frontiers in Pain Research

METHODS
published: 23 March 2022
doi: 10.3389/fpain.2022.764128

Combining Electrodermal Activity With the Peak-Pain Time to Quantify Three Temporal Regions of Pain Experience

Viprali Bhatkar[1]*, *Rosalind Picard*[2] *and Camilla Staahl*[3]

[1] *Digital Health Independent Consultant, Arlington, MA, United States,* [2] *MIT Media Lab, Cambridge, MA, United States,* [3] *Novo Nordisk A/S, R&D Business Development, Copenhagen, Denmark*

Background: Self-reported pain levels, while easily measured, are often not reliable for quantifying pain. More objective methods are needed that supplement self-report without adding undue burden or cost to a study. Methods that integrate multiple measures, such as combining self-report with physiology in a structured and specific-to-pain protocol may improve measures.

Method: We propose and study a novel measure that combines the *timing of the peak pain* measured by an electronic visual-analog-scale (eVAS) with continuously-measured changes in electrodermal activity (EDA), a physiological measure quantifying sympathetic nervous system activity that is easily recorded with a skin-surface sensor. The new pain measure isolates and specifically quantifies three temporal regions of dynamic pain experience: I. Anticipation preceding the onset of a pain stimulus, II. Response rising to the level of peak pain, and III. Recovery from the peak pain level. We evaluate the measure across two pain models (cold pressor, capsaicin), and four types of treatments (none, A=pregabalin, B=oxycodone, C=placebo). Each of 24 patients made four visits within 8 weeks, for 96 visits total: A training visit (TV), followed by three visits double-blind presenting A, B, or C (randomized order). Within each visit, a participant experienced the cold pressor, followed by an hour of rest during which one of the four treatments was provided, followed by a repeat of the cold pressor, followed by capsaicin.

Results: The novel method successfully discriminates the pain reduction effects of the four treatments across both pain models, confirming maximal pain for no-treatment, mild pain reduction for placebo, and the most pain reduction with analgesics. The new measure maintains significant discrimination across the test conditions both within a single-day's visit (for relative pain relief within a visit) and across repeated visits spanning weeks, reducing different-day-physiology affects, and providing better discriminability than using self-reported eVAS.

Conclusion: The new method combines the subjectively-identified time of peak pain with capturing continuous physiological data to quantify the sympathetic nervous system response during a dynamic pain experience. The method accurately discriminates, for both pain models, the reduction of pain with clinically effective analgesics.

Keywords: sympathetic nervous system, electrodermal, EDA, SCL, VAS, cold pressor, capsaicin

OPEN ACCESS

Edited by:
Kenneth Craig,
University of British Columbia, Canada

Reviewed by:
Hugo F. Posada-Quintero,
University of Connecticut,
United States
Eleonora Vecchio,
University of Bari Aldo Moro, Italy

***Correspondence:**
Viprali Bhatkar
viprali.b@gmail.com

Specialty section:
This article was submitted to Pain Research Methods, a section of the journal Frontiers in Pain Research

Received: *25 August 2021*
Accepted: *15 February 2022*
Published: *23 March 2022*

Citation:
Bhatkar V, Picard R and Staahl C (2022) Combining Electrodermal Activity With the Peak-Pain Time to Quantify Three Temporal Regions of Pain Experience. Front. Pain Res. 3:764128. doi: 10.3389/fpain.2022.764128

INTRODUCTION

Pain involves a subjective experience influenced by factors such as fear, emotion, anxiety, cognitions, autonomic responses and malaise (1). Self-reported pain intensity does not correlate well with the severity of the pathological condition (2). Thus, quantification of analgesic effects in clinical trials, even with established analgesics, is frequently inconclusive (3).

Today's standard for pain measurement, the visual-analog scale (VAS) or electronic VAS (eVAS), allows participants to self-report their subjective experience of pain either statically–by reporting a single number, or dynamically–by turning a dial or moving a slider, usually along a scale from 1 to 100. While such scales have become the gold standard, being quick and easy to use, they have long been recognized to have problems with accuracy and reliability, with many factors beyond pain that influence the scores people give (1, 4). While many efforts are made to optimize self-report measures, e.g., customizing how it is presented for a particular population such as older adults (5), a holy grail of pain measurement is to obtain a more objective measure that sensitively reflects changes in pain experience and is easy to use. It also needs to work reliably and repeatably, across different participants experiencing different levels of pain in a lab study, and also on different days and visits, with repositioned equipment making valid measures, across different types of pain and analgesic use.

Recent surveys reviewed a growing number of automated methods to quantify pain objectively using facial expressions, vocalizations, physiology, brain-activity sensing, and more, and indicated the need for personalization of measures (6), as well as many wearable sensing approaches that can help quantify pain more objectively (7). While all of these measures show promise, each fully-objective method has its limitations, typically ignoring user-dependent subjective information, and focusing only on the objective data for one type of pain model and only during one day's visit or assessment period. The same emotions in the same person can exhibit patterns of physiology that change from day to day (8), so it is important to make sure that any pain-sensing method can account for this day-based variation.

Methods to elicit pain in a controlled manner have been refined via a large number of human pain models (9). In this work we use two well-established methods to induce pain: (1) the cold pressor, placing a limb into icy-cold water and holding it there, known for deep intense pain activating the descending pain system and its sensitivity to opioids (10), and (2) intradermal injection of capsaicin, which generates stable, long-lasting, and reproducible primary and secondary hyperalgesia lasting 2 to 3 h (11–13).

While many attempts have been made to develop an objective measure of pain, we focus in this work on a new measure that can be used easily and efficiently deployed in a variety of environments including the emergency room, post-operative recovery space, etc. This requirement rules out EEG, MRI, MEG, and fNIRS, despite that there has been exciting progress with these brain-based methods, e.g., (14, 15). We choose a measure that can be assessed as easily as vitals are assessed today with a readily applied wearable sensor, and measure the sympathetic nervous system response using a new characterization of electrodermal activity (EDA), which can be obtained quickly and easily by placing a sensor on the surface of the wrist or lower leg. The sensor can optionally be worn for continuous monitoring 24/7. Unlike the heart, which receives both sympathetic and parasympathetic nervous system innervation, the skin receives only sympathetic innervation (16). EDA thus provides a sensitive measure of sympathetic nervous system activity that can be captured effortlessly, and that changes continuously during a pain experience.

Sometimes EDA is considered non-specific, because it can be influenced by changing humidity and sweating, hydration, and strong emotions. Our method addresses the specificity problem by synchronizing the quantification of the EDA temporally to two precisely defined moments: (a) the moment of onset when applying a painful stimulus, and (b) the moment, identified subjectively, of "peak pain" experience. By using relative values in the regions anchored by these time points, EDA-based measures are likely to be highly specific to pain because they occur during an elicited experience of pain, acknowledged by a self-reported peak pain. Also, changes due to humidity, sweating, hydration, and emotions-unrelated-to-pain are minimal within the time-frame measured. We evaluate the proposed measure across people, across different days, across two pain models, and across three treatments, showing it addresses these traditional concerns.

While objective physiological data often have the strong and helpful property of being able to be continuously measured, sometimes they are limited because they change only at a *subset* of the moments of interest during a pain experience; for example, facial expressions might be most likely to occur at the onset of a cold pressor task, but the expression might fade or disappear completely, even as pain continues to increase, an observation identified decades ago (17). We seek in this work to develop a measure that continuously represents the trajectory of pain's anticipation, response, and decay.

While the subjectively reported levels provided on a VAS or eVAS can vary because of many factors unrelated to severity of pain, it is still routinely used. In our work, we use it in a way that extracts the timing of its peak, but then we discard the actual eVAS values. More specifically, when self-reporting pain, the exact value selected is highly subjective: it might be low simply because the participant wants to appear stoic. However, when a dial is turned continuously after a painful stimulus, it usually will increase up to a point, before it falls. Thus, each participant shows a moment of peak pain—the highest value relative to their other values. In our work, we find that the time to arrive at this peak is stable across pain sessions, even on different days with different pain treatments. The temporal position of the peak eVAS value is used to delineate two regions: The region rising up to this peak, and the region recovering from this peak. Our new measure then quantifies the EDA in these regions.

We also choose to include in our measure one more region: the assessment of the physiology during a period of anticipation immediately before the pain onset. This choice was inspired by hearing pediatric nurses discuss how some children flinch as if in pain or utter "ouch" *before* the needle touches them and by work showing that pre-pain anxiety can predict self-reported

pain (18). Quantifying this pre-pain anxiety is not typically done in pain research, but we think it is important for better understanding patient pain experiences and we recommend its measurement, at least as a contextualizing factor before the actual pain stimulus occurs.

To summarize, the proposed new method precisely characterizes and quantifies physiology over three temporal regions:

I (Anticipation): From the announcement of an imminent painful stimulus to the pain stimulus onset
II (Response) From the stimulus onset to the moment of subjectively reported peak pain
III (Recovery) From the peak pain moment to recovery from pain, or for a fixed time after the peak

These three quantities characterize our three-region pain measure.

It is well-established that pain should be highest during a painful-stimulus condition when no treatment is provided, reduced slightly under a placebo treatment, and reduced the most by effective analgesics. On placebo effectiveness, see for example Colloca and Barsky (19) and also demonstrations that higher-priced placebos work better than lower-priced ones (20). Using this knowledge, we test the novel three-region measure in a rigorous study with a 3-armed, placebo-controlled, randomized crossover trial design including 24 healthy adults. We systematically compare each measure before and after the effects of placebo, oxycodone and pregabalin. We also examine temporal situations known to affect pain measures, including the heightened anxiety expected during a "first visit," which can be expected to translate into a report of higher pain on the first time than when the identical procedure is repeated later. Finally, we show that the new measure outperforms the eVAS in all of these tests, demonstrating excellent pain discriminability.

METHODS

The methods used in this study are designed to evaluate a new measure of pain in the context of a clinical trial setting. We use treatments of previously established efficacy against pain (pregabalin, oxycodone) in a design of a randomized control trial. The trial applies a double-blind placebo-controlled multi-treatment, multi-day design. Outcomes were compared for all treatments both within and across participants, across days and weeks, and across different placements of the sensors, in order to comprehensively evaluate if the new pain measure is robust to all of these important variations. All study procedures were pre-approved by an ethics review board and the study was registered by ICON Development Solutions, under registration number EudraCT 2012-000484-25.

Participants

We recruited 24 healthy male adults, with normal body mass indexes (18–30 kg/m^2) and normal laboratory health tests. Each committed to attend four visits experiencing pain stimuli on four different days within a two-month period. Participants were non-smokers or light smokers (up to 5 cigarettes or equivalent per day). We focused this study on males since resources were limited and we wanted to reduce gender-based interactions and effects, as well as avoid menstrual-cycle changes and their impact on pain and physiology, which is a complex topic of ongoing research (21–23). Properly controlling the complexity associated with the female physiology would require a larger and longer study, even if it results in the same measure working for women as what we study here for men. Informed consent was obtained before commencing the study.

Pain-Elicitation: Cold Pressor and Capsaicin

The Cold Pressor Test

After preliminary equilibration of the hand temperature, and after alerting the participant that the process would start in 2 min, the participant was instructed to put one hand (the one without the palmar EDA sensor) into a cold-water bath (2°C) for 2 min whilst continually recording the pain intensity using the eVAS with the other hand. The right hand and left hand were used alternatingly on different visits. At the end of 2 min, the participant was instructed to remove his hand from the water bath. Pain was scored continuously using the eVAS starting at the time of the immersion and continued throughout the immersion.

The Intradermal Capsaicin Test

Participants were familiarized with pain evoked from 100 μg of capsaicin at the Training Visit. A single intradermal injection of capsaicin (100 μg) was made into the volar surface of the upper forearm (Manufacturer: ICON Development Solutions Manchester. Composition: 1 mg/ml capsaicin in 10% v/v ethanol, 7.5% v/v Tween 80 in 0.9% sodium chloride solution (100 μg/100 μL).) The injection of intradermal capsaicin was announced to the participant 5–8 min before the injection. The right arm and left arm were used alternatingly on different visits. Pain was scored continuously using the eVAS starting just prior to the intradermal injection and continued for 15 min after the injection.

Pain-Measurement: eVAS and EDA

Recording of eVAS

Pain intensity was assessed using an eVAS with the left end (=0) being equivalent to "no pain" and the right end (=100) referring to "worst pain imaginable". Participants were asked to evaluate pain intensity continuously by selecting the point on the eVAS that corresponds to the pain intensity they have at that moment in time. Participants were instructed to take both pain intensity and unpleasantness into account when scoring pain. While these can be considered two different dimensions, many studies show similar behavior of both dimensions during experimental pain, e.g., Duncan et al. (24), and efforts to distinguish them are ongoing (25) and not addressed in our study design.

EDA

EDA was measured electrically as skin conductance, using the Affectiva Q sensor, which measures skin conductance level (SCL) in microSiemens using 1 cm Ag-AgCl dry electrodes. Sampling rates were 8Hz. Each participant wore synchronized Q sensors

on five different locations, left wrist (LW), right wrist (RW), left ankle (LA), right ankle (RA) and right or left palm (P). The palm side was alternated over the four visits and was worn on only one side because the cold pressor test required submersion of one hand into ice water. In the rest of this paper, only the data from the four limbs was used as the palm data was too often noisy from movement artifacts.

Protocol

The Protocol is illustrated in **Figure 1**. Each patient made four visits: An initial training visit (TV), followed by three treatment visits (Treatments A, B, and C) in randomized order. Treatments were applied double-blind to treatment condition, and all data analyses in this paper were conducted initially without the condition being revealed. Later, they were revealed to be: A=pregabalin, B=oxycodone, and C=placebo. All four visits had a similar structure: First the patient put on the five EDA sensors. Next, a baseline heat-pain stimulation on the non-dominant hand was performed (but is not analyzed in this work, as the timing of each part of the series of rapid stimulations was not reliably recorded for comparison to the EDA). Next, they experienced the cold pressor, while filling out eVAS continuously during the immersion. Then the treatment was applied in the form of an oral capsule, except during the first visit, the TV, when no treatment was made. Then, the patient rested for an hour, which allowed treatment A, B, or C to take effect. Next, they experienced again the same cold pressor test, while continuously reporting eVAS levels. Then, 10 minutes elapsed while they filled out the State Trait Anxiety Inventory (STAI) (26) (not analyzed here). Next, the capsaicin was administered while they continuously reported eVAS levels. Finally, the sensors were removed and the participant was dismissed.

Overall, this design enabled systematic examination of multiple important comparisons including: (1) measuring the same stimulus (cold pressor) before and after treatment (no treatment, placebo, oxycodone, or pregabalin) within the same day; and (2) measuring reported pain across different days (cold pressor and capsaicin) x (no treatment, placebo, oxycodone, pregabalin). Since a person's physiological patterns can vary a lot from day to day, it is important to see if the proposed eVAS-peak-anchored electrodermal measure shows consistent differentiation both across days as well as within days.

In an effort to mitigate the effects of anticipatory arousal, which is likely to increase with increasing uncertainty, the sequence of events was first shown to all participants up front during their first visit (TV), and then this same sequence of events was used in that visit and all subsequent visits. Only the treatment (blinded administration of A, B, or C) was randomized across the subsequent visits. All visits followed the same procedure to reduce the influence that uncertainty has on autonomic stress responses. Also, participants are given an indication 2 min before each cold pressor task that it is going to start in 2 min and similarly 5–8 min before the capsaicin injection, so that anticipatory effects and time periods are held as constant as possible across the procedures and days. This helps eliminate "surprise" effects on autonomic responses.

Data Processing

ICON recruited 27 healthy adult male participants. Of these, three men dropped out of the study early and we received data sets for 24 participants x 4 sensors (LW, RW, LA, RA) x 4 visits = 368 sets of physiological responses. One participant's data had the wrong sampling rate for visit 1, no eVAS for visit 2, and no data for visit 3, so we dropped his data, leaving 23 sets.

Each file was visually inspected to confirm that the data record contained quality signals throughout the entire visit. Some files needed to be omitted due to bad data quality (malfunctioning sensor or sensor placed too loosely to record, causing visibly high levels of noise). Also, a total of 9 participants missed some visits or dropped out at some point after completing the training visit. Overall, 295 of the potential 368 files from the four limbs and 92 visits were obtained with high quality (80.2%). These 295 are distributed as: TV = 76 files, A = 73 files, B = 73 files, C = 73 files. All of these are used in the analyses that follow.

EDA Filtering, SCL Normalization, and Down-Sampling

Electrodermal activity can be divided into the "tonic component," the slowly varying part of the signal usually referred to as skin conductance level (SCL), and the "phasic component," the relatively fast changing peaks usually referred to as skin conductance responses (SCR's). The SCL is usually measured over intervals ranging from tens of seconds to hours, while SCR's are usually measured within 1–6 s after a discrete event.

Our analysis over the cold and capsaicin regions used SCL's derived as follows:

To separate the tonic from phasic EDA, a 5th order, zero-phase, lowpass Butterworth filter was applied to the raw skin conductance signal. The filter's cutoff frequency was set to 0.05 Hz as tonic activity is observed in 0–0.05 Hz. The SCL for each 1-min epoch was estimated using a 1-min wide centered moving average filter.

We compared data from multiple bodily locations and from multiple people over multiple days as baseline physiology can vary from day to day. We needed a robust way to make the data values comparable across all these files. Also, to accurately assess the changes in SCL after an analgesic, it is necessary to compare the SCL before and after the treatment on a common scale. We chose to use Z-score normalization before making all of these comparisons. To perform Z-score normalization, the (low-pass filtered) SCL for each file (one sensor, one day's session) was used to compute the mean and standard deviation for that session. Then the file's SCL was normalized by subtracting the mean value for the day's session and dividing it by the standard deviation for that session, such that the normalized SCL for the day has zero mean and unit standard deviation. Thus, the two cold and one capsaicin session for a person's visit were normalized using the same mean and standard deviation for that day.

The normalized SCL was subsequently analyzed over each of the regions I, II, and III for each cold and capsaicin segment.

Computation of Three-Region Measure

Pain is a mix of psychologically perceived phenomena and physically experienced phenomena (13). In this work, we

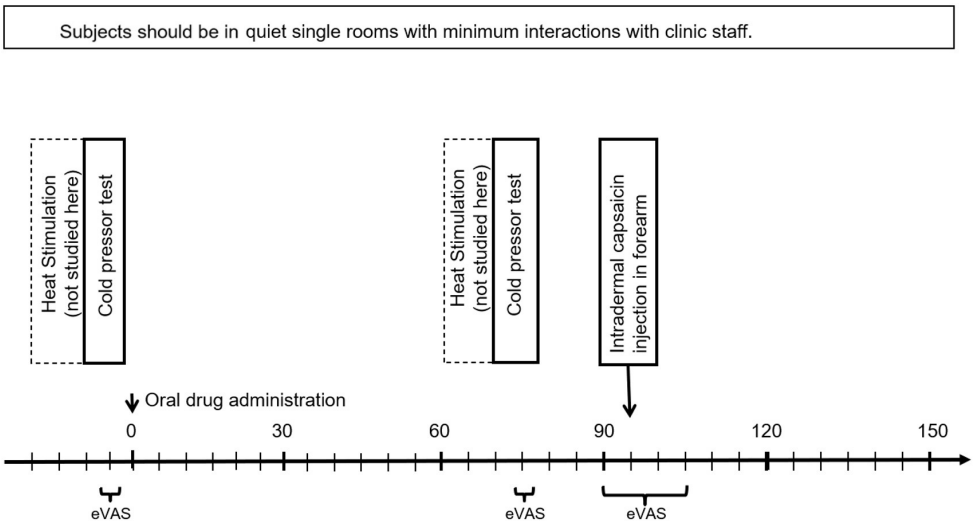

FIGURE 1 | Study protocol, showing three time periods where eVAS was measured. EDA was measured for the entire session (~3 h).

combine these two components in a novel way, using two time points—the objectively measured onset time of the pain stimulus and the subjectively measured time of the peak of the self-reported eVAS data—to structure the analysis of the physiological EDA data into three regions of the pain experience. The result gives a measure that improves on eVAS by adding objective data yet incorporates a valuable aspect of the self-reported pain experience—its peak pain moment as perceived by the participant in pain.

Here is how the three-region method works (See **Figure 2**): Using eVAS data and timing information of when the person was warned of the impending cold or capsaicin stimulus, we define three non-overlapping regions. These three regions separately quantify three regions of the pain response: I. Anticipation, II. Response, and III. Recovery.

Region I = Pain Anticipation

For the cold stimulus, participants were warned approximately 2 min before the cold pressor test. For the capsaicin stimulus, the warning period was from 5 to 8 min. We define Region I, "the anticipatory period", to be the region of time from the onset of the warning to the onset of the pain stimulus. We expect that SCL during this region is affected more by anticipatory anxiety than by physical pain. It is important to include responses during this region because sometimes people appear to actually experience pain before the stimulus touches them: For example, a child might jerk back and scream with "pain" before a needle touches them, and adults sometimes exhibit a facial grimace as if in pain before the onset of actual sensory pain. Thus, we include Region I, the subjective pain anticipatory experience, as part of the pain experience. The eVAS was not reported during region I so we cannot compare physiology with eVAS in that region. However, SCL is hypothesized to rise with anticipation, uncertainty, and anxiety, and our study data confirm that the SCL usually rises during Region 1, even sometimes taking on high values here.

Region II = Pain Response (Rising From Onset to Peak)

Region II is defined as the region of time that begins with the onset of the pain stimulus and ends when the person reports their peak pain level. In this study, the cold stimulus begins when the hand is placed in the ice water, and the capsaicin stimulus begins when the needle is inserted. The participant begins to report eVAS at this onset moment. Region II spans the time from the start of the pain stimulus and start of the eVAS recording to the peak reported eVAS level. The timing of this peak is clearly visible for capsaicin, which has eVAS that tends to follow the shape shown in **Figure 2** (green line = eVAS, blue line = SCL).

For cold pressor, we compute the peak location differently, as the eVAS often climbs monotonically and doesn't peak until the 2-min cold pressor test ends (See **Figure 3**). If we counted the peak as the right-most point, then we would often have just Region II and no Region III. We think it is valuable, even though the hand is still immersed, to examine this later portion of the cold pressor task where the eVAS tends to "level off" separately from the first portion of the immersion, where the eVAS typically climbs fast. Thus, for cold pressor pain we define the peak to occur at the time that the eVAS levels off–specifically, where it ceases to go up more than 0.005 units or 99.99% of the maximum value.

Region III = Pain Recovery (Sustain or Decay)

In this study, for both cold pressor and capsaicin, Region III is defined to begin at the peak identified in the eVAS. For cold pressor, Region III is measured until the cold pressor is ended (2 min from cold pressor onset), while for capsaicin, Region III is measured until 15 min following the onset of the capsaicin stimulus. For cold pain, this region is where the eVAS is usually leveling off–pain is "sustained." For capsaicin pain, this region tends to be where the eVAS values "decay" as the person is in recovery from the initial capsaicin injection.

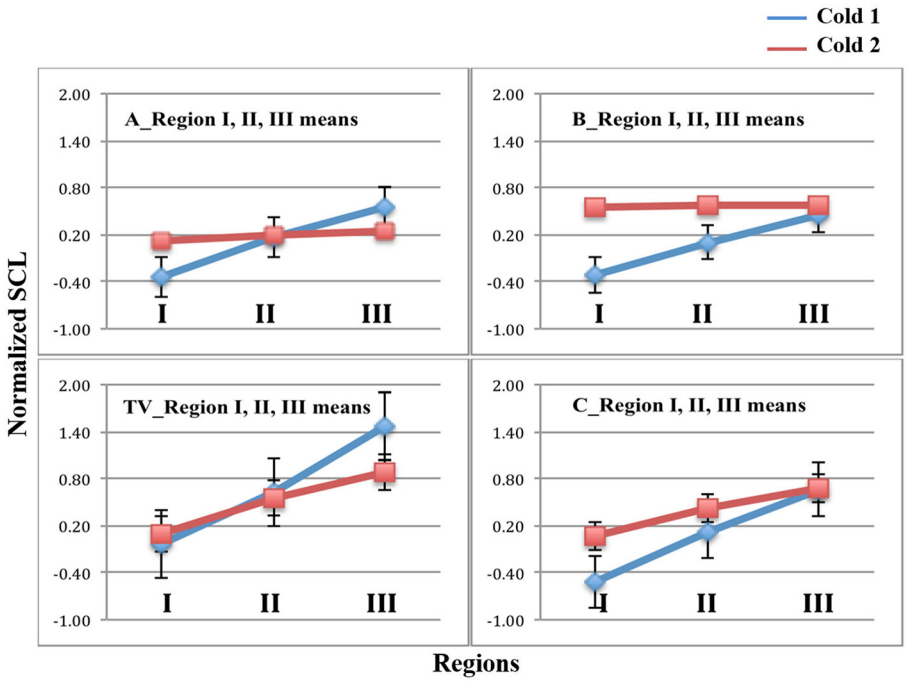

FIGURE 4 | Mean and standard error bars of normalized SCL in Regions I, II, and III. Blue = Cold1. Red = Cold2. Data are from the four limb sensors for n = 23 participants. Analgesics were applied in A and B, and are associated with a lack of increase across the Cold2 pressor.

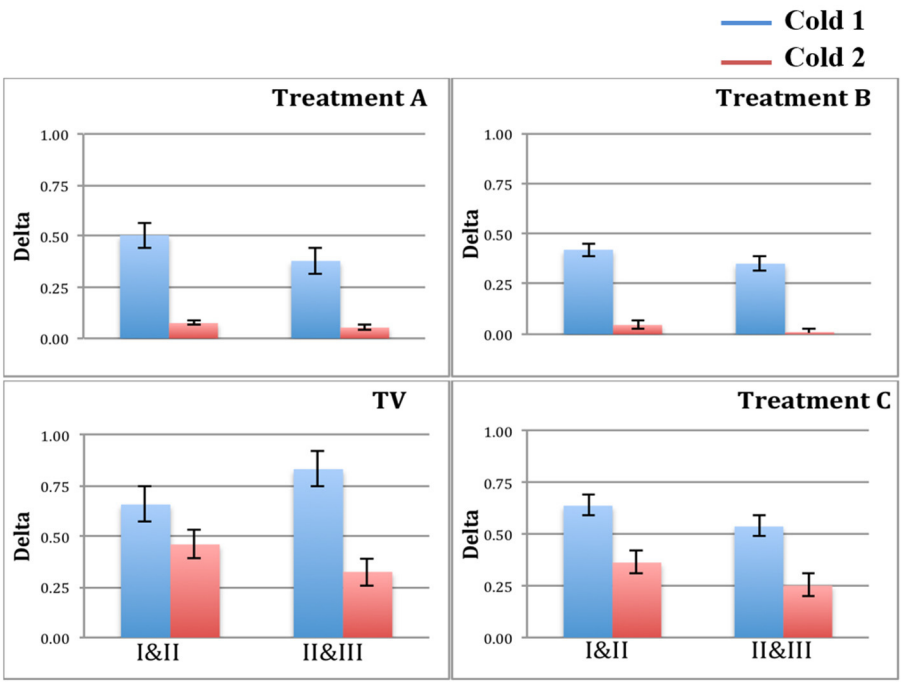

FIGURE 5 | Blue bars = delta values between regions for Cold1. Red bars = delta values between regions for Cold2. Treatments A and B show a significant reduction in the deltas, as hypothesized for these two analgesics.

confirm that the new measure shows these statistically significant reductions for Cold2. We see the significant effect of comparing analgesic conditions, A and B, to non-analgesic condition TV, and the non-significant effect of C's placebo compared to TV.

TABLE 1 | Testing for statistically significant changes in normalized SCL between adjacent regions during Cold1 (before treatment) and Cold2 (after treatment).

Δ	TV I and II	TV II and III	A I and II	A II and III	B I and II	B II and III	C I and II	C II and III
h	0	0	1	1	1	1	1	0
p	0.355	0.151	0.000	0.000	0.000	0.000	0.023	0.065
N	75	75	76	76	73	73	73	73

One-tailed Wilcoxon rank sum test (testing if delta Cold2 < delta Cold1 and assigning h = 1 if this is true). The significant effect of the analgesic is confirmed for treatments A and B, while a significant effect is also seen only at the start of the placebo C.

TABLE 2 | Testing for statistically significant changes in normalized SCL for Cold1 (before treatment) and Cold2 (after treatment) across sessions on different days.

Δ	TV vs. A Cold1_I and II	TV vs. A Cold1_II and III	TV vs. A Cold2_I and II	TV vs. A Cold2_II and III
h	0	0	1	1
p	0.485	0.436	0.000	0.001
N	75 vs. 76	75 vs. 76	75 vs. 76	75 vs. 76
Δ	**TV vs. B Cold1_I and II**	**TV vs. B Cold1_II and III**	**TV vs. B Cold2_I and II**	**TV vs. B Cold2_II and III**
h	0	0	1	1
p	0.213	0.142	0.000	0.000
N	75 vs. 73	75 vs. 73	75 vs. 73	75 vs. 73
Δ	**TV vs. C Cold1_I and II**	**TV vs. C Cold1_II and III**	**TV vs. C Cold2_I and II**	**TV vs. C Cold2_II and III**
h	0	0	0	0
p	0.545	0.788	0.651	0.659
N	75 vs. 73	75 vs. 73	75 vs. 73	75 vs. 73

Comparison is made between the first visit, TV (no treatment for Cold1 or Cold2), and later visits A, B, C. As desired in a measure, all of the no-treatment conditions do not differ over time. The effect of the analgesic is significant only in the diminished responses of SCL to Cold2 in conditions A and B (and not in Cold1 conditions or in placebo C).

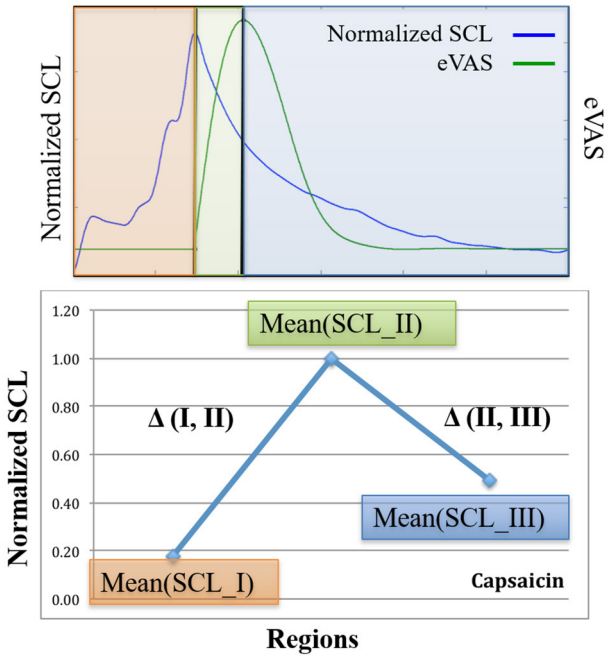

FIGURE 6 | Notation for Capsaicin regions and deltas.

Moreover, the new measure's significant differences cannot be attributed simply to day differences, as the study further confirms the presence of no such difference across the days during Cold1, before the analgesics are applied (where all h = 0).

Capsaicin Pain

For each visit, each participant experiences one inoculation of Capsaicin to elicit pain. We make similar tests for the Capsaicin pain model. The big difference in these tests is that now we have only one inoculation per visit in the second half of each visit, so we cannot compare pre- and post-drug within the same day's visit. Instead, we must evaluate the harder challenge of comparing across visits that have analgesics (A, B) and that don't have analgesics (TV, C), even though these occur on different days. Thus, to find a reliable, repeatable result for Capsaicin pain is a greater test of the new measure's robustness than when the measures are made within the same day's session.

We first characterize the changing pattern of mean SCL across Capsaicin regions I, II, and III, as this is a different kind of pain than cold pressor pain. The notation we use for Capsaicin is described in **Figure 6**, where we again denote the three regions relative to the time of onset of the needle (pain stimulus) and to the (subjective) eVAS-reported peak pain. Again, we show the eVAS in green, and we use its peak to separate regions II and III. The SCL is shown in blue, having an earlier peak at the end of the anticipatory region, the moment when the needle is applied. The first time we saw this "anticipatory" peak preceding the actual reported peak-pain we were surprised (This occurred in a prior pilot study with flu-shot data, where it occurred the moment before the needle was inserted). We find in this clinical trial data that such a peak sometimes occurs as in the example shown here, and sometimes occurs closer to the self-reported peak pain. This phenomenon is another reason to explicitly measure Region I.

In **Figure 7**, we show the mean normalized SCL for all four types of visits, during each of the three regions of the Capsaicin experience. First, we see a general arc across all the visits TV (blue), A (red), B (green) and C (purple): The anticipatory period

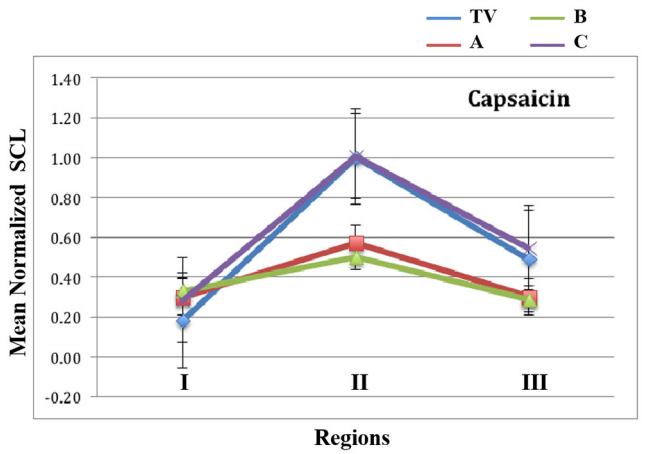

FIGURE 7 | Mean values of normalized SCL within regions I, II, and III for capsaicin. TV = blue, C = Purple, and the analgesics A = red, B = green. Data combine four limb locations from n=23 participants; bars are stderr.

TABLE 3 | Capsaicin pain: comparisons of normalized mean SCL in treatments A, B, and C vs. the training visit, TV, within each of regions I, II, III.

	TV vs. A		
	I	**II**	**III**
h	0	1	1
p	0.409	0.000	0.041
N	75 vs. 76	75 vs. 76	75 vs. 76
	TV vs. B		
	I	II	III
h	0	1	1
p	0.109	0.000	0.021
N	75 vs. 73	75 vs. 73	75 vs. 73
	TV vs. C		
	I	II	III
h	0	0	0
p	0.110	0.323	0.478
N	75 vs. 73	75 vs. 73	75 vs. 73

We see the hypothesized reduction of pain confirmed in regions II and III of the analgesic treatments A and B (h=1 for both). We also see the "no difference" hypothesis confirmed for the placebo treatment C, and for all anticipatory periods (before the needle is inserted).

is relatively low in all visits. In the middle, we see that the peak pain eVAS period is also in the region usually having the peak SCL. This property of this measure is seen to be robust for all four types of visits. Finally, the slow recovery of eVAS is similar to that of the SCL during Region III.

The capsaicin pain experience is divided into three regions: the anticipation of pain just before the injection, the needle pain with the injection and its feeling of pain increasing to a peak value, followed by the feeling of the burning wearing off slowly as the peak pain subsides.

As hypothesized, the proposed new measure shows that the arc of the three-region response is less severe for the two analgesic conditions A and B than for the non-analgesic TV and C conditions.

We examine the statistical significance of the measure by comparing the mean values of EDA in regions I and II and in regions II and III of treatments A, B, and C with those of the training visit TV. We apply the Wilcoxon rank sum test to examine the mean values within each region, across the conditions (**Table 3**).

Results show that the mean values of normalized SCL for region II are significantly different between A and TV, and between B and TV, and *not* between C and TV. These results are all in the hypothesized direction: The analgesics reduce the pain response more than placebo, which reduces it more than no treatment.

Importantly, the changes in our new measure are not due to an "overall reduction in SCL" from the analgesic because we confirm (**Table 3**) that the SCL is not different in Region I, before the onset of the pain stimulus, even though all treatments had been given more than 90 min before this time.

Note that these statistically significant effects, for both the capsaicin and the cold pressor pain models, were found before the team doing the data analysis was unblinded to conditions A, B, and C.

DISCUSSION

This paper presents a novel measure of characterizing pain response based on objectively identifying the time of onset of a pain stimulus, subjectively identifying the peak-pain moment (from the numerical peak of a self-reported eVAS), and then quantifying physiological changes in the three regions delineated by these two time points. The resulting quantitative measures are shown to provide statistically significant discrimination validating the effectiveness of well-known analgesics compared to placebo and no-treatment.

Does the new method work better than self-reported eVAS data alone, and if so, when might it replace it? Before showing this quantitative comparison, it is worth noting some of the features of traditional psychophysical methods of pain assessment, which request a report of subjective pain experience using either one-dimensional pain scales (like eVAS) or multidimensional pain scales; for a more complete picture of self-reported evoked pain response, various assessments must be used (6, 27–30). Different aspects of pain response such as psychological distress or anticipation, pain intensity, and pain recovery interact in complex ways to determine the perception and experience of pain (31–33). The proposed new three-region model summarizes these complex interactions quantitatively with three physiological values that capture meaningful differences in pain level across treatments both within a day and across days; however, the topic of how the measures of the three regions map to the many subjective aspects of pain, and their assessments by multidimensional pain scales, is not currently captured by the method in this paper. These topics remain a challenge for future studies.

The new method adds some complexity to eVAS: eVAS is only one modality, while combining it with EDA integrates a second. Thus, we directly test: Is the new combined EDA + eVAS method performing objectively better than using only eVAS across this data set? The answer is yes, as seen in **Figure 8** where we show the mean eVAS values across conditions TV, A, B, and C for Cold1 vs. Cold2, and **Tables 4**, **5** where statistical significance comparisons are made. We also tested the max eVAS values and the area under the curve of the eVAS, and the results were similar, with the only case of statistically significant discrimination occurring with eVAS and treatment B in the case of Cold pain, and with no significant discrimination with the Capsaicin model using eVAS alone. Another eVAS measure we tested was the time from the start of the stimulus to the max eVAS, which was found to not differ significantly across the visits for a given pain model. While this means that it fails as an eVAS measure at discriminating treatments that reduce pain, it does add strength to its use in our proposed new measure for defining Region II's endpoint, as it is stable across visits and across treatments. Thus, the value a person gives with the eVAS, used alone, fails to discriminate any pain reduction of using pregabalin for the more than 70 visits where eVAS measures compared Cold1 to Cold2, the latter after the treatment was given, and also fails to discriminate any pain reduction of either treatment with the Capsaicin model.

A limit of using only eVAS is also seen in the marginally significant difference found between TV and analgesic B (oxycodone) across visits when all measures are based on using only eVAS (**Table 5**). However, the three-region EDA + eVAS measure clearly distinguished both visits A and B from visits C and TV. Thus, the novel method outperforms traditional eVAS in a randomized control trial evaluating the cold-pressor model of deep pain. The new model is specific to pain (using eVAS to anchor the peak moment of pain) while being more discriminative than eVAS, even with a relatively small number of participants.

Note that it is possible that with a much larger number of participants, the difference between TV and A may eventually become significant when using only eVAS, as might at the same time the difference between TV and C. However, adding more patients adds substantial trial costs, and it requires inflicting pain on a lot more people. If the difference (Cold2 vs. Cold1) using the analgesic with a larger number of participants becomes significant, yet no greater than placebo's significance, then the drug will not be deemed effective. In contrast, the proposed new pain measure is significant in its discriminatory ability when using a small number of participants; thus, it may reduce both clinical trial costs and the ethical costs of inflicting pain on larger numbers of people.

EDA is traditionally recognized as responding to pain, but not specifically to only pain: It usually increases when the sympathetic nervous system is activated, with the fight or flight response, as well as with uncertainty and anticipation (16). Thus, an increase in EDA is usually expected with both anticipation of and experience of painful experiences. Using direct brain stimulation, researchers have shown that EDA is activated ipsilaterally by stimulation of the amygdala, anterior and posterior hippocampus, and anterior cingulate (34), key

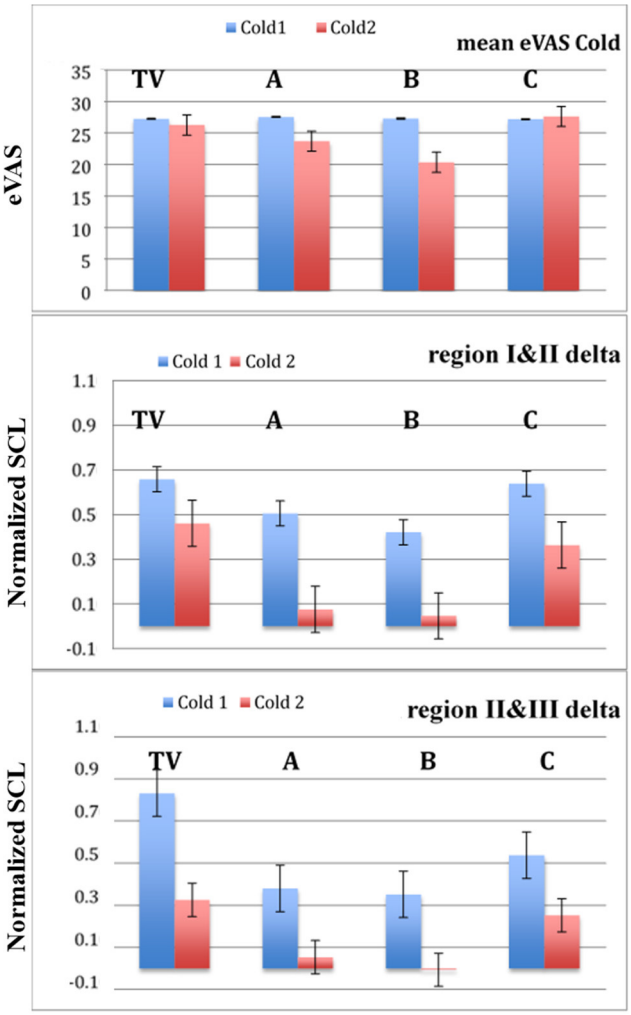

FIGURE 8 | The mean values of eVAS alone do not successfully discriminate both effective analgesics. The deltas comparing normalized SCL values across adjacent regions are more discriminatory. Cold 1 = blue, Cold2 = red, n = 23 participants. Bars are stderr.

regions involved in processing pain, emotion, and anxiety. Thus, the EDA measure in general will be sensitive to pain, changing when pain happens; however, it is not specific to only pain; for example, a significant increase in EDA may occur with brain activity during and soon after a grand mal seizure (35); also, it has been observed to be elevated at the time of death in the minutes following a grand mal seizure (36).

Our work here addresses the problem of specificity in several ways. First, like with early work showing that skin conductance responses reflect infant responses to painful heel sticks (37), we measure the level of pain objectively in a situation known to cause experience of pain, as would be expected in a clinical study, hospital, or recovery room, where contextual factors that might influence the pain measure are both observable and controllable. Second, and novel to our work, we specifically anchor the regions to-be-quantified by using the time point where the person