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RESEARCH REPORT

Influence of aging on thermal and vibratory thresholds of quantitative sensory testing

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Abstract Quantitative sensory testing has become a common approach to evaluate thermal and vibratory thresholds in various types of neuropathies. To understand the effect of aging on sensory perception, we measured warm, cold, and vibratory thresholds by performing quantitative sensory testing on a population of 484 normal subjects (175 males and 309 females), aged 48.61 ± 14.10 (range 20–86) years. Sensory thresholds of the hand and foot were measured with two algorithms: the method of limits (Limits) and the method of level (Level). Thresholds measured by Limits are reaction-time-dependent, while those measured by Level are independent of reaction time. In addition, we explored (1) the correlations of thresholds between these two algorithms, (2) the effect of age on differences in thresholds between algorithms, and (3) differences in sensory thresholds between the two test sites. Age was consistently and significantly correlated with sensory thresholds of all tested modalities measured by both algorithms on multivariate regression analysis compared with other factors, including gender, body height, body weight, and body mass index. When thresholds were plotted against age, slopes differed between sensory thresholds of the hand and those of the foot: for the foot, slopes were steeper compared with those for the hand for each sensory modality. Sensory thresholds of both test sites measured by Level were highly correlated with those measured by Limits, and thresholds measured by Limits were higher than those measured by Level. Differences in sensory thresholds between the two algorithms were also correlated with age: thresholds of the foot were higher than those of the hand for each sensory modality. This difference in thresholds (measured with both Level and Limits) between the hand and foot was also correlated with age. These findings suggest that age is the most significant factor in determining sensory thresholds compared with the other factors of gender and anthropometric parameters, and this provides a foundation for investigating the neurobiologic significance of aging on the processing of sensory stimuli.

Key words: aging, algorithms, cold threshold, method of level, method of limits, quantitative sensory testing, vibratory threshold, warm threshold

Introduction

Quantitative sensory testing has become a common approach to evaluate thermal and vibratory thresholds in various types of neuropathies. Age significantly influences the structures and functions of the nervous system. In addition, the effects of age sometimes differ on various parts of the nervous system.

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For example, the gray matter density of the cortex and the volume of different regions in the brain vary substantially with age *(Sowell et al., 2003; Sullivan et al., 2004)*. Such changes may cause differential effects on functions. Neuroanatomically, the components of the pathway for thermal perception include sensory receptors in the skin, peripheral nerves, dorsal root ganglia (DRG), dorsal horn neurons, spinothalamic tracts, the thalamus, and primary and secondary somatosensory cortices. Previous studies indicated that the sensitivity to noxious stimuli may change with aging *(Dyck et al., 1996; Edwards and Fillingim, 2001; Pickering et al., 2002; Edwards et al., 2003)*. However, those studies did not specifically address the issue of age on non-noxious thermal thresholds *(Merchut and Toleikis, 1990; Hilz et al., 1999)*, such as warm thresholds. Therefore, their results are sometimes controversial. Plasticity of dorsal horn neurons also changes with aging *(Iwata et al., 2002)*. All these findings suggest that the overall functional outcome of the pathways for thermal perception should also change with age. Although previous studies on thermal thresholds provided normative data of age-matched control subjects, the number of subjects and the range of ages were often limited *(Hagander et al., 2000a; 2000b; Djaldetti et al., 2004; Shun et al., 2004)*.

Sensory thresholds are usually evaluated with quantitative sensory testing, a psychophysical approach to measuring sensory thresholds *(Yarnitsky and Ochoa, 1991; Yarnitsky and Sprecher, 1994; Yarnitsky, 1997; Dyck and O'Brien, 2002)*. Two commonly used algorithms are the method of limits (Limits) and the method of level (Level). Thresholds measured by Limits are reaction-time-dependent, and those measured by Level are reaction-time-independent *(Gruener and Dyck, 1994; Yarnitsky, 1997; Zaslansky and Yarnitsky, 1998)*. Most studies on quantitative sensory testing have usually reported the results of one algorithm *(Hilz et al., 1999; Pan et al., 2003; Djaldetti et al., 2004)*. Correlations between both algorithms and the influence of age on the difference between both algorithms, however, have never been systemically evaluated.

Functionally, the sensory system can be classified into a thermal stimulus detection system and a vibratory stimulus detection system. Both systems have different components including sensory receptors, pathways in the spinal cord, and termination sites in the thalamus. Thermal stimuli are detected by free nerve endings of the superficial skin and conveyed by unmyelinated and small myelinated nerves, the extensions of small-diameter neurons in the DRG. Central terminals of small DRG neurons form synapses in the dorsal horn of the spinal cord and ascend through spinothalamic tracts. Vibratory stimuli are detected by Pacinian corpuscles in the subcutaneous tissues and transmitted by large myelinated nerves, the extension of large neurons in DRG. The central processes of large DRG neurons ascend in the dorsal column of the spinal cord. Both systems relay in the thalamus, mainly in the ventral posterior lateral nucleus, and finally reach the somatosensory cortex. It is not clear whether age has a similar effect on sensory thresholds of both systems. Several factors might influence sensory thresholds in addition to age, including gender, regional differences (upper extremity vs. lower extremity), and anthropometric parameters. Several groups and ours have demonstrated that skin innervation is reduced with aging and that differential regulation exists, for example, between males and females and between the upper and lower extremities *(McArthur et al., 1998; Periquet et al., 1999; Chang et al., 2004; Goransson et al., 2004)*. These findings implicate that sensory thresholds may be differentially affected by age between the upper and lower extremities. Previous studies have indicated that age has significant influence on sensory thresholds of different body parts *(Dyck et al., 1993a; 1995)*. A further issue is whether the differences in sensory thresholds between different body parts are also affected by age. Anthropometric parameters, such as body height and body mass index (BMI), are important modulators of physiologic functions, for example, parameters of nerve conduction studies *(Tong et al., 2004)*. It is not clear whether these anthropometric parameters affect the measurement of sensory thresholds.

We hypothesized that age has different effects on sensory thresholds of different body parts, and the differences in sensory thresholds measured by different algorithms are also affected by age. The purposes of the current study therefore were to study the following issues in a large-scale population across different ages. These include (1) the effects of age, gender, and anthropometric parameters on sensory thresholds of thermal and vibratory stimuli, (2) the effects of age on differences between algorithms, and (3) the effects of age on differences in sensory thresholds between the hand and foot.

Materials and Methods

Study population

Healthy subjects of different ages included subjects recruited from the community and subjects who visited National Taiwan University Hospital, Taipei, Taiwan for health examinations between January 1996 and December 2003 as a previously described cohort *(Lin et al., 1998)*. No hospital employees or their relatives participated in this study. In total, there were

484 subjects (175 males and 309 females), aged 48.61 ± 14.10 (range 20–86) years. Figure 1 is a histogram demonstrating the distribution of ages in decades. Staff physicians and neurologists (SC Hsieh, CC Chao, and ST Hsieh) examined each subject to ensure the absence of neurologic symptoms and signs. Systemic and neurologic diseases, such as diabetes mellitus, hypertension, and stroke, were excluded by physical and neurologic examinations and relevant laboratory examinations including plasma glucose levels and kidney and liver functions. Detailed history of medications was surveyed and medical charts were reviewed to ensure the absence of medical illness and medications. Subjects with history of neurologic disorders, sensory symptoms, and neurologic signs were excluded from this study. The Ethics Committee of National Taiwan University Hospital, Taipei approved this study.

Quantitative sensory testing: general principles

The facilities and procedures of quantitative sensory testing were the same as previously published principles and protocols from this laboratory *(Dyck, 1993; Chiang et al., 2002; Pan et al., 2003; Shy et al., 2003; Shun et al., 2004)*. Briefly, examinations were carried out in a quiet, air-conditioned room with the room temperature maintained at 21–24°C. Skin temperatures were 31–34°C in such an environment. Before testing, the examiner explained the procedures, and several trials were conducted so that subjects could be familiar with the tests.

We used two test algorithms: the Limits and the Level. Thresholds measured by Limits are reaction-time-dependent, and those measured by Level are independent of reaction time. For thresholds measured by Limits, the machine delivered stimuli of increasing intensities starting from the baseline value according to the default settings. When the stimulus was perceived, the subject immediately pushed a button, and the machine stopped delivering the stimulus. The next trial started from the baseline value again, with the average of four successive trials as the threshold of Limits *(Yarnitsky and Sprecher, 1994; Hagander et al., 2000a; Meier et al., 2001)*.

For sensory thresholds measured by Level, the device delivered a stimulus of constant intensity set by the algorithm. The intensity of the next stimulus was either increased or decreased by a fixed ratio according to the response of the subject, i.e., whether or not the subject had perceived the stimulus. Such procedures were repeated until a predetermined difference in intensity was reached. The mean intensity of the final two stimuli was the threshold of Level *(Zaslansky and Yarnitsky, 1998)*.

Sensory thresholds of each modality at two sites, the hand and foot, were measured. To eliminate potential influences of testing order on sensory thresholds, we randomized the sequences regarding modalities (warm, cold, vs. vibratory), sites (hand vs. foot), and methods (Limits vs. Levels). There were 12 possible sequences, and preliminary analysis did not reveal any order effect. Thermal thresholds were expressed as warm threshold and cold threshold temperatures in °C, and vibratory thresholds were expressed as micrometer displacement (μm). The study population was initially set up in 1996, and normative data of the first study population were similar to those reported in the literature *(Yarnitsky and Sprecher, 1994; Lin et al., 1998; Hagander et al., 2000b)*.

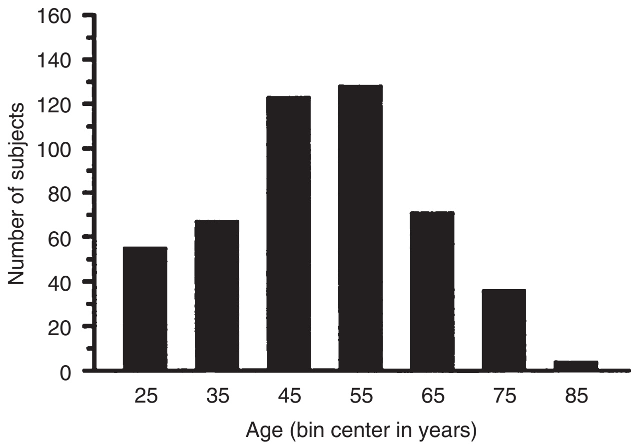

Figure 1. Distribution of age in the study population. The histogram shows the age distribution in the study population with each decade as an age group.

Quantitative sensory testing: measurement of thermal thresholds

We measured thermal thresholds with a Thermal Sensory Analyzer (TSA 2001, Medoc Advanced Medical Systems) following established protocols *(Pan et al., 2003)*. The thermode size was 3 × 3 cm, and the adaptation temperature of the thermode was set at 32°C. The stimulating surface of the thermode was placed in contact with the skin of the test site and was secured by a band without stretching. Test sites included the hand (thenar eminence) and the foot (foot dorsum). The rate of temperature change was kept at 1°C/s, with a return rate of 1°C/s. The temperatures rarely exceeded 42°C as measured by Level. During the test, subjects were instructed to give their feedback, and subjects with response of heat-pain were excluded from the analysis. All subjects in the current report rated their response as warm instead of heat-pain.

For thermal thresholds measured by Limits, the machine delivered stimuli of increasing intensities starting from the baseline value (a temperature of 32°C). When the thermal stimulus was perceived, the subject immediately pushed a button, and the sensory analyzer stopped delivering the stimulus. The next trial began again from 32°C, with the average of four successive trials taken as the threshold temperature of Limits.

For thermal thresholds measured by Level, the sensory analyzer delivered a stimulus according to a baseline temperature of 32°C with an initial increment (for warm stimuli) or decrement (for cold stimuli) of 1°C. The temperature of the next stimulus was either increased or decreased by a fixed ratio (2:1) according to the response of the subject, i.e., whether or not the subject had perceived the thermal stimulus. For example, the first trial temperature for measuring warm threshold temperature was 33°C. If the subject perceived the warm stimuli, the next trial temperature would be increased to 35°C (i.e., by adding twofolds of the previous change in temperature). If the subject did not perceive the warm stimuli at 33°C, the next trial temperature would be reduced to 32.5°C (i.e., by subtracting one-half of the previous change in temperature). Such procedures were repeated until a predetermined difference in temperature (0.2°C) was reached. The mean intensity of the final two thermal stimuli was the thermal threshold temperature of Level.

Quantitative sensory testing: measurement of vibratory thresholds

Vibratory thresholds were measured with a Vibratory Sensory Analyzer (VSA 3000, Medoc Advanced Medical Systems) following published protocols *(Pan et al., 2003)*. The diameter of the vibratory probe was 1.2 cm, and the stimulating surface of the vibratory probe was placed on the hand (the knuckle of the index finger) and the foot (lateral malleolus). The sensory analyzer delivered vibratory stimuli at a frequency of 100 Hz.

For vibratory thresholds measured by Limits, the sensory analyzer delivered stimuli of increasing intensities starting from the baseline value (0 μm of displacement) at a rate of 1 μm/s. When the vibratory stimulus was perceived, the subject immediately pushed a button, and the machine stopped delivering the vibratory stimulus. The next trial began again from the baseline value, with the average of four successive trials taken as the vibratory threshold of Limits.

For vibratory thresholds measured by Level, the sensory analyzer delivered a vibratory stimulus of constant intensity set by the algorithm. The initial search step was 1 μm of displacement. The intensity of the next vibratory stimulus was either increased or decreased by a fixed ratio of 2:1 according to the response of the subject, i.e., whether or not the subject had perceived the stimulus. Such procedures were repeated until a predetermined difference in vibratory stimuli (0.2 μm) was reached. The mean intensity of the final two vibratory stimuli was the vibratory threshold of Level.

Statistical analysis

Categorical variables were analyzed by Fisher's exact test. Numerical variables following a Gaussian distribution are expressed as the mean ± SD and were analyzed by ANOVA and a post-hoc test among the three age groups. Correlations were analyzed by two approaches: scattered plots and multiple linear regression. Sensory thresholds, the difference in thresholds between the two algorithms, and the difference in thresholds between the two test sites were plotted against age. Slopes and the 95% confidence interval (CI) were analyzed using GRAPHPAD PRISM (GraphPad Software). Both forward and backward stepwise linear regressions were performed using the statistical software SPSS (SPSS) to evaluate the effect of age on the above parameters. Results from both versions were similar, and the presentation was based on the backward version. In addition to age, gender and appropriate parameters were used as independent variables in the multivariate models with the listing of the correlation coefficients (α, t, p) for the model and standardized coefficients for each independent variable. Forward and backward stepwise linear regressions were applied in the multivariate analysis. Statistical results were considered significant if $p \leq 0.05$.

Sensations could change in an exponential pattern or as a natural log (ln) function, for example, the intensities of sounds *(von Békésy, 1959; Stevens, 1970; Johnson et al., 2002)*. In our preliminary analysis, we compared results of statistical analysis between sensory thresholds and their corresponding ln-transformed sensory thresholds. The findings were similar probably because changes in temperatures and displacements were in a narrower range compared with changes in the intensities of sounds. For simplicity, we presented authentic thresholds in the current report. When establishing normative values following the suggestions *(O'Brien and Dyck, 1995)*, we have previously calculated the percentile value of sensory thresholds in the study population for the comparison between controls and subjects with disease *(Pan et al., 2003; Shun et al., 2004)*.

Table 1. Demographic data.

	Groups			Statistics p-value
	Young	Middle age	Old	
Age range (years)	20–39	40–59	≥60	
n (%)	122 (25.2)	251 (51.9)	111 (22.9)	
Age (years)	29.90 ± 6.00	49.48 ± 5.67	67.18 ± 5.89	<0.0001
Sex (male/female)	50/72	87/164	38/73	0.438
Body height (cm)	164.7 ± 7.7	160.6 ± 7.3	159.1 ± 7.7	<0.0001
Body weight (kg)	59.27 ± 12.04	60.36 ± 9.84	60.13 ± 9.27	0.627
Body mass index (kg/m^2)	21.7 ± 3.3	23.3 ± 2.8	23.7 ± 3.1	<0.0001

Results

Effects of age on sensory thresholds by Level

The demographic data of the study population is listed in Table 1, with three age groups: young (20–39 years), middle aged (40–59 years), and old (60–80 years) by ANOVA and post-hoc tests (Table 1). The compositions of gender distribution and body weight were similar among the three groups. Body height and its derived parameter, BMI, however, differed among the three groups, suggesting that these parameters must necessarily be taken into consideration in analyzing the effect of age on sensory thresholds.

We first compared sensory thresholds measured by Level among the three age groups. Values of all three sensory thresholds by Level at the hand and foot differed among the three age groups (p < 0.0001 by

Table 2. Comparison of sensory thresholds measured by the methods of level and limits.

Sensory thresholds	Groups: Young	Middle age	Old	p-value: ANOVA	post-hoc
Method of level					
Warm thresholds					
Warm threshold of the hand (°C)	32.71 ± 0.22	32.81 ± 0.24	32.92 ± 0.26	<0.0001*	a: <0.001*, b: <0.001*, c: <0.001*
Warm threshold of the foot (°C)	35.70 ± 1.46	37.04 ± 1.74	37.96 ± 1.73	<0.0001*	a: <0.001*, b: <0.001*, c: <0.001*
Cold thresholds					
Cold threshold of the hand (°C)	31.39 ± 0.17	31.28 ± 0.23	31.22 ± 0.23	<0.0001*	a: <0.001*, b: <0.001*, c: 0.01*
Cold threshold of the foot (°C)	30.87 ± 0.52	30.59 ± 0.67	30.28 ± 0.83	<0.0001*	a: <0.001*, b: <0.001*, c: <0.001*
Vibratory thresholds					
Vibratory threshold of the hand (μm)	0.79 ± 0.23	1.19 ± 0.49	1.42 ± 0.67	<0.0001*	a: <0.001*, b: <0.001*, c: 0.001*
Vibratory threshold of the foot (μm)	1.75 ± 0.72	3.32 ± 1.45	4.89 ± 1.91	<0.0001*	a: <0.001*, b: <0.001*, c: <0.001*
Method of limits					
Warm thresholds					
Warm threshold of the hand (°C)	33.71 ± 0.68	33.96 ± 0.99	34.09 ± 0.77	<0.0001*	a: 0.008*, b: 0.001*, c: 0.218
Warm threshold of the foot (°C)	37.39 ± 2.02	38.83 ± 2.48	40.09 ± 2.39	0.003*	a: <0.001*, b: <0.001*, c: <0.001*
Cold thresholds					
Cold threshold of the hand (°C)	30.62 ± 0.62	30.41 ± 0.66	30.22 ± 0.76	<0.0001*	a: 0.005*, b: <0.001*, c: 0.015*
Cold threshold of the foot (°C)	29.38 ± 1.30	28.92 ± 1.56	28.59 ± 1.77	<0.01*	a: 0.009*, b: <0.001*, c: 0.069
Vibratory thresholds					
Vibratory threshold of the hand (μm)	1.94 ± 0.75	2.64 ± 1.14	3.02 ± 1.18	<0.0001*	a: <0.001*, b: <0.001*, c: 0.012*
Vibratory threshold of the foot (μm)	3.47 ± 1.33	5.20 ± 2.14	7.49 ± 3.06	<0.0001*	a: <0.001*, b: <0.001*, c: <0.001*

ANOVA: among the three groups; a: between young and middle age; b: between young and old; c: between middle age and old.
*Statistically significant.

ANOVA, Table 2). In addition, there were progressive differences from the young group to the old group by post-hoc test (Table 2).

To investigate the effects of age on sensory thresholds by Level, we plotted sensory thresholds against age (Fig. 2). Sensory thresholds by Level linearly changed with age, and sensory thresholds of different modalities at different locations had different slopes and intercepts. In general, the slopes for sensory thresholds of the foot were steeper than those of the hand. Slopes were 0.0616 ± 0.0053 (95% CI 0.0512–0.0720, $p < 0.0001$) for warm thresholds of the foot and 0.0048 ± 0.0008 (95% CI 0.0033–0.0068, $p < 0.0001$) for those of the hand, respectively (Fig. 2A). For cold thresholds, slopes were −0.0041 ± 0.0107 (95% CI −0.0054 to −0.0027, $p < 0.0001$) for the hand and −0.146 ± 0.0022 (95% CI −0.0189 to −0.0103, $p < 0.0001$) for the foot (Fig. 2B). Slopes of vibratory thresholds were 0.0174 ± 0.0018 (95% CI 0.0139–0.0208, $p < 0.0001$) for the hand and 0.0839 ± 0.0051 (95% CI 0.0739–0.0939, $p < 0.0001$) for the foot (Fig. 2C).

We then analyzed the effects of age on sensory thresholds by multiple regression analysis. In each model, one sensory threshold of the specified location, such as the warm threshold of the hand, was used as the dependent variable. In addition to age and gender, BMI was also used as an independent variable (Table 3). Age was the only parameter linearly associated with sensory thresholds in each model. Gender and BMI were associated with certain sensory thresholds at certain test sites. Age and gender therefore were used as independent variables in the following analyses with the model of multiple linear regression.

Correlations between algorithms: Limits vs. Level

To understand whether sensory thresholds measured by different algorithms were correlated, we also measured sensory thresholds by Limits and performed a linear regression analysis. Similar to those measured by Level, sensory thresholds measured by Limits differed among the three age groups and had progressive differences from the young to the old group according to the post-hoc test ($p < 0.0001$ by ANOVA, Table 2).

We then analyzed the correlation of sensory thresholds between both algorithms by multiple linear regression models. In each model, each sensory threshold by Level was defined as a dependent variable with its corresponding sensory threshold by the Limits (same modality and same location), age, and gender as independent variables (Table 4). Sensory thresholds measured by the two algorithms were highly correlated. Take the warm threshold of the foot as an example. The correlation coefficient, R, for the model was 0.900, and standardized coefficients for

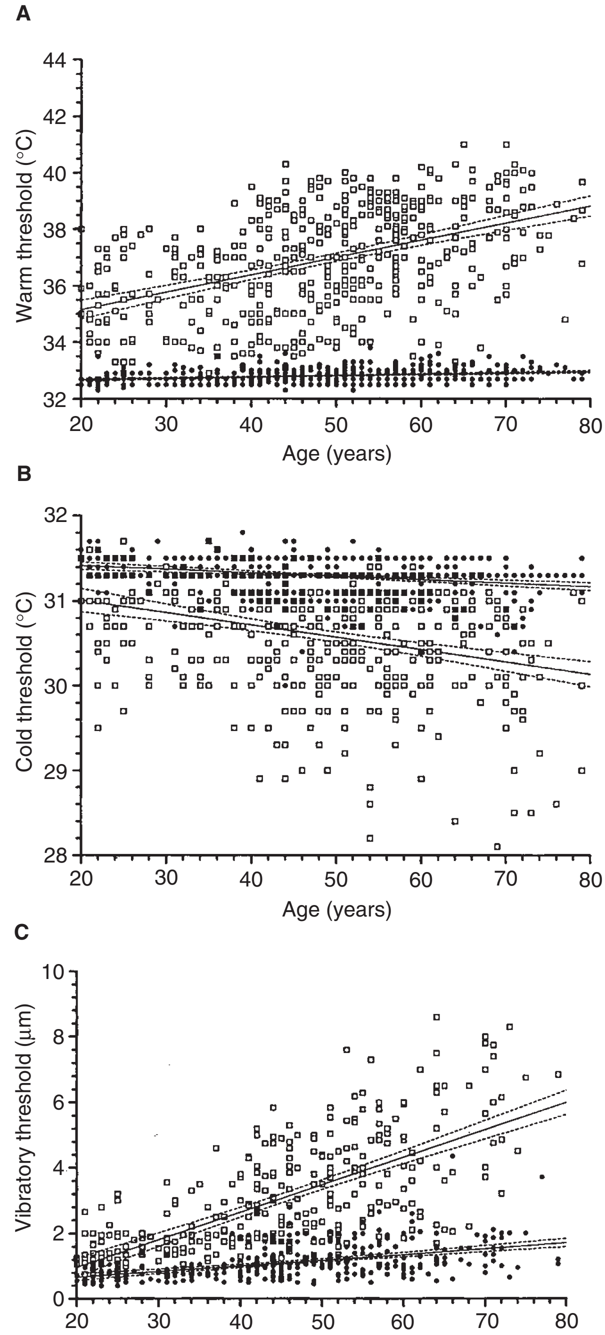

Figure 2. Effects of age on sensory thresholds. Sensory thresholds of each modality were plotted against age (●, for hand; □, for foot). (A) Warm thresholds were linearly correlated with age, with a slope of 0.0048 ± 0.0008 ($p < 0.0001$) for the hand and 0.0616 ± 0.0053 ($p < 0.0001$) for the foot. (B) Cold thresholds linearly changed with age, with a slope of −0.0041 ± 0.0107 ($p < 0.0001$) for the hand and −0.146 ± 0.0022 ($p < 0.0001$) for the foot. (C) Slopes of vibratory thresholds were 0.0174 ± 0.0018 ($p < 0.00021$) for the hand and 0.0839 ± 0.0051 ($p < 0.0001$) for the foot.

Table 3. Effect of age, gender, and body mass index on sensory thresholds by the method of level.

Location	Model (*R*, p)	Standardized coefficients (β, *t*, p)		
		Age	Gender	Body mass index
Hand				
Warm	0.351, <0.001*	0.250, 5.648, <0.001*	0.167, 3.757, <0.0001*	0.110, 2.401, 0.017*
Cold	0.273, <0.001*	−0.259, −5.685, <0.001*	−0.081, −1.782, 0.075	−0.011, −0.227, 0.821
Vibratory	0.487, <0.001*	0.469, 9.397, <0.001*	0.074, 1.435, 0.152	0.045, 0.844, 0.400
Foot				
Warm	0.511, <0.001*	0.484, 11.756, <0.001*	0.201, 4.895, <0.0001*	−0.032, −0.745, 0.457
Cold	0.295, <0.001*	−0.301, −6.587, <0.001*	−0.024, −0.533, 0.594	0.028, 0.585, 0.559
Vibratory	0.684, <0.001*	0.690, 16.198, <0.001*	0.094, 2.153, 0.032	−0.028, −0.613, 0.540

R, correlation coefficient for the model; β, standardized coefficient for the independent variable. Model of multiple linear regression: each sensory threshold of the specified location was the dependent variable, with age, gender, and one of the anthropometric parameters as the independent variable.
*Statistically significant.

thresholds by Limits and age were 0.831 and 0.124, respectively. There was a trend toward a higher correlation at the foot compared with that at the hand for each sensory threshold (standardized coefficient of 0.831 for warm threshold of the foot compared with standardized coefficient of 0.579 for warm threshold of the foot). Similar trends were observed for both cold and vibratory thresholds. These observation were substantiated by examining the 95% CI of coefficients for the same threshold by Limits. For example, the 95% CI of coefficients of the warm threshold for the hand (0.001–0.071) and the foot (0.568–0.633) were not overlapped (Table 4).

For each sensory modality at the same test site, sensory thresholds measured by Limits were higher than those measured by Level (Table 2). We then asked whether the difference in sensory thresholds between the two algorithms was age-related by plotting the differences against age (Fig. 3). Differences were linearly correlated with age, but the slopes differed. Slopes were 0.0141 ± 0.0039 (95% CI 0.0064–0.0218, $p = 0.0004$) for differences in warm thresholds of the foot and 0.0048 ± 0.0024 (95% CI 0–0.0095, $p = 0.0506$) for those of the hand (Fig. 3A). For differences in cold thresholds between algorithms, slopes were 0.0077 ± 0.0036 (95% CI 0.0006–0.0148, $p = 0.0335$) for the foot and 0.0069 ± 0.0019 (95% CI 0.0032–0.0106, $p = 0.0003$) for the hand (Fig. 3B). Slopes for differences in vibratory thresholds between algorithms were 0.0931 ± 0.0079 (95% CI 0.775–0.1087, $p < 0.0001$) for the foot and 0.0120 ± 0.0027 (95% CI 0.0067–0.0172, $p < 0.0001$) for the hand, respectively (Fig. 3C).

The effect of age on differences in sensory thresholds between the two algorithms was further analyzed by the multiple linear regression models with age and gender as independent variables (Table 5). Age was the most significant factor associated with the differences, particularly for vibratory thresholds compared with thermal thresholds despite a minor discrepancy between the simple linear regression model and the multiple linear regression model.

Differences in sensory thresholds between the hand and foot

For each subject, sensory thresholds of the foot were always higher than those of the hand (i.e., elevated warm threshold temperatures, reduced cold threshold temperatures, and elevated vibratory thresholds, $p < 0.0001$ by paired *t*-test, Table 2). We defined the parameter of the difference in each sensory threshold measured by Level between the foot and the hand for analysis. This value significantly differed from the hypothetical value of zero for each sensory threshold. For the warm threshold, the difference was 4.097 ± 1.790°C (95% CI 3.935–4.259°C, $p < 0.0001$). Differences were 0.7131 ± 0.6315°C (95% CI 0.6562–0.7701°C, $p < 0.0001$) for the cold threshold and 2.964 ± 1.625 μm (95% CI 2.779–3.149 μm, $p < 0.0001$) for the vibratory threshold. We then analyzed the effect of age on this parameter by plotting the difference in sensory threshold against age (Fig. 4). Age had a significant impact on this parameter for all sensory thresholds. The slope of the difference in warm thresholds between the foot and the hand was 0.0572 ± 0.0052 (95% CI 0.0470–0.0675, $p < 0.0001$, Fig. 4A). The difference in cold thresholds between the foot and hand was 0.0104 ± 0.0020 (95% CI 0.0065–0.0144, $p < 0.0001$, Fig. 4B). A similar observation was noted after analyzing the slope for the difference in vibratory thresholds between the foot and hand: 0.0785 ± 0.0050 (95% CI 0.0686–0.0883, $p < 0.0001$, Fig. 4C).

We performed multiple linear regression analyses on the differences in sensory thresholds (measured by

Table 4. Correlations between the method of limits and the method of level.

Thresholds and location	Model (R, p)	Standardized coefficients (β, t, p)			Unstandardized coefficient of the same threshold by Limits
		Age	Gender	Same threshold by Limits	
Hand					
Warm threshold by Level	0.657, <0.0001*	0.195, 5.548, <0.001*	0.072, 2.003, 0.046	0.579, 15.987, <0.0001*	0.036 (0.001–0.071)†
Cold threshold by Level	0.589, <0.0001*	−0.145, −3.803, <0.001*	−0.048, −1.276, 0.202	0.535, 13.976, <0.0001*	0.174 (0.150–0.198)
Vibratory threshold by Level	0.862, <0.0001*	0.182, 5.940, <0.001*	0.013, 0.461, 0.645	0.774, 25.097, <0.0001*	0.372 (0.343–0.401)
Foot					
Warm threshold by Level	0.900, <0.0001*	0.124, 5.517, <0.0001	0.050, 2.438, 0.015*	0.831, 36.377, <0.0001*	0.600 (0.568–0.633)
Cold threshold by Level	0.771, <0.0001*	−0.139, −4.609, <0.0001	−0.015, −0.511, 0.609	0.731, 24.226, <0.0001*	0.326 (0.300–0.353)
Vibratory threshold by Level	0.940, <0.0001*	0.188, 7.622, <0.0001*	−0.003, −0.167, 0.867	0.814, 32.824, <0.0001*	0.515 (0.512–0.577)

R, correlation coefficient for the model; β, standardized coefficient for the independent variable. Model of multiple linear regression: each sensory threshold of the specified location was a dependent variable, with age, gender, and one of the anthropometric parameters as an independent variable.
*Statistically significant.
†Unstandardized coefficient (95% confidence interval).

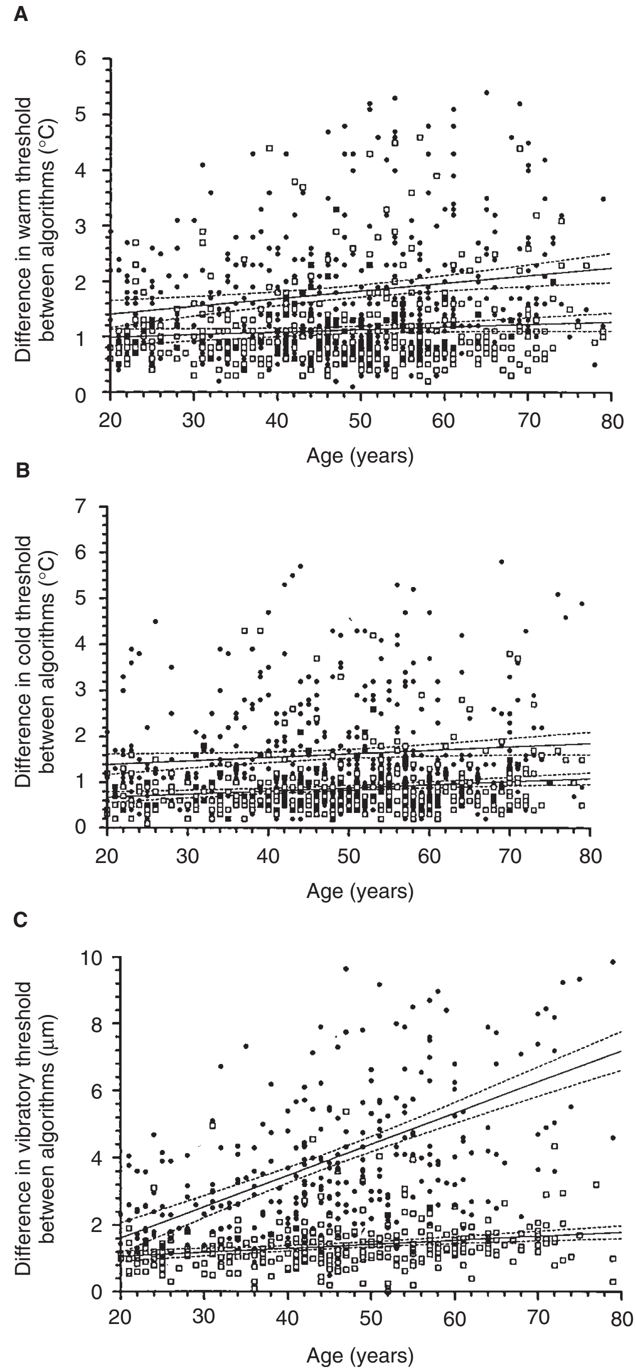

Figure 3. Effects of age on differences in sensory thresholds between the method of limits (Limits) and the method of level (Level). Differences in sensory thresholds between Limits and Level at each test site were plotted against age (●, for foot; □, for hand). (A) For differences in warm thresholds between Limits and Level, slopes were 0.0048 ± 0.0024 (p = 0.0506) for the hand and 0.0141 ± 0.0039 (p = 0.0004) for the foot. (B) Slopes of differences in cold thresholds between algorithms were 0.0069 ± 0.0019 (p = 0.0003) for the hand and 0.0077 ± 0.0036 (p = 0.0335) for the foot. (C) Slopes for differences in vibratory thresholds between Limits and Level were 0.0120 ± 0.0027 (p < 0.0001) for the hand and 0.0931 ± 0.0079 (p < 0.0001) for the foot.

Table 5. Multiple regression of differences in sensory thresholds between the method of limits and the method of level.

Thresholds and location	Model (*R*, p)	Standardized coefficients (β, *t*, p) Age	Gender
Hand			
Difference in the warm threshold	0.230, <0.001*	0.093, 2.088, 0.037*	0.212, 4.743, <0.0001*
Difference in the cold threshold	0.168, <0.001*	0.169, 3.661, <0.001*	0.030, 0.660, 0.509
Difference in the vibratory threshold	0.255, <0.001*	0.241, 4.481, <0.001*	0.086, 1.598, 0.111
Foot			
Difference in the warm threshold	0.180, <0.0001*	0.166, 3.636, <0.0001*	0.073, 1.587, 0.113
Difference in the cold threshold	0.099, 0.104	0.098, 2.129, 0.034*	−0.004, −0.077, 0.939
Difference in the vibratory threshold	0.573, <0.0001*	0.564, 11.954, <0.0001*	0.130, 2.749, 0.006*

R, correlation coefficient for the model; β, standardized coefficient for the independent variable. Model of multiple linear regression: each sensory threshold of the specified location was a dependent variable, with age, gender, and one of the anthropometric parameters as an independent variable.
*Statistically significant.

Level) between the foot and hand. Because body height might be potentially related to the difference, body height was also included as an independent variable for analysis in addition to age and gender (Table 6). Among these parameters, age was the single factor consistently correlated with these parameters. The same findings were obtained when comparing sensory thresholds measured by Limits (Table 6).

Discussion

Important observations in the current report are that (1) age is the most significant factor in determining sensory thresholds compared with other factors, such as gender and anthropometric parameters; (2) sensory thresholds measured by Level are highly correlated with sensory thresholds measured by Limits, and the difference between these two algorithms are correlated with age; and (3) sensory thresholds of the foot are higher than those of the hand, and differences in sensory thresholds between these two sites are also age-dependent. Because these findings come from an ethnic population other than the Caucasian population, such observations not only confirm previous reports *(Dyck et al., 1993a; 1995; Yarnitsky and Sprecher, 1994)* but also strongly suggest that age is the most significant factor in determining sensory thresholds. In addition, the new observations that the differences in sensory thresholds between sites and between algorithms were also age-dependent carry important implications regarding neurobiologic mechanisms and clinical applications.

Influence of age on sensory thresholds

Age was the single factor highly correlated with sensory thresholds of various modalities. The neurobiologic basis of age-dependent changes in sensory thresholds is an intriguing issue. First, thermal stimuli are detected by sensory receptors in the skin. Thus, an obvious explanation of age-dependent changes in sensory thresholds is age-related changes in the densities of sensory receptors or nerve terminals. Recent developments allow sensory nerve terminals in the skin to be studied by special staining of nerve terminals with specific neuronal markers *(Kennedy and Wendelschafer-Crabb, 1993; Pan et al., 2001)*. Quantitation of these neural structures in the skin indicated that skin innervation is reduced with age *(McArthur et al., 1998; Periquet et al., 1999; Chang et al., 2004)*. However, changes in nerve terminals can only account for a portion of the changes in sensory thresholds. Changes in other parts of the nervous system related to perceptions of sensory stimuli may also contribute to the changes in sensory thresholds, for example, central conduction through the spinal cord and the thalamus and processing of information in the sensory cortex. The incorporation of sensory nerve terminal studies and functional imaging studies may provide opportunities to understand the contributions of different structures to the effects of age on changes in sensory thresholds *(Disbrow et al., 1998; Peyron et al., 2000; Brooks et al., 2002)*. Nevertheless, quantitative sensory testing to measure sensory thresholds offers an approach for evaluating the functional integrity of the entire neural pathway for sensory perception.

The current report indicates that sensory thresholds changed linearly with age. In clinical studies, most reports interpreted sensory thresholds of patients according to normative data on a broad range of ages *(Yarnitsky and Sprecher, 1994; Shun et al., 2004)*. Taking the progressive difference among the three age groups into consideration, the reporting of sensory thresholds based on a smaller range of ages may provide more accurate information and comparisons. In the present report, the study population covered normal subjects in the range of 20–80 years of age. Several studies have indicated that changes in structures of the nervous system are not necessarily linear with aging

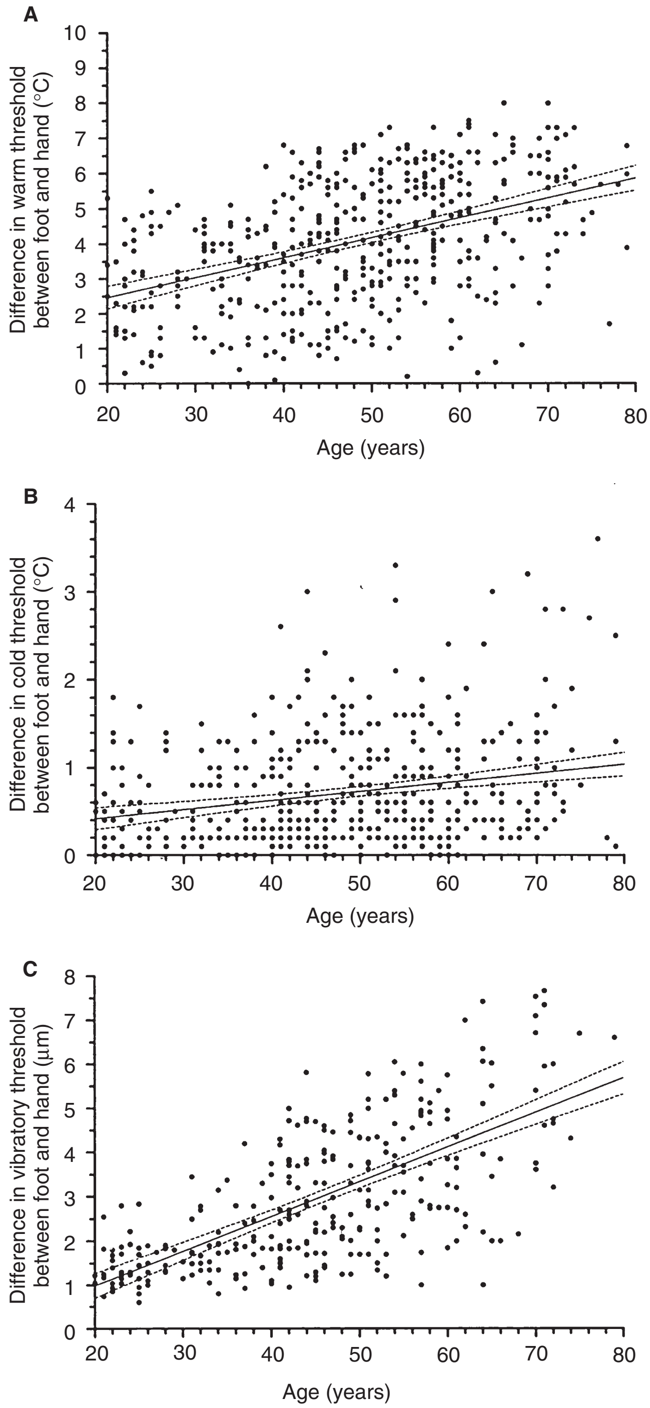

Figure 4. Effects of age on differences in sensory thresholds between the hand and foot. Differences in sensory thresholds measured by the method of level between the two test sites were plotted against age. (A) The slope of differences in warm thresholds between the foot and the hand was 0.0572 ± 0.0052 ($p < 0.0001$). (B) For the difference in cold thresholds between the foot and the hand, the slope was 0.0104 ± 0.0020 ($p < 0.0001$). (C) The slope of the differences in vibratory thresholds between the two test sites was 0.0785 ± 0.0050 ($p < 0.0001$).

(Green et al., 2000; Sowell et al., 2003; Luebke et al., 2004). A further issue is whether changes in sensory thresholds are linear for normal subjects aged >80 years. Determining this will require future studies on the oldest old group and comparison of results with those of the current study *(Green et al., 2000)*.

Finally, the effects of aging differ on various components of the sensory system, as well as between thermal and vibratory sensations. Even for the thermal system, the effect of aging differs for warm and cold thresholds. These findings extend previous observations, for example, cold thresholds of the hand and foot changed more with aging than same thresholds of the face in extensive studies to compare sensory thresholds of different body parts *(Dyck et al., 1993a)*. A further issue is whether the degree of the differences in sensory thresholds between hand and foot is also age-dependent (discussed below). Several possibilities may account for these differences: receptors, fiber tracts, and detection sensitivity of quantitative sensory testing.

Influence of age on sensory thresholds measured by different algorithms

The high correlations between sensory thresholds measured by Level and Limits have significant implications for both neurobiologic and clinical aspects. In addition, differences in thresholds of both algorithms were also correlated with age. Previous studies have reported on different algorithms separately, except for scattered studies which reported results of both algorithms *(Yarnitsky and Sprecher, 1994; Shun et al., 2004)*. The major difference between the algorithms of Level and Limits is reaction time *(Yarnitsky, 1997; Zaslansky and Yarnitsky, 1998)*. The current report suggests that the reaction-time component is also age-dependent. Previous studies on sensory thresholds did not elaborate on this issue, and the present study suggests that the comparison of sensory thresholds obtained by different algorithms provides opportunities to understand the neurobiology of sensory perception. Incorporation of motor-evoked potential studies for assessing the central motor conduction time may address this issue *(Di Lazzaro et al., 2004)*. In clinical practice, performing the Limits algorithm takes a much shorter testing time than performing the Level algorithms.

Effect of age on regional differences in thermal perception

The current report indicates the higher sensory thresholds in the foot than those in the hand, and the differences in sensory thresholds between the two sites are also age-dependent. These results extend

Table 6. Multiple regression analysis on differences in sensory thresholds between the hand and foot by different algorithms: the method of limits and the method of level.

Location	Model (*R*, p)	Standardized coefficients (β, *t*, p)		
		Age	Gender	Body height
Level				
Difference in the warm threshold	0.493, <0.0001*	0.492, 11.455, <0.0001*	0.067, 1.160, 0.247	0.152, 2.528, 0.012*
Difference in the cold threshold	0.239, <0.0001*	0.250, 5.216, <0.0001*	−0.046, −0.173, 0.473	0.056, 0.835, 0.404
Difference in the vibratory threshold	0.687, <0.0001*	0.705, 15.492, <0.0001*	0.036, 0.570, 0.569	0.113, 1.743, 0.082
Limits				
Difference in the warm threshold	0.415, <0.0001*	0.430, 9.508, <0.0001*	−0.023, −0.377, 0.706	0.182, 2.894, 0.004
Difference in the cold threshold	0.125, 0.063	0.130, 2.636, 0.009*	−0.070, –1.064, 0.288	0.064, 0.927, 0.354
Difference in the vibratory threshold	0.558, <0.0001*	0.580, 11.328, <0.0001*	0.010, 0.147, 0.883	0.174, 2.409, 0.017*

R, correlation coefficient for the model; β, standardized coefficient for the independent variable. Model of multiple linear regression: each sensory threshold of the specified location was a dependent variable, with age, gender, and one of the anthropometric parameters as an independent variable.
*Statistically significant.

previous findings that the influence of age on sensory thresholds are site- and modality-specific, for example, higher in foot than in the hand and face *(Dyck et al., 1990; 1993a; 1993b; Bell-Krotoski et al., 1993; Burns et al., 2002)*. One potential determinant of thermal thresholds is the difference in densities of sensory receptors or nerve terminals in the skin *(Dyck et al., 1993b)*. As observed in a previous study, the density of nerve terminals in the skin of the lower extremities is lower than that of the upper extremities *(Chang et al., 2004)*. However, differences in sensory nerve terminals of the skin between the upper and lower extremities are not age-dependent *(Chang et al., 2004)*. This is in contrast to the observation that differences in sensory thresholds between the hand and the foot are age-dependent. Certainly, the skin type, glabrous skin vs. hairy skin, may contribute to a difference in the abundance of cutaneous nerve terminals *(Nolano et al., 2003)*. Alternatively, the pathways traveled from sensory receptors to the sensory cortex differ in length, being longer for the foot than for the hand. This can be demonstrated by the much higher sensory thresholds measured by Limits than by Levels. In addition, differences in sensory thresholds between the two algorithms being much larger in the foot than in the hand may partially account for this phenomenon. How sensory information dissipates during conduction is another intriguing issue. Future studies combining various neurophysiologic approaches with quantitative sensory testing may unravel the underlying neurobiologic significance.

In conclusion, the present study provides normative data of aging on sensory thresholds by Limits and Level in a large population. The results suggest that age is the most single determinant of sensory thresholds among all parameters studied; these are important references for the interpretation of clinical data on sensory thresholds. Quantitative sensory testing is an easily performed, non-invasive assessment, and these approaches could be applied clinically *(Zaslansky and Yarnitsky, 1998; Burns et al., 2002; Magda et al., 2002; Shy et al., 2003)*, including screening of sensory disorders *(Dyck et al., 1987; 2000; Lipton et al., 1987; Nurmikko, 1991; Gulevich et al., 1992; Dyck and O'Brien, 1999; Sindrup et al., 2001)* and monitoring of disease progression or therapeutic effects *(Simovic et al., 2001; Wellmer et al., 2001; Wallace et al., 2002; Hilz et al., 2004; Windebank et al., 2004; de la Cour and Jakobsen, 2005)*.

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