in the connectivity of the nociceptive system and the ANS in pain processing. While this review only summarizes current evidence on autonomic reactivity to nociceptive stimulation in healthy adults, the contributions of autonomic dysregulation to pain perception in patients with conditions of recurrent or chronic pain are of interest (Tousignant-Laflamme et al., 2006). Furthermore, experimental studies on HRV and acute pain can help standardize and establish HRV methods in the use of routine clinical monitoring (Paris et al., 2001; Mazzeo et al., 2011).

5. Conclusion

The ANS is sensitive to induced acute pain. HRV is a promising measure of autonomic reactivity to nociceptive stimulation. In healthy adults, studies investigating changes in HRV in response to pain induction report an increase in baroreflex activity as indexed by LF domain measures and a decrease in parasympathetic activity as indexed by HF domain measures of HRV. This influence is moderated by certain psychological and physiological factors that were identified by different studies. Besides IS, experimental conditions that distract from (e.g., stressors such as CPT or PASAT) or focus the subject's attention on the pain experience have major contributions to changes in HRV. Furthermore, in the case of induced muscle pain,

MSNA explains interindividual differences in HRV changes. Since the method of nociceptive stimulation (the pain stimuli) might have a different effect on the autonomic parameters regardless of the pain experience itself (Treister et al., 2012), comparisons of painful experimental stimuli (i.e., mechanical vs. electrical) should be studied. Future studies need to focus on investigating BP, baroreflex activity and HRV to further clarify their relationship and contribution to clinical phenomena such as hypertension-related hypoalgesia. Of additional interest is the ability of individual differences in resting autonomic activity (i.e., HRV baseline measures) to explain possible variance in pain sensitivity and HRV changes to pain induction.

Findings from these studies may have important clinical implications as a large variety of health conditions are associated with changes in ANS function that can be indexed by HRV (Rajendra Acharya et al., 2006). Addressing the field of pain, reduced HRV is reported in patients with complex regional pain syndrome (Terkelsen et al., 2012), fibromyalgia patients (Mork et al., 2013), patients with chronic neck pain (Kang et al., 2012), irritable bowel syndrome (Mazurak et al., 2012) or headache (Micieli et al., 1993; Tubani et al., 2003). Furthermore, lower HRV is associated with extended pain-related sick leave in employees (Kristiansen et al., 2011). Thus, HRV is of interest as a potential biomarker for specific pain-related diseases (Lerma et al., 2011) and a potential outcome measure for the relief of pain due to therapeutic interventions (Storella et al., 1999; Zhang et al., 2006; Toro-Velasco et al., 2009). Evidence on the relation of HRV and experimentally induced pain in healthy subjects may help gain further insights on changes in autonomic function in patients with pathological pain states.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Search strategy by database.

Table S2. Frequently used HRV measures, table data based on Thayer et al. (2008), Task Force (1996), Goldstein et al. (2011) and Moak et al. (2009).