Research Article

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Reference Values of Touch Sense Threshold from an Adult Brazilian Cohort

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ABSTRACT

Semmes-Weinstein monofilaments have been widely used in clinical practice to evaluate touch sense in healthy subjects and in the population of risk of neuropathies as Diabetes Mellitus and leprosy patients. It is an effective and low-cost clinical tool indeed, however, it is an instrument of low sensitivity with subjective responses. In the 1980s, a procedure was proposed for the psychophysical assessment of touch sense by sine-wave electric current stimulation. This assessment was based on studies that suggested sinusoidal electric stimuli of several different frequencies would excite sensory fibers of different diameters, increasing the selectivity of the stimulation. This study aims to evaluate and describe touch sense perception threshold of a healthy Brazilian cohort using sine-wave electric stimulation. Reference values of Current Perception Threshold (CPT) were registered in upper limb nerves of 100 healthy subjects, 57 (male) and 43 (female). All subjects had the ulnar, median, and radial nerves evaluated with a sine-wave electric stimulator called NEUROSTIM® to quantify the CPT for the frequencies 1Hz, 250Hz and 3000Hz.

The CPT reference values for the Ulnar Nerve varied between 484µA - 1003µA for the 3000Hz frequency, 168µA - 322µA for the 250Hz and 122µA - 571µA for the 1Hz frequency. For the Median Nerve varied between 468µA - 1321µA for the 3000Hz frequency, 168µA - 386µA for the 250Hz and 168µA - 437µA for the 1Hz frequency. For the Radial Nerve varied between 516µA - 1350µA, 144µA - 533µA and 173µA - 342µA for each frequency respectively.

The NEUROSTIM evaluation protocol seems to be effective, objective, and able to be replicated for touch sense evaluation in healthy subjects. Having CPT reference values to a Brazilian adult healthy cohort can help professionals in the clinics to have a better understanding, management and treatment of diseases affecting touch sense, such as leprosy, diabetes mellitus and others.

Keywords

Current Perception Threshold, Touch Sense, Sine-Wave stimuli, Reference Value, Brazilian Cohort.

Introduction

Since the 1980s, a procedure has been proposed for the psychophysical assessment of skin sensitivity by sine-wave electric stimulation [1].

Unlike the pulsating electric current, such as used in electroneuromyography (ENMG) which evaluates the nerve conduction velocity, the sinusoidal current is able to detect the electrical threshold of sensory perception at a minimum amount of current [1-3].

The touch evaluation using this new method - Current Perception Threshold (CPT) - was based on studies that suggested sinusoidal stimuli of different frequencies would excite sensory systems related to fibers of different diameters, thus increasing the neuronal selectivity of the stimulation [1,3,4].

Sensory fibers can be classified into three major groups: A-β, A-δ and C [5]. Type C fibers do not have myelin and their diameter is less than 1.5 µm, presenting a lower conduction velocity of nerve impulses (between 0.5 and 2 m/s). These fibers are related to the sensations of pain, temperature and itchiness [6,7].

Type Aδ fibers are thin myelinated and conduct pain and temperature sensations, however, at higher speeds that can reach 30 m/s. On the other hand, touch sensations are transmitted by fibers composed of Aβ-type axons, which are thick myelinated fibers and can present conduction speeds of up to 75 m/s [6,7].

Literature has suggested that the 5Hz frequency would stimulate non-myelinated (C) fibers, 250Hz fine myelinated fibers (Aδ) and 2000Hz myelinated fibers of medium caliber (Aβ) [1,4,8]. Aβ fibers conduct the senses of touch, pressure, and vibration, while both Aδ fibers and C fibers conduct the senses of pain and temperature, and C fibers also serve as post-sympathetic fibers [8].

Posterior studies have shown that the correlation between the 5Hz frequency and clinical neurologic evaluation are poor, suggesting that the 1Hz frequency is more selective to evaluate the non-myelinated (C) fibers and 3000Hz myelinated fibers of medium caliber (Aβ) [8,9].

Thus, it would be natural to use the neuroselective characteristic of the sine-wave electric stimulation for early diagnosis of peripheral neuropathies of progressive evolution, such as leprosy. In this case, it might be expected that the Current Perception Threshold (CPT) to low frequencies (associated with the neural fibers of thin caliber) could be altered before the CPT for high frequencies (associated with the coarse fibers) [9-11].

The evaluation of the sensory nerve fiber's function through the touch sense is important in the diagnosis and follow-up of certain diseases involving the sensory conducting pathways, such as diabetes, leprosy, carpal tunnel syndrome, and others. Such as the Semmes-Weinstein monofilaments (SWM), used in the detection and monitoring of peripheral neuropathies, quantifying the skin touch-pressure threshold [12,13], the Sensory Nerve Conduction Study is an important tool in the assessment of peripheral nervous system disorders through the velocity of an electrical impulse in the nerve, as well as the Somatosensory evoked potentials [14,15]. Likewise other clinical tests such as Voluntary Muscle Testing, Grip Dynamometry, Motor Nerve Conduction Measurements, Vibration Perception Thresholds, Thermal Detection Thresholds are largely used to assess nerve function [16-18], Different from other examination tools, the CPT can evaluate the functioning of the sensory nerve fibers through touch sense in a quantitative form and achieve differential neuro-excitatory effects of the sensory fibers depending on the different frequency of stimuli [1,4].

CPT has been used by other studies instead of using ENMG for evaluation and follow-up of touch sense in patients affected by different sensory pathologies, also to understand how normal touch sense is processed in subjects with no pathologies [2,3,10,11,19].

This study aims to evaluate and describe the CPT reference values for three upper limb nerves in a healthy Brazilian cohort using sine-wave electric stimulation.

Material and Methods

Subjects

One hundred healthy subjects (57 male and 43 female, mean age 48 ± 20 years) with no diagnosis or complaints of sensory dysfunction were assessed. The exclusion criteria were sensory loss in SWM (>0.05g), low tolerance/adaptation to electrical current, wounds, ulcers or metal prosthesis on the hands and arms, cardiac pacemaker, any diagnosis of peripheral neuropathy, central nervous system disorder, as well as other orthopedic injuries on the arms, and use of any centrally acting drugs.

All subjects were submitted to the CPT Protocol.

The electrocutaneous stimulation was applied on the dermatomes related to the Ulnar, Median and Radial nerves with the frequencies 3000Hz, 250Hz and 1Hz [20] (Figure 1). To prevent any experimental bias, the order of evaluation of nerve, current frequency, and hand (right or left) were chosen randomly using a computer software *Microsoft® Excel.*

In the setup room, subjects were all comfortably seated with their arms resting on an armrest chair (elbow flexed at 90°), while the tactile electrical stimulus was applied on one hand at a time.

CPT Protocol

The CPT sine-wave electric current was measured by the NEUROSTIM®, a secure device capable of generating electrical stimuli with controlled current and programmable waveform, with intensity up to 8 *m*A [9].

The test was divided into 2 steps: The first step is a rapid assessment, called RAMP test, in which the amplitude value is continuously incremented until the volunteer presses the Stimulus Perception Button (SPB). At that time, the amplitude value is stored as Ramp Threshold (RT) in *m*A and the first step of the test comes to an end. The RT value is used as a reference to systematically determine the values of the parameters "initial amplitude" (iA) and "initial increment" (INC) used in the CPT evaluation, the second stage of the evaluation.

From the values of the parameters iA, INC, the duration of the stimuli (T_ON), the resting time between stimuli (T_OFF) and the stimulation frequency determined by the user, the CPT searching process is started, which is the lower value of intensity felt by the patient during the electrical stimulation assessment.

Two gold electrodes with a diameter of 10 mm were used to stimulate the palmar face of the phalanges of the 5th finger to evaluate the ulnar nerve, on the palmar face of the phalanges of the 2nd finger for evaluation of the median nerve and in the anatomical radial snuff for evaluation of the radial nerve, separated by 2 cm between the centers (Figure 1).

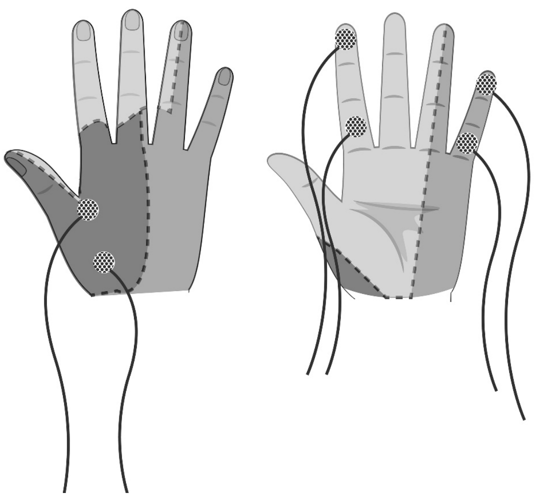

Figure 1: CURRENT PERCEPTION THRESHOLD PROTOCOL. Second Finger corresponds to the territory of the Median nerve, Fifth Finger corresponds to the territory of the Ulnar nerve, Radial Snuff corresponds to the territory of the Radial nerve.

The assessment protocol used is according to Martins et al. [10,11]. Three different types of frequencies were tested for each upper limb nerve (ulnar, median and radial): 1Hz, 250Hz, and 3000Hz. The frequencies were randomly tested to avoid adaptation to the stimulus.

The CTP for each site was determined as the minimum intensity at which the subject reported feeling the stimulus applied.

Data Analysis

Before the statistical treatment of the data, the Shapiro-Wilk test was applied. The test indicated non-normality for all variables evaluated.

Non-parametric statistics such as Wilcoxon and Mann-Whitney were used to analyze all variables. The level of significance (α) used was equal to 0.05.

Prism GraphPad 9 **was the software used to analyze all data.**

Reference Value

To establish the range of CPT reference values for normal touch sense for every frequency and nerve measured, the interval between 2.5% percentile and 97.5% percentile of the results was used [21]. This technique was used to calculate the values which are in the 95% confidence interval of the results [22].

At the result session, the graphs box and whiskers are used. The bottom of the box means the 25% percentile, the top of the box means the 75% percentile, the line inside the box indicates the median. The whiskers indicate the interval between the 2.5% percentile and the 97.5% percentile. That is the reference value for each nerve and frequency.

Results

The general CPT values for each frequency from the different nerves are shown in table 1.

Table 1: General CPT Values.

	Median	2.5% - 97.5% Percentile	Min - Max
3000Hz Ulnar	897μA	484μA - 1003μA	468μA - 1012μA
Median	1099μA	468μA - 1321μA	423μA - 1321μA
Radial	1096μA	516μA - 1350μA	484μA - 1456μA
250Hz Ulnar	288μA	168μA - 322μA	168μA - 322μA
Median	368μA	168μA - 386μA	144μA - 476μA
Radial	366μA	144μA - 533μA	112μA - 533μA
1Hz Ulnar	442μA	122μA - 571μA	184μA - 627μA
Median	276μA	168μA - 437μA	168μA - 453μA
Radial	227μA	173μA - 342μA	168μA - 347μA

In relation to the CPT value, the mean between both hands from each of the 100 healthy subjects were analyzed and described below:

The CPT reference values for the Ulnar Nerve varied between 484μA - 1003μA for the 3000Hz frequency, 168μA - 322μA for the 250Hz and 122μA - 571μA for the 1Hz frequency (Figure 2).

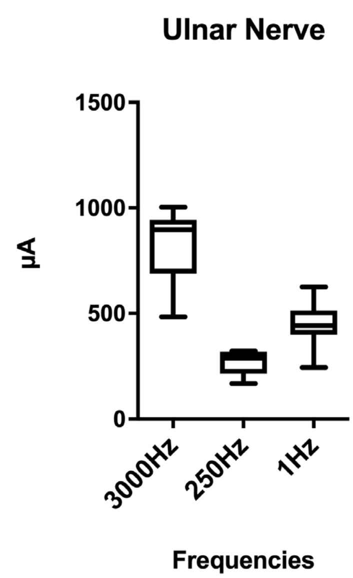

Figure 2: ULNAR. The bottom of the box means the 25% percentile, the top of the box mens the 75% percentile, the line inside the box indicates the median. Whiskers indicate the interval between the 2.5% percentile and the 97.5% percentile.

The CPT reference values for the Median Nerve varied between 468μA - 1321μA for the 3000Hz frequency, 168μA - 386μA for the 250Hz and 168μA - 437μA for the 1Hz frequency (Figure 3).

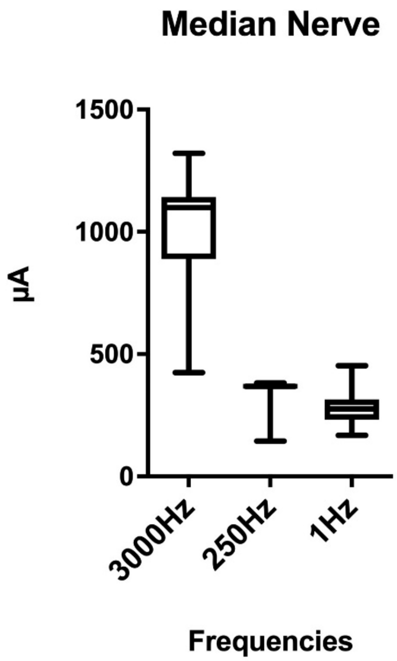

Figure 3: MEDIAN. The bottom of the box means the 25% percentile, the top of the box mens the 75% percentile, the line inside the box indicates the median. Whiskers indicate the interval between the 2.5% percentile and the 97.5% percentile.

The CPT reference values for the Radial Nerve varied between 516µA - 1350µA, 144µA - 533µA and 173µA 342µA for each frequency respectively (Figure 4).

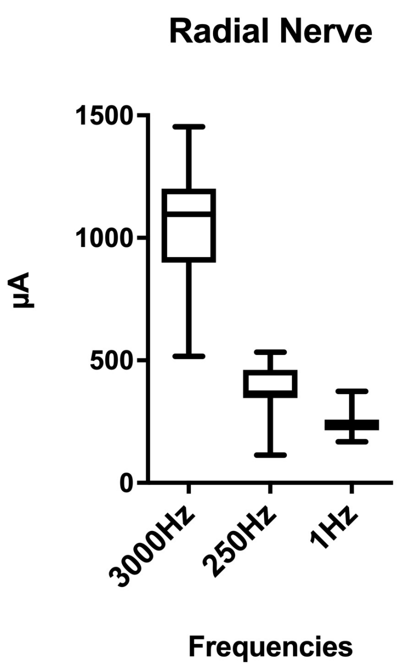

Figure 4: RADIAL. The bottom of the box means the 25% percentile, the top of the box mens the 75% percentile, the line inside the box indicates the median. Whiskers indicate the interval between the 2.5% percentile and the 97.5% percentile.

No statistically significant difference *(Wilcoxon p> 0.05)* was found in the comparison between the CPT values from men and women (Table 2). Also, no significant difference *(Mann-Whitney p> 0.05)* was found between CPT values from the left and right side of the same subject (Table 2).

Table 2: Gender and Laterality CPT Values.

	Median Gender Men | Women	**Median Laterality** Left hand | Right Hand
3000Hz Ulnar	800µA | 897µA	897µA | 897µA
Median	1099µA | 990µA	1099µA | 990µA
Radial	1096µA | 1096µA	1096µA | 1096µA
250Hz Ulnar	288µA | 274µA	288µA | 288µA
Median	368µA | 368µA	368µA | 368µA
Radial	366µA | 366µA	366µA | 366µA
1Hz Ulnar	478µA | 433µA	442µA | 438µA
Median	276µA | 276µA	276µA | 276µA
Radial	226µA | 229µA	226µA | 229µA

Also no correlation was found between CPT values for men and women nor left and right hand *(p>0,05)*.

There is a low negative correlation between CPT and age for frequencies 250Hz and 1Hz in the ulnar nerve, the frequency 250Hz in the medial nerve and for the frequency 3000Hz in the radial nerve. No correlation was found for the frequency 3000Hz in the ulnar nerve, the frequencies 3000Hz and 1Hz in the medial nerve and for the frequencies 250Hz and 1Hz in the radial nerve (Figure 5).

The 100 subjects were divided in 5 groups, according to the age, for comparison: *group A* (18-25 years old) had 18 subjects, *group B* (26-35 years old) had 22 subjects, *group C* (36-45 years old) had 22 subjects, *group D* (46-55 years old) had 20 subjects and *group E* (56-65 years old) had 18 subjects.

When comparing the different age ranges, most of the frequencies to each nerve had no statistical difference between the different groups *(Kruskal-Wallis p>0,05)*, but the groups with older ages (Groups D and E) have higher coefficient of variation (CV) for all frequencies and nerves when compared to the groups with newer ages (Groups A, B and C) (Table 3).

When Groups A, B and C (n=62) were grouped together and compared with groups D and E (n=38) grouped together *(Mann-Whitney test)*, only the Ulnar nerve in the frequency of 250Hz and 1Hz and the Median nerve in the frequency of 250Hz showed statistical difference between newer and older people. The other frequencies for each nerve didn't show statistical difference (p>0.05) (Table 4).

Compliance with Ethical Requirements

Statement of Human and Animal Rights

The study was approved by the Local Ethics and Research Committee from the Clementino Fraga Filho Hospital/ Federal University of Rio de Janeiro/Brazil under the number

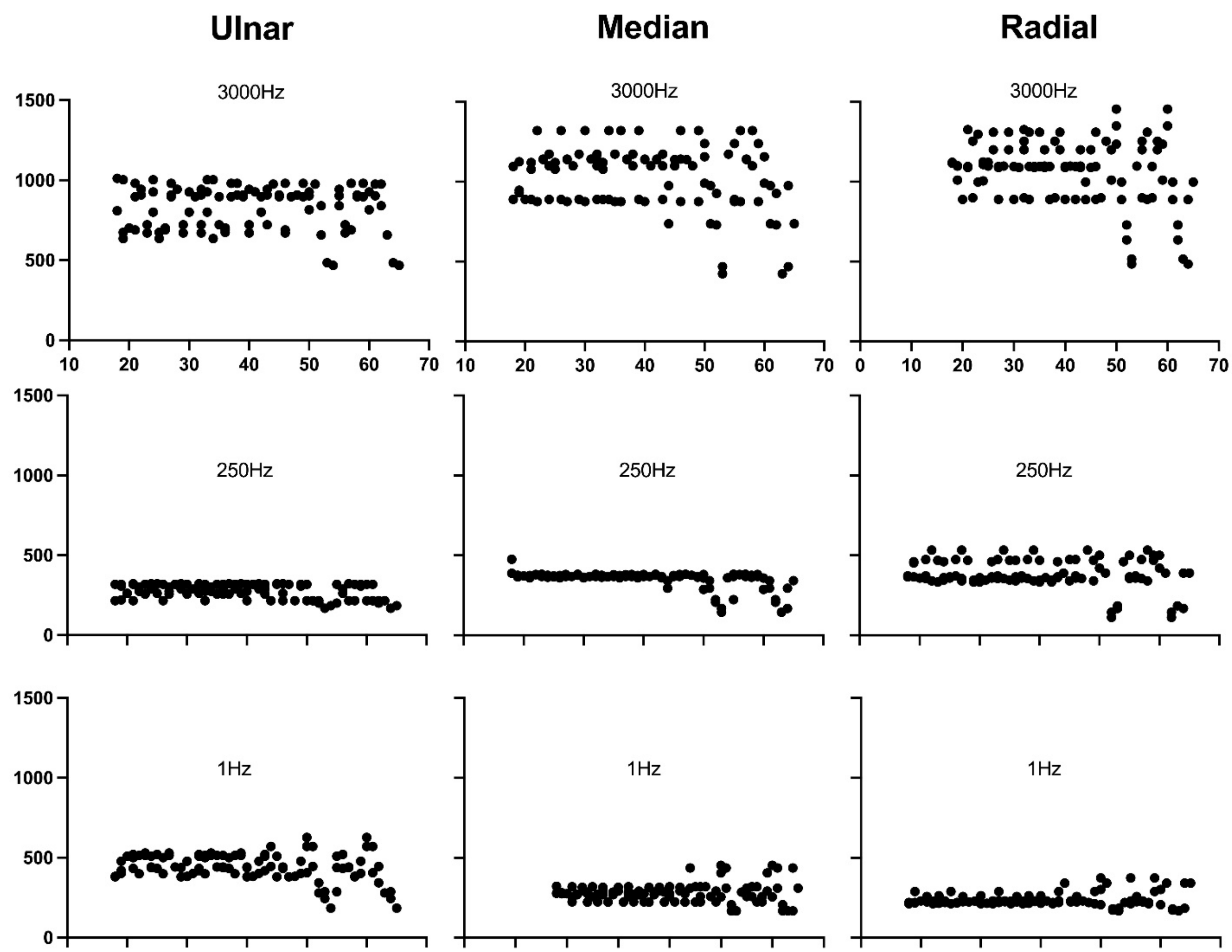

Figure 5: CORRELATION. Correlation between the Current Perception Threshold protocol and age for the ulnar, median and radial nerves for the 3000Hz, 250Hz and 1Hz frequencies.

Table 3: Groups of Age CPT Values and Coefficient of Variation [CV].

	Median Group A	**[CV]**	**Median Group B**	**[CV]**	**Median Group C [CV]**		**Median Group D [CV]**	**Median Group E [CV]**	
3000Hz Ulnar	804,5µA	[17.4%]	897µA	[14.9%]	902µA [13.4%]		897µA [22.6%]	868,5µA [22.6%]	
Median	1087µA	[12.3%]	1110µA	[14.7%]	1119µA [14.9%]		982,5µA [26.9%]	975µA	[27.4%]
Radial	1099µA	[10.5%]	1096µA	[13.1%]	1096µA [11.9%]		1054µA [28.1%]	998µA	[28.4%]
250Hz Ulnar	460µA	[11.4%]	489µA	[11.7%]	443,5µA [11.8%]		419µA [28.4%]	419µA	[28.5%]
Median	372µA	[6.7%]	368µA	[2.1%]	368µA	[5.3%]	361µA [24.9%]	350µA	[24.9%]
Radial	366µA	[15.1%]	361µA	[17.1%]	363µA	[15.1%]	380,5µA [35.7%]	389µA	[35.4%]
1Hz Ulnar	304µA	[13.7%]	294,5µA	[11.8%]	288µA	[13.3%]	215µA [23.6%]	215µA	[23.1%]
Median	276µA	[10.2%]	273µA	[11.1%]	286µA	[17.7%]	267µA [30.7%]	275µA	[32.3%]
Radial	225µA	[10.4%]	226,5µA	[8.1%]	229µA	[15.9%]	225µA [25.3%]	28,5µA	2 [26.7%]

Table 4: Comparison Groups of Age.

	18-45 years	46-65 years	p Value
3000Hz Ulnar	897µA	897µA	0.38
Median	1099µA	975µA	0.14
Radial	1096µA	1005µA	0.13
250Hz Ulnar	461µA	419µA	0.01µA
Median	368µA	358µA	0.001µA
Radial	366µA	389µA	0.74µA
1Hz Ulnar	288µA	215µA	0.001µA
Median	276µA	267µA	0.80µA
Radial	227µA	226µA	0.96µA

3001499/2018 and is in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

The participation was voluntary, and all subjects of this study provided informed consent through a written document.

Discussion

The aim of this study was to establish reference values for the Current Perception Threshold (CPT) using the sine-wave electric stimulation for the evaluation of skin sensitivity as touch sense in healthy Brazilian subjects.

This study discusses the potential contribution in early diagnosis of peripheral neuropathies. Having a reference value in a healthy population is determinant to contrast with the assessment of touch sense in patients in initial development of neuropathies such as Leprosy's disease, Diabetes Mellitus and others.

In the present study, the CPT values were recorded for ulnar, median, and radial nerves on both upper limbs for three different frequencies 3000Hz, 250Hz, and 1Hz in a sample of 100 healthy subjects.

This study shows the interval of confidence of 95% (2,5-97,5%) of the sample of 100 healthy subjects to the touch sense threshold to hand nerves corresponding to the normal reference values in a Brazilian healthy cohort, which is something that still has not been done before as far as we know.

The data show a variability of touch sense threshold even in healthy subjects. The samples that are above or below from this interval of confidence of 95% are far from median but still have no complaints or diagnosis of nerve impairments, revealing an expected variability in touch sense perception. Differently from previous studies [3,9-11], this study reveals CPT values for the Ulnar nerve (cohort 100 healthy subjects), known as the first to be affected at the onset of neural damage in many neuropathies [18].

The CPT values found in the present study for the Radial nerve at the frequencies of 1Hz, 250Hz and 3000Hz tend to be lower than the previous CPT values found using the same frequencies [10,11]. That can be explained based on the difference of the sample between the studies.

Likewise, the Median nerve CPT values for the frequencies of 1Hz, 250Hz and 3000Hz also follow the same tendency to be lower than the values found by Neurotron Inc [2,3]. That can be also explained based on the difference of frequencies (5Hz, 250Hz, 2000Hz) used in each study.

The finding of a reference value for hand touch sense in Brazilian healthy cohorts using these more neuroselective frequencies as CPT does is something new in the literature [8,9]. It also has the advantage of stimulating thin caliber axons, the most and firstly fibers involved in touch sense loss in different neurologic diseases. On the other hand, the ENMG protocol stimulates the large fibers in the nerve's axons, those are normally the latest to be affected.

In line with this, CPT might contribute to early diagnosis of diseases that initiate nerve impairments in thin fibers. The study's findings have significant implications for the diagnosis and treatment of peripheral neuropathies. The use of CPT to evaluate touch is non-invasive, quantitative and seems to be a reliable method that can provide touch sense threshold to understand how upper limb nerves are working.

Having reference values in the CPT of Brazilian healthy adults can help professionals in the clinics to have a better understanding, management and treatment of diseases that affect touch sense, such as leprosy [23,24], diabetes [25], Brachial Plexus Injury [26], burns [27,28], carpal tunnel [29] and many others.

An important information this study brings is about the difference between different hand sides, genders and also groups of age. As shown in the results section, there was no significant difference between left and right hand not between men and women in line with other studies [6,30].

In general, no significant difference was found between groups as well. Nonetheless, it seems that the first three groups (A, B and C) have always a tendency to have lower CPT variability when compared to the last two groups (D and E). Groups A, B and C seem more alike to each other, and groups D and E also seem more alike to each other.

For some frequencies in all three nerves, a negative correlation was found. The low negative correlations were found for the 250Hz in the median nerve (r=-0.3919) and in the ulnar nerve (r=-0.3091), followed by the 3000Hz frequency in the radial nerve (r=-0.2177) and lastly by the 1Hz frequency in the ulnar nerve (r=-0.2161). Based on that, it seems that in our sample older people have the tendency to show more nonspecific CPT values, with more variability when compared to newer people.

Another finding that corroborates this data is the higher coefficient of variation for the groups D and E for every nerve and frequency, meaning a bigger dispersion of CPT results around the median.

The 3000Hz frequency in ulnar (r=-0.04873) and median nerve r=-0.1426), the 250Hz frequency in the radial nerve (r=--0.01217) and the 1Hz frequency in the median (r=-0.01884) and radial (r=0.06321) nerve didn’t show any correlation between age and CPT values.

One explanation for this is the progressive loss of cutaneous afferent axons and changes to cutaneous receptors with age [11,19]. At a given stimulus strength, fewer sensory axons will be stimulated in elderly subjects compared with the young, as the available pool of sensory axons is diminished. This means that in the elderly a greater stimulus intensity is required to recruit a critical number of sensory axons.

The number of mechanoreceptors and density of nerve fibers in the skin start to decrease with the older age [11,31,32], meaning that they need more stimulation to have a touch sense feeling, leading to a higher CPT value. The use of CPT for the early diagnosis of peripheral neuropathies could potentially lead to earlier intervention and better patient outcomes.

In conclusion, the use of CPT for the touch sense evaluation could be a useful tool for both early diagnosis and follow-up of diseases involving the sensory conducting pathways. The study's reference values for the CPT in healthy Brazilian subjects using sine-wave electric stimulation provide a benchmark for future research and could potentially lead to earlier intervention and better patient outcomes. Further research is necessary to evaluate the efficacy of CPT in diagnosing and following up peripheral neuropathies.

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Additionally, we would like to disclose that a portion of this research was presented at the Brazilian Congress of Biomedical Engineering in 2019, as one of the best studies of the congress, winning an honorable mention. However, the manuscript submitted now represents a significantly expanded and refined version of the conference presentation.

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