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Commentary

Multi-parameter autonomic-based pain assessment: More is more?

The ability to accurately measure pain represents the foundation for successful clinical management of this vexing symptom. Applications of pain assessment tools are not only relevant to diagnosis but also to the development of novel analgesic therapies, to basic research of the neural correlates of pain processing and even to legal/regulatory aspects of pain management [3].

As of today, pain assessment still relies primarily on self-report (e.g., ratings on a visual analogue scale), both in the clinical and experimental settings. Self-reports are generally easy to obtain, require practically little to no equipment, allow for collection of comprehensive information (e.g., regarding the intensity, unpleasantness, quality and spatio-temporal characteristics of the pain sensation), and generally exhibit good reliability [21]. These pain ratings represent the gold-standard for assessing different therapeutic interventions and are sensitive to a wide variety of factors (e.g., psychological manipulations [14,15]). As pain is by definition a subjective experience [16], patients' self-report will likely remain an integral and irreplaceable aspect of pain assessment.

Self-reports of pain, however, are subjective by nature, and can be influenced by a variety of psychosocial factors. For instance, individuals vary in the levels of pain expressivity deemed culturally acceptable, a characteristic that renders some individuals more comfortable to report pain than others [9,20,23,27]. Even more importantly, verbal pain measures cannot be easily (if at all) obtained from certain populations, such as preverbal children or demented/paralyzed patients. Thus, objective surrogates of the pain experience would provide a critical complement to self-reports or, when these are not available, may replace them. For example, a growing number of studies have explored functional neuroimaging markers as brain-derived surrogate measures of pain [3,25]. While several potential functional magnetic resonance imaging (fMRI) markers have shown promising results [1,2,18,19], such techniques may be limited by infrastructure costs and patient access.

An alternate option for objective markers of pain, with possible bedside applications, may be found through investigations of pain-related autonomic reactivity. Autonomic measurements can be acquired with equipment that is relatively inexpensive and easy to transport, and a growing body of knowledge suggests that autonomic activity is significantly altered by pain states. For example, studies have shown that the application of pain stimuli induces significant heart rate acceleration [7,11–13,17,24], through either increased sympathetic or decreased parasympathetic outflow to the sinoatrial node of the heart. Other studies have demonstrated that pain increases skin conductance [4–6,8,13,22], via sympathetically driven sudomotor activity. However, the use of autonomic parameters to infer pain presents significant limitations. Indeed, we have recently shown that, while autonomic-derived measures on average respond robustly to pain stimuli, the extent to which such pain-related autonomic responses individually reflect the magnitude of pain experienced varies significantly across individuals [13].

In this issue of PAIN, Treister and colleagues [26] asked whether the linear combination of multiple autonomic parameters allows better estimation of the magnitude of pain perceived in response to stimuli of various intensities, compared to the use of each parameter independently. The authors first identified, among a pool of 55 subjects, 45 who demonstrated stable and reliable ratings in response to painful stimuli of different intensities. From these subjects, they then measured five different autonomic parameters while subjects received 1-minute heat stimuli of four levels (high, medium, low and no pain): heart rate (HR), heart rate variability – high frequency spectral power (HRV-HF), skin conductance level (SCL), number of skin conduction fluctuations (NSCF) and photo-plethysmographic pulse wave amplitude (PPGA). These peripherally-derived signals reflect a multi-organ autonomic response that covers both sympathetic and parasympathetic branches of the autonomic nervous system (ANS). Importantly, the ANS, contrary to previous belief, is not an all-or-none multi-organ response system, but rather demonstrates variable outflow to different end-organs [10]. Such variability provides a degree of independence for these different ANS-derived metrics, and makes a multi-dimensional model-based marker a very reasonable approach to identify ANS based markers for pain.

In their current study, Treister and colleagues observed that all ANS parameters differentiated 'no pain' from 'pain': as expected, HR, SCL and NSCF were significantly higher during painful compared to innocuous stimulation, while HRV-HF and PPGA were significantly lower. However, no parameter was able to independently distinguish between the three different pain levels. In contrast, when the authors linearly combined the signal from all five autonomic parameters, by fitting an ordinal cumulative logit model to the data, they observed that the integrated signal was not only able to distinguish 'no pain' from 'pain' stimuli, but also differentiated across the pain levels (high pain > medium pain > low pain > no pain).

The results from this study are promising and suggest that autonomic-based pain assessment can benefit from the integration of multiple parameters. Although reactivity to evoked experimental pain may also differentiate chronic pain patients from healthy volunteers, future research needs to explore how the results of Treister et al. can be applied to characterize clinical pain in a patient population. In broader terms, this study suggests that integrating data from a variety of sources (e.g. multiple autonomic outflow metrics, or even combined ANS, functional imaging, behavioral metrics) should allow us to achieve a more accurate estimation of the pain experience. Successful chronic pain management is only as good as the tools used for accurate pain assessment. Future

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development of objective measures of pain that can complement or, in some cases, even serve as alternatives to patient self-report, promise to improve significantly how pain is managed in the clinical setting.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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