Literature Review

Exploring the Abilities of Peripheral Autonomic Parameters to Describe Pain: Another Dead End?

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Background: Pain is essential for survival, but it is also a major clinical, social, and economic problem that demands adequate management. The latter involves timely and accurate assessment, so several efforts have been made to develop accurate and reliable pain assessment tools. Advances in objective pain assessment include a large body of work focused on determining whether autonomic-mediated peripheral responses can be used to predict pain intensity. However, there is still no clinically validated autonomic marker for objective pain assessment.

Objectives: In order to identify possible causes of this situation, the present study reviews the most recent advances examining peripheral autonomic markers' ability to describe pain intensity.

Study Design: Systematic literature review.

Methods: We conducted an online search on PubMed using terms such as "pain assessment," "experimental pain," "autonomic arousal," "heart rate," "heart rate variability," "electrodermal activity," "pupillary diameter," and "blood pressure." Articles published from 2010 through 2020 examining the abilities of peripheral autonomic markers to describe experimental pain intensity were collected and reviewed. From each of the included studies, we extracted information regarding autonomic parameters and stimulation modalities used by experimenters, as well as the sample size, gender, and health condition of the patients.

Results: Twenty-six articles were included for analysis, from which only 2 studies reported the use of multiple modalities. Half of the documents reported sample sizes ranging from 20 to 50 patients, and only 3 studies used formal power calculation to determine the sample size. Most of the articles included only healthy patients, so the influence of age, gender, and pre-existing health conditions on the autonomic peripheral parameters' capabilities to reflect the experience of pain remains unexplored.

Limitations: It is possible that several documents were not retrieved due to a potential search engine bias or the use of very specific terms. Furthermore, only studies reporting pain intensity as a unique measure of its severity were included.

Conclusion: The measurement of autonomic responses elicited by experimentally induced pain is one crucial step toward the development of reliable pain assessment tools. Still, several issues need to be addressed before continuing to explore the use of autonomic parameters for the assessment of pain. It is also recommended that future research endeavors in capturing the singularity of the pain experience involve the measurement of both peripheral (end organs) and central (brain) autonomic responses to pain.

Key words: Pain assessment, autonomic nervous system, experimental pain research, peripheral autonomic markers, painful stimulation

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As a multidimensional experience, pain can be described from different angles. For instance, from an evolutionary standpoint, pain is essential for survival. It drives us to seek care and/or relief and teaches us to avoid harm in the future. Conversely, individuals with insensitivity to pain may fail to notice injuries or harmful events that might lead them to self-mutilation and even death (1). On the other hand, pain is also a major clinical, social, and economic problem, with musculoskeletal conditions (e.g., low back pain) being one of the main causes of disability and absence at work (2). In the United States alone, for instance, more than 100 million workdays are lost each year due to several disabling conditions, and total annual costs have been estimated between $119-$238 billion per year (3). This underlines the necessity for adequate pain management, which in turn involves timely and accurate assessment.

Advances in objective pain assessment include a large body of work focused on determining whether autonomic-mediated responses can be used to predict pain intensity. To this end, several devices and techniques for painful stimuli administration have been employed (4), providing researchers with control over the physical properties of the stimulus (e.g., magnitude, duration) and the possibility to associate quantifiable levels of manipulated variables to patients' pain ratings.

Given the fundamental role that the autonomic nervous system (ANS) plays in coping with life-threatening events, not surprisingly a stimulus that may evoke pain can modulate autonomic activity. Multiple end organs are innervated by the ANS through the sympathetic and parasympathetic branches, so it is reasonable to expect that painful stimuli may produce changes in measures describing the activity of those organs. Heart rate (HR), heart rate variability (HRV), electrodermal activity (EDA), pupillary diameter (PD), and blood pressure (BP) have been found to be influenced by experimentally induced pain (5). However, and despite some remarkable efforts, there is no clinically validated autonomic marker for objective pain assessment. In an attempt to identify issues preventing researchers from being conclusive about peripheral autonomic markers' abilities to reflect pain intensity, this study reviews the most recent advances on this topic. Current trends and the global distribution of research focused on exploring the utility of peripheral autonomic parameters as pain markers are also highlighted. Some recommendations that might be relevant for future research endeavors are outlined at the end of this paper.

Methods

Search Strategy

The PubMed database was used to collect and identify the salient and most recent literature regarding research on whether peripheral autonomic markers are capable of describing experimental pain intensity. The search was conducted in September 2020 and it was limited to the period from June 2010 through June 2020. The terms "pain assessment," "assessing pain," "pain intensity," "experimental pain," "induced pain," "nociceptive pain," "autonomic arousal," "autonomic responses," "heart rate," "heart rate variability," "electrodermal activity," "skin conductance," "galvanic skin response," "pupillary diameter," "pupil dilation," and "blood pressure" were used in combination to perform the literature search.

Selection of Relevant Studies

Documents were screened for title and abstract. Titles not related to the assessment of perceived pain intensity were immediately excluded. A study was considered eligible for inclusion if it aimed to explore the ability of HR, HRV, EDA, PD, or BP to vary as a function of experimentally induced stimuli labeled as painful; or if the study aimed to use HR, HRV, EDA, PD, or BP measures as a form of comparison between groups that explicitly identified painful stimuli.

We systematically excluded any study in which none of the aforementioned autonomic markers was used to estimate pain intensity; or in which autonomic responses were used to explore the effects of a substance, device, method, or ritual for pain relief on the perceived intensity of experimentally induced pain; or in which researchers aimed to use autonomic measures for automatic pain assessment using machine learning techniques; or in which researchers used noxious stimuli whose physical properties could not be controlled, as occurs with several procedures commonly performed in acute and critical care settings (e.g., surgical incisions, patient turning, endotracheal suctioning and extubation, catheterization, venipuncture, capillary blood sampling, lumbar punction). We also excluded studies reporting the use of autonomic markers to merely differentiate between patients with an acute or chronic pain condition and pain-free control groups, as well as those including populations unable to self-report pain intensity, such as newborns and deeply anesthetized patients. When important details could not be retrieved from the abstract, the document was included for full-text reading. Animal studies, meta-analyses, and reviews were also excluded, although reference lists of the latter were

used to retrieve any relevant study. The remaining documents were excluded if they were in a language other than English or Spanish, or if the study was published in the form of an abstract or poster.

Results

By applying the search strategy depicted in the Methods section, 26 articles were included in the analysis (Fig. 1), all of which are summarized in Table 1. As can be seen, most of the studies published from 2010 through 2020 included multiple autonomic parameters in their efforts to determine whether these measures are capable of reflecting experimentally induced pain. On the other hand, only 8 studies limited their scope to examine one single marker.

Among the autonomic parameters chosen for this study, HR achieved the highest number of documents reporting its use (16 articles), whereas PD had the lowest number of documents (3 articles), as shown in Fig. 2. HRV and EDA achieved the second and third highest number of articles, respectively. Moreover, 5 studies (6-10) explored the ability of the phasic component of the electrodermal phenomena (i.e., the skin conductance response - SCR) to reflect pain intensity, whereas a minor number of studies reported the use of the tonic component of the electrodermal phenomena (i.e., the skin conductance level - SCL: [8,11,12]) and the number of skin conductance fluctuations (NSCF: [11-13]). Only 2 studies (14,15) did not specify which component of EDA was assessed in terms of its ability to describe pain intensity. Despite not being systematically included, the blood volume pulse (i.e., the amplitude of the pulsatile component of the photoplethysmographic waveform) appeared in 4 studies (6,12,16,17).

All the documents included in this review were in English. However, some of them were published by

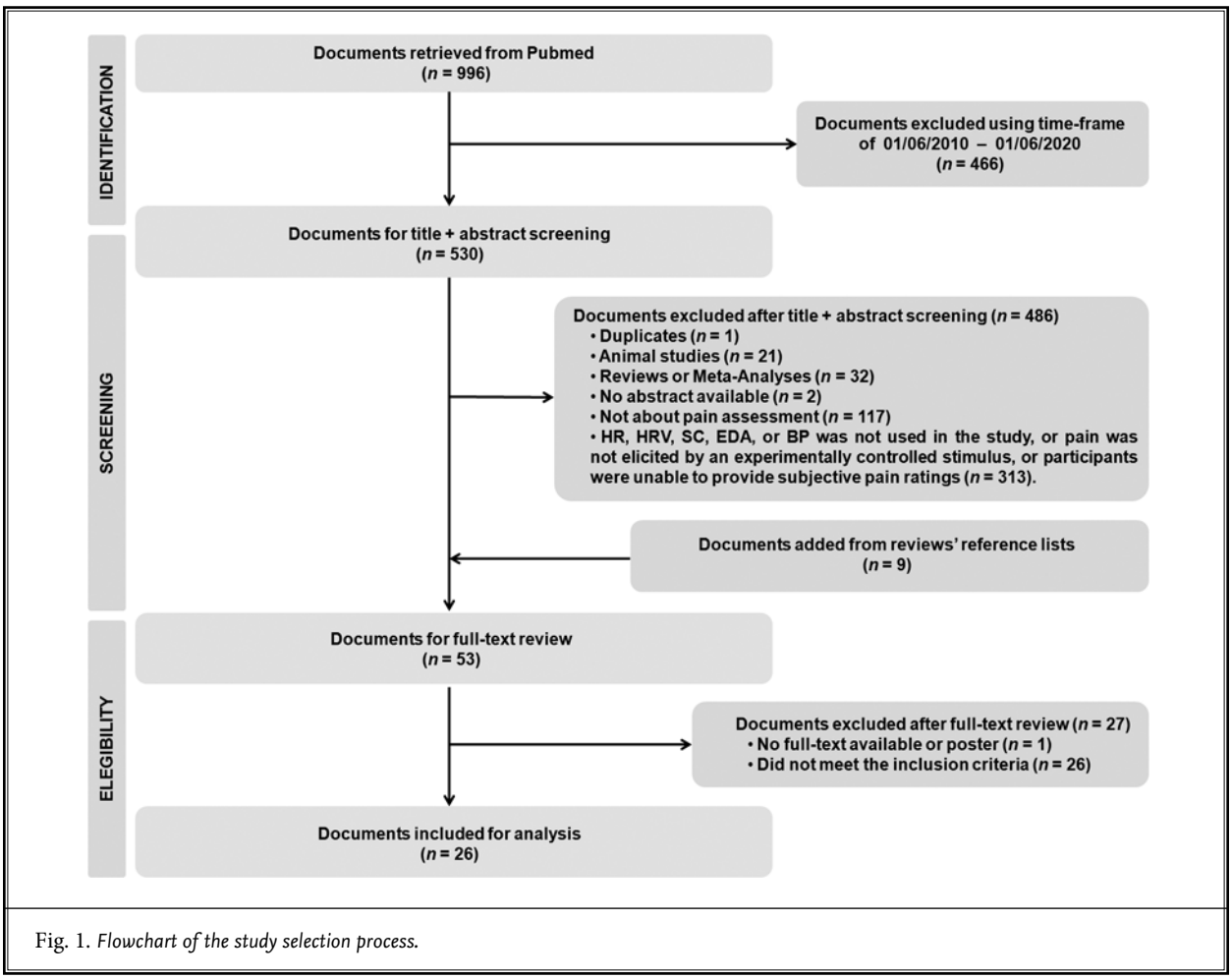

Fig. 1. *Flowchart of the study selection process.*

Table 1. *Summary of the 26 studies included in this review.*

Author(s); (reference); year	Autonomic marker(s)	Patients' condition (n); mean age ± SD or [age range] in years; women %	Stimulus modality	Key finding	Was a statistical comparison made between autonomic measures and pain scores?
Beach et al.; (27); 2015	HR	Alzheimer disease (n = 38) – Healthy (n = 33); 79.5 ± 8.9 – 74.4 ± 6.6; 63.6 % – 73.7 %	Mechanical (pressure)	Patients with severe Alzheimer disease (AD) show diminished HR responses to painful pressure in comparison with healthy and mild/ moderate patients with AD.	No
Benromano et al.; (6); 2016	HR, HRV, EDA (SCR), PA	Cerebral palsy (n = 18) – Healthy (n = 15); 34.5 ± 4.9 – 31.3 ± 7.7; 44.4 % – NR	Mechanical (pressure)	Despite the lack of correlation between stimulation intensity and the autonomic variables, PA was significantly higher and SCR significantly lower in patients with cerebral palsy (CP) with intellectual disability (ID) than controls. However, the patients with CP without ID exhibited autonomic values similar to healthy controls.	No
Breimhorst et al.; (7); 2011	EDA (SCR)	Healthy (n = 42); [22-36]; 50 %	Electrical (intradermal electrode), Mechanical (impact), Thermal (laser-induced heat)	Heat and mechanical, but not electrical stimulus intensities were successfully discriminated by SCR.	No
Chalaye et al.; (26); 2012	HR, HRV	Fibromyalgia (n = 10) / Irritable Bowel Syndrome (n = 13) – Healthy (n = 10); 46.7 ± 7.1/ 37 ± 15.8 – 41 ± 8.5; 100 % / 100 % – 100 %	Thermal (cold pressor test)	Patients with fibromyalgia showed a significant and sustained increase in HR and cardiac sympathetic activity, as well as a decrease in cardiac parasympathetic activity, regardless of the similar pain levels showed by the 3 groups.	No
Devoize et al.; (30); 2016	HR, BP	Healthy (n = 26); 26.0 ± 0.9; 50 %	Thermal (hot and cold water immersion test)	No relationship between the variations of cardiovascular responses and pain intensity was identified.	Yes
Eisenach et al.; (19); 2017	PD	Healthy (n = 28); [24-46]; 60.7 %	Thermal (heat)	Autonomic parameters were correlated with pain intensity, but only when cognitive processes remain unaltered.	Yes
Etherton et al.; (31); 2014	HR, BP (systolic, diastolic)	Healthy (n = 38); 21.7 ± NR; 44.7 %	Thermal (cold pressor test)	Pain catastrophizing was found to be correlated with pain ratings but not with cardiovascular autonomic measures.	Yes
Geuter et al.; (8); 2014	EDA (SCL, SCR), PD (PDL, PDR)	Healthy (n = 54); [21-39]; 0 %	Thermal (heat)	The tonic components of SC and PD were linearly related to pain ratings and less to stimulus intensity. Conversely, no correlation was found between the phasic components of these measures and stimulus intensity or pain rating.	Yes
Girard et al.; (18); 2011	HR	Schizophrenia (n = 35) – Healthy (n = 35); NR – NR; NR – NR;	Mechanical (pressure; ischemia)	Mean HR at 5-10 seconds after applying noxious pressure was significantly higher in schizophrenic patients than in controls. However, no significant differences were found between groups regarding how HR changed from baseline after pressure application.	No
Grant et al.; (28); 2017	HR, BP	Skin picking disorder (n = 14) – Healthy (n = 14); 32.0 ± 11.0 – 31.0 ± 7.8; 64.3 % – 78.6 %	Thermal (cold pressor test)	Although pain ratings were comparable between groups, patients with skin picking disorder (SPD) showed a diminished autonomic response during the cold pressor test compared to healthy controls.	No

Table 1 (cont.). *Summary of the 26 studies included in this review.*

Author(s); (reference); year	Autonomic marker(s)	Patients' condition (n); mean age ± SD or [age range] in years; women %	Stimulus modality	Key finding	Was a statistical comparison made between autonomic measures and pain scores?
Hamunen et al.; (16); 2012	HR, PA	Healthy (n = 29); [18-28]; 0 %	Thermal (heat at 43°C and 48°C, cold pressor test)	Although heat and cold stimuli produced a significant change in physiological parameters, only cold pain intensities were correlated with the magnitude of the respective changes in those parameters.	Yes
De Kooning et al.; (14); 2015	HR, HRV, EDA (SC)	Whiplash-associated disorder (n = 47) – Healthy (n = 31); 42.5 ± 8.47 – 43.45 ± 15.87; 67.4 % – 77.4 %	Mechanical (pressure)	Similar autonomic-mediated cardiac responses to pain in patients with whiplash-associated disorder (WAD) and healthy controls were observed. However, SC showed a slightly stronger response to painful stimulation in subjects with acute WAD.	Yes
Jess et al.; (23); 2016	HRV	Healthy (n = 20); 24.20 ± 1.91; 0 %	Electrical (transcutaneous)	Although the analgesia nociception index derived from HRV showed diminished values after the application of a random stimulus, it did not show significant differences between painful, non-painful or sham stimuli.	Yes
Jiang et al.; (20); 2017	HRV	Healthy (n = 30); [21-45]; 50 %	Electrical (transcutaneous), Thermal (heat)	Several ultra-short-term HRV measures changed in agreement with the intensity of experimental painful stimulation. However, they did not prove to be reliable indicators of pain intensity.	Yes
Léonard et al.; (29); 2015	HR, HRV	Trigeminal neuralgia (n = 12) – Healthy (n = 12); 60 ± 12 – 65 ± 10; 58.3 % – 25 %.	Thermal (cold pressor test)	In response to the cold pressor test, patients with trigeminal neuralgia showed greater sympathetic arousal and parasympathetic withdrawal than healthy controls.	No
Loggia et al.; (15); 2011	HR, EDA (SC)	Healthy (n = 39); [19-34]; 0 %	Thermal (heat)	While HR could predict between-patient differences in pain better than SC, the latter predicted variations in pain ratings within a given individual better than HR.	Yes
Meeuse et al.; (21); 2013	HRV	Healthy (n = 73); [19-41]; 60.3 %	Thermal (heat)	HRV measures may detect responses to heat-driven pain but they may not be suitable to assess pain intensity.	No
Mischkowsky et al.; (9); 2019	EDA (SCR), PD	Healthy (n = 116); [18-50]; NR	Thermal (heat)	The subjective experience of pain may play a crucial role in modulating spinal or supraspinal autonomic responses to noxious stimulation.	Yes
Nickel et al.; (11); 2017	HR, HRV, EDA (SCL, NSCF)	Healthy (n = 39); 24.3 ± 5.6; 35.9 %	Thermal (heat)	SC responses to heat-driven pain were correlated to the stimulus amplitude but not to the perceived pain intensity. No correlation was found between HR and stimulus intensity or pain intensity.	Yes
Reyes del Paso et al; (24); 2011	HRV, BP (systolic, diastolic)	Fibromyalgia (n = 35) – Healthy (n = 29); 50.5 ± 6.7 – 49.4 ± 9.4; 91.4 % – 93.1 %	Thermal (cold pressor test)	Results do not allow being conclusive on whether changes in autonomic-mediated cardiovascular responses were due to pain or the vasoconstriction directly induced by the cooling of the skin.	No
Saxena et al.; (22); 2015	HR, BP (systolic, diastolic)	Healthy (n = 79); [8-70]; 0 %	Thermal (cold pressor test)	Although highly significant differences in pain threshold and pain tolerance between age groups were observed, no significant differences regarding pain ratings and cardiovascular reactivity were found.	No

Table 1 (cont.). *Summary of the 26 studies included in this review.*

Author(s); (reference); year	Autonomic marker(s)	Patients' condition (n); mean age ± SD or [age range] in years; women %	Stimulus modality	Key finding	Was a statistical comparison made between autonomic measures and pain scores?
Shankar et al.; (10); 2019	HRV, EDA (SCR), BP (systolic, diastolic)	Healthy (n = 15); [20-22]; 0 %	Mechanical (pressure)	Both the cardiac and electrodermal parameters showed significant differences between pain and no pain conditions.	No
Silberberg et al.; (25); 2015	HR, BP (systolic, diastolic)	Healthy (n = 15); [21-33]; 0%	Chemical (capsaicin injection)	There were no significant differences between pain ratings at different depths. However, there was a significant trend for an increase in blood pressure and decrease in pulse with deeper injections.	No
Treister et al.; (12); 2012	HR, HRV, EDA (SCL, NSCF), PA	Healthy (n = 55); [18-35]; 38.2 %	Thermal (heat)	Although all of the parameters were able to differentiate between pain and no pain, none of them was able to differentiate between pain intensities. Conversely, the linear combination of parameters was able to differentiate not only between pain and no pain but also between all pain intensities.	Yes
Ye et al.; (17); 2017	HR, HRV, PA	Healthy (n = 40); 22.5 ± 1.6; 47.5 %	Thermal (heat)	Changes in autonomic parameters during the pain production and relief processes showed trends that may be used for continuous monitoring of pain intensity.	No

BP: blood pressure; EDA: electrodermal activity; HR: heart rate; HRV: heart rate variability; NSCF: number of skin conductance fluctuations; NR: not reported; PA: pulse amplitude; PD: pupillary diameter; PDL: pupillary diameter level; PDR: pupillary diameter response; SCL: skin conductance level; SCR: skin conductance response.

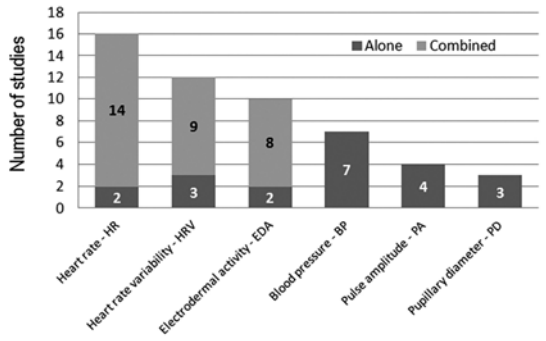

Fig. 2. *Total of studies reporting the use of the autonomic parameters chosen in this study.*

several authors from different countries. To provide more detailed information about the geographical distribution of the included studies, countries that have conducted significant research on the use of autonomic markers for pain assessment over the last decade are highlighted in Fig. 3. If a study was published by multiple authors from different countries, one point was given to each country. Thus, the top 3 contributing countries are the United States of America, Germany, and Canada, which collectively produced 73% of the publications.

Patients' ages were reported as the mean age ± the standard deviation in approximately half of the studies, so it was very difficult to determine whether patients were mainly children (< 10 years), adolescents (10-18 years), young adults (19-35 years), middle-aged adults (36-55 years), or older adults (> 56 years) for each of the included articles. One study (18) did not even report patients' mean age or age range. All the studies reporting the patients' age range involved younger adults while only 7 (8,9,13,19-22) included middle-aged adults and only one (22) involved patients younger than 18, even though studies with children and adolescents were not systematically excluded. As shown in Fig. 4a, half of the studies reported sample sizes ranging from 20 and 50 patients, while only one document (9) reported a sample size greater than 100. Regarding the sample gender, patients of only one gender were recruited in 8 studies (only men patients: [8,10,15,16,22-25]; only women patients: [26]), and 2 studies (9,18) did not even report pateints' gender, although patients from both genders were involved in the majority of the studies (Fig. 4b).

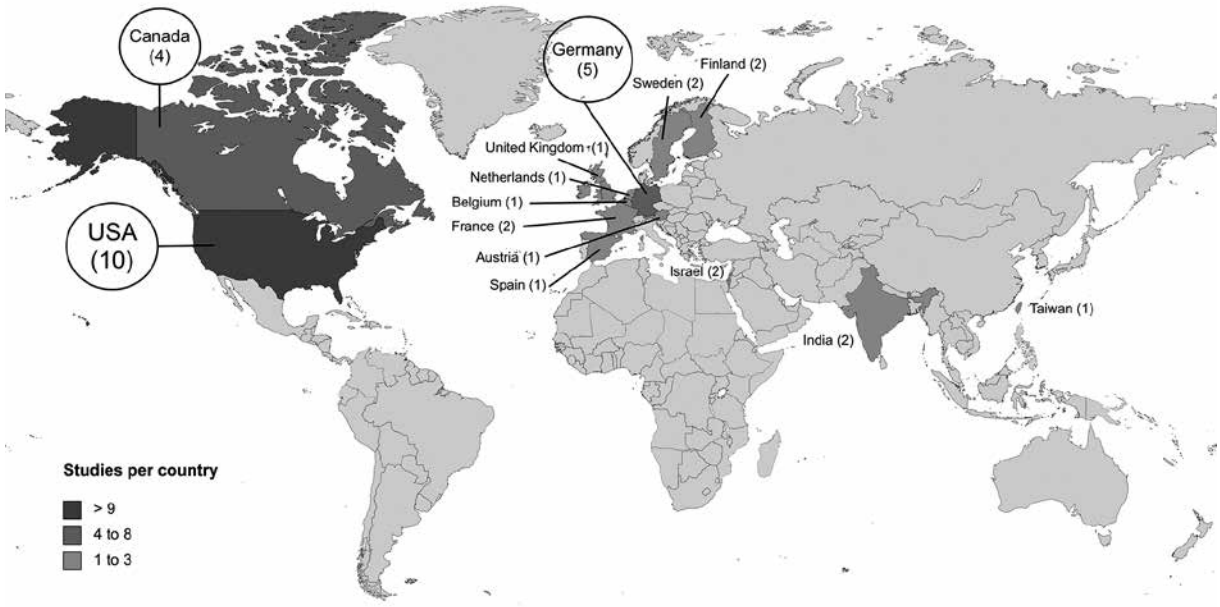

Fig. 3. *Leading countries exploring the peripheral autonomic markers' ability to describe the pain experience (from June 2010 to June 2020).*

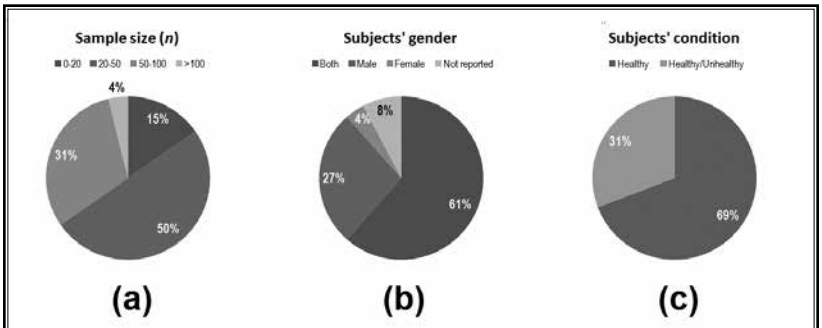

Fig. 4. *Pie charts showing the sample size (a), gender (b), and health condition (c) of the participants involved in the studies published between June 2010 and June 2020.*

Moreover, most of the articles also recruited only healthy patients, while only 8 studies (approximately 31%) involved both healthy and unhealthy patients (Fig. 4c), including those with Alzheimer disease (27), cerebral palsy (6), fibromyalgia (22,26), schizophrenia (18), skin pricking disorder (28), whiplash-associated disorder (14), and trigeminal neuralgia (29).

The vast majority of studies (24/26 = 92.3%) reported the use of one single nociceptive stimulation modality (i.e., thermal, mechanical, electrical, or chemical), and only 2 articles (7,20) reported the use of multiple modalities. Thermal stimuli, either heat, cold, or both, were used in more than half of the included studies (18/26 = 69.2%; Fig. 5), and while only cold water immersion (i.e., cold pressor test) was used for inducing pain by cold, different techniques were used to deliver noxious heat stimuli (contact heating element: [8,9,11,12,15,16,19-21]; hot water immersion: [17,30]; laser-induced heat: [7]). Mechanical, electrical, and even chemical stimulation were used in only 6 (6,7,10,14,18,27), 4 (7,13,20,23), and one (25) study, respectively.

Regarding results provided by the studies on this topic, we found that a high proportion of the total documents (19/26 = 73%) failed to identify significant correlations between autonomic responses to painful stimuli and subjective pain ratings (Table 1). Interestingly, the authors of some of those studies reported such findings based on the lack of correlation between autonomic measures and stimulation intensity, and not between the former and pain ratings (6,7,10,17,18,22,24-29). In other words, no statistical comparison between autonomic measures and subjective pain ratings was performed, and conclusions consequently provided were only inferential. Conversely, all the studies reporting

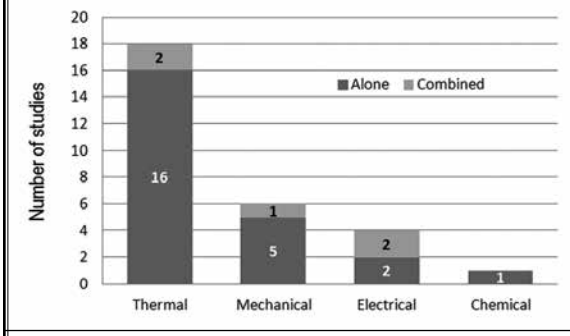

Fig. 5. *Total of studies reporting the use of one or more nociceptive stimulation modalities for experimental pain research.*

significant correlations between autonomic responses and pain ratings included a statistical comparison between these 2 measures (8,9,12,13,15,16,19).

Discussion

The ability of painful stimuli to provoke autonomic responses has already been discussed in previous work. Several years ago, Kyle and McNeil (5) synthesized more than 4 decades of research demonstrating that the kind of stimuli that usually leads to pain can also increase HR, BP, EDA, respiratory rate, and skin temperature, as well as decrease HRV and skin blood flow. However, several issues were found in that body of work regarding its experimental design, methodology, and statistical analysis. One of the aims of this review is to determine whether those issues have been addressed during the last decade (2010 – 2020) or, on the contrary, they are still preventing research from being conclusive about the use of autonomic markers for pain assessment.

A lower proportion of studies (16/26 = 61.5%) have explored HR's ability to reflect pain intensity during the last decade when compared with the period from 1970 through 2012 (28/39 = 71.8%, according to [5]). Still, HR continues to be the most frequently examined autonomic marker in experimental pain research (only followed by HRV and EDA with 12 and 10 studies, respectively).

Unlike other autonomic parameters (e.g., PD), HR is one of the major routine clinical indexes and a relatively easy measure to obtain. Therefore, it is not surprising that there is still considerable interest in examining HR capabilities for reflecting pain intensity. Furthermore, whereas EDA, BP, and skin blood flow, which are primarily influenced by the sympathetic branch of the ANS, HR provides information regarding the relative contributions of sympathetic and parasympathetic activity (32). Interestingly, such an argument has been raised by several authors (6,11,14) to explain why significant correlations were observed between sympathetic-driven measures (e.g., skin conductance) and stimulus intensity, but not between the latter and HR. As pointed out in Lee et al, (32), different autonomic markers should be considered for monitoring fluctuations in autonomic response to experimental pain. However, from the total of studies that have explored the ability of multiple autonomic parameters to reflect pain intensity during the last decade, only one study (12) has been able to combine them. As a result, the authors successfully differentiated between pain and no pain, as well as between 3 different pain intensities (low, mild, and severe).

Regarding the type of stimuli used to elicit pain, there is still a tendency to use only one sensory modality, as only 2 recent studies (7,20) reported the use of multiple modalities (Fig. 5). Because of this, results can hardly be generalized and, therefore, they can lose their utility. In turn, among the studies reporting the utilization of one single modality, thermal stimulation (heat, cold, or both) has been the most frequently used method to induce pain during the last decade. Specifically, a lower proportion of recently published studies (6/26 = 23.1%) have used the cold pressor test to elicit pain when compared with the period from 1970 through 2012 (15/39 = 38.5%, according to Kyle and McNeil [5]). Conversely, the proportion of studies reporting the utilization of heat pain stimuli has increased over the last decade (12/26 = 46.2% versus 8/39 = 20.5%). The reasons for this apparent preference for thermal stimulation remain unclear, but overreliance on this modality could limit the reliability and significance of the findings.

Previous functional magnetic resonance imaging (fMRI) studies (33,34) have shown that innocuous heat and cold may produce a significant activation of several cortical regions (the primary and secondary somatosensory cortices, the insular cortex), which in turn has been found to correlate with autonomic-mediated responses to pain across different end organs (35). Regarding the hot- or cold-water immersion test, it also has been found that cardiovascular changes induced by the cold pressor test are more likely to be related to a thermoregulatory rather than a nocifensive response (24,36). In those studies, even though changes in cardiovascular parameters were more pronounced during the cold pressor test than those observed during the

hot-water immersion test, no correlation was found between cardiovascular measures and pain ratings during the cold-water immersion test, which was in line with previous findings (37). All this suggests that thermal stimuli might influence autonomic activity regardless of the pain experience. Nevertheless, from the 18 studies reporting the use of thermal stimuli, only 3 (9,12,31) have acknowledged this limitation.

As in Kyle and McNeil (5), issues regarding the size, men/women ratio, and age range of the sample were found in several articles. For instance, in only 5 studies (13,16,21,25,27) the sample size was determined by formal power calculation, and for the rest of the studies it is not clear how sample size (or the effect size) was calculated. If a sample size is determined by any historical precedent (i.e., a previous study), the statistical power will decrease and results can hardly be replicated by other authors (38,39). Furthermore, although most of the reviewed studies report the involvement of patients of both genders, only 2 report gender-based differences in the autonomic responses elicited by noxious stimulation (7,19). This proportion of studies is even lower than that previously observed in Kyle and McNeil (5), and neither of those 2 studies recruited enough patients to conduct statistical analyses with appropriate power.

As the autonomic activity is partly influenced by age (40,41), autonomic pain responses may also be different across the lifespan. On the other hand, only one study examined this issue, and no significant differences were found between age groups regarding their cardiovascular reactivity to painful stimulation (22). In addition, only 8 of the included studies involved patients with some health condition or disorder, and while it has been shown that diseases like fibromyalgia and Alzheimer disease may interfere with autonomic-mediated responses to experimental pain (24,26,27), no study has been conducted to examine whether these responses are also influenced by several other illnesses. For instance, while BP has shown to be less sensitive to the cold pressor test in patients with skin picking disorder (28), little is known about its responsiveness to cold pain in hypertensive subjects. Pulse amplitude depends on vascular compliance; its ability to describe pain was examined in 4 of the included studies (6,12,16,17). The latter may be, in turn, affected by several factors like age, ethnicity, drug use, and illnesses like diabetes (42), thereby hindering its utility as a pain marker. As in many other experimental fields, patients with some health conditions are often excluded because they could be physically or mentally challenged (or even threatened) by laboratory settings. However, excluding patients with health disorders in experimental pain research not only may contravene the ethical principle of justice (43) (i.e., not only those who are healthy should benefit from research participation) but also may hamper generalization.

After several decades of experimental pain research, no valid autonomic marker for assessing pain has been identified. The lack of conclusive evidence suggests that further research may not solve this, at least, not before revisiting the theoretical basis in light of the available data. In an attempt to contribute with this process, the following sections point out several issues that should be addressed before continuing to explore the use of autonomic parameters for the assessment of pain.

Are the Autonomic Markers Sensitive to Pain?

Although the pain experience and the neurophysiological reaction to a damaging or potentially damaging stimulus (i.e., nociception) are usually associated, it is necessary to consider that they are different and one can exist without the other (44). Despite the significant correlations observed between perceived pain intensity and autonomic measures (8,9,12,15,19), several other studies have reported that such measures are significantly related to the physical properties of the stimulus but not to pain intensity (11,16,21,25). This seeming contradiction begs the question of whether pain or nociception is what elicits autonomic responses. One major issue in this regard is that several authors reporting no significant correlations between autonomic responses and subjective pain ratings did not perform statistical comparisons between these 2 measures (6,7,10,17,18,22,24-29). Instead, they compared each separately with the stimulus intensity, so the lack of correlation between them was inferred rather than observed. In addition, only a smaller proportion of studies have reported significant correlations between autonomic responses and pain ratings (8,9,12,13,15,16,19). As a result, we cannot affirm (or deny) that autonomic parameters are actually able to reflect pain intensity.

To provide clarification regarding this issue, some considerations need to be made. First, the International Association for the Study of Pain (IASP) links autonomic responses to nociception by referring to them as a potential consequence of the neural process of encoding nociceptive stimuli (45). To date, there is no reference made

by the IASP to a possible linkage between autonomic responses and pain (46). Second, there is some evidence of the functional and anatomical overlap between the ANS and the nociceptive pathways (47,48). These 2 systems interact at peripheral, spinal, and supraspinal levels, so an injury might trigger an autonomic response as part of a coordinated defensive mechanism, regardless of the conscious pain experience. This is the rationale for the use of autonomic-mediated responses in monitoring the occurrence of nociceptive events during surgery. In this regard, several approaches have been proposed, some of which are commercially available (for a review, see [49]). However, there is still no standardized and widely accepted autonomic marker for the assessment of the nociceptive response during operative procedures. A possible explanation is that, while stronger autonomic responses to noxious stimuli have been observed in patients with some chronic disorders when compared with healthy patients (14,18,26,29), other health conditions have shown to diminish the sensitivity of the same autonomic markers (6,27,28). Taken together, these observations suggest that 1) changes in peripheral autonomic measures tend to reflect nociceptive rather than painful events, and 2) this ability might be compromised by preexisting health conditions and illnesses.

Are the Autonomic Markers Specific to Pain?

Just as important as determining whether autonomic responses are, or are not, sensitive to the experience of pain, is addressing whether such responses are also pain-specific. Since autonomic responses can also be elicited by any stimulus that stands out above others, regardless of its sensory modality (i.e., a salient stimulus), quantitative comparisons between pain-driven responses and those evoked by nonpainful but salient stimuli should be performed. Yet, from the total of studies included in this review, only 2 documents report the use of nonpainful stimuli, and no salience-based comparison between painful and nonpainful stimuli was made (13,23). Furthermore, while it was found that SC responses to electrical-driven pain can be differentiated from those triggered by emotion-inducing pictures and sounds (13), the other study found that the analgesia nociceptive index derived from HRV do not even allow to differentiation between painful, nonpainful, and sham stimuli (23).

Although it is still a matter of debate, several authors have suggested the existence of pain-specific brain patterns (50-52), also collectively referred to as the "cerebral signature of pain." This signature is somehow encoded by the ANS through sympathetic and parasympathetic branches and transmitted to different end organs. In that case, pain-specific information could be isolated from peripheral autonomic markers by using data analysis techniques like machine learning and feature extraction (53). One study showed that features extracted from HR, HRV, SC, skin temperature, and skin blood flow can be used to discriminate pain from other emotional states such as boredom and surprise (54). However, that study involved only healthy patients, so the possibility that severe diseases and health disruptions may interfere with the ability of peripheral markers to reveal pain-specific information cannot be ruled out. If this is so, overreliance on peripheral autonomic measures could result in misleading interpretations, which in turn may interfere with adequate management of pain.

Clinical Implications

As mentioned previously, one key element for appropriate pain management is an early and accurate assessment. On the other hand, pain assessment can become a very difficult task when the patient cannot provide the physician with a self-report of pain. Because of this, it is important to have nonverbal pain markers through which it is possible to accurately estimate how much it hurts for the patient and, therefore, to give the patient the proper doses of analgesics.

For decades, researchers have explored the abilities of different autonomic markers to discriminate not only between the presence and absence of pain but also between different pain intensities. Nevertheless, it is necessary to fulfill some conditions to extrapolate results provided by that body of work to clinical practice. One of them is related to the researchers' abilities to reproduce clinical (acute or chronic) pain conditions. In some studies (12,17,31), authors have used nociceptive thermal stimulation (either heat or cold) under the assumption that it can reflect clinical pain conditions. However, those researchers applied the stimulus for one minute (12), 5 minutes (31), and 10 minutes (17), which could be insufficient to elicit nociceptive processes equivalent to those associated with clinical pain (55). Longer-lasting and broad-covering, rather than brief and much more localized stimuli, can activate temporal and spatial nociceptive mechanisms observed in several acute and chronic pain conditions. Thus, results yielded by experimental pain studies could be extrapolated to clinical pain assessment and management.

Another key condition to apply experimental pain

results to clinical settings is the inclusion of different stimulation modalities and paradigms. An earlier study (56), for instance, showed that propofol can increase the nociceptive reflex threshold to single stimuli but has no effect when stimuli are repetitive. Conversely, ketamine does not affect the nociceptive reflex threshold for single stimuli but increases it for repetitive stimuli (57). Together, these observations suggest that one single stimulation paradigm could be insufficient to test several classes of analgesic substances, which, in turn, is essential for pain management. From the studies included in this review, none report the use of repetitive stimuli for pain induction.

How to Measure Well the Right Thing?

Some studies have shown that changes in peripheral autonomic measures can reveal the specificity of the painful experience (13,54). In turn, peripheral markers impose only a few constraints on experimental design and are affordable for several studies, which might explain, to some extent, the continuous search for readily available pain markers. Other techniques such as electroencephalogram (EEG) and fMRI are often expensive and impractical to be implemented in experimental or laboratory settings. On the other hand, if the search for pain-specific responses is limited to observing only peripheral parameters, we might get a "good measure of the wrong thing" (58).

In a recent fMRI study, both painful and nonpainful stimuli were used to observe whether some brain regions showed activity preferentially associated with experimentally induced pain (59). While SCR was used to match 6 different intensities of painful heat and auditory stimuli in terms of their salience, pain-specific responses were identified from the secondary somatosensory cortex (SII). Specifically, it was found that SII activity showed a significant correlation with pain ratings and nociception but not with salient, nonpainful stimuli. In the same year, voxel-wise a general linear model analysis and region-wise model-free analysis were combined to identify differences between brain responses elicited by laser-induced heat (painful) and saliency-matched electrical (nonpainful) stimuli (60). Results showed that several brain regions (e.g., the bilateral opercular cortex and the right frontal middle and inferior areas) exhibited stronger responses to painful stimuli with strictly matched perceived intensity, and even for lower painful stimulation intensity, the response was more pronounced in certain brain regions (e.g., the right frontal middle area).

In another study (61), the authors were able to successfully distinguish painful heat stimuli from intensity/salience-matched nonpainful tactile, auditory, and visual stimuli at the brain level. Although additional modalities and more autonomic parameters are required for a complete demonstration, those findings suggest that the uniqueness of the pain experience might be better identified directly from the brain, and that autonomic arousal, rather than pain, is more likely to be described by peripheral autonomic parameters. After all, and like any other perceptual experience, pain occurs in the brain, which also has the last word in the interpretation of sensory information, including that potentially associated with such experience (62).

Recommendations for Future Endeavors

The lack of conclusive evidence supporting the use of peripheral autonomic responses as pain markers, along with recent work reporting pain-specific responses at the brain level (59-61), suggests that analyzing the activity of several brain regions rather than peripheral autonomic measures might allow identifying the experience of pain. Thus, future research endeavors in capturing the singularity of the pain experience should involve the measurement of both peripheral (end organs) and central (brain) autonomic responses to pain. Given that painful stimuli are often more salient than most nonpainful stimuli, it is reasonable to expect that pain-evoked responses are more pronounced than those elicited by nonpainful stimuli. Therefore, salience-matched nonpainful stimuli should also be included as a control condition in further studies. This suggestion should also be extended to the creation of databases for validating automated pain recognition. Despite the efforts made by some authors in this direction (63-65), only painful stimulation modalities have been included (and therefore, no salience-based comparison between painful and nonpainful stimuli was made) and only thermal and electrical stimuli have been used. Because of this, and so results can be extrapolated to clinical practice, different stimulation modalities and paradigms need to be included in experimental pain studies. It is also recommended that pain be distinguished from nociception by measuring relationships between pain responses and subjective pain ratings. Likewise, a more rigorous examination of how gender, age, and preexisting health conditions influence autonomic responses' ability to describe pain should be performed. Last but not least, standardization of experimental protocols could be useful to reduce experimental design differences that may limit comparison between studies and results'

reproducibility. In this regard, the contribution provided by Gruss et al (65) seems to be a promising step.

Limitations

The search was conducted on only one database (PubMed) to avoid inaccuracies that may result from translating a search strategy into different interfaces and search syntaxes (e.g., proximity operators and field codes differ between databases). Therefore, it is possible that several documents were not retrieved due to a potential search engine bias or the use of very specific terms. However, some documents could be identified from the reference lists of review articles, which possibly reduced the number of studies that could have been missed in the search.

Another limitation of this work is that only studies reporting pain intensity as a unique measure of its severity were included. As a sensory and emotional experience, pain also needs to be described in terms of the level of distress or arousal that it provokes (i.e., pain affect). Accounting for affective components of the pain experience is crucial for adequate assessment and management (66). Moreover, some studies have reported significant correlations between autonomic markers, such as HRV, and the perceived physical impairment caused by the pain experience (67,68). Nevertheless, it has been found that different methods for measuring pain intensity are more correlated than those used for assessing pain effect, which makes the latter more difficult to compare (69). Thus, it was decided to cope with one problem at a time and focus on examining only those studies that used pain intensity to describe the magnitude of the experience.

Conclusion

Undoubtedly, the measurement of autonomic responses elicited by experimentally induced pain is one key step toward the development of accurate and reliable pain assessment tools. But while the literature on the topic is increasing day by day, there is still no evidence supporting the use of autonomic markers for pain assessment. After reviewing the most recent advances regarding this matter, it has been found that most of the issues previously identified by other authors remain unaddressed. As long as this situation continues, results provided by experimental pain research can hardly be extrapolated to clinical (acute or chronic) pain conditions. On the other hand, some recent efforts suggest that peripheral autonomic measures might be used to match painful and nonpainful stimuli in terms of their salience and that pain-specific responses are more likely to be acquired directly from several brain regions. Certainly, the utilization of standardized techniques for monitoring brain activity (e.g., EEG, fMRI) may impose several restrictions on experimental pain research. Yet, our interest in finding easily available pain markers should not limit our efforts to search for the uniqueness of the pain experience by examining only relatively easy measures to obtain. Instead, we should consider the use of methods to monitor brain activity and ensure that experimental stimuli can reflect acute or chronic pain conditions. The more pain researchers are able to fulfill these requirements, the more useful the results will be for clinical practice.

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