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REVIEW ARTICLE

# Prediction of pain using electrocardiographic-derived autonomic measures: A systematic review

**Anne-Marie Wegeberg**[1,2,3] | **Trine Hyttel Sejersgaard-Jacobsen**[4] | **Christina Brock**[2,3,5] | **Asbjørn Mohr Drewes**[1,3,5]

[1]Thisted Research Unit, Aalborg University Hospital Thisted, Thisted, Denmark

[2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[3]Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark

[4]Department of Anesthesiology, Aalborg University Hospital Thisted, Denmark

[5]Steno Diabetes Center North Denmark, Aalborg, Denmark

**Correspondence**
Anne-Marie Wegeberg, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Mølleparkvej 4, Aalborg 9000, Denmark.
Email: a.wegeberg@rn.dk

## Abstract

**Background and Objective:** Pain is a major clinical challenge, and understanding the pathophysiology is critical for optimal management. The autonomic nervous system reacts to pain stimuli, and autonomic dysfunction may predict pain sensation. The most used assessment of autonomic function is based on electrocardiographic measures, and the ability of such measures to predict pain was investigated.

**Databases and Data Treatment:** English articles indexed in PubMed and EMBASE were reviewed for eligibility and included when they reported electrocardiographic-derived measures' ability to predict pain response. The quality in prognostic studies (QUIPS) tool was used to assess the quality of the included articles.

**Results:** The search revealed 15 publications, five on experimental pain, five on postoperative pain, and five on longitudinal clinical pain changes, investigating a total of 1069 patients. All studies used electrocardiographically derived parameters to predict pain assessed with pain thresholds using quantitative sensory testing or different scales. Across all study modalities, electrocardiographic measures were able to predict pain. Higher parasympathetic activity predicted decreased experimental, postoperative, and long-term pain in most cases while changes in sympathetic activity did not consistently predict pain.

**Conclusions:** Most studies demonstrated that parasympathetic activity could predict acute and chronic pain intensity. In the clinic, this may be used to identify which patients need more intensive care to prevent, for example postoperative pain and develop personalized chronic pain management.

**Significance:** Pain is a debilitating problem, and the ability to predict occurrence and severity would be a useful clinical tool. Basal autonomic tone has been suggested to influence pain perception. This systematic review investigated electrocardiographic-derived autonomic tone and found that increased parasympathetic tone could predict pain reduction in different types of pain.

## 1 | INTRODUCTION

Acute pain is a crucial survival mechanism that helps us notice harmful events and teaches us to avoid future harm. Contrary, chronic pain is a major social, economic, and clinical problem, leading to decreased quality of life, increased work absence, and disabilities (Argüello et al., 2022). Chronic pain is probably the most common symptomatic reason to seek medical consultation (Loeser & Melzack, 1999) and affects more than 1.5 billion people worldwide (Yeater et al., 2021). However, the complexity underlying pain pathophysiology makes it challenging to determine the cause of pain and complicates management (Benarroch, 2006; Huang et al., 2021).

More than five decades of research underline that acute noxious stimuli elicit a response in the autonomic system (Argüello et al., 2022; Kyle & McNeil, 2014; Mischkowski et al., 2019). However, within the central nervous system, the nociceptive and autonomic systems converge, allowing them to interact and maintain homeostasis in response to internal or external environmental challenges (Benarroch, 2001, 2006). Still, it is unclear whether an autonomic response is only a reflective product of noxious stimuli or if autonomic dysfunction present before pain induction is an integrated part of pain pathogenesis. Nevertheless, most chronic pain conditions, including musculoskeletal pain, fibromyalgia, chronic pancreatitis, and neurofibromatosis, are associated with some form of autonomic dysfunction, including decreased heart rate variability (Benarroch, 2001; Buscher et al., 2010; Schlereth & Birklein, 2008; Tracy et al., 2016; Yeater et al., 2021). This may result in diminished modulatory capacity in response to sensory threats, thus potentially increasing pain (Forte et al., 2022; Tracy et al., 2016). Furthermore, increasing or preserving the cardiovagal base tone through deep breathing, meditation, or vagal nerve stimulation has been used as pain treatment (Forte et al., 2022; Patel et al., 2022).

Heart rate and its derivatives continue to be the most frequently examined autonomic marker in pain research. They are believed to reflect both sympathetic and parasympathetic activities contrary to other autonomic measures (Argüello et al., 2022). Heart rate variability measures the time intervals between succeeding heartbeats. It can be analysed in time-domain-derived measures such as RR, SDNN, and rMSSD (see Table 1), with the latter representing parasympathetic tone through integrative vagal mediated control of the heart (Malik, Bigger, et al., 1996). Heart rhythm can also be transformed into spectral content of the oscillations into high- and low-frequency components related to blood pressure regulation and vasomotor tone. High-frequency power is strongly believed to represent parasympathetic activity through respiratory arrhythmia and cardiovagal regulation (Malik, Bigger, et al., 1996; Pomeranz et al., 1985). Contrarily, the meaning and utility of low-frequency power are debated, as some suggest that it exhibits both sympathetic and parasympathetic neurocardiac activity (Akselrod et al., 1981; Grasso et al., 1997). In contrast, a large body of evidence suggests a minor effect or lack of sympathetic activity (Eckberg, 1997; Goldstein et al., 2011; Reyes del Paso et al., 2013).

Obtaining a way to predict pain from electrocardiographic (ECG) activity as a simple measure available in clinical settings could have many implications. Unfortunately, due to the heterogeneous nature of the data and the lack of a systematic review of ECG's ability to predict pain, there is no consensus on whether such measures can predict pain. We hypothesize that autonomic dysfunction, displayed in altered ECG-derived measures, plays a part in pain perception. Thus, we aim to summarize studies investigating the ability of ECG-derived measures to predict experimentally or surgical-induced pain or changes in chronic pain conditions.

## 2 | LITERATURE SEARCH METHODS

A systematic review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009). This systematic review's research question was whether ECG measurements can predict pain perception in different settings.

### 2.1 | Eligibility criteria

Eligibility for inclusion in the review was assessed after applying the inclusion and exclusion criteria and considering full-text articles. Original research articles were considered if they met the following inclusion criteria: (I) studies predicting pain by baseline ECG measures before pain induction and (II) pain alterations over time in pain conditions predicted by ECG measures. Prediction was also defined as correlations performed between ECG measures obtained before pain induction and the pain result from pain induction. Studies with any of the following conditions were excluded: studies which did not investigate ECG measures, studies where ECG measures were the outcome, case reports, editorials, letters, protocol papers, abstracts, review/meta-analyses or proceedings, animal studies, and non-English full texts.

**TABLE 1** Overview of ECG-derived parameters. Based on Malik, Bigger, et al. (1996), Shaffer & Ginsberg (2017), and Tiwari et al. (2021) if not otherwise referenced.

| Abbreviation | Explanation | Unit | Autonomic interpretation | Study |
|---|---|---|---|---|
| HR | Heart rate: Number of heartbeats per minute | bpm | HR decelerates with parasympathetic activity and accelerates with sympathetic activity. | 8, 12 |
| RRi (HP) | RR-interval (heart period): Interval between heartbeats, more specifically interval between R peaks in QRS complexes due to depolarization of sinus node. | ms | RR-interval increases with parasympathetic activation and decreases with sympathetic activity. | 8, 10 |
| NN-interval | Intervals between successive normal R peaks in QRS complexes, defined as normal-to-normal | ms | Similar effects to RR-interval | |
| H.R.V. | Heart rate variability – variability in RRi: Time and frequency derived calculations based on the variability of NN interval | various | | |
| S.D.N.N. | The standard deviation of all NN-intervals. Time-domain H.R.V. | ms | Reflects all the cyclic components responsible for variability in the period of recording. | 6, 11, 14 |
| rMSSD | The square root of the mean of the sum of the squares of differences between adjacent NN-intervals. Time-domain H.R.V. | ms | Estimate the parasympathetic mediated changes reflected in HRV | 1, 4, 8, 11, 12, 14 |
| Total power | Power spectral analysis of heart rate fluctuations, more specifically the distribution of variance as a function of frequency resulting in a power spectrum between 0 and 0.5 Hz | Hz | Reflects all the cyclic components responsible for variability in the period of recording. | 11 |
| VLF | Very low-frequency power. Power at very-low-frequency range (0.003–0.04 Hz). Frequency-domain H.R.V. | $ms^2$ | The exact physiological mechanisms are uncertain but may relate to the renin-angiotensin-aldosterone system, thermoregulation, and/or peripheral vasomotor tone (Butruille et al., 2015; Draghici and Taylor, 2016). | 11 |
| LF | Low-frequency power. Power at low-frequency range (0.04–0.15 Hz). Frequency-domain H.R.V. | $ms^2$ | Controversial interpretation: influenced by both sympathetic and parasympathetic activity. May reflect parasympathetic activity in resting conditions. | 2, 4–6, 8, 11, 14, 15 |
| HF | High-frequency power. Power at a high-frequency range (0.15–0.4 Hz). Frequency-domain H.R.V. | $ms^2$ | Reflects parasympathetic activity. | 1, 2, 4, 5, 7, 8, 11, 12, 14, 15 |
| LF/HF ratio | The ratio between low- and high-frequency. Frequency-domain H.R.V. | | Controversial interpretation: Considered by some to mirror sympathovagal balance or reflection of sympathetic modulations. | 4, 11, 12, 14 |
| Deep breathing | RRi is measured during deep breathing at a frequency of 6 breaths per minute. The ratio is calculated from the mean of the longest RRi during expiration to the mean of the shortest RRi during inspiration (Ewing et al., 1980). | | Assess primarily parasympathetic function, though the involved reflex pathways are extremely complex and include both parasympathetic and sympathetic fibres to a greater or lesser extent (Ewing et al., 1980, 1985). | 1, 4 |

**TABLE 1** (Continued)

| Abbreviation | Explanation | Unit | Autonomic interpretation | Study |
|---|---|---|---|---|
| Valsalva maneuver | RRi measured during blowing against pressure (40 mmHg pressure) for 15 s. The ratio is calculated from the longest RRi after the maneuver (reflecting the overshoot bradycardia) to the shortest RRi during the maneuver (reflecting the bradycardia during strain) (Ewing et al., 1980). | | Assess primarily parasympathetic function, though sympathetic influences can also alter this response (Ewing et al., 1980, 1985). | 4 |
| ANI | Analgesia/Nociceptive index. The surface area between local minima and maxima in a normalized high-frequency RR series is automatically detected, with the area under the curve $(AUC)_{min}$ defined as the smallest sub-surface. ANI is calculated using the formula: $ANI = 100 \times [(5.1 \times AUC_{min} + 1.2)/12.8]$ (Logier et al., 2010) | 0–100 | Derived from the high-frequency component of heart rate variability reflecting the analgesia/nociception balance. High ANI reflects the dominant parasympathetic tone and low ANI sympathetic activation (Logier et al., 2010). | 3 |
| NIPE | Newborn Infant Parasympathetic Evaluation Index. Measured and calculated similarly to the ANI (Butruille et al., 2015; Logier et al., 2010) | 0–100 | Similar interpretation as ANI, by assessing the parasympathetic/sympathetic tone balance. | 13 |
| RSA | Respiratory sinus arrhythmia. Extracted from RRi, using a 12.75-s duration, moving polynomial filter to remove variance associated with complex aperiodic shifts and oscillations slower than the respiratory frequency. The residual output is band-passed and the RRi variance associated with spontaneous breathing was extracted, and the natural log was transformed to reduce skewness (Kovacic et al., 2020; Lewis et al., 2012). | $\ln(ms^2)$ | A measure of cardiac vagal tone (Kovacic et al., 2020) | 10 |
| VE | Vagal efficiency. Calculated as the slope from regression analyses between the total set of all sequential 15-sec epoch estimates of RRi and RSA (Kovacic et al., 2020). | $\ln(ms^2)/ms$ | A measure of the influence of cardiac vagal tone on heart rate (Kovacic et al., 2020) | 10 |
| pPPS | Predicted patient's pain score. A mathematical model based on analysis of all components within low- and high-frequency bands in RRi. | | Reflect parasympathetic/sympathetic balance as it incorporates both high- and low-frequency components | 9 |

*Note*: [1]Baron et al. (1997), [2]Appelhans & Luecken (2008), [3]Boselli et al. (2014), [4]Nahman-Averbuch et al. (2014), [5]Adjei et al. (2017), [6]Bossmann et al. (2017), [7]Allen et al. (2018), [8]Tracy, Koenig, et al. (2018), [9]Powezka et al. (2019), [10]Kovacic et al. (2020), [11]Caton et al. (2021), [12]Mathersul et al. (2021), [13]Verweij et al. (2021), [14]Jiang et al. (2022), [15]Umeda & Okifuji (2022).

## 2.2 | Search strategy

We conducted a detailed search on PubMed and EMBASE for relevant publications reporting data on pain prediction through ECG-derived measures. The last search was conducted on December 13, 2022. The search strategy was developed in consultation with a librarian specializing in literature searches. Results were combined by the Boolean operator 'AND' or 'OR' with search terms. The search strategy for PubMed and EMBASE can be found in Appendix 1. We extracted the records to Mendeley to sort and remove duplicates, and the list of potential articles produced by systematic research was independently screened for eligibility by two authors (AMW & THSJ). Disagreement was adjudicated by an additional independent reviewer (AMD). The bibliography of identified articles was cross-referenced to check for additional studies to include in the review. The study selection can be seen in the CONSORT diagram in Figure 1.

## 2.3 | Data extraction

Full articles that met the inclusion criteria were retrieved. Study information on the primary author, year of publication, country, study cohort, type of investigation (experimental pain, surgery type or follow-up period), sample size, gender ratio and age of participants were extracted from the articles retrieved in full text. Furthermore, details regarding the method of ECG measures and pain assessments were extracted and summarized within comprehensive tables and with the interpretation of these (see Tables 1 and 2). Findings and interpretations of the reported effects were derived from the papers retrieved in full text.

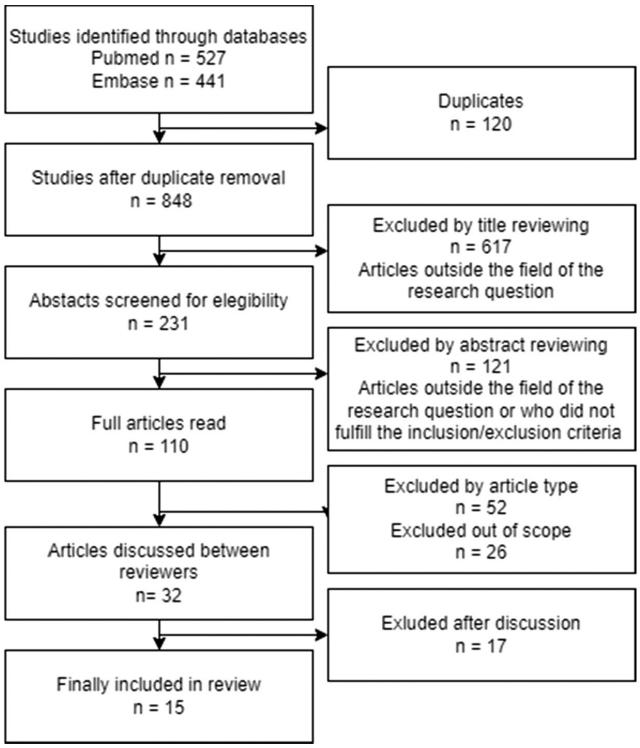


**FIGURE 1** Consort diagram of study selections.

## 2.4 | Risk of bias assessment

The Quality in Prognosis Studies (QUIPS) (Hayden et al., 2006, 2013) tool was independently used by two authors (AMW & THSJ), and disagreement was adjudicated by an additional author (AMD) to assess the quality and the methods of the included articles. More specifically, the overall risk of bias in each study was assessed, focusing on 6 bias domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

# 3 | RESULTS

## 3.1 | Literature search

The initial literature search identified 968 studies published between 1973 and 2022, and after removing duplicates, reviewing the titles and abstracts, and reading the full texts, 15 studies were selected. Five investigated experimental pain (Appelhans & Luecken, 2008; Jiang et al., 2022; Nahman-Averbuch et al., 2014; Tracy, Koenig, et al., 2018; Umeda & Okifuji, 2022), five investigated postoperative pain (Adjei et al., 2017; Boselli et al., 2014; Caton et al., 2021; Powezka et al., 2019; Verweij et al., 2021) and five investigated longitudinal changes in clinical pain (Allen et al., 2018; Baron et al., 1997; Bossmann et al., 2017; Kovacic et al., 2020; Mathersul et al., 2021). However, the heterogeneity within these studies did not allow for a meta-analysis. Details were recorded regarding the number of studies found, the number of studies meeting the specified inclusion criteria, the number of studies excluded, and the reasons for exclusion, which can be found in the CONSORT diagram in Figure 1.

## 3.2 | Demographic characteristics of the sample

Characteristics of the 15 selected studies can be found in Table 3. The studies were published between 1997 and

**TABLE 2** Overview of pain assessment tools.

| Name | Explanation | Scoring | Interpretation | Study |
|---|---|---|---|---|
| VAS | Visual analogue scale. A unidimensional, graphical pain scale | Assessed with pictures from 0 to 10 | Higher VAS scores indicate greater pain experience. | 1 |
| NRS | Numeric rating scale. A unidimensional, numeric version of the visual analogue scale. | Assessed on a Likert scale from 0 = no pain to 10 = worst pain imaginable or 0 = no pain to 100 = pain as intense/unpleasant as it could be | Higher NRS scores indicate greater pain experience | 2–7, 9, 11, 15 |
| PFSD | Pain Frequency-Severity-Duration questionnaire. Developed to assess multiple aspects of pain, focused on more than pain intensity. It consists of five questions, and over the last 14 days investigate the number of days pain is experienced, unusual and worst pain intensity, and the average duration of these (Salamon et al., 2014). | Q1: number of days 0–14<br>Q2/4: Likert scale from 0 (no pain) to 10 (worst pain).<br>Q3/5: 1–2, 3–5, 6–8, 9–12, 12–18, or 18–24 h. | A higher score equals worse pain experience | 10 |
| B.P.I. | Brief pain inventory questionnaire. Consist of pain severity (four items) and pain interference (nine items) | Assessed on Likert scales from 0 = "no pain" to 10 = "pain as bad as you can imagine" or 0 = "does not interfere" to 10 = "completely interferes". | Higher BPI scores indicate greater pain severity and pain interference | 12 |
| F.L.A.C.C. | Face, legs, activity, cry, consolability tool. A behavioural tool to assess pain in young children. The clinician selects the number that most closely matches the observed behaviour, described in each category (Merkel et al., 2002). | Assessed on a 0–2 Likert scale, resulting in a score from 0 to 10. | A higher score indicates behaviours associated with higher discomfort/pain. | 11, 13 |
| Pain threshold | Quantitative sensory testing pain-induced threshold. Pain induction is increased until a threshold is met, either pain detection or pain tolerance. | Pain measure at pain detection or pain threshold. | A higher threshold indicates higher pain tolerance. | 4, 8, 14 |

*Note*: [1]Baron et al. (1997), [2]Appelhans & Luecken (2008), [3]Boselli et al. (2014), [4]Nahman-Averbuch et al. (2014), [5]Adjei et al. (2017), [6]Bossmann et al. (2017), [7]Allen et al. (2018), [8]Tracy, Koenig, et al. (2018), [9]Powezka et al. (2019), [10]Kovacic et al. (2020), [11]Caton et al. (2021), [12]Mathersul et al. (2021), [13]Verweij et al. (2021), [14]Jiang et al. (2022), [15]Umeda & Okifuji (2022).

2022 and included 1069 participants, of which 58% (range 24%–100%) were women. The average age within studies ranged from 8 months to 69 years, with three studies conducted on infants (Verweij et al., 2021) or adolescents (Allen et al., 2018; Kovacic et al., 2020). Studies originated from Europe ($n = 8$), North America ($n = 5$), the Middle East ($n = 1$) and Oceania ($n = 1$).

## 3.3 | Risk of bias assessment

The overall risk of bias assessment can be found in Table 3 and the entire assessment in Appendix 2. Overall, three studies had a low risk of bias, one had a high risk of bias and the remaining had a moderate risk of bias.

The study participation was mainly biased due to missing population identification and recruitment period data. Study attrition was the highest contributor to bias, as information about the samples available for analysis and drop-out characteristics were non-existent in most included articles, leading to a moderate overall score for most. The main reason for bias in prognostic factor measurements and study confounding was a lack of information on data available for analysis and methods for missing data or identification and measures of

**TABLE 3** Characteristics of selected studies.

| Reference | Year | Country | Cohort | Experimental pain, surgery type, or follow-up | Sample (F/M) | Age (years) | Risk of bias assessment |
|---|---|---|---|---|---|---|---|
| Adjei et al. | 2017 | The United Kingdom | Surgery | Various vein surgery | 16 (7/9) | 60 ± 9<br>54.8 ± 16.3 | Moderate |
| Allen et al. | 2018 | The United States | Neurofibromatosis type 1 | 8 weeks follow-up | 39 (23/16) | 23.9 ± 2.1 | Low |
| Appelhans et al. | 2008 | The United States | Healthy | Cold pain stimulation | 59 (37/22) | 19.7 ± 1.8 | Moderate |
| Baron et al. | 1997 | Germany | Zoster infection | 6-month follow-up | 34 (18/16) | 67.9 ± 12.4 | Moderate |
| Boselli et al. | 2014 | France | Surgery | Ear, nose, throat, or orthopaedic lower limb surgery | 200 (92/108) | 44 ± 18<br>51 ± 17 | Moderate |
| Bossmann et al. | 2017 | Germany | Surgery | 6 months follow-up | 56 (37/19) | 68.9 ± 9.3 | Low |
| Caton et al. | 2021 | France | Surgery | Stereotactic Surgery | 30 (16/14) | 27.3 ± 15.7 | Moderate |
| Jiang et al. | 2022 | Finland/ Germany | Healthy | Electrical and heat pain stimulation | 117 (117/0) | Unknown | Moderate |
| Kovacic et al. | 2020 | The United States | Functional abdominal pain disorder | 3 weeks follow-up | 92 (83/9) | 15.2 ± 2 | High |
| Mathersul et al. | 2021 | The United States | Gulf War illness | 34 weeks follow-up | 75 (18/57) | 52.5 ± 6.7 | Moderate |
| Nahman-Averbuch et al. | 2014 | Israel | Chemotherapy-induced neuropathy | Heat pain stimulation, conditioned pain modulation | 27 (20/7) | 56.6 ± 7.9 | Moderate |
| Powezka et al. | 2019 | The United Kingdom | Surgery | Varicose vein surgery | 29 (19/10) | 48.8 ± 14.9 | Moderate |
| Tracy et al. | 2018 | Australia | Healthy | Heat pain Stimulation | 51 (26/25) | 21.9 ± 3.5<br>21.8 ± 3.6 | Moderate |
| Umeda et al. | 2022 | The United States | Healthy | Conditioned pain modulation through a cold pressor test | 123 (75/48) | 22.4 ± 2.9 | Moderate |
| Verweij et al. | 2021 | The Netherlands | Surgery | Various Surgeries | 121 (37/84) | 8.3 ± 5.3 (months) | Low |

confounding factors. Outcome measurements and statistical analysis contributed the least to the risk of bias, as the subcategories herein were consistently provided by all included articles, except for one with a high overall risk of bias.

## 3.4 | Electrocardiographic assessments

The different ECG-derived measures used in the included studies and how they are thought to reflect autonomic function can be found in Table 1. Ten studies used standard heart rate variability time and frequency domain measures, with the majority investigating low- and high-frequency power or variants hereof (log, ln, permutation entropies), and also including rMSSD, low/high-frequency power ratio (LF/HF) and SDNN. Six followed the European Society of Cardiology and the North American Society guidelines (Malik, John Camm, et al., 1996). Two studies used cardiovascular autonomic reflex test (Ewing et al., 1980) of Valsalva maneuver (Nahman-Averbuch et al., 2014) and deep breathing (Baron et al., 1997; Nahman-Averbuch et al., 2014) while one used respiratory sinus arrhythmia amplitude and vagal efficiency (Kovacic et al., 2020). The Analgesia/Nociception Index and the Newborn Infant Parasympathetic Evaluation Index, calculated based on the integrative influence of the respiratory cycle on the RR interval derived from ECG readings and measured on a 0–100 index, were each used in one study (Boselli et al., 2014; Verweij et al., 2021). Lastly, one study calculated predictive patient pain score models based on ECG frequency data (Powezka et al., 2019).

## 3.5 | Pain assessment

The different pain assessment tool and their interpretation can be found in Table 2. Nine studies assessed pain using a numerical rating scale (NRS) and one the visual analogue scale (VAS) (Baron et al., 1997). Two studies, including children (Caton et al., 2021; Verweij et al., 2021), used the Face, Legs, Activity Cry, and Controllability (FLACC) scale, a behavioural tool that scores observations within each category from 0 to 2. The Pain Frequency Severity Duration (Kovacic et al., 2020) and Brief Pain Inventory (Mathersul et al., 2021) were also used. In three experimental studies (Jiang et al., 2022; Nahman-Averbuch et al., 2014; Tracy, Koenig, et al., 2018), the pain was assessed by heat pain threshold, where a thermode was placed on the participant's forearm, and the temperature was increased until the threshold was reached.

## 3.6 | Predicting experimental pain

All studies predicting experimentally induced pain used thermal stimulation, either cold (Appelhans & Luecken, 2008; Umeda & Okifuji, 2022) or heat (Jiang et al., 2022; Nahman-Averbuch et al., 2014; Tracy, Koenig, et al., 2018), to elicit pain. Four studies investigated the sensory response in healthy participants while the last study measured pain in chemotherapy-treated cancer patients without previous pain (Nahman-Averbuch et al., 2014). All studies succeeded in predicting pain using ECG measures. See Table 4 – Experimental.

Detailed analysis of heart rate variability showed that higher levels of parasympathetic activity assessed with rMSSD, high-frequency power or Valsalva ratio predicted hypoalgesia evident as higher thermal heat pain thresholds (Jiang et al., 2022; Nahman-Averbuch et al., 2014) and tolerance (Jiang et al., 2022), increased pain endurance (Umeda & Okifuji, 2022) and higher pain modulation (Nahman-Averbuch et al., 2014). Altogether, higher levels of parasympathetic activity seem to predict lower intensity of induced experimental pain. However, not all studies found that high-frequency power could predict pain ratings and thresholds (Appelhans & Luecken, 2008; Tracy, Koenig, et al., 2018; Umeda & Okifuji, 2022). Instead, these studies showed that higher levels of low-frequency power, likely containing a mixture of parasympathetic and sympathetic activity (Eckberg, 1997; Goldstein et al., 2011; Reyes del Paso et al., 2013), also predicted less pain (Appelhans & Luecken, 2008; Jiang et al., 2022; Tracy, Koenig, et al., 2018). Similarly, a higher low-frequency/high-frequency power ratio predicted higher thermal heat pain thresholds and tolerance (Jiang et al., 2022).

## 3.7 | Predicting postoperative pain

Five studies predicted pain after various surgical procedures, including vein surgery, ear, nose, and throat surgery, orthopaedic lower limb surgery and stereotactic surgery. Across studies, the pain was measured in the early postoperative settings on arrival at the post-anaesthesia care unit. The studies showed that more parasympathetic activity and a lower low-frequency/high-frequency power ratio predicted decreased postoperative pain, see Table 4 – Postoperative.

Detailed analysis of heart rate variability showed that higher levels of parasympathetic activity assessed with rMSSD and high-frequency power predicted less postoperative pain through lower pain ratings following various vein and stereotactic surgery (Adjei et al., 2017; Caton et al., 2021). However, these studies also showed that higher low-frequency power, possibly primarily mediating

**TABLE 4** Finding and interpretations of studies.

| | Study | Findings | Interpretation |
|---|---|---|---|
| Experimental | Jiang | An increase in SDNN, rMSSD, LF and LF/HF ratio is associated with an increased pain threshold. | Increased parasympathetic activity, sympathetic or parasympathetic activity, and sympathovagal balance predict decreased pain sensitivity through higher pain tolerance. |
| | Umeda | An increase in HF is associated with an increased chance of pain test completion. LF and HF did not associate with pain threshold and rating. | Increased parasympathetic activity predicts a higher pain endurance, but not pain threshold or pain ratings. |
| | Tracy | An increase in LF is associated with an increased pain threshold. RRI, HF and rMSSD did not associate with pain threshold. | Increased sympathetic or parasympathetic or predicts decreased pain sensitivity through higher pain tolerance. |
| | Nahman-Averbuch | An increase in rMSSD is associated with an increased pain threshold. A decrease in the Valsalva ratio is associated with increased pain rating and decreased changes in pain rating. HF, LF, LF/HF ratio and deep breathing did not associate with pain threshold or pain ratings. | Increased parasympathetic activity predicts decreased pain sensitivity through higher pain tolerance, lower pain ratings and higher pain modulation. |
| | Appelhans | An increase in LF is associated with increased unpleasantness ratings, pain, and moderate pain detection thresholds. LF and HF did not associate with pain. | Increased sympathetic or parasympathetic activity predicts decreased pain sensitivity through higher pain tolerance. |
| Post-operative | Caton | An increased LF/HF ratio and decreased rMSSD, HF, SDNN, and LF are associated with increased postoperative pain. HR did not associate with postoperative pain. | Increased parasympathetic activity and sympathetic or parasympathetic activity predicted decreased pain. Increased sympathovagal balance predicted increased postoperative pain. |
| | Verweij | NIPE did not associate with pain ratings. | Sympathovagal balance did not predict pain |
| | Powezka | An increased pPPS associated with pain ratings | Increased sympathovagal balance predicted decreased pain sensitivity through lower pain ratings. |
| | Adjei | An increased LF and HF are associated with decreased pain ratings. | Increased parasympathetic activity and sympathetic or parasympathetic activity predicted decreased pain sensitivity through lower pain ratings. |
| | Boselli | An increase in ANI is associated with decreased pain ratings. | Increased parasympathetic activity predicted decreased pain sensitivity through lower pain ratings. |
| Long-term | Mathersul | An increase in rMSSD, and HF and a decrease in HR are associated with decreased pain severity. LF/HF ratio did not associate with pain severity. | Increased parasympathetic activity predicted decreased pain sensitivity through increased pain severity. |
| | Kovacic | An increased VE is associated with an increase in pain. | Increased parasympathetic activity predicted increased pain sensitivity through an increase in pain severity. |
| | Allen | An increase in HF is associated with decreased pain intensity. | Increased parasympathetic activity predicted decreased pain sensitivity through improvement in pain intensity. |
| | Bossmann | LF and SDNN did not associate with pain intensity. | Increased sympathetic or parasympathetic activity did not predict pain intensity. |
| | Baron | rMSSD, HF and deep breathing did not associate with pain persistency. | Parasympathetic activity did not predict pain. |

parasympathetic activity, decreased postoperative pain ratings (Adjei et al., 2017; Caton et al., 2021). Similarly, a mathematical pain model based on analysis of all components within low- and high-frequency powerbands suggested that higher levels of parasympathetic activity predicted decreased pain sensitivity (Adjei et al., 2017). In contrast, a higher low-frequency/high-frequency power ratio predicted higher postoperative pain ratings (Caton et al., 2021), which could suggest an influence of sympathetic-mediated hyperalgesia.

Studies using the analgesia/nociception index (Boselli et al., 2014), and the newborn infant parasympathetic evaluation index (Verweij et al., 2021), based on heart rate variability and suggestive of vagal tone, showed some controversies. Higher scores using both indices are believed to reflect high parasympathetic tone, and low scores reflect sympathetic activation (Logier et al., 2010), though calculations are based on high-frequency bands, which mainly asses parasympathetic activity. The study in adults using the analgesia/nociception index (Boselli et al., 2014) showed that scores reflecting parasympathetic tone predicted less postoperative pain, similar to the results from rMSSD and high-frequency power analysis. However, no such prediction could be made in infants, though a higher parasympathetic tone could distinguish between comfort and discomfort (Verweij et al., 2021).

### 3.8 | Predicting long-term clinical pain changes

Five studies predicted long-term pain alterations, with timeframes ranging from 3 weeks to 9 months. Two randomized controlled trials investigated the effects of cognitive behaviour therapy versus yoga (Mathersul et al., 2021) or percutaneous electrical nerve field stimulation versus sham (Kovacic et al., 2020) while the remainder investigated the long-term effects of knee replacement surgery (Bossmann et al., 2017), long-term pain in zoster infections (Baron et al., 1997) and the psychological flexibility in neurofibromatosis type 1 (Allen et al., 2018). The studies showed that higher levels of parasympathetic activity could predict decreased pain in most instances but not all, see Table 4 – Long-term.

Detailed analysis of heart rate variability showed that higher levels of parasympathetic activity assessed with rMSSD and high-frequency power predicted an improvement in pain severity after 8 weeks in Neurofibromatosis Type 1 (Allen et al., 2018) and after 34 weeks of therapy in veterans with Gulf War illness regardless of treatment (Mathersul et al., 2021). This suggests that higher parasympathetic activity before treatment can predict a better response to interventions.

In contrast, low to moderate baseline vagal efficacy predicted decreased pain intensity after 3 weeks of auricular neurostimulation (Kovacic et al., 2020). However, this was only in the group receiving neurostimulation and not in the placebo group. Interestingly, in observational studies without intervention, the low-frequency/high-frequency power ratio did not predict changes in pain severity following knee replacement surgery (Bossmann et al., 2017). Similarly, measures of parasympathetic activity using high-frequency power and deep breathing could not predict pain persistency after zoster infections (Baron et al., 1997).

## 4 | DISCUSSION AND CONCLUSIONS

The relationship between nociceptive input and perceived pain is complex, continuously modulated and influenced by internal and external factors. An altered autonomic function, represented in ECG analysis, may alter pain circuits, resulting in a diminished modulatory capacity of the pain response. Thus, identifying dysfunctional neurocardiac regulation can potentially be used to predict the expression and intensity of a painful response. We collected the existing literature, which suggested that a higher parasympathetic tone could predict pain relief, while the potential of sympathetic activity, measured with the current ECG-derived methods, is more challenging to interpret.

### 4.1 | Pain and the autonomic nervous system

Heart rate variability is the most commonly used measure to assess neurocardiac regulation as a proxy for autonomic functioning. Various parameters are generally viewed to quantify the parasympathetic activity (rMSSD and high-frequency power), sympathetic regulation with parasympathetic influences (low-frequency power) or sympathovagal balance (low-frequency/high-frequency power ratio) (Malik, Bigger, et al., 1996). However, a large body of evidence (Eckberg, 1997; Goldstein et al., 2011; Reyes del Paso et al., 2013) suggests that low-frequency power in the ECG most likely represents parasympathetic activity with minor or no sympathetic activity. Hence, neither sympathetic blockade nor pharmacological and physical manipulations changed low-frequency power (Eckberg, 1997; Goldstein et al., 2011; Reyes del Paso et al., 2013). Thus, heart rate variability may not be an optimal measure of sympathetic activity when using low-frequency power. However, should a sympathetic component exist within the low-frequency power band and

low-frequency/high-frequency power ratio, this could still support the results, as sympathetic enhanced activity can increase and decrease pain sensitivity (Binder et al., 2004; Donello et al., 2011; Rhudy & Meagher, 2001; Yaksh et al., 2017), making it much less specific than parasympathetic activity.

Interconnected at a central level, the autonomic and pain systems also integrate into the stress response, a key player in maintaining homeostasis through adaptive behavioural or mental response to environmental signals. Among others, periaqueductal grey area and the hypothalamus-pituitary–adrenal are important in this interplay (Lamotte et al., 2021). Pain conditions can thus arise in a context of a deregulated stress response, which may also contribute to the persistence of such conditions. Chronic dysfunction in stress response can limit adaptability to everyday events, leading to secondary disturbances, particularly in pain control mechanisms. This has been illustrated in painful conditions with dysautonomia, where hyporeactivity to stress has been implicated (Woda et al., 2016).

## 4.2 | Autonomic function and experimental pain prediction

Experimental methods to induce pain are widely used to provide a mechanistic understanding of pain and its alterations in diseases associated with chronic pain (Petersen-Felix & Arendt-Nielsen, 2002). Experimental pain stimuli activate the nociceptive process in controlled conditions without causing tissue damage and are usually set at a level of discomfort that can be tolerated (Petersen-Felix & Arendt-Nielsen, 2002; Umeda & Okifuji, 2022). Thus, an experimental pain setup is ideal for investigating the connections between acute pain and heart rate-derived parameters. As such, the effect of experimentally induced pain on heart rate variability has been extensively studied (Forte et al., 2022; Koenig et al., 2014). However, our systematic search only found five studies predicting experimental pain by heart rate-derived measures.

The connection between the autonomic nervous system's adaptability and pain sensitivity has previously been studied, finding that subjects unable to complete experimental pain tests had more dysfunctional autonomic functions than those who could complete the tests (Umeda et al., 2013). This is supported by the compilation of studies in this review, which confirm the assumption that increased baseline parasympathetic activity predicted hypoalgesia (Nahman-Averbuch et al., 2014; Umeda & Okifuji, 2022). A higher sympathovagal balance predicted less pain sensitivity following a noxious cold (Appelhans & Luecken, 2008) and heat pain (Tracy, Jarczok, et al., 2018). Interestingly, the studies did not show effects in the high-frequency and low-frequency power bands simultaneously, underlining the complex nature of the system, as they may represent different physiological processes, for example respiratory sinus arrhythmia and baroreceptor activity, respectively. Nevertheless, the compilation suggests that increased heart rate variability measures, reflecting parasympathetic activity, predicted less pain to experimental stimulations.

## 4.3 | Autonomic function and postoperative pain prediction

In contrast to experimental pain, surgery leads to actual tissue damage, which may result in various processes leading to pain and autonomic responses. Even with adequate pain management, as many as 30% of patients undergoing surgery may develop chronic postoperative pain (Boselli et al., 2014; Pogatzki-Zahn et al., 2017; Wilder-Smith & Arendt-Nielsen, 2006). Consequently, objectively predicting pain sensitivity after surgery would be invaluable. Hence, previous studies and reviews have attempted to predict preoperative determinants of postoperative pain using sociodemographic and psychosocial determinants and quantitative sensory testing (Lungu et al., 2016; Werner et al., 2010).

This compilation of studies showed that those with increased low-frequency or high-frequency power had reduced pain after surgery (Adjei et al., 2017; Caton et al., 2021; Powezka et al., 2019), consistent with the above results for experimental pain. However, one study showed that an increased low/high-frequency power ratio increased pain, contrary to the experimental finding (Caton et al., 2021). This is interesting as it was an isolated result contradictory to the high- and low-frequency power results in the same article.

The analgesia-nociceptive index (Boselli et al., 2014) showed similar results to the other parasympathetic measures, though this was not the case for the newborn infant parasympathetic evaluation index (Verweij et al., 2021). This suggests that though there is a reaction in the heart rate when pain is elicited, it is impossible to predict the perceived pain in infants as in adults. This could be because the applied scales were not specific enough for this type of measurement, as they may assess reactions mediated by other external factors. Alternatively, children's nervous systems are not yet fully developed and do not process neural input in the same manner as adults, and it could be speculated that autonomic regulation would increase with age and maturation. In conclusion, these investigations suggest that preoperative heart rate-derived parameters could predict postoperative pain in adults,

highlighting which patients need specialized pre-and postoperative care to prevent pain.

### 4.4 | Autonomic function and prediction of long-term clinical pain

Unlike acute pain, chronic pain conditions are characterized by losing protective function from painful sensations (Cohen et al., 2021). This results in neuronal sensitisation, plasticity and reorganization of the pain system (Arendt-Nielsen et al., 2018), as reported in many chronic pain conditions (Gibler & Jastrowski Mano, 2021), and results in altered pain perception (Gibler & Jastrowski Mano, 2021). The autonomic systems also appear to be altered, primarily with sympathetic dominance and decreased parasympathetic activity (Tracy et al., 2016). However, it is essential to emphasize that the autonomic nervous system is not a "zero-sum" system, and the general perception of reciprocity is too simplistic in chronic conditions (Berntson et al., 1991).

Long-term alterations are more complex to quantify, as they can be influenced by many factors including different disease pathophysiology, pre-existing alterations of the pain and autonomic systems or influences from, among others, stress. Thus, the interactions within the neural pathways may not function as in health. This may aid in explaining the discrepancy found in the studies looking at clinical pain, where only some of the studies showed that higher parasympathetic baseline heart rate variability parameters predicted improved pain over time.

The studies investigating autonomic neuromodulating treatments (yoga or of auricular neurostimulation) showed a better effect of the treatments in those with higher baseline parasympathetic activity. This suggests that the neuromodulation could have a significant effect when the autonomic system functions better, and even that autonomic function outweighs the effects of treatment. Investigations of long-term pain in conditions (neurofibromatosis type 1 and zoster infection) associated with increased chances of chronic pain interestingly showed different abilities of predicting pain. In neurofibromatosis, greater autonomic flexibility predicted a better pain outcome, possibly as the disease does not affect the autonomic system but is more located near the skin. Contrary, in zoster infections, ECG-derived measures could not predict pain, possibly because the zoster infections influence the functioning of the autonomic system (Sakakibara et al., 2022). Thus, even though these studies investigated different types of long-term pain alterations, most conclude that a functioning autonomic system is needed and that a greater autonomic adaptivity is vital for preventing prolonged altered pain perception.

Interestingly, the results on knee replacement surgery (Bossmann et al., 2017) suggest that though pain can be predicted postoperative, other factors may influence the long-term pain level. One possibility could be psychological stress. However, this was tested and showed no influence in that particular study.

### 4.5 | Limitations

There are several limitations to this study. First, the heterogeneity of the studies was very high, particularly for the findings on long-term and chronic pain, and thus, did not allow for a meta-analysis. Therefore, we chose to combine studies investigating similar forms of pain, for example experimental, post-surgical and long-term, to provide the most cohesive analysis. Secondly, the measures of heart rate variability themselves have some limitations. Long-term recordings (24 h or more) are generally considered more robust than short-term recordings (5 min or less) (Shaffer & Ginsberg, 2017). However, shorter recordings were used mainly in the experimental and operative settings. Additionally, it is worth noting that frequency content-derived measures are more vulnerable to the utilized software with predefined filter settings than the time domain-derived parameters and thus may vary between systems and publications. Thirdly, there is a discrepancy in the literature about interpreting heart rate variability measures. The general belief is that low-frequency power and low-frequency/high-frequency power ratios reflect a vital sympathetic component, though not all literature supports this notion. However, one could argue that defining parasympathetic (and sympathetic function) based on calculations based on heartbeats is a proxy upon a proxy. Considering the controversies, other heart rate-derived measures such as deceleration capacity, T-wave repolarisation dynamics or even provocative pain tests might provide more in-depth information (Liao et al., 2023), though, they were not applied in the selected articles.

## 5 | CONCLUSION

Based on the information compiled in this review, an increased parasympathetic activity seems to be able to predict a decrease in perceived pain across all three types of pain investigated, whereas results for the sympathetic activity are more dubious. The results suggest a potential for heart rate-derived measures as a simple and physiological index of pain response. This could have significant clinical implications, as it would provide an objective way to anticipate pain and support pain management in clinical care.

## AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: AMW, CB, AMD; data collection: AMW, THSJ; analysis and interpretation of results: AMW, THSJ, CB, AMD; draft manuscript preparation: AMW; revising it critically for important intellectual content AMW, THSJ, CB, AMD. All authors reviewed the results and approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

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## ORCID

*Anne-Marie Wegeberg* https://orcid.org/0000-0002-8323-4843
*Trine Hyttel Sejersgaard-Jacobsen* https://orcid.org/0000-0002-6586-4235
*Christina Brock* https://orcid.org/0000-0002-3381-1884
*Asbjørn Mohr Drewes* https://orcid.org/0000-0001-7465-964X

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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