Research Paper

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Normative data for Aδ contact heat evoked potentials in adult population: a multicenter study

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Abstract

There has been a significant increase over recent years in the use of contact heat evoked potentials (CHEPs) for the evaluation of small nerve fiber function. Measuring CHEP amplitude and latency has clinical utility for the diagnosis and assessment of conditions with neuropathic pain. This international multicenter study aimed to provide reference values for CHEPs to stimuli at 5 commonly examined body sites. Contact heat evoked potentials were recorded from 226 subjects (114 females), distributed per age decade between 20 and 79 years. Temperature stimuli were delivered by a thermode (32°C-51°C at a rate of 70°C/s). In phase I of the study, we investigated side-to-side differences and reported the maximum normal side-to-side difference in Aδ CHEP peak latency and amplitude for leg, forearm, and face. In phase II, we obtained normative data for 3 CHEP parameters (N_2P_2 amplitude, N_2 latency, and P_2 latency), stratified for gender and age decades from face, upper and lower limbs, and overlying cervical and lumbar spine. In general, larger CHEP amplitudes were associated with higher evoked pain scores. Females had CHEPs of larger amplitude and shorter latency than males. This substantive data set of normative values will facilitate the clinical use of CHEPs as a rapid, noninvasive, and objective technique for the assessment of patients presenting with neuropathic pain.

Keywords: CHEPs, Nociceptive evoked potentials, Normative data

1. Introduction

The clinical evaluation of patients complaining of pain requires documentation of lesion or dysfunction in peripheral or central somatosensory nerve pathways, as a step toward diagnosing a neuropathic condition. In this domain, conventional electrodiagnostic tests seldom provide direct specific data. Therefore, neurophysiologists may instead rely on the assessment of nociceptive cerebral evoked potentials. These can be obtained by applying radiant heat, delivered through laser beams[5]; contact heat, conveyed through thermofoil thermodes[11]; or specially designed electrodes using electrical stimulation.[28,29] Examples of the utility of these tools can be found in the literature for postherpetic neuralgia,[49] trigeminal neuralgia,[15] meralgia paresthetica,[40] central neuropathic pain,[21] facial neuropathic pain,[47] Fabry disease,[50] HIV,[35] hepatitis C infection,[56] painful diabetic neuropathy,[10,34,36] and other conditions presenting with neuropathic pain,[8,37,45,55] as well as in studies of healthy volunteers.[1,30,46]

Nociceptive evoked potentials have been recommended by various authors for the diagnosis of neuropathic pain and the evaluation of thermal pain pathways.[17,25,31,32] Although laser evoked potentials (LEPs) have been the most studied to date, they require precautions to avoid eye damage and skin burns. This is not the case for contact heat evoked potentials (CHEPs), which have been shown to have a similar dipolar modelling with brain electrical source analysis to those evoked by radiant heat (laser) stimulation.[52] The clinical utility of CHEPs is currently well accepted in many situations: they have been used to detect early Aδ fiber damage in diabetic patients with minimal neuropathy,[37,54] to support the clinical diagnosis in incomplete spinothalamic tract damage[26,27,51] and to predict the pain-relieving effect of spinal cord simulation.[38] However, the lack of standardized methods and robust reference values might have been major drawbacks limiting the clinical use of CHEPs.

The most common condition for which the clinician may require use of such neurophysiological techniques is the assessment of small fibre polyneuropathies.[7,18] In these neuropathies, pain is usually the main symptom and physical examination may not show conclusive signs. Both decrease of CHEP amplitude and increase of CHEP latency correlate with the reduction of intraepidermal nerve fiber density in neuropathic conditions.[1,7,8] The analysis of CHEPs can, therefore, be considered an objective method of assessing neurological deficits, particularly when skin biopsy to determine intraepidermal nerve fiber density is not available. We reasoned that the neurophysiologist facing this challenge should have normative data available to evaluate the suspected lesion or dysfunction in Aδ fibre pathways.

Previously, 2 groups reported CHEP normative values, one for Asian[9,12] and another for Dutch populations.[31] These studies in

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relatively small numbers of individuals, limited to upper and lower limb stimulation sites, demonstrated the correlation of CHEP amplitude and latency with age and gender. In the study reported here, we recruited a larger number of healthy subjects to obtain reference data for a population in sites across continents. The primary aim of our study was to determine the CHEP normative data to stimulation of face, upper and lower limbs, and cervical and lumbar spines. We also investigated the possibility of laterality effect and determined the maximum normal limits for side-to-side differences in CHEP latency and amplitude.

2. Methods

2.1. Subjects

Healthy adult subjects of both genders participated in this multicenter international study. The investigations were conducted in 2 phases in 5 institutes: (1) Neurology Department, Universidade Federal Fluminense, Rio de Janeiro, Brazil; (2) Neurology Department, Rambam Health Care Campus and Technion Medical School, Haifa, Israel; (3) Anesthesiology Department, Osaka University, Osaka, Japan; (4) Neurology Department of the Hospital Clinic, Barcelona, Spain; and (5) Neurology Department, Mayo Clinic, Scottsdale, AZ. Identical systems were used in each study center. Formal training was provided at investigator meetings with principal investigators and senior technicians from each center, which defined a protocol of clinical evaluation in healthy subjects to rule out signs of peripheral neuropathy and to standardize technical aspects of the study, including the experimental procedure and familiarization with the stimulation and recording systems. Study design required each center to test 48 subjects equally distributed for decades between 20 and 79 years. The study was conducted in 2 phases. During phase I, each center was to test 12 subjects (6 males, 6 females; 1 male and 1 female per age decade) bilaterally; phase II was based on the assessment of 36 subjects (18 males, 18 females; 3 males and 3 females per age decade) tested unilaterally. The participants were recruited from hospital volunteers and through advertisements. All subjects underwent a neurological examination following the protocol established at the investigator meetings.

The exclusion criteria were as follows:

(1) Known chronic or systemic neurological or psychiatric diseases.
(2) Findings suggesting a neurological disorder on neurological examination. Specifically, subjects were questioned about feeling of any sensory phenomenon, either positive (paresthesias, pain) or negative (hyposthesia).
(3) Chronic use of central nervous system (CNS) drugs (eg, antidepressants, psychoactive, antiepileptic drugs), medications that can cause peripheral neuropathy (eg, isoniazid, vincristine, taxanes, thalidomide, statins), or analgesics (except for aspirin).
(4) Alcohol use of more than 14 units per week, or alcohol/recreational substance intake during the 24 hours before the test.
(5) Communication barriers or cognitive dysfunction.

All participants underwent a standardized interview before signing the consent form. The study conformed to the Helsinki Research Convention rules and was approved by the ethics or institutional research board committee of each institute.

2.2. Experimental setup

We chose 5 stimulation sites, described below. The location sites of the thermode are shown in **Figure 1**.

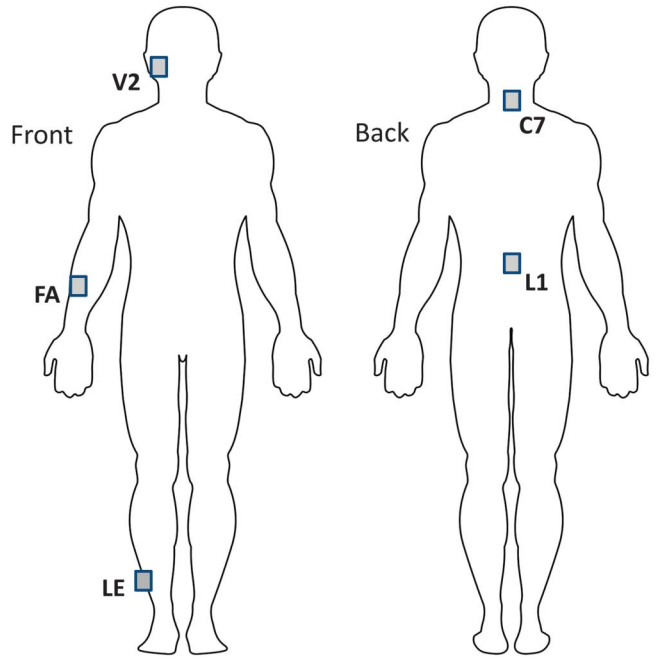

Figure 1. Stimulation sites: FA, forearm; LE, leg; V2, cheek; C7, cervical spine, over C7; L1, lumbar spine, over L1.

(1) Forearm (FA): At the distal volar forearm, within an area delimited by the upper border of the distal third of the forearm and the ulnar styloid.
(2) Leg (LE): At the lateral surface of the distal leg, within an area delimited by the upper border of the distal third of the leg and the lateral malleolus.
(3) Cervical spine (C7): At the spinous process of C7.
(4) Lumbar spine (L1): At the spinous process of L1.
(5) Face (V2): At the mid-cheek, below the malar bone.

We chose to use the sites described because they gave us a distribution of data from several parts of the body, are comfortable sites for the subject not to undress, and provide adequate skin surfaces for keeping the thermode in full contact with the skin and for changing the stimulation site slightly between stimuli. Although the feet are commonly involved in polyneuropathies, we chose not to use dorsum of the feet in our study because of the possibility to have no responses in some normal subjects, particularly in elderly subjects.

2.3. Stimulation parameters

Contact heat stimuli were delivered by increasing the temperature from baseline (32°C) to a fixed temperature of 51°C at a rate of 70°C/s with a round thermode of 27-mm diameter that covered an area of 572.5 mm^2 (PATHWAY, Sensory Analyzer System; Medoc, Israel). The stimulator was programmed to deliver a series of 7 stimuli, which were applied with an interstimulus interval of 8 to 12 seconds, onset-to-onset. The position of the thermode over the skin was slightly varied after each stimulus. Two stimulus series were given for each body site (on both the right and left sides in phase I and on either the right or the left side, chosen at random, in phase II). The randomization procedure excluded consecutive testing at the same site. A pause of more than 30 seconds was required between each series of stimuli. Three additional, manually triggered, stimuli were permitted to complement the results obtained after each series of 7 stimuli in case of

artifacts or other stimulation or recording interference. The investigators took care to keep the thermode pressure light and uniform over the stimulated skin surface, in accordance with the training protocol.

Before testing, every subject underwent familiarization with the study by receiving 2 stimuli per each tested body site. Subjects unable or unwilling to tolerate the stimulus at any body site were considered screening failures.

2.3.1. Contact heat evoked potential recording

All recordings were performed at a room temperature between 20°C and 24°C. Subjects were lying, prone, supine, or on their side, as appropriate for the stimulation site. Contact heat evoked potentials were recorded from electrodes placed at Fz, Cz, T3 (for right hemibody stimulation), or T4 (for left hemibody stimulation), referenced to linked earlobes. The ground electrode was placed on the nasion. An electrooculographic electrode was placed near the right eye to detect unwanted blinking. We used the MEB-9400 EMG/EP system (Nihon Kohden, Japan) to record and analyze the waveforms using a sensitivity of 20 μV/div and a bandpass filter between 0.1 and 50 Hz. Impedance was tested at least twice during the experiment and was always kept below 5 kOhm.

Subjects were asked to provide a mean pain score at the end of each series of 7 stimuli, using the 0 to 10 verbal numerical pain scale.

2.3.2. Contact heat evoked potential analysis

We decided to analyze the recordings from Cz because this was the site where the Aδ CHEPs consistently exhibited the largest amplitudes. Subject data were included in the statistical analysis for all stimulation sites in which we recorded at least 10 well-identified evoked potential waveforms, free from blinking, eye movement, or muscle artifacts, within the 250- to 800-ms time window after stimulus onset. We determined the latency of the N_2 and P_2 peaks, and the N_2P_2 amplitude, on each individual trace and obtained the average waveform from all artifact-free traces. Data were obtained bilaterally in phase I and unilaterally in phase II.

2.3.3. Statistical analysis

We collected, collated, error-checked, and organized data on CHEPs recorded from Cz, after stimuli to 5 body sites in 5 study centers in both genders and 6 age groups, between 20 and 79 years. To minimize measuring errors, we excluded from the analysis recordings with N_2P_2 amplitude less than 5 μV, which would have been of similar amplitude as the background electroencephalographic activity. The effect of laterality (left vs right side differences) was explored using the data collected in phase I, designed specifically to evaluate whether laterality effects needed to be taken into consideration for further analyses. Data from bilateral V2, FA, and LE were analyzed using *t* tests. To this aim, we had to exclude some data from one of the centers because of technical issues unrelated to the normative values or statistical processing. To determine whether there were significant side-to-side differences, we calculated the coefficient of repeatability[4] as the value of 1.96 times the SD of the differences between pairs of readings, taken in both sides in the same subject under otherwise equivalent conditions. The coefficient of repeatability was determined separately for N_2 and P_2 latencies, and N_2P_2 amplitude, as the 95% precision limit for differences between right and left side stimulation. Using this approach, we obtained the maximum expected difference between sides due to chance. Subsequently, any statistically significant difference from chance would indicate significant differences between sides.

Data from phases I and II were combined for normative value determination. Analyses were performed separately on N_2 latency, P_2 latency, and N_2P_2 amplitude for 5 recording body sites (V2, FA, LE, C7, and L1) in males and females.

Analysis proceeded in a planned stepwise fashion:

(1) Regression analysis began with models using age and gender, as well as their interaction as independent variables. These models were used for initial hypothesis tests regarding age and gender effects, and as the basis for development of reduced statistical normative models, that is, efficient models containing only statistically significant effects which contribute to amplitude and latency. Examination of regression diagnostics (particularly residuals) indicated that use of a logarithmic transformation was required for amplitude data to meet regression analysis requirements; therefore, a $\log_{10}$ (N_2P_2 amplitude) transformation was used in this and subsequent analyses.
(2) As none of the interactions was significant, analysis continued with models using both age and gender as independent variables.
(3) If these models did not show significant associations of gender in addition to age with the CHEP parameters, we ran another model with both genders combined, using only age as factor.
(4) If no significant age association with CHEP parameters was found either, then analyses proceeded considering possible gender-only differences, based on the overall distribution of data for that parameter, with determination of parametric and nonparametric confidence intervals.

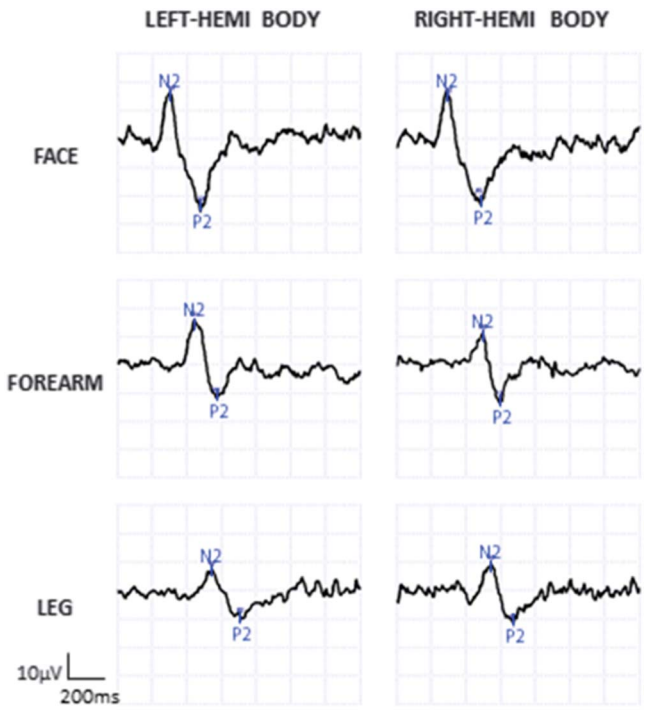

Figure 2. Examples of individual Aδ waveforms of contact heat evoked potentials recorded from Cz (referenced to linked earlobes) in response to stimuli delivered to right and left sides for each of the stimulation sites listed in the left column. Note the similarities between waveforms from both sides and the progressive increase in latency and decrease in amplitude from face to leg.

Table 1

Data on laterality.

Stimulation site	Parameter	Right	Left	CR
V2	N_2 latency	354.7 (71.0)	362.2 (69.5)	88.7
	P_2 latency	487.1 (67.1)	497.6 (80.0)	122.3
	N_2/P_2 amplitude	25.2 (13.1)	26.1 (12.6)	15.0
FA	N_2 latency	467.0 (43.1)	463.7 (48.9)	65.7
	P_2 latency	591.3 (90.3)	593.8 (69.3)	78.6
	N_2/P_2 amplitude	23.8 (14.9)	23.9 (14.6)	13.0
LE	N_2 latency	514.7 (65.5)	529.5 (56.9)	159.8
	P_2 latency	641.3 (77.2)	648.7 (77.7)	162.5
	N_2/P_2 amplitude	17.5 (9.8)	19.5 (12.1)	10.5

Data are the mean and 1 SD value (in parenthesis) for N_2 latency, P_2 latency, and N_2/P_2 amplitude in face, forearm (FA), and leg (LE) for right and left sides. CR, coefficient of repeatability. There were no significant side-to-side differences (paired *t* test; $P > 0.05$ for all comparisons).

(5) If no significant gender-only differences were found, determination of parametric and nonparametric confidence intervals would be based on the distribution of data for that parameter, collapsed across gender, with determination of parametric and nonparametric confidence intervals.

At each stage of regression modeling, outliers were identified using the Cook D statistic, with the conventional outlier threshold definition of >4/N. Such outliers were removed from each model to improve fit.

To summarize, any of the regression analyses that yielded significant models ($P < 0.05$) with significant fit for both age and gender were used to determine the following:

(1) Back-transformed from log10 values, the 95% 2-tailed normative value cutoffs for N_2P_2 amplitude data, and
(2) The 1-tailed 95% upper normative value cutoffs for N_2 and P_2 latency data.

Those parameter combinations that did not exhibit age dependence were retested in models based only on gender. Those parameter combinations that did not exhibit gender dependence were retested in models based only on age. The same procedure of outlier removal and determination of significance was used to yield final models and normative limits based on those models. For those parameter combinations that exhibited neither age nor gender dependence, we calculated the 95th percentile scores.

The relationship between CHEP parameters and subjective pain scores was examined for each body site separately for males and females. Gender differences were assessed using median tests and are presented as medians and minimal–maximal values range.

Finally, we ran an analysis to assess diagnostic reproducibility of data among centers. For this, we applied the normative cutoff criteria to the original data obtained from each site to determine the proportion of abnormal values with respect to the total number of recordings for each site. This was considered an index of diagnostic reproducibility of data among centers, which was used for comparison by χ^2 tests.

3. Results

Two hundred forty subjects were recruited for the study. There were very few screening failures, ranging between 0 and 2 subjects per center. However, because of problems with recording, storing the data, or the presence of artifacts, the final study sample was based on data from 226 subjects (114 females). Specific aspects of the analysis were based on a different number of subjects, reported as "N" in the following paragraphs.

3.1. Side-to-side differences

Responses from left and right sides were assessed in 48 subjects (24 females) in V2, FA, and LE stimulation sites. Representative waveforms of Aδ CHEPs are shown in **Figure 2**. The repeatability observed between sides is reported in **Table 1** for all variables and all stimulation sites after pooling together subjects of different ages and genders. In no parameter was significant side bias found for any stimulation site. Side-to-side repeatability was generally narrower for amplitude than for latency at all sites. There were also no significant between-sides differences in pain scores.

3.2. The influence of age and gender on contact heat evoked potential characteristics

Females had significantly lower height than males (161 ± 7.0 vs 174 ± 7.7; *t* test, $P < 0.001$) and overall they had higher amplitudes and shorter latencies than males (**Table 2**).

The regression analysis procedure for determination of normative values showed no significant gender × age interaction

Table 2

Influence of gender, age, and the interaction of gender × age on contact heat evoked potential parameters for each body site.

Parameter	Site	Female		Male		*P*		
		Mean	SE	Mean	SE	Gender	Age	Gender × age
N_2P_2 amplitude	C7	27.2	1.8	21.4	1.5	<0.0001	<0.0001	0.6408
N_2P_2 amplitude	Cheek	27.8	1.9	22.4	1.6	<0.0001	<0.0001	0.2102
N_2P_2 amplitude	Forearm	24.5	1.2	17.9	1.3	<0.0001	<0.0001	0.078
N_2P_2 amplitude	L1	26.5	1.9	19.2	1.5	<0.0001	<0.0001	0.1882
N_2P_2 amplitude	Leg	19.5	1.8	14.6	1.6	<0.0001	<0.0001	0.9968
N_2 latency	C7	400.2	3.9	407.1	4.1	0.2256	<0.0001	0.81
N_2 latency	Cheek	352.8	4.7	379.1	4.7	0.0001	<0.0001	0.5301
N_2 latency	Forearm	446.1	3.1	476.6	3.5	<0.0001	0.004	0.7134
N_2 latency	L1	438.7	3.9	452.0	4.0	0.0182	<0.0001	0.2574
N_2 latency	Leg	503.5	3.9	538.3	4.6	<0.0001	0.001	0.3592
P_2 latency	C7	531.6	3.8	543.8	4.0	0.0283	0.0002	0.4429
P_2 latency	Cheek	486.5	3.7	510.5	3.8	<0.0001	<0.0001	0.1101
P_2 latency	Forearm	558.0	3.8	597.9	4.3	<0.0001	0.004	0.8939
P_2 latency	L1	566.7	3.9	588.4	4.0	0.0001	0.0002	0.6548
P_2 latency	Leg	630.0	4.8	660.5	5.6	<0.0001	0.161	0.4581

Data are the mean and SEM for each parameter and stimulation sites listed in the left columns. All models were overall significant at $P < 0.01$. *P* values are given separately for gender, age, and gender × age interaction. C7, cervical spine; L1, lumbar spine.

for any parameter (**Table 2**). Subsequent planned regressions showed significant effects of age and gender on each of the CHEP parameters, of age only on L1 and C7 and of gender only on P_2 latency to leg stimulation. **Figure 3** shows the data plot for N_2 latency against age, separated for males and females for all stimulation sites except for C7 and L1, which are shown together for males and females. Similar distribution was observed for P_2 latency (graphs shown in **Figure 1** of the supplementary material, available online at http://links.lww.com/PAIN/A222). Data are not plotted for P_2 latency for leg stimulation, which was not dependent on age but on gender (Wilcoxon rank-sum test, $P = 0.0005$) and was not normally distributed. Its upper limit value (1-tailed 95%) was 738 milliseconds for females and 758 milliseconds for males.

Figure 4 shows the data plot for N_2P_2 amplitude against age, separated again for males and females. Simple inspection of data distribution shows a tendency to reduced amplitude and increased latency with increasing age. The percentage of outliers along all analyses ranged from 5% to 7%.

3.3. Pain ratings

The median pain ratings for the entire study population are presented in **Table 3** separated for females and males. In each group, the distribution of scores always included the 0 and 10

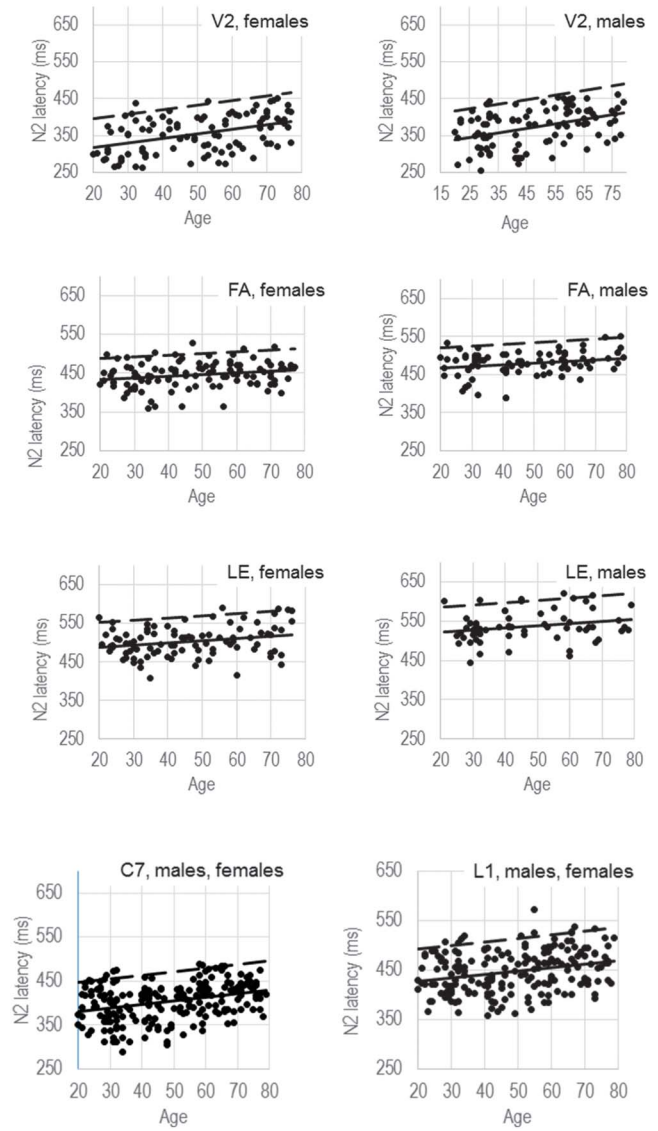

Figure 3. Normative values for N_2 latency for the 5 stimulation points as a function of age. Data are presented separately for males and females for all stimulation sites except for cervical spine (C7) and lumbar spine (L1) where there was no gender effect. The continuous line indicates the mean, and the broken line indicates 95% individual upper confidence limit. All model *P* values were significant at $P < 0.0001$. V2, face; FA, forearm; LE, leg.

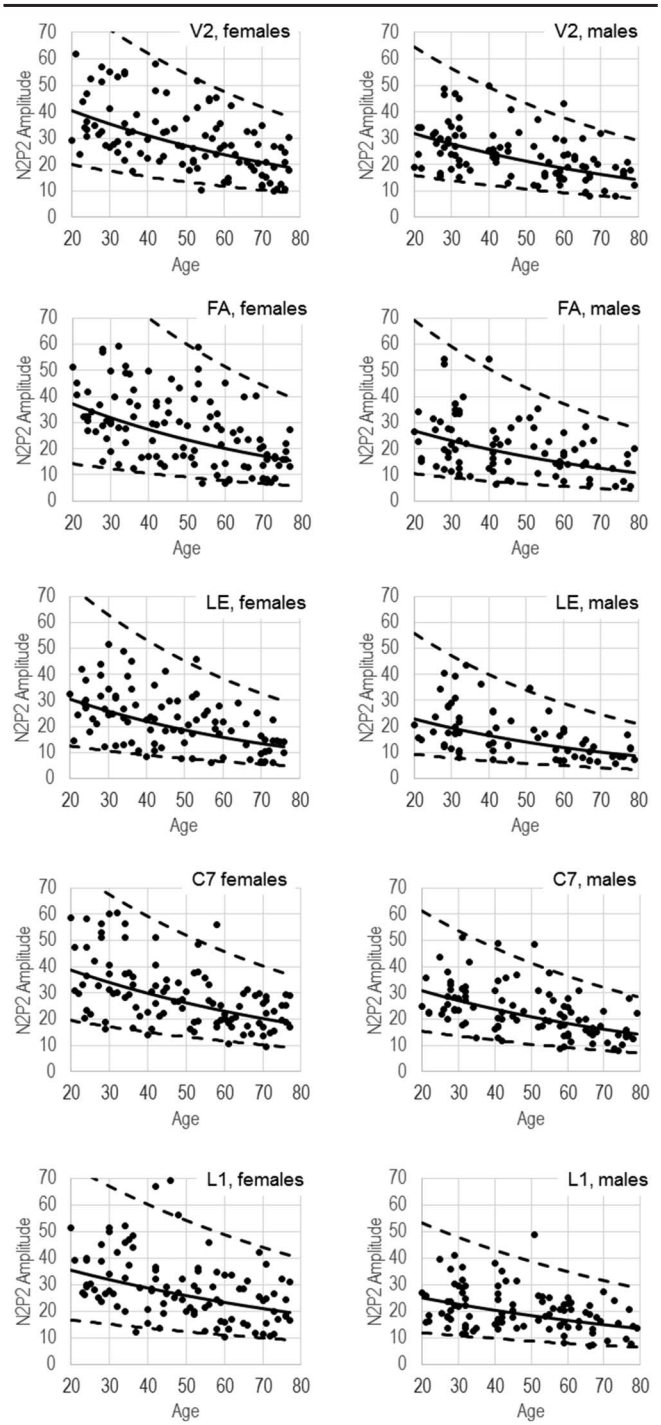

Figure 4. Normative values for N_2P_2 amplitude for all 5 stimulation sites, plotted against age, separated again for males and females. The continuous line indicates the mean and the broken lines indicate 95% individual upper and lower confidence limits. All model *P* values were significant at $P < 0.0001$. V2, face; FA, forearm; LE, leg.

Table 3

Subjective rating of pain.

Body site	Overall	Females	Males	*P*
C7	5.0 (3.0-7.0)	5.0 (3.0-7.0)	5.0 (3.0-6.0)	0.846
V2	6.0 (4.0-7.0)	6.0 (4.0-8.0)	5.0 (4.0-7.0)	0.068
FA	5.0 (3.5-6.0)	5.0 (4.0-6.0)	4.0 (3.0-6.0)	0.288
L1	5.0 (3.0-7.0)	5.0 (4.0-7.0)	5.0 (3.0-6.4)	0.300
LE	4.0 (2.1-5.0)	4.0 (3.0-6.0)	4.0 (2.0-5.0)	0.131

Data are the median pain ratings and the 25th to 75th percentile (within parenthesis) to stimuli applied to the body sites listed in the left column, C7, spinous process of C7; V2, cheek; FA, ventral forearm; L1, spinous process of L1; LE, distal lateral leg. The interquartile range is reported as the full range. In each case, it ranged from 0 to 10, the scale endpoints.

endpoints, that is, at least 1 subject reported the minimum possible value, and at least 1 subject reported the maximum possible value for the same stimulus. Overall, no gender differences were observed. Spearman correlation analysis revealed a significant correlation between higher pain scores and higher N_2P_2 amplitudes in males and in females for most body sites tested. No significant correlation was observed between the pain scores and CHEP latencies.

3.4. Diagnostic reproducibility of data among centers

The percentage of original cases beyond the limits of our own criteria ranged between 0% and 24%. Parameters and body sites in which there were significant differences among centers were N_2 latency in V2 and C7, and P_2 latency in L1, whereas there were no statistically significant differences in N_2 latency and N_2/P_2 amplitude for FA and LE (**Table 4**).

4. Discussion

We report normative data for CHEPs collected in a multicenter international study of a large group of adult subjects over a wide range of ages. These normative values refer to several body sites—face, upper and lower limbs, and cervical and lumbar spines, in both males and females. The analysis allows evaluation of both lower and upper limits of normality for N_2P_2 amplitudes and upper normal limits for N_2 and P_2 latencies. Most of the CHEP parameters were dependent on age and gender.

The application of these normative values to the raw data obtained at each center yielded some differences among centers, ie, not all centers would score the same in percentage of abnormal values. Indeed, we anticipated some degree of intercenter variability because evoked potential characteristics may be sensitive to demographic factors and subtle methodological differences in examination or evaluation, despite extensive investigator training. P_2 latency differences could be explained because of response jitter due to long conduction distance. However, the main (if not sole) generator of the P_2 component is located in the anterior cingulate cortex, the activity of which is strongly related to individual psychological characteristics.[41] Therefore, P_2 latency variability among centers could in part be due to differences in emotional and cognitive characteristics of subjects recruited in different centers, an aspect that would deserve further study.

Table 4

Ratio of values beyond norms across centers.

Body site	N_2P_2 amp (μV)	N_2 latency (ms)	P_2 latency
C7	20/194	11/203*	19/195*
V2	14/193	11/196*	13/194*
FA	6/195	13/188	17/184
L1	18/190	13/195	20/188*
LE	10/157	17/150	7/160*

Figures are the number of values out-of-norm for that particular site for each of the relevant parameters.
* Indicate significant differences among centers ($P < 0.01$).
FA, forearm; LE, leg; V2, cheek; C7, cervical spine; L1, lumbar spine.

The first phase of this project focused on the question of the effect of laterality (right vs left assessment) on CHEP parameters. Although the results of several studies did not reveal laterality effect of pain perception,[13,33,44] no systematic analysis has been published to date. The results of this study did not show hemibody laterality effect for any CHEP parameter or for pain scores. Contact heat evoked potential peak latencies were similar on both sides of the body and in accord with the expected afferent conduction time in Aδ peripheral nerve fibers and spinothalamic tracts. These findings are in line with those of Chen et al.,[12] who found no CHEP latency difference in response to stimulation of left and right forearms and suggest that unilateral assessment is both reliable and sufficient for normative data collection. Contact heat evoked potential amplitudes were also similar in both sides for all stimulation points. The upper limits of chance differences between sides in healthy subjects are also established. Differences in latency were rather wide. However, the combination between latency and peak amplitude data (the latter with much smaller repeatability index) may be clinically meaningful for the assessment of unilateral damage.

Contact heat evoked potential parameters are known to be affected by age. Prolonged latency and reduced CHEP or LEP amplitudes are associated with aging and correlated with the age-related changes in thermal pain perception. These results are in accord with previously published reports.[9,14,16,22,31] In our subjects, 26 of 30 CHEP parameters were dependent on subject age, showing amplitude reduction and latency prolongation as a function of age. This may be due to a mild neuronal loss or dysfunction in the peripheral nerves and/or a length-dependent desynchronization of the ascending nociceptive volleys. Therefore, including the age variable in the calculation of CHEP normative values is clearly important.

The normative values for CHEPs for this study were analyzed separately for males and females. The approach used here is based on the widely reported gender-related differences in experimental pain perception.[3,19,39] Several authors reported on higher amplitudes and shorter latencies of pain-evoked potentials in females.[9,31] Others, however, did not demonstrate gender differences.[12,48] The results of our study are concordant with the reports of Chao et al.[9] and Lagerburg et al.,[31] in which females responded with higher N_2P_2 amplitudes independently of the stimulated site. Further gender differences were found for most N_2 and P_2 latencies, which were consistently shorter in females than in males. Despite a significant gender effect on CHEPs, females and males reported similar pain scores. Furthermore, higher perceived pain was associated with larger amplitudes at all body sites tested, but was unrelated to gender. We might thus conclude that larger Aδ amplitudes in females are unrelated to perceived pain and may be attributed to activity in cortical and subcortical limbic brain structures, which might result in larger pain-evoked potentials amplitudes.[6,23,43,53]

4.1. Study limitations

It is worth noting that the reported normative values are valid only when using the equipment, setup, and stimulation parameters reported in this study. We did not evaluate C-fiber evoked potentials in this study, although C fibers are likely involved in the pathophysiology of small fiber neuropathies. The normative values reported here for Aδ CHEPs should be considered as

a set of reference data available for checking and comparison with values from healthy control subjects obtained at each laboratory. Particularities of each case and setup could lead to some divergence from these values. Using shorter interstimulus interval might potentially decrease the amplitude of pain-evoked potentials.[42] Furthermore, higher stimulation intensity contributes to larger CHEP amplitudes.[11,24] The stimulation intensity used in this study (51˚C) was bearable for most subjects, evoked reproducible waveforms, and therefore may be safely used for a wide range of clinical applications.

The effect of height on CHEP data has not been examined. In comparison to the effect of age, the influence of height has been explored to a lesser extent in pain neurophysiology. The few studies on this issue report disparate results, and it may actually be an inaccurate surrogate for nerve length. Although Truini et al.[48] and Lagerburg et al.[31] showed that the LEP latencies but not amplitudes evoked by foot and arm stimulation were positively correlated with height, Chen et al.[12] found no CHEP parameter to be associated with height, for stimuli to the dorsum of the hand and foot, forearm, and peroneal area. Gender differences in height might have contributed in our study to the latency differences reported according to gender.

5. Conclusions

The study of nociceptive evoked potentials has been recommended recently in guidelines for the assessment of neuropathic pain[17,25] and for the neurophysiological evaluation of temperature and pain pathways.[2,20,37] The large data set reported in this study on normative values will facilitate the implementation of CHEPs as a useful diagnostic test for a range of neurological and chronic pain conditions and, in particular, for the assessment of small fiber neuropathies.

Conflict of interest statement

Yelena Granovsky and Elliot Sprecher are paid consultants of Medoc Ltd. Praveen Anand has been a paid consultant of Medoc Ltd, but has not received funding for the preparation of this manuscript. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A222.

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