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Normative Values for Contact Heat and Cold Evoked Potentials

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ABSTRACT

Objective: To establish normative values for contact heat evoked potentials (CHEP) and cold evoked potentials (CEP), providing a reference for evaluating small fibre neuropathy (SFN) and spinothalamic tract (STT) function.

Methods: Thermal quantitative sensory testing and sensory nerve conduction studies were conducted for screening subjects. CHEP and CEP were recorded from the distal volar forearm and foot dorsum of 80 healthy participants (26–75 years) using a 1.2 cm^2 contact thermal stimulator (ramp: 300°C/s, heat: 60°C, cold: 10°C, duration: 200 ms). Age-grouped descriptive statistics were computed. Results between age groups, stimulation sites and sex were compared.

Results: Upper limb CEP showed >90% detection rates across all ages. N2P2 amplitudes were larger in upper compared to lower limbs (CHEP: $p = 0.032$; CEP: $p < 0.001$). N2P2 amplitudes decreased with age for CHEP ($p < 0.001$) and CEP ($p = 0.002$). Latencies did not vary between age groups or between limbs (CHEP: $p = 0.600$; CEP: $p = 0.351$).

Conclusions: This normative dataset will support the clinical integration of CHEP and CEP as an objective and non-invasive technique for evaluating small fibre and STT function.

Significance Statement: Normative data for contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) were established across age groups in healthy adults, marking a key step toward their use in routine clinical neurophysiology. CHEP and CEP N2P2 amplitudes were consistently larger in upper than lower limbs, with the greatest age-related decline in the feet. Notably, CEP from the upper limbs showed the highest visualisation rates (>90%) across all ages.

1 | Introduction

The diagnosis and follow-up of small fibre neuropathy (SFN) and spinothalamic tract (STT) lesions require specific tools that assess the function of thermonociceptive pathways (Devigili et al. 2008; Hubli and Leone 2024). Although multiple diagnostic techniques are available, each presents advantages and limitations.

Quantitative sensory testing (QST) provides a non-invasive approach to evaluating small fibre and STT function. However, its reliance on subjective patient feedback, susceptibility to attentional and emotional influences, lengthy testing duration and requirement for trained personnel substantially limit its clinical practicality (Rolke et al. 2006; Backonja et al. 2013). Conventional nerve conduction studies and somatosensory evoked potentials primarily assess large myelinated fibres and

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therefore lack sensitivity to small fibre pathology. In contrast, evoked potentials elicited by stimuli selectively activating thermosensitive skin afferents—including laser-evoked potentials (LEP), contact heat-evoked potentials (CHEP) and cold-evoked potentials (CEP) – enable the objective assessment of small fibre and STT function (Ragé et al. 2011; Garcia-Larrea and Hagiwara 2019). LEP have been validated for assessing SFN and STT dysfunction (di Stefano et al. 2017; Hatem et al. 2010; Valeriani et al. 2012), but their clinical use remains limited due to high equipment costs, safety considerations associated with laser use and the need for skilled operators.

Recent technological developments have introduced safe and portable devices for recording CHEP and CEP with thermal contact stimulation. CHEP demonstrates high diagnostic value for both SFN and STT assessment, as reduced amplitudes and prolonged latencies correlate with decreased intraepidermal nerve fibre density—an early indicator of Aδ fibre dysfunction (Atherton et al. 2007; Casanova-Molla et al. 2011; Chao et al. 2008). CHEP can also identify STT abnormalities that may be overlooked by conventional methods (Haefeli et al. 2014; Jutzeler et al. 2017; Scheuren et al. 2021). Similarly, CEP can effectively identify spinothalamic dysfunction (Perchet et al. 2023; Rosner et al. 2015) and small fibre impairment as in polyneuropathy and Fabry disease (Kersebaum et al. 2024).

Despite these advantages, widespread clinical implementation of CHEP and CEP has been constrained by the limited availability of stimulators capable of generating sufficiently rapid heating and cooling ramps required for synchronous thermonociceptor activation and time-locked cortical responses (Hüllemann et al. 2019; de Keyser et al. 2018; Leone et al. 2019). The 2018 introduction of the TCSII stimulator (QST.Lab) addressed this limitation by enabling ultrafast heating and cooling rates of up to 300°C/s, facilitating reproducible CHEP and CEP responses (de Keyser et al. 2018; Lejeune et al. 2023; de Schoenmacker et al. 2022). Portable, reliable and easy to operate, this device supports scalable applications in both research and clinical settings.

Although reference values exist for LEP and CHEP, none are available using the ultrafast TCSII stimulator and no normative data are available for CEP. This study therefore aimed to establish normative values for CHEP and CEP using a standardised stimulation protocol to facilitate their clinical application in diagnosing and monitoring small fibre and STT function.

2 | Materials and Methods

2.1 | Participants

This study was conducted with approval from the Comité d'Éthique Hospitalo-Facultaire des Cliniques Universitaires Saint-Luc (UCLouvain) (B4032022000138, approved on January 12, 2023) and adhered to the Declaration of Helsinki.

Healthy participants were recruited voluntarily between January and April 2023 via advertisements on the laboratory's website, university bulletin boards and word-of-mouth. Written informed consent was obtained from all participants prior to the start of the study.

Eligible participants met the following inclusion criteria: (1) aged between 26 and 75 years, (2) absence of any known neurological or metabolic disorders, (3) no current or historical acute/chronic nociceptive or neuropathic pain conditions, (4) no prior or current use of medications that could influence evoked potential recordings (e.g., analgesics, psychotropic substances, antiepileptics), (5) ability to complete the study tasks, (6) no history of chemotherapy, (7) no alcohol abuse (> 21 units/week for men, > 14 units/week for women) and (8) non-volleyball players (due to potential altered sensitivity in the volar forearm skin). We aimed to recruit 80 participants across five age groups (26–35, 36–45, 46–55, 56–65 and 66–75 years), with 16 individuals per group (8 males and 8 females) and invited them accordingly for the initial assessment.

2.2 | Initial Assessment

Participants who met the inclusion criteria underwent an initial assessment consisting of a basic neurological examination, sensory nerve conduction studies (SNCS) and thermal quantitative sensory testing (QST). Any abnormal findings led to the exclusion of the participant from further analysis.

2.2.1 | Basic Neurological Examination

The neurological assessment included testing vibratory sensation using a 128 Hz tuning fork on two locations (external malleolus and radial styloid process), assessing distal dermatome sensation using a fine brush and testing deep tendon reflexes (bicipital, tricipital, patellar and ankle reflexes). Distal muscle strength was evaluated using the Medical Research Council (MRC) scale and plantar reflexes were examined bilaterally (O'Brien 2023).

2.2.2 | Sensory Nerve Conduction Studies (SNCS)

Antidromic SNCS were performed on the distal upper and lower limbs using a Synergy Medelec EMG system (Synergy, Medelec) to identify any electrophysiological evidence of polyneuropathy. The radial nerve was tested bilaterally in the upper limbs, with the active electrode placed over the extensor pollicis longus tendon and the reference electrode 2 cm proximally on the thumb. Stimulation was delivered 8 cm proximally over the radius. The sural nerves were tested bilaterally in the lower limbs, with the active electrode placed posterior to the lateral malleolus and the reference 2 cm distally. Electrode positioning was adjusted slightly to optimise responses. Peak latencies and peak-to-peak amplitudes were recorded and compared to reference values (Fournier 2013).

2.2.3 | Thermal Quantitative Sensory Testing (QST)

Thermal detection and thermal pain thresholds were assessed for cold and heat using the method of limits following the

German Research Network on Neuropathic Pain (DFNS) protocol (version 2.1-08.07.2010) (Rolke et al. 2006).

A Peltier thermode (probe T06, TCS II, QST.Lab, Strasbourg, France) with a surface area of 10 cm^2 was applied to the skin to deliver continuous heating or cooling stimuli at a ramp rate of 1°C/s. Participants pressed a button upon perceiving the targeted sensation. The baseline temperature was set to 32°C and maximal stimulus intensities were 0°C for cooling and 50°C for heating. QST was performed contralateral to the side used for CHEP and CEP stimulation and testing order was randomised to avoid bias. Results were compared to pre-established normative values from the DFNS protocol (version 2.1-08.07.2010).

2.3 | Contact Heat and Cold-Evoked Potentials

Upon confirmation of normal SNCS and QST assessment, CHEP and CEP were recorded using contact heat and cold stimulation, delivered to the distal volar forearm (upper limb stimulation) and the contralateral foot dorsum (lower limb stimulation). Participants were seated comfortably in a reclining chair, with their volar forearms facing upwards and feet resting on a footstool. The side and order of stimulation were randomised across participants to reduce potential biases.

2.3.1 | Stimulation Protocol

All thermal stimuli were administered using a contact thermal stimulator (TCS model II.1, QST.Lab, Strasbourg, France). The thermode used (model T03) comprises 15 micro-Peltier elements arranged on a 3 cm diameter disk, with each Peltier element having a surface area of 7.7 mm^2, resulting in a total stimulation area of approximately 1.2 cm^2. The baseline temperature was set at 32°C. For CEP, the target temperature was set to 10°C, whereas it was set to 60°C for CHEP. Both temperatures were achieved with a rapid heating or cooling rate of 300°C/s and the duration of each stimulus was 200 ms.

The thermode was manually held against the participants' skin, with the investigator ensuring light and consistent pressure throughout stimulation. Following previous studies (de Keyser et al. 2018; Courtin and Mouraux 2022), upper limb stimuli were delivered to the distal volar forearm because it offers better probe-skin contact than the hand dorsum due to softer subcutaneous tissue and the absence of bony prominences. Lower limb stimuli were delivered to the contralateral foot dorsum. Each site and temperature received 30 stimuli, with side and sequence randomised to minimise bias. To minimise habituation, the location of the stimuli was slightly shifted after each stimulus.

2.3.2 | EEG Recording

The EEG was recorded using 32 actively shielded Ag-AgCl electrodes mounted in an elastic electrode cap and arranged according to the International 10–20 system (WaveGuard 32-channel EEG cap; Advanced Neuro Technologies). Participants were instructed to keep their gaze fixed slightly below eye level and to remain as still as possible during the recording. Impedances were kept below 10 kΩ at all leads. The electrooculogram (EOG) was recorded using a pair of surface electrodes on the left zygomatic process and on the glabella.

The recordings were digitised and amplified with a 1000 Hz sampling rate and an average reference (HS64, Advanced Neuro Technologies).

2.3.3 | EEG Recordings Pre-Processing

The EEG recordings were analysed offline using Matlab 2023 (The MathWorks) and the Letswave 6 and 7 toolboxes for EEG data analysis (https://letswave.org).

The signal was filtered using a 50 Hz multi notch FFT filter and then a 0.3–30 Hz bandpass Butterworth filter.

Signals were segmented into epochs lasting from −500 to +1500 ms relative to the stimulus onset. Artefacts due to eye blinks or eye movements were then removed using a validated method based on an independent-component analysis (FastICA algorithm). After baseline correction (reference interval: −500 to 0 ms), epochs with amplitude values exceeding ±100 μV were rejected due to the likeliness of them being contaminated by artefacts. Signals were then rereferenced to the average of the mastoid electrodes M1 and M2 or to the frontal midline electrode Fz.

Evoked potential extraction was performed through visual inspection. Three distinct peaks (N1, N2, P2) were consistently identified within the averaged waveforms across all participants and experimental conditions. The N1 component manifested as a negative deflection over the contralateral posterior-parietal region, with polarity reversal observed at frontal electrodes. The N1 was obtained from centroparietal and temporal electrodes contralateral to the stimulated forearm (T7/T8, C3/C4, CP1/CP2, CP5/CP6 for right/left stimulation), referenced to Fz. For the statistical analyses, we used N1 parameters assessed at the contralateral electrode T7/T8, where the maximal N1 amplitude was consistently observed in our study population. Thus, the N1 emerged as the first negative deflection within a 160–220 ms post-stimulus latency window, preceding the N2 component. The later N2 and P2 components were analysed at the vertex electrode Cz (referenced to M1-M2). The N2 was defined as the largest negative peak within a 220–300 ms window, while the P2 was identified as the first positive deflection following the N2 component.

2.4 | Statistical Analyses

Statistical analyses were conducted in JASP 0.19.1.0. Descriptive statistics were computed for all variables. To satisfy assumptions of normality of the residuals, Warm Detection Threshold (WDT), Cold Detection Threshold (CDT), peak-to-peak amplitudes of the N2P2 complex and N1 peak, CHEP P2 latencies and CEP N1 were log-transformed.

An ANOVA was used to compare heights across groups. Repeated measures ANOVAs were used to examine the effects

of the factors AGE (5 groups: 26–35, 36–45, 46–55, 56–65, 66–75 years old), SITE (upper vs. lower limb) and SEX on each of the dependent variables of interest: CHEP N1 latency, N1 amplitude, N2 latency, P2 latency and N2-P2 amplitude; CEP N1 latency, N1 amplitude, N2 latency, P2 latency and N2-P2 amplitude. Moreover, a binary logistic regression analysis was conducted to assess the effect of age on the likelihood of obtaining detectable CHEP and CEP signals within the study population.

The significance level was set at 0.05. For post hoc analyses, the significance level was adjusted using Holm's correction to account for the multiplicity of tests. Additionally, a Pearson correlation analysis was conducted between QST measures and CHEP/CEP variables. The significance level was set at 0.05. Since this was an exploratory analysis, we did not correct for multiple comparisons.

3 | Results

3.1 | Study Population

A total of 85 participants were recruited for the initial assessment. All underwent the SNCS and QST. In two cases, the median nerve measurements were substituted for radial nerve measurements due to prior trauma and in two others, superficial fibular nerve recordings replaced sural nerve measurements due to past ankle surgeries. All participants had SNCS values within the normal range. Due to abnormal QST values, five participants were excluded from the CHEP and CEP recordings. The final dataset included data from 80 participants. Table 1 summarises the demographic characteristics of the study population. The mean height was 171.6 ± 7.89 cm, with no significant difference observed between men and women (ANOVA: $F(4,79) = 0.420$, $p = 0.794$). Descriptive data for SNCS and QST are provided in the Tables S1 and S2.

3.2 | Contact Heat and Cold Evoked Potentials

3.2.1 | Visual Identification of CHEPs and CEPs

Figure 1 displays the percentage of waveforms in which the examiner could visually identify the N1 peak and the N2P2 complex, stratified by stimulation modality (CHEP, CEP), age group and tested limb.

For heat stimulation, the N2-P2 complex was identified in 81%–100% of waveforms of the upper limb and 63%–94% of waveforms of the lower limb. The N1 peak was identified in 75%–100% of waveforms of the upper limb and 56%–100% of waveforms of the lower limb.

For cold stimulation, the N2-P2 complex was identified in 94%–100% of waveforms of the upper limb and 69%–94% of waveforms of the lower limb. The N1 peak was identified in 88%–100% of waveforms in both upper and lower limbs.

The logistic regression analysis revealed no significant effect of age on the visualisation rates of either CHEP or CEP peaks (CHEP N2P2: $p > 0.996$; CEP N2P2: $p > 0.998$; CHEP N1: $p > 0.994$; CEP N1: $p > 0.996$).

Figure 2 shows the grand-average waveforms of CHEP and CEP elicited from the upper and lower limbs at the vertex electrode Cz and at the contralateral electrode T7/T8 per age group.

3.2.2 | Analysis of Latency and Amplitude

Table 2a,b present the obtained normative values for CHEP and CEP, including the peak latencies and amplitudes for the N1, N2, P2 and N2-P2 peak-to-peak components, categorised by age group and limb.

The ANOVA analyses for the factors LIMB, AGE GROUP and SEX are shown in Table 3.

3.2.2.1 | CHEP. The ANOVA revealed significant effects of both LIMB ($F(1,4) = 4.879$, $p = 0.032$) and AGE ($F(1,4) = 7.525$, $p < 0.001$) on the N2-P2 amplitude of CHEPs. Post hoc analyses showed that N2-P2 amplitudes were significantly larger in the upper limbs compared to the lower limbs ($p = 0.032$).

For the factor AGE, post hoc analyses corrected using Holm's method revealed that the 26–35 years group displayed significantly larger N2-P2 amplitudes compared to both the 56–65 years group ($p = 0.002$) and the 66–75 years group ($p < 0.001$). No other pairwise comparisons between age groups were statistically significant after correction for multiple testing (all p values > 0.031).

A significant effect of the factor LIMB was found for the N1 amplitude ($F(1, 4) = 4.064$, $p = 0.049$), with greater N1 amplitudes recorded in the upper limbs relative to the lower limbs.

No significant effects of AGE, LIMB or SEX were found for the N1, N2 and P2 latencies.

3.2.2.2 | CEP. The ANOVA revealed a significant effect of the factor LIMB on the N2P2 amplitude of CEP

TABLE 1 | Demographic characteristics of the study population.

Age group	All	26–35 years	36–45 years	46–55 years	56–65 years	66–75 years
$N =$	80	16	16	16	16	16
Mean age (in years)	49.7 (13.80)	29.7 (1.40)	40.3 (3.34)	51.4 (3.16)	59.1 (2.36)	67.8 (1.97)
Sex (F/M)	40/40	8/8	8/8	8/8	8/8	8/8
Mean height (in cm)	171.6 (7.89)	170.3 (9.06)	171.8 (8.17)	170.4 (8.07)	172.4 (8.15)	173.3 (6.33)

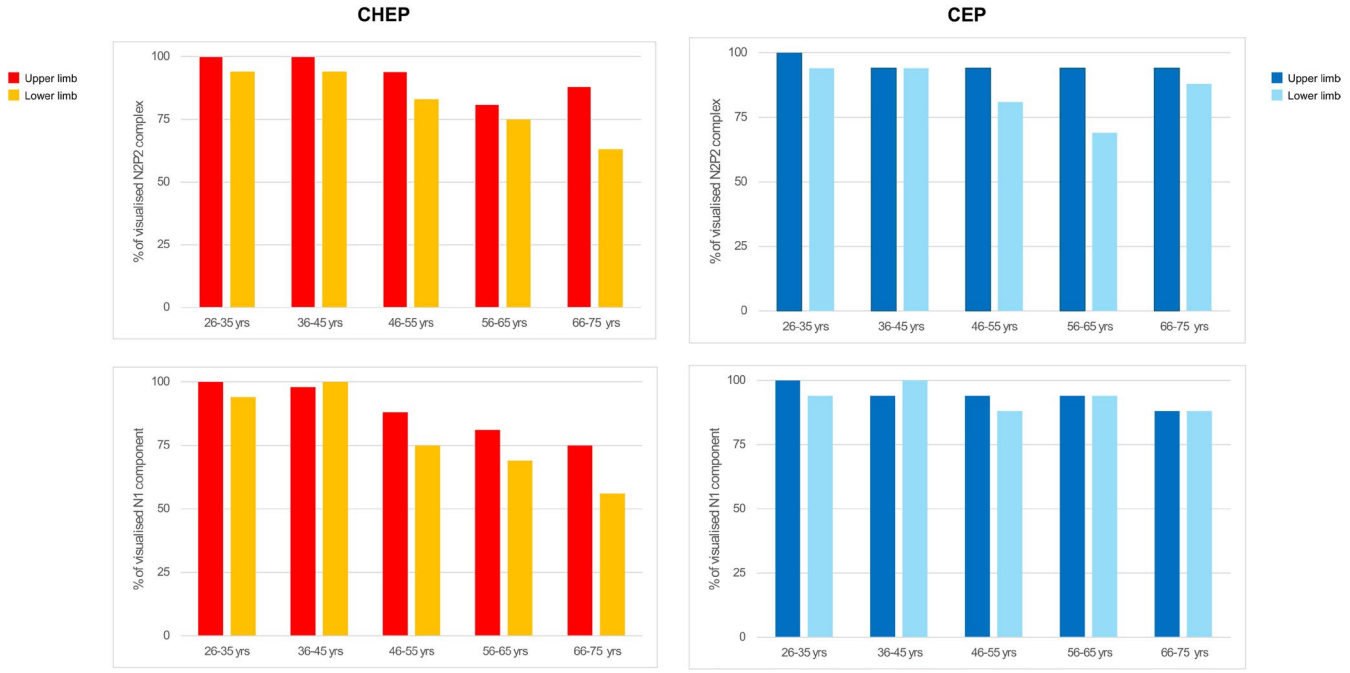

FIGURE 1 | Frequency (in percentage) of visualised N2P2 complexes and N1components of contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) per age group and per limb.

($F(1,4) = 55.891$, $p < 0.001$), with significantly larger amplitudes observed in the upper limbs compared to the lower limbs.

Additionally, a significant effect of the factor AGE was observed ($F(1,4) = 4.624$, $p = 0.002$). Post hoc analyses indicated that the 26–35 years group exhibited larger N2-P2 amplitudes compared to the 66–75 years group ($p = 0.003$). No other pairwise comparisons between age groups reached statistical significance after the correction for multiple comparisons (all p values > 0.016).

For the N1 amplitude, a significant effect of LIMB was observed ($F(1,4) = 12.406$, $p < 0.001$), with larger N1 amplitudes recorded in the upper limbs compared to the lower limbs.

No significant effects of AGE or LIMB were found for the latencies of the different components (N2 peak latency, P2 peak latency, N1 peak latency).

3.2.3 | Correlation Between QST and CHEP/CEP Amplitudes

Figure 3 shows the scatter plots of QST thresholds compared to the N2-P2 amplitude of CHEP and CEP at the upper and lower limbs.

For the amplitude of the N2-P2 component of CHEP, a significant negative correlation was observed with the thermal thresholds in both limbs (lower thresholds were associated with greater N2-P2 amplitudes). In the upper limb, the warm detection threshold (WDT) correlated with the N2-P2 amplitude ($r = -0.351$, $p = 0.003$). In the lower limb, both the WDT ($r = -0.354$, $p = 0.004$) and the heat pain threshold (HPT) ($r = -0.430$, $p < 0.001$) correlated with the N2-P2 amplitudes.

The amplitude of the N2-P2 component of CEP also showed significant negative correlations between cold detection thresholds (CDT) and N2-P2 amplitudes in both limbs. The correlation was present in the upper limb ($r = -0.259$, $p = 0.024$) and the lower limb ($r = -0.294$, $p = 0.013$).

For CHEP, no significant correlations were observed between thermal thresholds and N1 amplitude, neither in the upper limb (all $p > 0.754$) nor in the lower limb (all $p > 0.353$). For CEP, the amplitude of the N1 peak was significantly correlated with thermal detection thresholds, but only in the upper limb (CDT: $r = -0.282$, $p = 0.013$; CPT: $r = -0.283$, $p = 0.013$).

4 | Discussion

The use of contact heat and cold evoked potentials (CHEP and CEP) to assess small fibre and spinothalamic tract (STT) function has gained considerable interest in recent years with the introduction of a portable stimulation system (TCSII) which allows recording of responses having a signal-to-noise ratio comparable to that of laser-evoked potentials owing to its ultra-fast heating and cooling ramps. The present study reports normative values for CHEP and CEP elicited by stimulation of the distal volar forearm and foot dorsum as a function of age. The presence/absence of evoked potentials is described as well as the variability in latency and amplitude of the waveform components across five age groups ranging from 26 to 75 years.

Our findings underline the diagnostic utility of recording CEP from the upper limbs, as the visualisation rate of these evoked potentials exceeds 85% in any age group of the healthy population sample. Thus, the absence of a recordable CEP waveform following upper limb stimulation may offer a valuable clue for

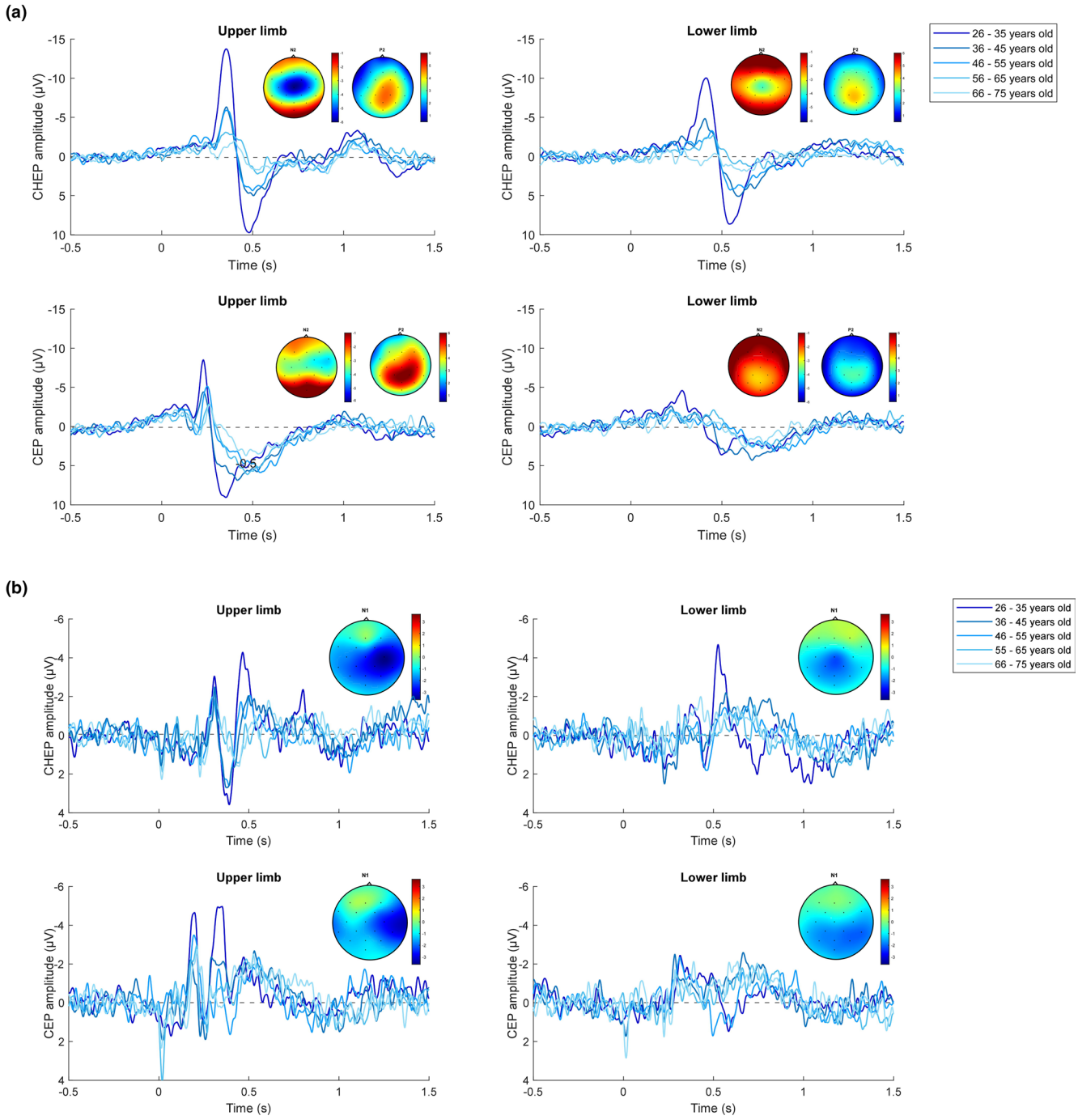

FIGURE 2 | Grand-average waveforms of contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) elicited from the upper and lower limbs (a) at the vertex electrode Cz and (b) at the T8 electrode. Colour coding refers to each examined age group. The insets illustrate the topography of the peaks for the grand average waveform, including all participants, regardless of age.

diagnosing specific neuropathic conditions. For instance, in trigeminal neuropathic pain, cold stimuli have failed to elicit CEP from the face, while Aδ-fibre-mediated LEP remained present albeit with reduced amplitudes and delayed latencies (Leone et al. 2019). The differential involvement of cold perception in neuropathic pain has been evidenced in many studies using psychophysical assessments. For example, the cold detection threshold is a sensitive marker for peripheral sensory neuropathy, with evidence supporting its diagnostic value in both Type 1 (Hyllienmark et al. 2009; Lysy et al. 2014) and Type 2 diabetes (Farooqi et al. 2016; Huang et al. 2023). In line with these findings, Courtin et al. (2020) demonstrated that cold detection is more effective than warm detection in identifying early sensory alterations in diabetic patients who lack overt clinical signs of neuropathy, consistent with previous studies in diabetic and HIV-related neuropathies (Løseth et al. 2008; Sorensen et al. 2006; Zhou et al. 2007). Cold detection may be more affected than heat detection due to its reliance on small myelinated fibres (Schepers and Ringkamp 2010) and the lower abundance of cold-sensitive TRPM8-expressing fibres compared

TABLE 2 | Normative values for (a) contact heat evoked potentials (CHEP) and (b) cold evoked potentials (CEP).

(a)

		All	26–35 years	36–45 years	46–55 years	56–65 years	66–75 years
Upper limb							
N1 latency (ms)	Mean (1 SD)	315.70 (66.96)	299.44 (31.11)	318.81 (68.91)	306.75 (66.50)	350.54 (69.72)	307.42 (90.51)
	Median [IQR]	308.00 [46.50]	308.50 [36.25]	304.50 [43.75]	305.00 [37.75]	337.00 [65.00]	302.50 [84.25]
N2 latency (ms)	Mean (1 SD)	371.54 (63.27)	353.00 (31.41)	367.50 (63.82)	365.36 (46.50)	408.62 (63.81)	368.67 (96.79)
	Median [IQR]	364.00 [52.00]	351.00 [42.50]	358.00 [50.50]	366.00 [47.75]	405.00 [69.00]	381.00 [103.50]
P2 latency (ms)	Mean (1 SD)	552.42 (142.90)	488.56 (35.17)	41.50 (166.94)	579.21 (175.33)	601.08 (156.65)	68.17 (130.64)
	Median [IQR]	512.00 [127.00]	486.5 [48.50]	491.00 [138.75]	544.00 [187.75]	530.00 [248.00]	543.00 [203.25]
N1 amplitude (μV)	Mean (1 SD)	−3.35 (3.95)	−4.21 (3.57)	−3.73 (6.84)	−3.69 (2.19)	−3.12 (2.89)	−1.99 (2.55)
	Median [IQR]	−2.49 [2.32]	−3.98 [4.83]	−1.44 [3.09]	−3.01 [3.43]	−2.49 [2.06]	−1.78 [2.51]
P2 amplitude (μV)	Mean (1SD)	8.90 (6.11)	14.25 (9.09)	8.83 (4.82)	8.24 (5.45)	6.43 (2.98)	6.76 (3.13)
	Median [IQR]	6.81 [5.68]	9.68 [13.34]	8.25 [7.85]	6.88 [5.78]	5.15 [3.18]	6.45 [4.09]
N2 amplitude (μV)	Mean (1 SD)	−9.17 (7.17)	−15.80 (10.95)	−8.94 (5.54)	−8.77 (5.95)	−6.80 (2.28)	−5.52 (3.49)
	Median [IQR]	−6.39 [5.69]	−17.42 [18.27]	−7.04 [5.45]	−5.98 [6.94]	−6.93 [3.47]	−4.57 [3.43]
N2P2 amplitude (μV)	Mean (1 SD)	18.07 (12.44)	30.05 (18.99)	17.77 (9.10)	17.02 (9.99)	13.23 (4.42)	12.27 (6.13)
	Median [IQR]	13.82 [11.82]	25.30 [34.76]	14.86 [8.87]	12.33 [18.03]	12.96 [7.03]	10.87 [7.77]
Lower limb							
N1 latency (ms)	Mean (1 SD)	361.02 (89.21)	362.07 (44.80)	348.31 (111.46)	349.92 (89.21)	381.82 (71.84)	371.22 (127.52)
	Median [IQR]	368.00 [107.00]	362.00 [84.00]	341.50 [128.25]	384.50 [119.50]	409.00 [73.00]	383.00 [207.00]
N2 latency (ms)	Mean (1 SD)	402.97 (82.31)	412.06 (42.98)	382.93 (88.79)	402.42 (92.42)	431.27 (48.07)	388.00 (130.51)
	Median [IQR]	426.00 [96.00]	425.00 [50.00]	403.00 [170.00]	441.50 [148.75]	439.00 [60.00]	408.50 [221.00]
P2 latency (ms)	Mean (1 SD)	609.97 (118.70)	588.81 (83.58)	608.33 (84.61)	574.50 (124.40)	683.82 (117.88)	607.60 (179.84)
	Median [IQR]	584.50 [127.00]	563.00 [82.75]	577.00 [132.00]	574.00 [155.50]	650.00 [117.00]	634.50 [219.75]
N1 amplitude (μV)	Mean (1 SD)	−2.24 (2.40)	−3.54 (2.46)	−1.65 (2.50)	−1.96 (2.54)	−2.10 (2.38)	−1.95 (1.90)
	Median [IQR]	−2.05 [1.85]	−3.46 [2.32]	−1.12 [2.07]	−1.04 [3.05]	−1.67 [3.14]	−1.85 [1.82]

(Continues)

TABLE 2 | (Continued)

(a)

		All	26–35 years	36–45 years	46–55 years	56–65 years	66–75 years
P2 amplitude (μV)	Mean (1 SD)	7.50 (4.49)	11.67 (4.98)	7.82 (3.82)	7.76 (4.44)	5.03 (2.67)	5.22 (3.05)
	Median [IQR]	6.44 [5.76]	12.18 [8.15]	8.10 [4.48]	6.91 [6.59]	4.73 [3.35]	4.35 [4.06]
N2 amplitude (μV)	Mean (1 SD)	−7.40 (6.44)	−12.77 (9.15)	−7.37 (5.55)	−7.55 (5.52)	−5.25 (3.99)	−4.07 (3.19)
	Median [IQR]	−5.19 [5.44]	−8.70 [13.50]	−5.76 [6.27]	−6.74 [4.68]	−4.02 [2.08]	−3.30 [2.86]
N2P2 amplitude (μV)	Mean (1 SD)	14.90 (9.40)	24.45 (11.88)	15.18 (4.63)	15.31 (9.08)	10.28 (6.18)	9.30 (5.32)
	Median [IQR]	12.89 [11.58]	20.15 [21.21]	15.40 [8.00]	14.72 [11.46]	9.04 [5.55]	7.33 [5.88]

(b)

		All	26–35 years	36–45 years	46–55 years	56–65 years	66–75 years
Upper limb							
N1 latency (ms)	Mean (1 SD)	211.99 (76.31)	189.69 (19.21)	215.13 (138.54)	204.00 (34.66)	219.87 (42.07)	234.00 (80.83)
	Median [IQR]	200.50 [47.00]	190.50 [31.25]	181.00 [43.50]	200.00 [37.00]	204.00 [62.00]	233.00 [68.50]
N2 latency (ms)	Mean (1 SD)	257.25 (51.81)	231.88 (18.39)	236.53 (66.07)	259.87 (30.86)	270.40 (46.27)	289.27 (63.81)
	Median [IQR]	251.50 [47.50]	233.50 [22.75]	231.00 [59.00]	252.00 [56.00]	264.00 [58.00]	293.00 [78.00]
P2 latency (ms)	Mean (1 SD)	439.42 (116.31)	379.94 (94.03)	394.60 (108.58)	454.13 (115.36)	474.20 (89.45)	498.20 (135.90)
	Median [IQR]	445.50 [179.50]	349.00 [127.25]	408.00 [177.00]	445.00 [161.00]	473.00 [88.00]	469.00 [192.00]
N1 amplitude (μV)	Mean (1 SD)	−4.43 (3.76)	−6.40 (4.19)	−3.96 (4.80)	−4.75 (2.81)	−4.27 (3.06)	−2.78 (3.03)
	Median [IQR]	−3.85 [2.55]	−5.04 [5.00]	−3.84 [1.41]	−5.17 [3.07]	−3.41 [4.80]	−2.52 [2.76]
P2 amplitude (μV)	Mean (1 SD)	10.22 (5.40)	14.42 (6.91)	10.77 (4.58)	8.98 (3.70)	9.40 (5.90)	7.52 (2.62)
	Median [IQR]	9.79 [5.76]	10.81 [12.95]	10.80 [2.71]	8.69 [4.98]	7.10 [10.38]	7.41 [4.54]
N2 amplitude (μV)	Mean (1 SD)	−7.27 (5.38)	−11.20 (7.52)	−6.45 (3.67)	−7.93 (5.79)	−5.04 (3.39)	−5.75 (3.42)
	Median [IQR]	−6.02 [6.74]	−9.37 [11.74]	−5.85 [3.77]	−6.12 [8.08]	−4.59 [6.94]	−5.56 [6.94]
N2P2 amplitude (μV)	Mean (1 SD)	17.44 (9.07)	25.62 (13.51)	17.22 (6.15)	16.91 (7.32)	14.44 (5.81)	13.03 (4.82)
	Median [IQR]	15.91 [9.16]	18.99 [24.15]	16.46 [7.82]	16.26 [11.71]	14.32 [9.12]	11.73 [6.26]
Lower limb							

(Continues)

TABLE 2 | (Continued)

(b)

		All	26–35 years	36–45 years	46–55 years	56–65 years	66–75 years
N1 latency (ms)	Mean (1 SD)	312.01 (128.74)	289.73 (110.17)	314.38 (198.93)	295.38 (105.67)	365.07 (94.56)	299.14 (98.25)
	Median [IQR]	302.00 [177.00]	300.00 [85.00]	275.00 [224.25]	291.00 [196.25]	358.00 [142.50]	320.00 [172.50]
N2 latency (ms)	Mean (1 SD)	347.75 (110.29)	314.53 (95.94)	96.08 (100.26)	350.40 (113.77)	409.07 (98.00)	367.14 (119.84)
	Median [IQR]	348.00 [182.00]	311.00 [96.00]	222.00 [178.50]	310.00 [210.00]	415.00 [135.50]	381.00 [204.00]
P2 latency (ms)	Mean (1 SD)	652.44 (159.55)	612.80 (166.55)	618.23 (114.11)	689.40 (171.10)	85.43 (150.08)	654.07 (188.15)
	Median [IQR]	652.00 [256.00]	567.00 [286.00]	627.00 [202.50]	09.00 [257.00]	665.50 [277.50]	657.00 [243.25]
N1 amplitude (μV)	Mean (1 SD)	−2.81 (3.10)	−3.86 (4.83)	−2.24 (2.81)	−2.50 (2.46)	−3.06 (2.83)	−2.38 (1.80)
	Median [IQR]	−2.06 [1.57]	−2.22 [2.30]	−1.63 [3.61]	−2.09 [2.15]	−2.45 [3.19]	−2.10 [2.82]
P2 amplitude (μV)	Mean (1 SD)	6.88 (3.17)	8.09 (2.91)	8.07 (4.08)	6.18 (1.72)	5.87 (3.89)	6.19 (2.16)
	Median [IQR]	6.63 [3.78]	7.30 [2.89]	7.01 [5.41]	6.28 [3.08]	4.36 [4.94]	6.53 [3.98]
N2 amplitude (μV)	Mean (1 SD)	−5.31 (4.09)	−7.32 (5.11)	−6.93 (5.75)	−4.24 (2.63)	−4.38 (2.52)	−3.68 (1.88)
	Median [IQR]	−4.57 [1.62]	−5.75 [3.74]	−6.11 [2.88]	−3.61 [3.64]	−3.93 [2.79]	−3.32 [3.35]
N2P2 amplitude (μV)	Mean (1 SD)	12.18 (6.17)	15.40 (6.40)	15.00 (8.49)	10.43 (3.06)	10.24 (6.06)	9.83 (2.87)
	Median [IQR]	11.83 [4.90]	13.36 [5.03]	12.92 [5.10]	9.92 [3.98]	8.61 [7.60]	9.49 [4.77]

Note: Mean (1 standard deviation) and median [interquartile range] values are reported in the entire study population as well as in separate age groups, for the upper and lower limbs.

TABLE 3 | Analysis of variance (ANOVA) for N1, N2, P2 variables of contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) with between-subject factor age group and within-subject factors limb and sex.

	Factor limb		Factor age group		Factor sex		Limb × age group		Limb × sex	
Variable	***F***	***p***	***F***	***p***	***F***	***p***	***F***	***p***	***F***	***p***
CHEP										
N1 latency	0.426	0.517	0.846	0.502	0.014	0.908	0.283	0.888	0.118	0.732
N2 latency	0.278	0.600	1.650	0.176	0.062	0.804	0.780	0.544	0.265	0.609
P2 latency	0.074	0.786	1.898	0.125	2.004	0.163	2.282	0.073	0.504	0.481
N1 amplitude	**4.064**	**0.049***	1.128	0.353	1.679	0.201	0.194	0.941	0.674	0.415
N2P2 amplitude	**4.879**	**0.032***	**7.525**	**<0.001***	0.906	0.346	0.542	0.706	0.064	0.804
CEP										
N1 latency	0.198	0.658	1.451	0.227	**7.589**	**0.008***	0.335	0.854	0.653	0.422
N2 latency	0.883	0.351	**3.396**	**0.014***	0.804	0.373	0.676	0.611	0.024	0.877
P2 latency	2.912	0.093	1.668	0.169	0.182	0.671	0.536	0.710	0.230	0.633
N1 amplitude	**12.406**	**<0.001***	1.523	0.206	0.015	0.903	1.670	0.167	0.292	0.591
N2P2 amplitude	**55.891**	**<0.001***	**4.624**	**0.002***	0.016	0.900	**2.752**	**0.036***	3.022	0.087

Note: Values indicated in bold are statistically significant. The table provides *F* values and *p* values for each factor and interaction.
*$p < 0.050$.

to heat-sensitive TRPV1 fibres, making it more vulnerable to progressive nerve fibre loss (Axelsson et al. 2009; Jeon and Caterina 2018; Weyer-Menkhoff et al. 2019).

Recording CEP from the lower limbs has been reported to be challenging in a small sample of healthy subjects over 50 years of age even with a steep cooling ramp of −300°C/s (Scheuren et al. 2022). The present database, with a much larger group of elderly healthy individuals, confirms that the visualisation rate and N2-P2 peak-to-peak amplitudes of CEP elicited from the foot dorsum significantly decrease with age. This likely arises from the longer peripheral conduction distances from the lower limbs, leading to greater signal dispersion and reduced afferent synchronisation, similar to LEP findings (Truini et al. 2005). Additionally, the lower density of intraepidermal nerve fibres at distal sites (Lauria 1999; McArthur et al. 1998) further diminishes signal transmission. These combined factors –greater signal dispersion and reduced receptor density—complicate the acquisition of reliable cortical responses from the lower limbs. It has been suggested previously that methodological adaptations such as a larger stimulation area could overcome the technical difficulty of acquiring CEP from the lower limbs (Scheuren et al. 2022).

While in clinical neurophysiology, the assessment of somatosensory evoked potentials typically relies on several factors, including the presence or absence of waveform components, their latencies and their amplitudes (Cruccu et al. 2008), a significant challenge remains in translating these principles to the clinical application of CHEP and CEP. It is currently unclear whether amplitude or latency measurements should take precedence in the clinical interpretation of CHEP and CEP. Previous studies have shown that the N2-P2 amplitude and the N2 latency are linked to intraepidermal nerve fibre density, offering insight into small fibre integrity (Wu et al. 2017; Casanova-Molla et al. 2011; Chao et al. 2008). In our study, we observed a significant age-related decline in evoked potential amplitudes, consistent with previous findings in CHEP, CEP and LEP studies (Truini et al. 2005; Rosner et al. 2018; Scheuren et al. 2022). The pronounced amplitude reductions and even the absence of any visible evoked potential observed in older adults when recording from the foot dorsum, align with the documented greater age-related decline in thermal sensitivity at the feet compared to the hands (Guergova and Dufour 2011). This could be further explained by age-related declines in axonal transport efficiency and cumulative signal attenuation in longer nerve fibres (Lautenbacher and Strian 1991). Our findings are also consistent with Scheuren et al. (2022), who reported significantly reduced CEP amplitudes in older adults, even with rapid cooling rates.

Interestingly, our study found no significant age-related differences in N2 and P2 latencies for both CHEP and CEP, consistent with previous LEP findings (Truini et al. 2005), even when comparing age groups separated by 40 years. This contrasts with earlier established normative CHEP studies (Jutzeler et al. 2016; Rosner et al. 2018; Granovsky et al. 2016) that reported age-related increases in CHEP latencies. This discrepancy likely results from differences in stimulation parameters. When slow heating ramps are used ($\leq$70°C/s, compared with 300°C/s in the present study), higher thermal activation thresholds in older individuals will translate into a delayed activation of thermonociceptors relative to stimulus onset, as more time is required for the skin temperature to reach threshold—thereby increasing CHEP latencies. In contrast, with very steep heating ramps, the temperature rises quickly above threshold and is likely to produce a more synchronous afferent volley, thus minimising

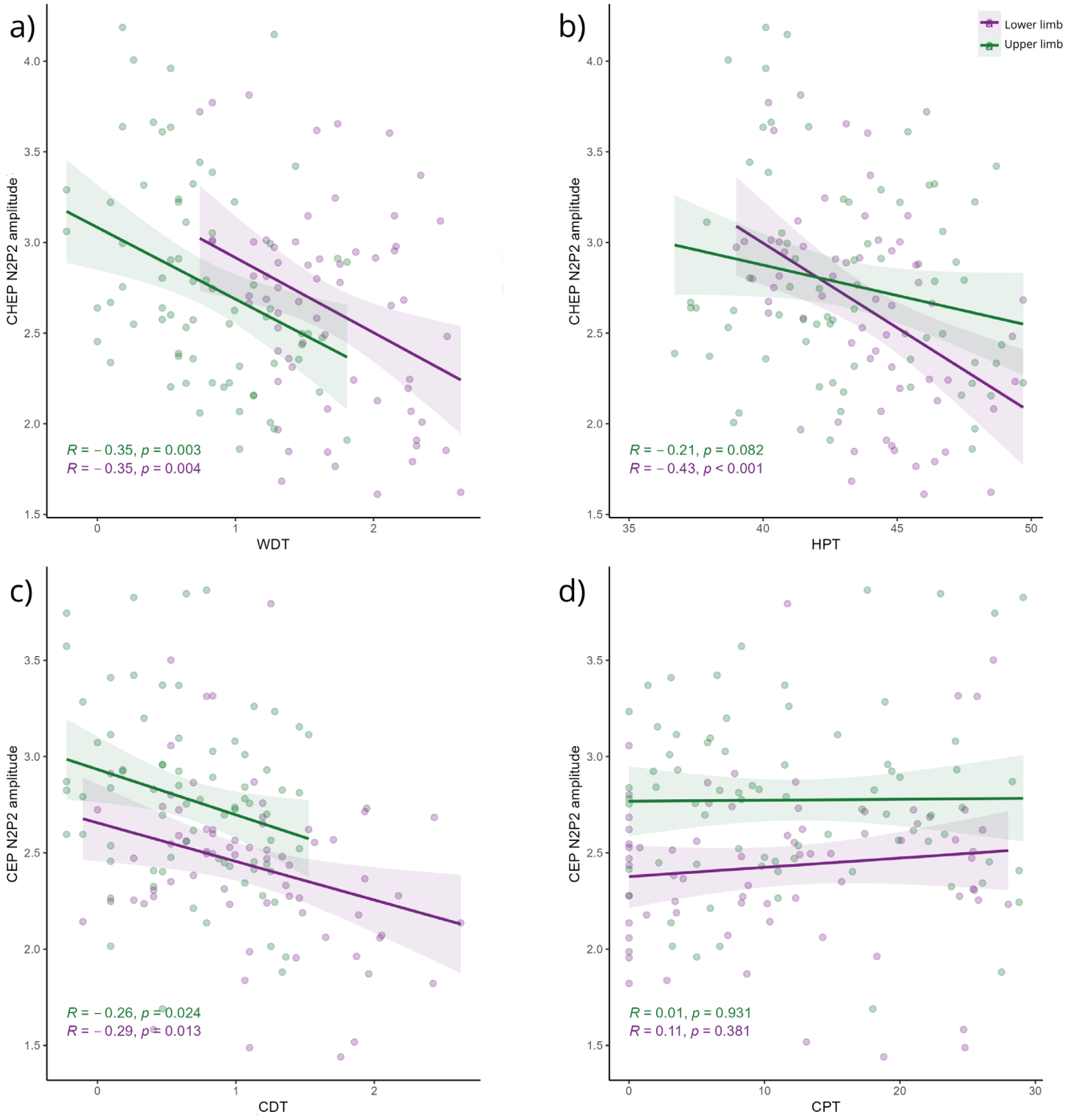

FIGURE 3 | Scatter plots showing correlations between quantitative sensory testing threshold and N2P2 amplitudes of contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) in upper and lower limbs. Panels represent (a) warm detection threshold (WDT), (b) heat pain threshold (HPT), (c) cold detection threshold (CDT) and (d) cold pain threshold (CPT). Regression lines are shown for each limb, with shaded areas representing the 95% confidence interval.

the influence of individual threshold variability on response latency. These findings suggest that, when steep heating ramps are used, CHEP latencies are not significantly affected by age and clinical normative latency ranges may not require age-based adjustments. Sex did not influence amplitudes or latencies in our study, differing from the mixed results of previous research (e.g., larger amplitudes in female participants reported by Granovsky et al. 2016 and Staikou et al. 2016 and longer latencies in male participants described in Jutzeler et al. 2016).

The N1 component is thought to reflect early cortical sensory processing (Garcia-Larrea 2012; Lee et al. 2009) and to be less influenced by cognitive factors (Garcí-Larrea et al. 1997; Siedenberg and Treede 1996; Zaslansky et al. 1996). However, clinical use remains difficult due to its small amplitude and overlap with N2 (Treede et al. 2003; Iannetti et al. 2006; Wydenkeller et al. 2008). The lateralization of the N1 component necessitates a more complex recording setup, including a contralateral temporal electrode to enhance detection accuracy

(Valeriani et al. 2012). Furthermore, because the cortical representation of the lower limb lies deep within the interhemispheric fissure, it produces smaller and less lateralized signals, making it possibly harder to differentiate N1 from the midline N2 during lower-limb stimulation.

4.1 | Implications for Clinical Practice

Our findings demonstrate that CEP recorded from the upper limbs consistently yield high detection rates (> 90% N2P2 waveforms) in all age groups, supporting their utility. In contrast, amplitude values appear to be more affected by age, particularly in lower limb recordings. These findings hold significant implications for clinical diagnostics, particularly in SFN, where proximal–distal comparative assessments are diagnostically pertinent and in spinal pathologies, where analogous comparative analyses may offer diagnostic guidance (Terkelsen et al. 2017; Jutzeler et al. 2016). Importantly, clinicians should exercise caution in interpreting amplitude values, particularly in older populations, to avoid confounding age-related changes with pathological alterations. The normative data presented here provide clinicians with valuable reference values for both upper and lower limbs, enhancing interpretation in individual patients. To further support clinical use, preliminary 5th–95th percentile cut-offs (Table S3) offer an initial framework for distinguishing normal from abnormal findings, though they should be applied cautiously as they derive from healthy participants only. Future patient-inclusive studies are needed to validate these thresholds. Finally, to ensure diagnostic accuracy and inter-patient comparability, clinicians are encouraged to employ fast ramp-rate stimulators and standardised protocols with consistent target temperatures and testing sites, pending validation in patient populations.

4.2 | Study Limitations

One limitation of this study is the use of the distal volar forearm as the testing site, which may limit the direct clinical applicability of our normative dataset, as the hand dorsum is typically examined in SFN diagnostics to assess the most distal limb regions. CHEP and CEP responses from the forearm likely differ from those at the hand dorsum, so these normative data should not be used for interpretation at that site. Nonetheless, a previous proof-of-concept study showed that transient cold detection thresholds at the forearm discriminated diabetic patients without neuropathy from controls (Courtin et al. 2020), suggesting this site remains clinically relevant. Another limitation concerns the TCSII stimulator, which currently lacks CE certification for clinical use in the European Union, restricting it to research settings. However, by establishing normative reference values across age groups, this study supports future investigations into the diagnostic performance of CHEP and CEP elicited by the TCSII—an important step toward certification and clinical implementation.

5 | Conclusion

This study establishes normative values for CHEP and CEP using a contact thermode able to achieve very steep heating and cooling ramps, offering a reference for assessing STT function using the same stimulation parameters (stimulation site, target temperature, heating- and cooling-ramp, stimulation surface). Our findings highlight the diagnostic value of recording CEP from the upper limbs, which consistently achieved waveform detection rates exceeding 90% across all age groups. The larger N2-P2 amplitudes observed in the upper limbs compared to the lower limbs likely reflect the impact of longer conduction distances and lower receptor densities in distal regions. Age-related reductions in amplitudes, particularly in the lower limbs, emphasise the importance of incorporating age into clinical interpretations. The diagnostic utility of the N1 component remains constrained by challenges in obtaining reliable recordings, especially for CHEP.

Author Contributions

This study was designed by Samar M.Hatem André Mouraux and Arthur Courtin. The experiments were performed by Yoshnee Foolchand. The data were analysed by Yoshnee Foolchand, Avgustina Kuzminova, Marc-Henri Louis, Arthur Courtin André Mouraux, Samar M. Hatem and the results were critically examined by all authors. Yoshnee Foolchand had a primary role in preparing the manuscript, which was edited by Samar M.Hatem André Mouraux, Arthur Courtin and Patricia Dessart. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Scatter plots showing correlations between quantitative sensory testing threshold and N1 amplitudes of contact heat evoked potentials (CHEP) and cold evoked potentials (CEP) in upper and lower limbs. Panels represent (a) warm detection threshold (WDT), (b) heat pain threshold (HPT), (c) cold detection threshold (CDT) and (d) cold pain threshold (CPT). Regression lines are shown for each limb, with shaded areas representing the 95% confidence interval. **Table S1:** Descriptive data for sensory nerve conduction studies. **Table S2:** Descriptive data for quantitative sensory testing (QST). **Table S3:** Cut-off values of normative dataset.