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Objective Correlate of Subjective Pain Perception by Contact Heat-Evoked Potentials

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Abstract: The method of pain-evoked potentials has gained considerable acceptance over the last 3 decades regarding its objectivity, repeatability, and quantifiability. The present study explored whether the relationship between pain-evoked potentials and pain psychophysics obtained by contact heat stimuli is similar to those observed for the conventionally used laser stimulation. Evoked potentials (EPs) were recorded in response to contact heat stimuli at different body sites in 24 healthy volunteers. Stimuli at various temperatures were applied to the forearm (43°C, 46°C, 49°C, and 52°C) and leg (46°C and 49°C). The amplitudes of both components (N2 and P2) were strongly associated with the intensity of the applied stimuli and with subjective pain perception. Yet, regression analysis revealed pain perception and not stimulus intensity as the major contributing factor. A significant correlation was found between the forearm and the leg for both psychophysics and EPs amplitude.

***Perspective:** Contact heat can generate readily distinguishable evoked potentials on the scalp, consistent between upper and lower limbs. Although these potentials bear positive correlation with both stimulus intensity and pain magnitude, the latter is the main contributor to the evoked brain response.*

***Key words:** Evoked potentials, pain, contact heat.*

The difficulty of objective, quantifiable pain measurement presents an obstacle in the investigation of mechanisms of pain processing and in the assessment of pain therapy. Brain imaging via fMRI and PET have demonstrated an association between perceived experimental pain and the extent of brain response for certain cortical and subcortical structures.[1,6,9,18,26,38,41]

Pain-evoked potentials (pain EPs) reflect the endogenous processing of pain information in response to an external stimulus. The most widely used technique to generate pain EPs is via application of very short radiant heat stimuli delivered by a laser that selectively stimulates small-caliber sensory fibers, allowing synchronization of the stimuli with EEG recording (time-locking).[7,8,25] Several studies have shown a decrease in the amplitude of the N2-P2 component of the pain EPs in conditions of painful neural lesions with sensory deficit, such as postherpetic neuralgia,[44] trigeminal neuralgia,[17] syringomyelia,[42] central neuropathic pain,[22] and neuropathic pain of unknown etiology.[46] Moreover, a decrease in the pain EP vertex amplitude in response to analgesic interventions has been found in parallel to a decrease in reported pain scores.[3,14,29-31,40] Yet, an increase in the pain EP that might have been expected in pain syndromes expressing hyperalgesia has not been reported, except in the case of fibromyalgia.[23,28]

The positive correlation between the level of perceived pain scores and the EPs amplitude in studies using laser stimulation[11-13,33] supports the hypothesis that pain EPs may serve as a quantitative tool for pain measurement of the normal nervous system. In turn, it has been demonstrated that this relationship does not hold in (i) experimental setups that change perception, such as with the administration of benzodiazepines[47] or shifts in attention,[5,34] and (ii) some clinical conditions, such as neuropathic pain syndromes.[22,43,46] Therefore, the use of pain EPs as a method for the objective evaluation of pain perception requires that the user is aware of the conditions under which measurements are taken and that ap-

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propriate interpretation of the data is subsequently performed.

The present study examined the relationship between the neurophysiological and the psychophysical aspects of a recently introduced type of somatosensory stimulation, using contact heat stimuli. Since a strong similarity was found between the cerebral dipoles activated by contact heat stimuli and by laser pulses,[45] it was expected that a similar stimulus-response relationship would prevail. The main goal of this study was to define and characterize the contact heat EPs by measuring the interrelations between stimulus intensity, perceived pain, and EP amplitudes. An additional aim was to evaluate the patterns of response in the upper limbs as compared with the lower limbs.

Materials and Methods

Subjects

The participants in this study were 24 healthy volunteers (10 men and 14 women, aged 20–52 years). The Rambam Medical Center institutional review board approved the study protocol, and consent was obtained from each subject.

Stimulator

We used a contact heat-evoked potential stimulator (CHEPS; Medoc Ltd., Ramat Yishai, Israel), with a round thermode that contacts a cutaneous area of 572.5 mm^2 (27-mm diameter). The thermode is composed of a heating thermofoil (Minco Products, Inc., Minneapolis, MN), which is covered with a 25-μm layer of thermoconductive plastic (Kapton, thermal conductivity at 23°C of 0.1 to 0.35 W m^{-1} K^{-1}). Two thermocouples are embedded 10 μm within this conductive coating, which contacts the skin directly, thus providing an estimate of the skin temperature at the thermode surface. The thermofoil permits a heating rate of up to 70°C/sec, and the Peltier device allows a cooling rate of 40°C/sec.[24]

Procedure

Subjects sat comfortably in a quiet room with an ambient temperature near 22°C. We applied heat stimuli, at 1 of 4 peak intensities of 43°C, 46°C, 49°C, and 52°C per block, to the proximal volar forearm of the nondominant hand, followed by 2 blocks of 46°C and 49°C stimuli, applied to the ipsilateral medial aspect of the lower leg. To avoid sensitization, the temperature of the initial block of stimuli was randomly determined between the

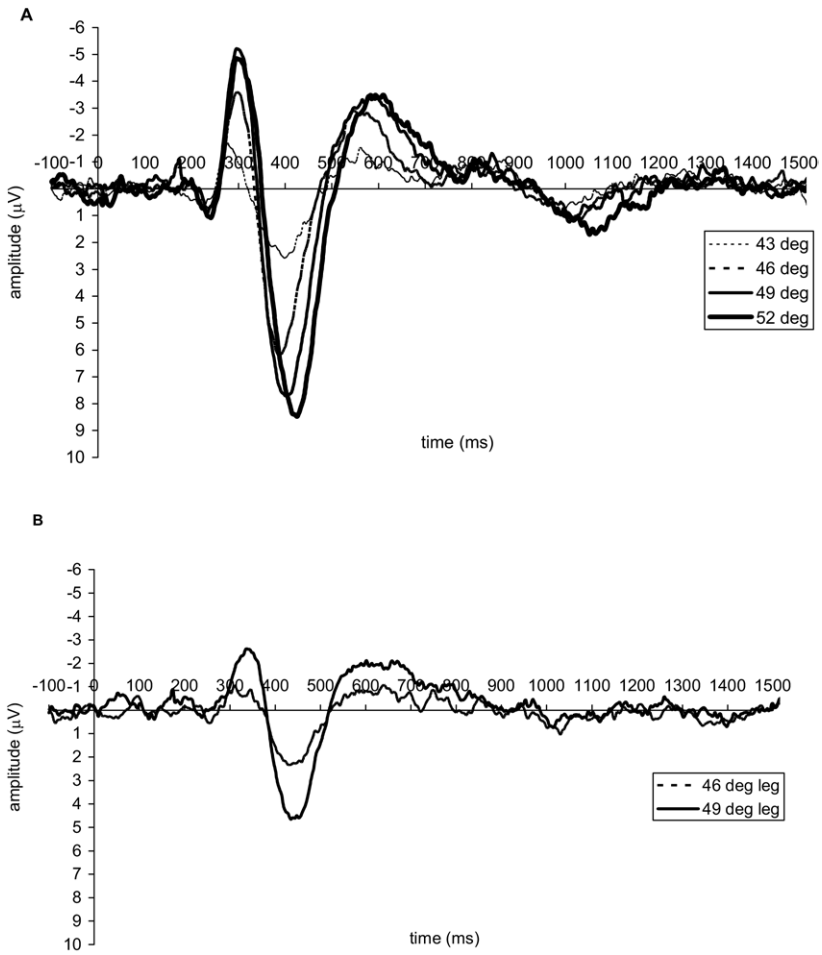

Figure 1. Grand averaged waveforms (n = 24) evoked by forearm **(A)** and leg **(B)** contact heat stimulation. EEG recordings were performed at the Cz position.

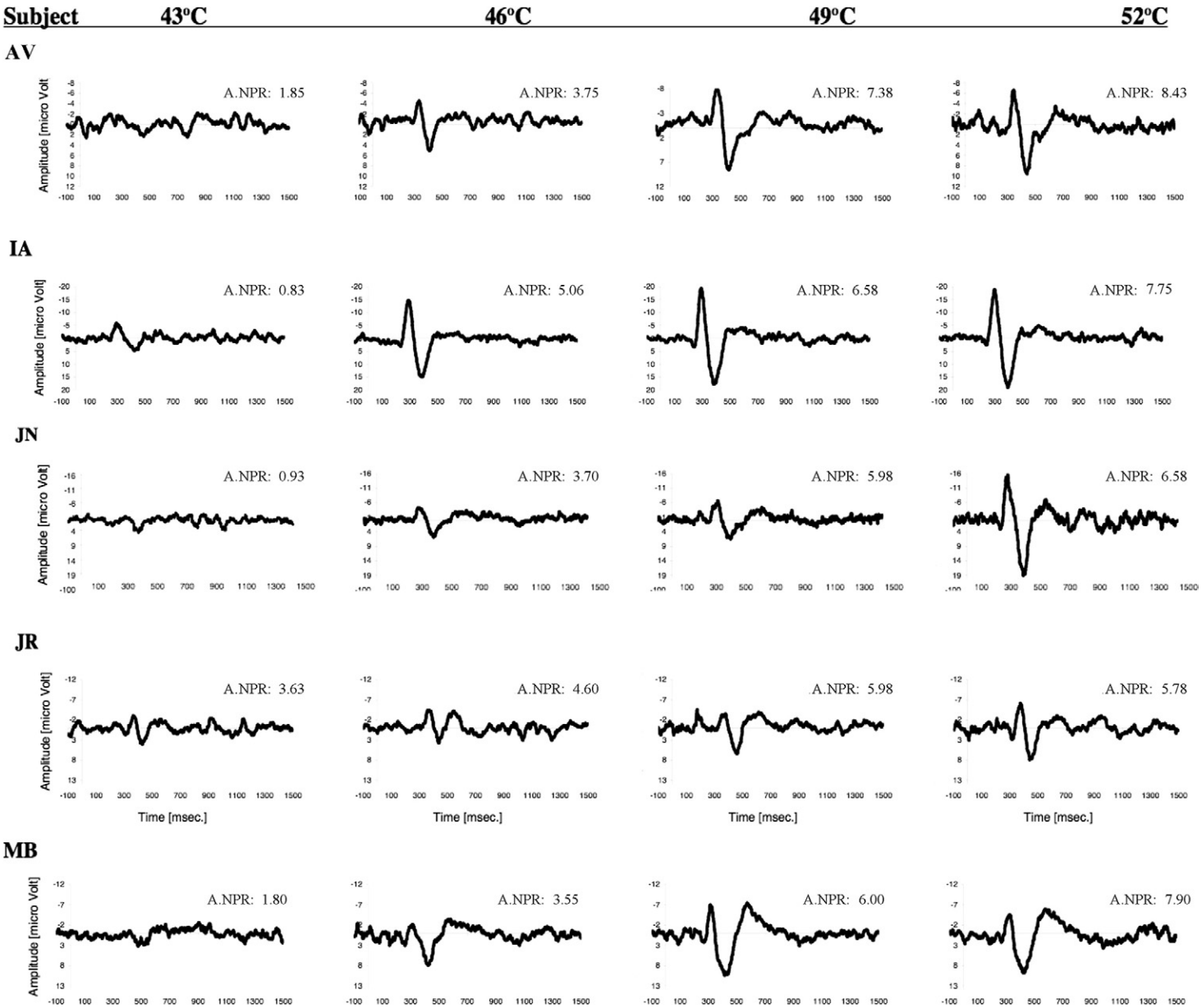

Figure 2. Waveforms and heat perception/heat pain scores to the 4 temperatures applied to the forearm in 10 randomly chosen subjects. The *y*-axis represents voltage; *x*-axis represents latency. A.NPR, Averaged Numerical Pain Rating.

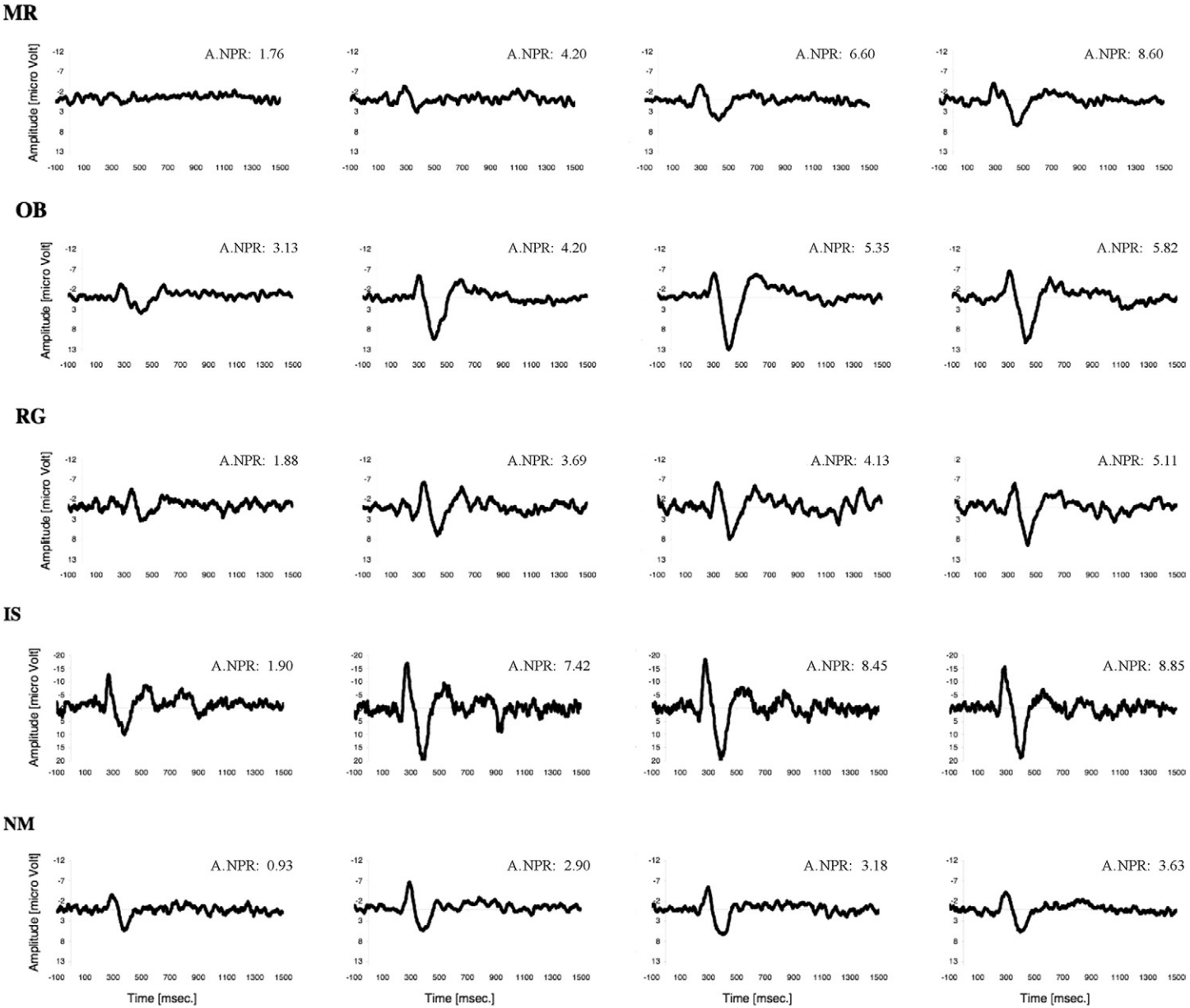

Figure 2. Continued

Table 1. Contact Heat-Evoked Potentials Characteristics [Mean Amplitude and Latency of Both Positive (P), Negative (N), and Peak-to-Peak Components] and Pain Scores (±SD) to Contact Heat Stimuli Delivered to the Forearm (a) and Leg (b)

A.	*43°C*	*46°C*	*49°C*	*52°C*
N	−3.1 ± 2.6 μV	−5.8 ± 4.2 μV	−7.1 ± 5.0 μV	−7.0 ± 4.2 μV
	309.2 ± 34.2 ms	310.6 ± 34.8 ms	312.20 ± 27.8 ms	320.4 ± 28.4 ms
P	3.6 ± 2.7 μV	7.8 ± 5.1 μV	9.3 ± 5.2 μV	9.6 ± 4.3 μV
	388.3 ± 48.8 ms	400.9 ± 43.0 ms	405.3 ± 31.4 ms	425.4 ± 31.0 ms
Peak-to-peak	6.7 ± 4.6 μV	13.7 ± 9.1 μV	16.4 ± 9.7 μV	16.7 ± 8.0 μV
Pain	2.2 ± 1.2	4.0 ± 2.1	5.6 ± 2.3	6.5 ± 2.3

B.	*46°C*	*49°C*
N	−3.4 ± 3.1 μV	−5.0 ± 3.4 μV
	374.2 ± 56.4 ms	340.5 ± 31.2 ms
P	5.1 ± 3.8 μV	6.0 ± 3.7 μV
	468.6 ± 43.4 ms	451.1 ± 34.3 ms
Peak-to-peak	8.5 ± 6.5 μV	11.0 ± 6.6 μV
Pain	2.6 ± 1.8	4.4 ± 2.7

lower temperatures (43°C and 46°C), followed by randomly delivered temperatures of 49°C and 52°C. Baseline temperature was 32°C; subjects were blinded to stimulation sequence. The temperature increase and decrease rates for all 4 intensities were the same: 70°C/sec and 40°C/sec, respectively. The average latency from onset to peak temperature was 147 ± 4.5 ms, 188 ± 7 ms, 214 ± 3 ms, and 242 ± 5 ms for 43°C, 46°C, 49°C, and 52°C, respectively. The average pulse duration (from onset to offset) for all for intensities was 509 ± 11 ms, 571 ± 8 ms, 746 ± 8 ms, and 798 ± 8 ms for 43°C, 46°C, 49°C, and 52°C, respectively. Due to the possible effect of the thermode pressure on the perception of delivered heat intensity, the researcher who was conducting the experiment was instructed specifically to try to maintain constant thermode pressure during the stimulation.

Each stimulation block consisted of 20 constant-intensity stimuli applied to the same body region at interstimulus intervals of 10 seconds, with a 15-minute break between blocks. The thermode was moved to an adjacent area after each stimulus, in a random manner, within an approximate area of 6 × 8 cm. To avoid initial expectation effects and to reduce the novelty effect on heat-evoked potentials, we applied several training stimuli before beginning evoked potential recording.

Subjects were asked to rate their pain perception for each stimulus on a 0 to 10 numerical ranking scale 3 seconds after stimulus onset. A level of 4 was defined as the threshold for a pinprick-like pain sensation.

Contact Heat-Evoked Potential Recording

Contact heat-evoked potentials (CHEPs) were recorded from Fz, Cz, Pz, C3, C4, T7, and T8. This was done by using an electrode cap (Easy Cap Q40; FMS Falk Minow Services, Herrsching, Germany), without external reference (the average of all selected channels was used as the reference). The EPs was recorded and analyzed on a Quick Amp EEG system (Brain Products GmbH, Munich, Germany) within a 0.15 and 100 Hz bandpass at sampling rate of 500 Hz. The impedance from all electrodes was kept below 5 kΩ. Visual artifacts were controlled by an artifact rejection program, with 50 μV set as a maximal allowed voltage step. Each recording epoch of 2100 ms included a period of 100 ms for baseline correction of single trials. Stimulus onset was marked by a TTL pulse from the CHEPs to the Quick Amp at the beginning of the temperature increase.

Data Analysis

The recorded EEG data from Cz was analyzed. The amplitude of negative (N2) and positive (P2) vertex potentials was measured from baseline to peak, and the peak-to-peak N2-P2 amplitude was then calculated. The latencies were measured at the peak of response. The determination of N2 and P2 amplitudes was based on our previous experience with contact heat pain potentials.[24] We identified the peak in a time window of 200 to 400 ms for the N2 component and a time window of 300 to 500 ms for the P2 component. For the identification of N2 and P2 components after leg stimulation, we used the time windows of 300 to 500 ms and 400 to 600 ms, respectively. Statistical analyses were performed with JMP (SAS Institute, Cary, NC). The effect of temperature on pain scores were analyzed by 1-way mixed model ANOVAs. Temperature was treated as a nominal factor with multiple levels, in part because only 2 temperatures were used in testing the leg. The effect of stimulus temperature and pain rating on pain EPs was assessed by regression analysis, where both factors were expressed as continuous variables. Pearson correlation analyses were used to explore the associations between EP amplitude and pain scores at various temperatures; correlation analyses were conducted after data were averaged across all of a participant's responses to a specific temperature. In addition, these correlations were performed to evaluate the relationships between pain scores and EP

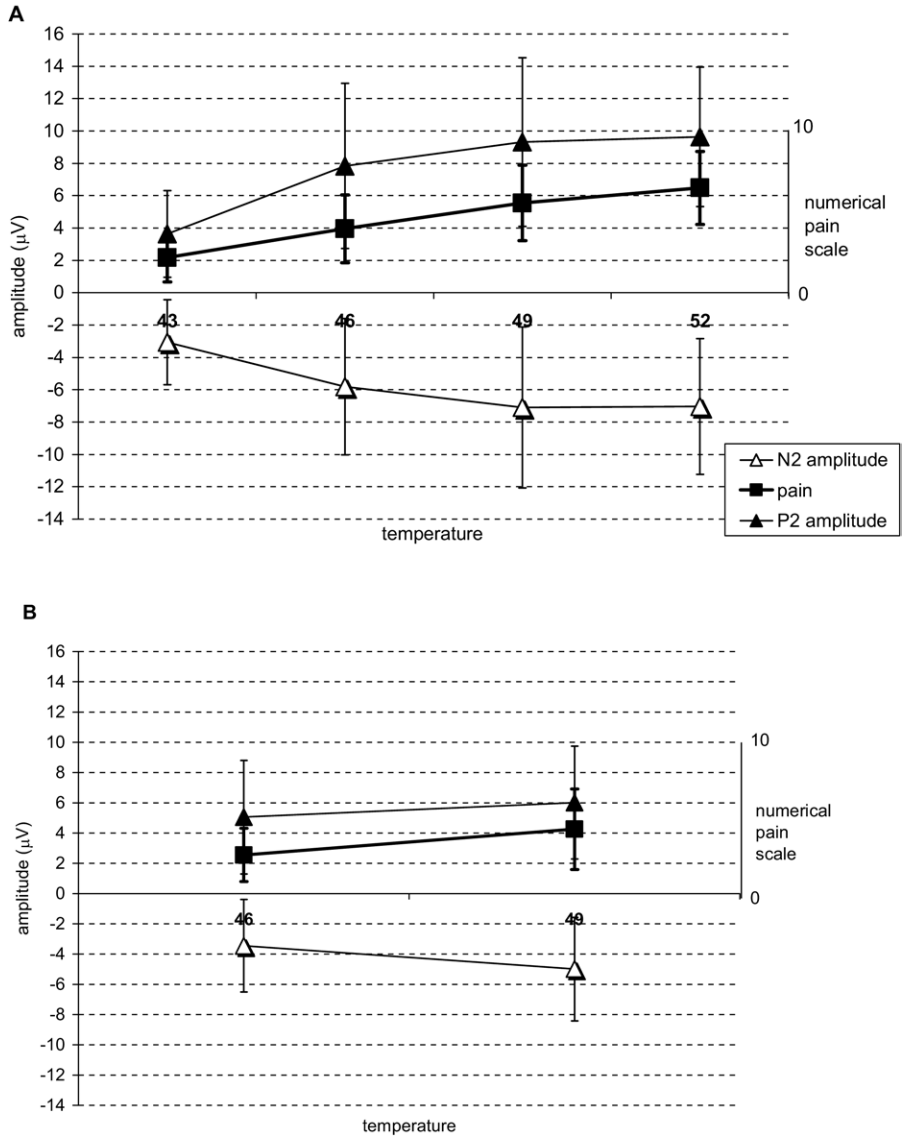

Figure 3. Averaged EP amplitudes of both negative and positive components and heat perception/heat pain scores for the 4 temperatures applied to the forearm **(A)** and 2 temperatures applied to the leg **(B)**.

data in the leg and the forearm. The data are presented as mean ± standard deviation. Statistical significance was defined as $P \leq .05$.

Results

The application of contact heat stimuli resulted in well-perceived heat sensation, ranging from nonpainful heat (at 43°C) to strong pinprick-like heat pain sensation at higher temperatures. Stimulus temperatures were found to have a significant effect on pain scores for both the forearm ($P < .0001$) and for the leg ($P < .0001$) (1-way mixed-model ANOVA). For the forearm, a post hoc Tukey test indicated that the pain scores produced by each temperature were all significantly different from each other ($P < .05$).

Brief contact heat stimulation evoked well-defined potentials, which were more distinct visually in response to temperature intensities that evoked pain sensation (above 43°C for the forearm and above 46°C for the leg) (Fig 1 and Fig 2). The average pain ratings, N2 and P2 amplitudes and latencies, at each temperature are presented in Table 1.

Regression analyses indicated that the amplitude of both N2 and P2 components increased significantly ($P = .0006$ and $P < .0001$, respectively) as a function of applied temperature. Similarly, the amplitude of both components increased significantly ($P < .0001$ for each) as a function of pain score (Fig 3).

To assess the simultaneous impact of both stimulus intensity and pain scores, and their interaction on each of the EP components evoked at the forearm, another regression analysis was performed, with stimulus intensity (temperature), pain score, and their interaction as independent variables. The results (Table 2) demonstrate

Table 2. Linear Regression Model Assesses the Contribution of Pain Perception and Stimulation Temperatures on the Amplitude of N2 and P2 Components of Contact Heat-Evoked Potentials (Forearm Stimulation)

Term	*Estimate*	*SE*	*P*
N2 Amplitude			
Intercept	−0.918962	4.752621	.8471
VAS	−0.852332	0.19368	< .0001
Temperature	−0.023666	0.113445	.8352
VAS × temperature	0.0289064	0.029044	.3230
P2 Amplitude			
Intercept	−4.971594	5.908541	.4023
VAS	0.970202	0.236569	< .0001
Temperature	0.1753956	0.140677	.2157
VAS × temperature	−0.027943	0.037106	.4539

NOTE: Subject was included as a random effect in these models.

Pain magnitude but not stimulus intensity was the correlate of both components' amplitude.

that the magnitude of evoked pain but not the stimulus intensity or the interaction was the major factor influencing the EP amplitudes of both components ($P <$ .0001). The absence of a main effect for stimulus intensity or of an interaction between stimulus intensity and perceived pain indicates that the previously suggested effect of temperature is subsumed within the effect of pain itself on the degree of EP response.

To establish the relationship between the pain EPs and perceived pain, separate correlation analyses were performed for each of the stimulus temperatures delivered at forearm and leg. To minimize individual score variability, all of the responses derived from a single temperature were averaged for each subject. Results of this analysis indicated that the pain scores positively correlated with both N2 and P2 amplitudes evoked by stimulation at painful heat intensity (46°C and higher for the forearm, 49°C for the leg). The *r* and *P* values of the pain scores—amplitude correlation—are presented in Table 3. The individual data scatter plots for the 49°C stimulus are presented in Fig 4.

To assess the interbody region consistency of the EP responses, we plotted the pain scores and EP responses evoked in the forearm and in the leg (no leg EPs were detectable in 4 of 24 subjects, after stimulation with 46°C; in 2 of these subjects, no EPs were observed to the stimulation with 49°C). Our results demonstrated a significant correlation between the EPs from the leg and forearm (Fig 5), confirming our assumption about the individual within-subject consistency of pain EP responses. Similarly, the pain scores to forearm and leg stimulations were significantly correlated (46°C forearm-to-leg: $r = .45$; $P = .028$; 49°C forearm-to-leg: $r = .63$; $P = .001$).

Discussion

The results of our study demonstrate that well-defined pain EPs can be induced by contact heat skin stimulation using various temperatures applied to different body sites. EP amplitudes were strongly associated with the intensity of the applied stimuli as well as subjective pain perception, but the perceived pain was the major factor influencing brain response, as indicated by ANOVA. For each of the pain-generating temperatures the amplitudes of both N2 and P2 components were significantly associated with the magnitude of perceived pain. In addition, the significant correlation between the forearm and the leg indicates consistency of the EP response across body sites.

The relationship between the amplitude of brain potentials evoked by laser stimuli and perceived pain was described about 30 years ago by the Carmon group.[10,33] This relationship was further clarified by Carmon et al, who applied 2 laser intensities evoked painful and nonpainful sensations, demonstrating that the increased magnitude of subjective sensation was accompanied by increased EPs amplitude, mostly based on the increase of the positive component.[11] Similar to LEPs, Chen et al demonstrated the relationship between the painfulness

Table 3. Correlation Between Pain EPs Amplitude [Negative (N) and Positive (P) Components] and Pain Scores at Each Stimulus Temperature Applied on the Forearm (a) and Leg (b)

a. Site	*43°C*	*46°C*	*49°C*	*52°C*
Forearm				
N	$r = -.01$	$r = -.52$	$r = -.61$	$r = -.39$
	NS	$P = .0089$	$P = .0014$	trend ($P = .0576$)
P	$r = -.33$	$r = .52$	$r = .54$	$r = .38$
	NS	$P = .0089$	$P = .0061$	trend ($P = .0652$)

b. Site	*46°C*	*49°C*
Leg		
N	$r = -.60$	$r = -.43$
	$r = .006$	$P = .047$
P	$r = .75$	$r = .70$
	$r = .0002$	$P = .0003$

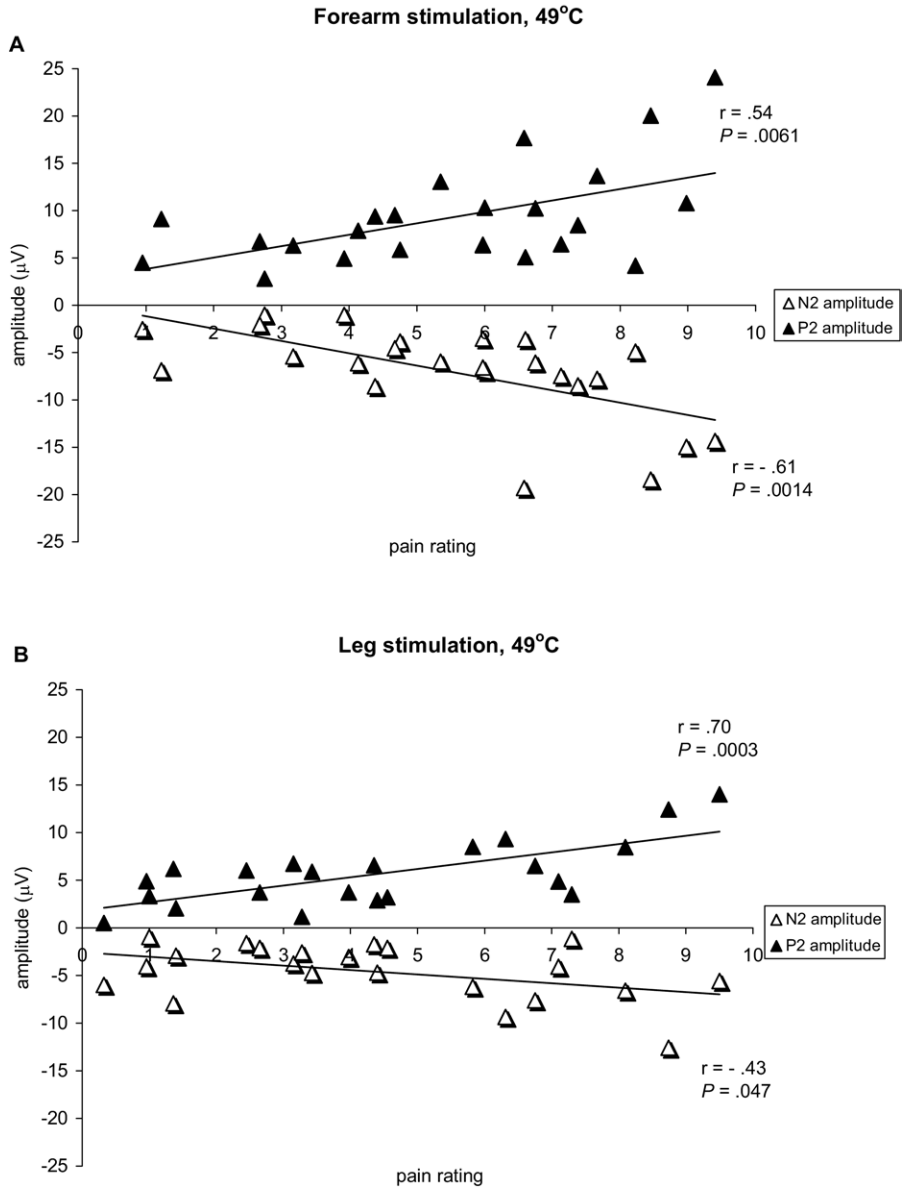

Figure 4. Correlation of evoked potential amplitudes with individual pain scores evoked by stimulation temperature of 49°C applied to the forearm **(A)** and leg **(B)**.

of dental electrical stimulation and EPs amplitudes in response to 5 different intensities, for both positive and negative late components.[13] Moreover, the pain perception was found to have more of an impact on EPs amplitude as compared with the stimulus intensity.[11-13]

The relationship between pain EPs and perceived pain magnitude is widely accepted and has become a postulate in clinical pain neurophysiology. However, the results of the above described studies were based on relatively small sample sizes (up to 10), and the association between pain and amplitude were based on the combined data of multiple sessions among the same few subjects. In the present study, the individual character of the association between pain experience and evoked brain response was tested in a sample of 24 subjects from whom we obtained single responses to each applied temperature.

We have noted that the association of pain and stimulus intensity on one hand and CHEP amplitude on the other, while consistent for the lower temperature, failed at the highest temperature of 52°C. This might be related to a ceiling neuronal effect for SII responses to increasing painful laser stimuli.[21] In line, the level of SII activity was a matter attentional modulation with markedly increased SII activity from the low attention to the mid-attention tasks, whereas further increase of attention demands was not accompanied by additional enhancement of SII activity.[35] The similar scalp distributions of CHEPs and LEPs[45] led us to suggest that SII located dipole is likely to contribute to the N2-P2 component. It might be, therefore, that under the specific stimulation conditions of this study, a ceiling effect of SII for the 52°C attenuated further increase of pain EPs amplitude.

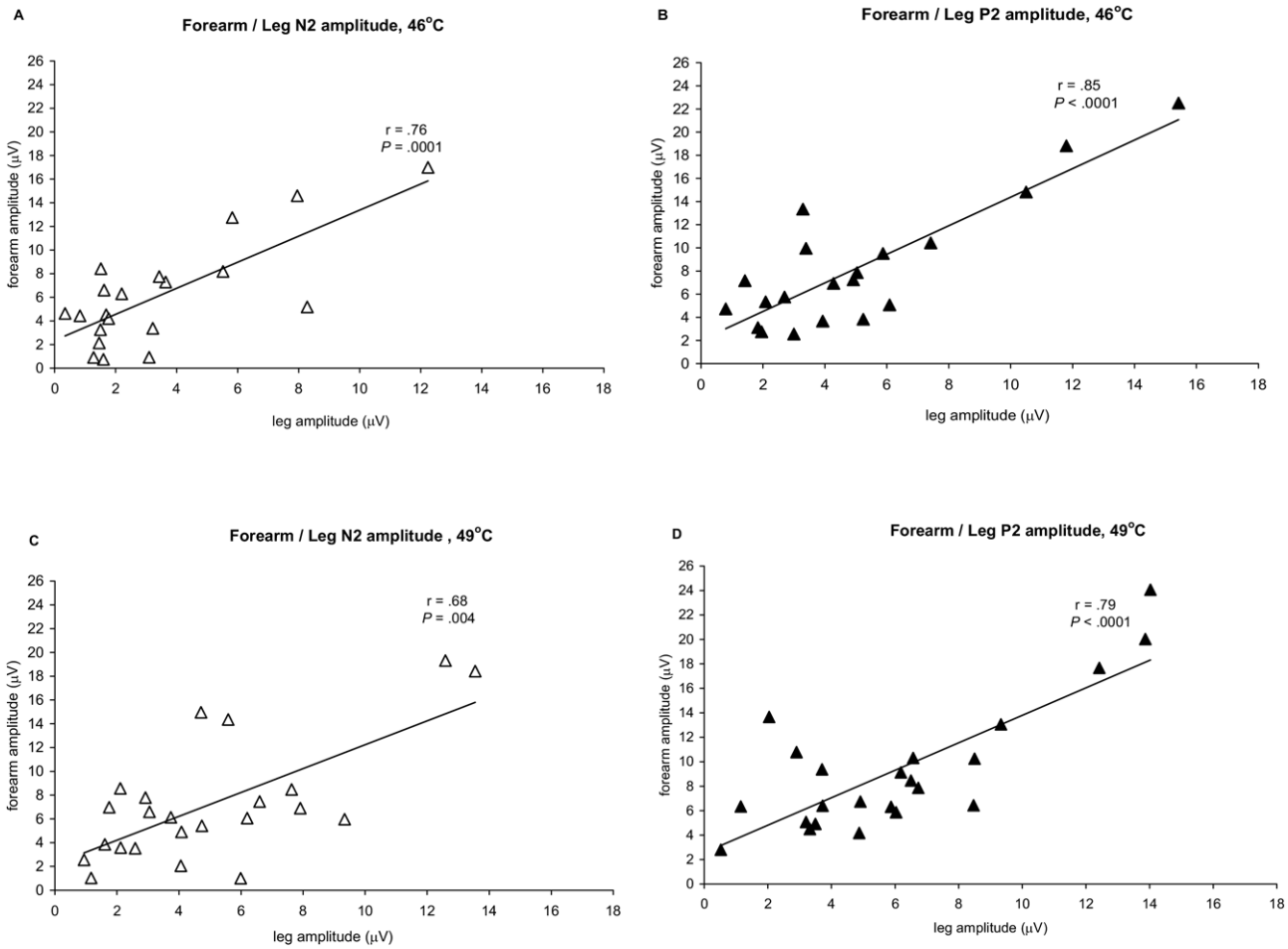

Figure 5. Significant correlation of evoked potentials amplitudes to the forearm and leg stimulation (N2, absolute values, open triangles; P2, filled triangles) evoked by stimulation temperature of 46°C (**A** and **B**) and 49°C (**C** and **D**).

The novelty of the present study is the comprehensive approach to evaluating the association between the subjective and the objective pain dimensions. This study applied not only a wide stimulus intensity range, from non-noxious to moderately noxious sensations, but also used 2 different body sites, using a novel method to evoke pain EPs by rapidly increasing contact heat stimuli.[15,16,24,27,45] Both the contact and the laser stimuli generate a heat pain sensation and are believed to generate the same brain activity. Indeed, the waveform characteristics, the maximal EPs amplitude over vertex, and the association between the pain ratings and amplitudes over the 3 applied intensities[15] are very similar to the currently reported data and point to the reliability of contact heat EPs. Despite the lack of direct studies comparing LEPs and contact heat EPs, these same characteristic criteria may be applied, and significant similarity of results would be expected.

The biophysics underlying the heat-skin interactions for contact heat and for radiant laser stimuli are quite different. For the laser, the temperature rises to several thousand degrees centigrade per second, allowing nociceptors activation within a few milliseconds. The resulting afferents activation is thus very synchronized and therefore allows the recording of good time-locked neuronal responses; the energy absorption is nearly complete, and transparency is very low. For contact heat, the increase in cutaneous temperature is much slower[32]; therefore, the peripheral and central neuronal responses are less synchronized. In addition, the extent of pressure between the probe and the skin, and the flatness of the stimulated skin determine energy transfer.[37] The uncertainty regarding the extent of heat transfer into the depth of the skin was raised by Baumgärtner et al,[4] suggesting a less efficient heat penetration for the contact stimulus. The fact that appropriate EPs are consistently recorded in response to contact heat stimuli legitimates the use of this stimulation methodology.

Although heat pain produced by LEPs has been extensively studied, the small stimulation area (3–5 mm diameter) and very short stimulus duration for most laser devices (<50 ms, though pulse width up to 200 ms were reported) may be a disadvantage, making the stimulus somewhat unnatural in comparison to the general real life experience of thermal pain. We believe that if a longer stimulus that still produced a clear EP could be given, then the advantage of a sound psychophysical stimulus would override the disadvantage of a less dis-

persed barrage of impulses that generate this waveform. Another disadvantage of laser stimulation is the frequent appearance of superficial burns lasting up to several weeks, occurring mainly after the use of a CO_2 based laser. In addition, the use of laser stimulator poses difficulties in operation and the constant need for calibration, as well as the safety precautions required for laser use.

Contact heat stimulation, on the other hand, offers some advantages. First, the use of a larger stimulation area evoked a higher number of primary afferent nociceptors, evoking brain responses of a higher signal-to-noise ratio, in addition to the more natural pain sensation quality. Indeed, an increase in pain sensation with enlargement of the stimulation area was described for the pain threshold[19] and suprathreshold heat stimuli,[39] at within- and between-dermatome levels.[20,36] Furthermore, increased cortical activity for larger thermode size was confirmed in brain imaging experiments.[2] An additional advantage of this method is selective stimulation of C-fibers and evoking the ultra-late EPs without any additional manipulation.[24]

One potential drawback of the contact heat method relates to latency jitter—that is, the effect of the relatively slow rate of stimulus rise, on peak latencies of averaged waveforms. Whereas stimuli of the same temperature will result in EPs with similar latency, longer latencies will result from higher target temperatures, simply because as stimulus temperature keeps rising, the evoked potential's amplitude keeps rising as well, generating waves of higher amplitude and consequent longer latency. In our study, in which averaging was only done within the same temperature stimuli, this factor is not relevant, though future contact heat EPs-based studies will have to take into consideration this procedure-based relation between stimulus temperature and wave latency.

The demonstrated significant correlation of pain rating and of EP components to pain stimuli applied on upper and lower limbs indicates the consistency of individual pain EP responses and the reliability of this stimulation method. The reliability of LEPs was demonstrated in terms of correlation to body parameters.[44] By assessing the responses over different body sites, we conclude that despite wide variability in pain experience, the magnitude of pain psychophysics and EP responses has some intra-individual consistency, serving a target for the assessment of pain treatment/pharmacological interventions.

The present study findings expand our understanding regarding brain processing of the pain experience. The fact that the subjective response to noxious stimuli was associated with the objective measure in response to this pain event, regardless of the methodology used for stimulation, further supports the role of pain EPs in the study of mechanisms of human pain processing.

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