

Original Research Article

Age Differences in Multimodal Quantitative Sensory Testing and Associations With Brain Volume

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Abstract

Background and Objectives: Somatosensory function is critical for successful aging. Prior studies have shown declines in somatosensory function with age; however, this may be affected by testing site, modality, and biobehavioral factors. While somatosensory function declines are associated with peripheral nervous system degradation, little is known regarding correlates with the central nervous system and brain structure in particular. The objectives of this study were to examine age-related declines in somatosensory function using innocuous and noxious stimuli, across 2 anatomical testing sites, with considerations for affect and cognitive function, and associations between somatosensory function and brain structure in older adults.

Research Design and Methods: A cross-sectional analysis included 84 “younger” ($n = 22$, age range: 19–24 years) and “older” ($n = 62$, age range: 60–94 years) healthy adults who participated in the Neuromodulatory Examination of Pain and Mobility Across the Lifespan study. Participants were assessed on measures of somatosensory function (quantitative sensory testing), at 2 sites (metatarsal and thenar) using standardized procedures, and completed cognitive and psychological function measures and structural magnetic resonance imaging.

Results: Significant age \times test site interaction effects were observed for warmth detection ($p = .018$, $\eta_p^2 = 0.10$) and heat pain thresholds ($p = .014$, $\eta_p^2 = 0.12$). Main age effects were observed for mechanical, vibratory, cold, and warmth detection thresholds ($ps < .05$), with older adults displaying a loss of sensory function. Significant associations between somatosensory function and brain gray matter structure emerged in the right occipital region, the right temporal region, and the left pericallosum.

Discussion and Implications: Our findings indicate healthy older adults display alterations in sensory responses to innocuous and noxious stimuli compared to younger adults and, furthermore, these alterations are uniquely affected by anatomical site. These findings suggest a nonuniform decline in somatosensation in older adults, which may represent peripheral and central nervous system alterations part of aging processes.

Translational Significance: Sensory function is critical to healthy aging. While there is a general consensus that sensory function, such as vision and hearing, declines with age, less is known about changes in other important sensory modalities, such as touch and pain sensitivity. This article adds to the literature by investigating age-related changes in somatosensory functions necessary for maintaining mobility and independence through the life course and provides evidence for specific, rather than global, sensory decline that is related to central nervous system function.

Keywords: Central nervous system, Cold detection threshold, Heat pain threshold, Mechanical threshold, Vibration detection threshold

Background and Objectives

The loss of main sensory modalities (vision, hearing, taste, and smell) is considered a normal part of aging; however, less is known about age-related changes in somatosensory function (1,2). Somatosensory function (eg, mechanoreception, thermoreception, pain perception) provides important information about the internal and external environment, necessary for maintaining health and independence during aging (3–5). The ability to sense touch, regulate temperature, and discriminate between innocuous and potentially damaging stimuli are important protective defenses that, when impaired, place individuals at a greater risk for isolation, injury, and negative health outcomes (3,5,6). While prior research indicates somatosensory function may be negatively affected in older adults, findings are inconsistent (1).

Multimodal quantitative sensory testing (QST) is a method that can be used to quantify somatosensory function across the life span. During QST, innocuous and noxious stimuli can be applied to quantify a loss or gain of sensory function, as well as pain sensitivity and pain modulatory capacity (7). Research has demonstrated older adults exhibit increased detection thresholds for both thermal and mechanical stimuli, indicating a general decline in somatosensory functioning (8). However, these findings are inconsistent (9). For example, Yang et al. (10) demonstrated differential detection thresholds to cold, warmth, mechanical, and vibratory stimuli among healthy adults such that all detection thresholds were influenced by the testing site (face and hand), but only warmth and mechanical detection were influenced by age. Moreover, 2 studies assessing age-related changes across multiple somatosensory modalities demonstrated that thermal detection thresholds were significantly affected by both age and testing site, with older adults demonstrating greater thermal detection thresholds in the lower extremities (11,12), while other researchers have failed to find age-related declines detection responses to innocuous stimuli (13). Collectively, these findings suggest that somatosensory function is not only affected by age, but also by the testing site in humans, supporting the theory that sensory declines in aging are specific, rather than global, events (14).

The strongest evidence for age-related changes in somatosensory function is in response to noxious stimuli (15). Findings from several studies indicate older adults may be less sensitive to painful heat stimuli compared to young adults (16,17). Interestingly, these age-related differences do not appear to be universal across testing sites. For example, Riley et al. (16) reported age-related differences in response to heat pain at the knee, but not at the forearm. Other studies provide evidence for diminished pain modulatory capacity in older adults, which may reflect declines in endogenous inhibitory systems (18). Moreover, Cruz-Almeida et al. (19) recently showed that an older epigenetic age (based on an epigenetic aging biomarker) was significantly associated with heat pain thresholds ($r = -0.48, p < .05$) and pressure pain thresholds (PPTs) at the trapezius ($r = -0.57, p < .01$), but not PPTs at the quadriceps, again highlighting potential site-specific alterations. These findings are in line with a previous systematic review indicating that age effects on somatosensory functioning are most robustly observed for pressure stimuli compared to thermal and electrical (20). However, other researchers have found the opposite, with thermal pain detection being affected by age but not PPTs (10,16,17).

Evaluation of age-related changes in somatosensory function will also necessitate consideration of biobehavioral factors such as cognitive and psychological function. Population-based studies have reported significant associations between cognitive decline, depression, and sensory deficits (eg, vision and hearing) (21,22). Also, research has shown that depressed mood states (23) and psychological distress (24) can influence responses to noxious stimuli. Furthermore, recent research implicates the somatosensory cortex, responsible for processing sensory information from various parts of the body, in emotional processing, generation of emotional states, and emotional regulation (25,26).

Age-related changes in somatosensory function are likely due to changes in both the peripheral and central nervous systems (2,9). Previous research has demonstrated that brain volume decreases with aging (27), which may help to explain declines in somatosensory function. However, little is known regarding the relationship between age-related

differences in somatosensation and specific brain structure characteristics. The brain is not static, and research indicates that compensatory responses in the brain may confer sensory maintenance in older adults (28). Given the conflicting findings of how somatosensory function is influenced by age and testing site, and the importance of somatosensory function in successful aging, examination is warranted to further identify mechanisms contributing to age-related declines.

Therefore, the purpose of this study was to (a) systematically examine somatosensory function by age and test site using a validated multimodal QST battery and (b) explore associations between somatosensory function in older adults and brain structure. Given the prior literature, we hypothesized that older adults would demonstrate higher thermal and mechanical sensory detection thresholds and greater pain sensitivity, compared to young adults, and that brain structure would be associated with somatosensory function across multiple sensory modalities.

Research Design and Methods

Study Design

Participants were recruited as part of the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) study, aimed at examining the neurobiology of age-related differences in pain modulation and its impact on function, conducted at the University of Florida (UF) between 2015 and 2020. Data for this study were obtained during separate laboratory sessions conducted approximately 1 week apart. The measures and procedures described below are limited to those involved in this study. All procedures were reviewed and approved by the UF Institutional Review Board, and all participants provided written and verbal informed consent.

Participants

Community-dwelling healthy younger adults aged 18–28 years ($n = 22$) and older adults older than 60 years ($n = 62$), who were native English speakers were recruited through posted flyers, newspaper ads, and word of mouth. Specific pain conditions were not included as part of the eligibility criteria as the NEPAL study aimed to include a broad representation of aging adults. Individuals with the following conditions were excluded from participation in the study: (a) Alzheimer's, Parkinson's, or other condition directly affecting the brain; (b) serious psychiatric condition (eg, schizophrenia, major depression, bipolar disorder); (c) uncontrolled hypertension, heart failure, or history of acute myocardial infarction; (d) systemic rheumatic disorders (ie, rheumatoid arthritis, fibromyalgia, systemic lupus erythematosus); (e) HIV/AIDS; (f) hospitalization within the past year for a psychiatric condition; (g) chronic opioid use; (h) excessive anxiety about the study protocol; (i) contraindications to magnetic

resonance imaging (MRI); and (j) and cognitive impairment (Modified Mini-Mental State Examination score ≤ 77 (29)), as previously published (19).

Study Procedures

Individuals were screened for eligibility by phone and in person. Following screening and informed consent, participants completed a health assessment session (HAS) that included standard demographic and health questionnaires, psychological questionnaires, and measures of self-reported pain, followed by a multimodal QST session to assess somatosensory functioning, basal pain sensitivity, and modulation and an MRI session. Sessions were scheduled no more than 1 week apart. Full study procedures have been previously reported (19).

Health Assessment Session

During the HAS, participants were screened for cognitive impairment and asked to complete demographic questionnaires (eg, age, sex, ethnicity/race, education) and were interviewed about their clinical pain history and completed psychological measures. Participants also completed the Edinburgh Handedness Inventory (EHI) to assess dominance and laterality.

Depression

The *Center for Epidemiologic Studies—Depression (CES-D)* scale is a 20-item measure on which participants rate the frequency of depression-related symptoms ranging from 0 “rarely or none of the time” to 3 “most or almost all of the time” (30). The CES-D scale has been shown to be a reliable and valid measure of depressive symptomology in the general population (30).

Affect

The *Positive and Negative Affect Scale (PANAS)* was also administered and consists of two 10-item subscales designed to examine positive and negative affects. High positive affect (PA) scores indicate “high energy, full concentration, pleasurable engagement,” while high negative (NA) scores indicate “subjective distress and unpleasurable engagement” (31). The PANAS has demonstrated adequate internal consistency, validity, and test–retest reliability in the general population (31). Both state (“you feel this way right now”) and trait (“you generally feel this way”) PA and NA were assessed.

Cognitive function

The 30-item *Modified Mini-Mental State Examination (3MS)* was used to assess cognitive status (29) and has been widely used as a screening tool for dementia. The 3MS displays high interrater reliability and internal consistency (32).

Self-reported pain

Current baseline pain at the time of somatosensory testing (prior to QST procedures) was assessed on a 0 “no pain” to 100 “the most intense pain imaginable” numerical rating scale (NRS).

QST Session

All testing was conducted in a quiet room with a controlled temperature, mean = 22.21°C, with participants seated in a comfortable chair. Procedures were explained to the participant with instructions delivered just before the start of the testing. A demonstration of testing procedures followed by at least one practice trial ensured participants’ understanding of the testing protocol. PPT was conducted at the trapezius and quadriceps; all other QST procedures were conducted at the thenar eminence and at the first metatarsal head of the foot, following standardized procedures. QST procedures followed a standardized protocol consistent with the German Research Network on Neuropathic Pain protocol (7,33). Testing algorithms included a method of limits for detection and pain thresholds and methods of levels for temporal summation (34).

Thermal testing

Thermal detection and pain thresholds. A 30 × 30 thermode attached to the TSA-II Neurosensory Analyzer was applied to both test sites. The thermode temperature started at 32°C and either gradually decreased (ie, cold detection) or increased (ie, warmth detection) at a rate of 1°C/second until the participant stated the stimulus was first perceived as cold or warm, respectively. This procedure was repeated until the participant reported the stimulus as first painful (ie, cold pain threshold and heat pain threshold) with a cutoff value of 0°C for cold pain threshold and 50°C for heat pain threshold. Participants were asked to rate the pain intensity of each cold and heat pain threshold trial on a 0–100 NRS, where 0 represents “no pain” and 100 represents “the most intense pain imaginable.” The thermal detection and thermal pain procedures were each repeated 3 times for both cold and warmth at each site and the average obtained for each test. Cold detection threshold and cold pain threshold values were Z-transformed so that a higher Z-value indicated a higher cold detection/pain threshold (ie, less sensitivity). Warmth detection and heat pain threshold values were Z-transformed and reversed so that a higher Z-score indicated a lower warmth detection or heat pain threshold (ie, more pain sensitivity or gain of function).

Mechanical testing

Mechanical detection threshold. A standard set of Semmes–Weinstein monofilaments (Touch Test™ Sensory Evaluator; North Coast Medical, Inc., Morgan Hill, CA) were used to assess mechanical detection threshold (MDT)

at both testing sites. Participants were instructed to close their eyes and respond “yes” when they could first feel the test stimulus or “no” if they could not feel it. “Catch trials” were randomly completed in which the monofilament was moved closer to the skin without actually touching it in order to document potential reporting bias. Test stimuli ranged from 0.008 to 300 g monofilament probes. Four series of stimuli were applied to each site using the method of limits to capture detection thresholds. Average MDT was calculated as follows: (a) 2 series of descending stimuli—average calculated using the force for the last monofilament that was detected and the force for the first monofilament that was not detected; and (b) 2 series of ascending stimuli—average calculated using the force for the last monofilament that was not detected and the force for the first monofilament that was detected. Threshold values for MDT at each test site (ie, thenar eminence and metatarsal) were defined as the geometric mean obtained over the 4-stimulus series based on the raw MDT scores. Geometric means were converted to Z-scores and reversed so that a higher Z-score indicated a lower MDT (ie, more pain sensitivity or gain of function).

Pressure pain threshold. A handheld digital pressure algometer (AlgoMed; Medoc Ltd., Ramat Yishai, Israel) was applied to the right quadriceps and right trapezius muscles at a constant rate of 30 kPa/second up to a maximum pressure level of 1000 kPa. Participants indicated when the pressure first became painful by pressing a button. The order of testing site was randomized and counterbalanced. Each trial was repeated 3 times at each site and averaged. PPT values were Z-transformed and reversed for analysis so that higher Z-scores indicated a lower PPT (ie, more pain sensitivity).

Mechanical temporal summation. A calibrated nylon monofilament with 300 g of force was applied to each site (ie, thenar eminence and metatarsal) in a randomized order. First, a single stimulus was delivered and participants rated the pain intensity using a 0–100 NRS. Next, a series of 10 punctate stimuli were administered twice at a rate of one contact/second and participants verbally rated the highest pain intensity. The pain intensity ratings were averaged by site, and the averages of the single pain ratings were subtracted from this number at each location. Mechanical temporal summation (MTS) magnitude was Z-transformed so that a higher Z-score indicated a higher MTS magnitude (ie, more pain sensitivity).

Vibratory detection threshold. A handheld VSA-3000 circular probe with a 1.22 cm² circular probe attached to a TSA-II Neurosensory Analyzer with accompanying software (Medoc Ltd, Ramat Yishai, Israel) measured vibratory detection threshold (VDT) for a 100 Hz stimulus frequency at both the thenar eminence and first metatarsal

head. Vibratory sensations began at 0 μm and increased at 0.5 $\mu\text{m}/\text{second}$ until a maximum of 130 μm was reached. Each participant indicated when s/he first felt a vibratory sensation, and this value was recorded. This procedure was conducted 3 times at each site and averaged. VDT values were Z-transformed and reversed so that a higher Z-score indicated a lower VDT (ie, gain of function).

Neuroimaging

MRI data were collected on the Advanced Magnetic Resonance Imaging and Spectroscopy facility’s Philips (Best, the Netherlands) 3-T scanner with a 32-channel radiofrequency coil at the University of Florida’s McKnight Brain Institute. A high-resolution, T1-weighted (T1w), turbo field echo, anatomical scan was collected with the following parameters: repetition time = 7.1 ms, echo time = 3.2 ms, 170 slices acquired in a sagittal orientation, flip angle = 8°, and resolution = 1 mm³. The head was secured via cushions positioned inside the head coil to minimize movement. Each T1w image was preprocessed using the “recon-all” function in Freesurfer Software Suite 7.1.0 (<http://surfer.nmr.mgh.harvard.edu/>), with a default configuration for the general cortical reconstruction process. This procedure included calculating the volume of the cortical areas using the Destrieux atlas (35) (Freesurfer’s *aparc.2009s*).

Statistical Analysis

Data analysis was conducted in SPSS v.26 (IBM, Armonk, NY). Age was transformed into a bivariate categorical variable (19–28 years old and ≥ 60 years old). These categories were selected as these age ranges were part of the eligibility criteria for participation in the study. Descriptive statistics were calculated and group differences were assessed using

t-tests for continuous/discrete ordinal variables and chi-square for nominal variables. Assumptions underlying each statistical test were examined. Listwise deletion was employed for missing data. All QST variables were transformed to Z-scores prior to analysis. To examine QST differences by age and test site, repeated measures analyses of covariance with age group as the between-subjects factor and test site as the within-subjects factor were conducted, controlling for race, affect, and cognitive function. Unadjusted (ie, no covariates), partially adjusted (ie, controlling for race and affect), and fully adjusted (ie, controlling for race, affect, and cognitive function) models were examined using a forward stepwise approach, as these variables differed significantly ($p < .05$) between age categories (Table 1). An effect size of 0.01, 0.06, and 0.14 was considered to be small, medium, and large effect sizes, respectively, with an alpha of less than 0.05 considered statistically significant. Statistically significant interaction effects ($p < .05$; two-tailed) were followed with simple effects decomposition and Bonferroni correction to examine main effects.

Brain imaging analysis

Using a linear model, we examined the association between QST measurements and the volume of the cortical areas segmented by Freesurfer, using the latter as the independent variable, the former as the dependent variable, and sex, EHI, and intracranial volume as covariates. This analysis was done using Freesurfer, with Cluster-wise Correction for Multiple Comparisons ($p < .05$; two-tailed).

Results

Demographic and Clinical Characteristics

A total of 84 participants were included in this secondary analysis. Individuals in the younger age category ($n = 22$)

Table 1. Demographic and Clinical Characteristics of the Sample

Characteristic	Younger Adults ($n = 22$)	Older Adults ($n = 62$)	<i>p</i>
Age (years), <i>mean</i> \pm <i>SD</i>	21.31 \pm 1.54	72.12 \pm 6.69	<.001
Sex, <i>n</i> (% female)	12 (54.5)	41 (66.1)	.441
Race, <i>n</i> (%)			
Caucasian	13 (59.1)	58 (93.5)	<.001
African American	1 (4.5)	3 (4.8)	.720
Asian/Pacific Islander	2 (9.1)	1 (1.2)	.066
Hispanic	6 (27.3)	0 (0)	<.001
Education	14.54 \pm 1.41	15.74 \pm 2.84	.062
CES-D scale, <i>mean</i> \pm <i>SD</i>	7.35 \pm 5.71	7.23 \pm 5.17	.930
PANAS State Positive, <i>mean</i> \pm <i>SD</i>	29.42 \pm 7.47	34.28 \pm 8.79	.033
PANAS State Negative, <i>mean</i> \pm <i>SD</i>	11.74 \pm 2.62	11.12 \pm 1.98	.275
PANAS Trait Positive, <i>mean</i> \pm <i>SD</i>	36.21 \pm 8.44	36.93 \pm 6.33	.700
PANAS Trait Negative, <i>mean</i> \pm <i>SD</i>	13.42 \pm 3.44	11.68 \pm 2.58	.024
3MS, <i>mean</i> \pm <i>SD</i>	100.90 \pm 2.67	98.82 \pm 3.36	.014
Baseline Pain rating, <i>mean</i> \pm <i>SD</i>	0.00 \pm 0.00	7.95 \pm 13.87	.030

Notes: CES-D = Center for Epidemiologic Studies—Depression; PANAS = Positive and Negative Affect Scale; 3MS = Modified Mini-Mental State Examination. Bold values represent statistical significance at $\alpha = 0.05$.

ranged from 19 to 24 years with mean (*SD*) age = 21.31 (1.54). All individuals in this age category were pain-free based on the clinical pain history and self-reported pain ratings at the time of testing. Individuals in the older age category ($n = 62$) ranged from 60 to 94 years with mean (*SD*) age = 72.11 (6.69) years. Within the older age participants, mean (*SD*) baseline pain intensity at the time of sensory testing was low (mean (*SD*) = 7.95 (13.87); [Table 1](#)). Ethnicity/race representation differed significantly between young and older adults ($p < .001$). While depressive symptoms (*CES-D scale*) did not differ by age cohorts ($p = .913$), state positive affect (*PANAS State PA*) was statistically higher ($p = .033$) and trait negative affect (*PANAS Trait NA*; $p = .024$) was statistically lower in older adults compared to young adults. Cognitive function was also statistically significantly lower in older adults compared to young adults ($p = .014$; [Table 1](#)).

Somatosensory Function

Thermal testing

Cold detection thresholds and pain thresholds and ratings. A significant main effect of age was observed for cold detection thresholds (fully adjusted model: $F(1,54) = 10.706$, $p = .002$, $\eta_p^2 = 0.165$), with older adults displaying a lower cold detection threshold (ie, older adults required more temperature stimulus for cold detection threshold), at both sites ([Tables 2 and 3](#)). Cold pain threshold ratings during testing did not differ by age or test site, and interaction effects were not observed ($ps > .05$; [Figure 1](#)).

Warmth detection thresholds and heat pain thresholds and ratings. Statistically significant age \times test site interaction effects were observed for warmth detection threshold (fully adjusted models: $F(1,53) = 5.95$, $p = .018$, $\eta_p^2 = 0.10$) and heat pain threshold ($F(1,47) = 6.55$, $p = .014$, $\eta_p^2 = 0.12$). Warmth detection threshold and heat pain threshold were significantly higher at the metatarsal (ie, foot) in older adults compared to younger adults, indicating a loss of somatosensory function with age ([Tables 2 and 3](#); [Figure 1](#)). Age differences in these measures were not observed at the hand (warmth detection threshold: $p = .092$; heat pain threshold: $p = .917$). Heat pain threshold ratings differed by age in the unadjusted model ($p = .029$); however, this effect was mitigated with the addition of covariates ([Tables 2 and 3](#); [Figure 1](#)).

Mechanical testing

Mechanical detection threshold. There was a significant main effect of age on punctate MDT (fully adjusted model: $F(1,52) = 21.609$, $p < .001$, $\eta_p^2 = 0.294$), with older adults displaying higher MDTs, or a loss of sensory function, relative to younger adults (mean difference (*SE*) = 0.64 (0.14); [Tables 2 and 3](#); [Figure 1](#)).

Pressure pain threshold. Significant age \times test site interaction effects were observed for PPT in the unadjusted and partially adjusted models ([Table 3](#)); however, this effect was no longer statistically significant after controlling for race, affect, and cognitive function ($p = .217$). PPTs were lower among older adults at the quadriceps compared to younger adults ([Figure 1](#)).

Mechanical temporal summation. Main and interaction effects were not observed for MTS across all models ($ps > .05$; [Tables 2 and 3](#); [Figure 1](#)).

Vibratory detection threshold. There was a significant main effect of age on VDT (fully adjusted model: $F(1,53) = 11.674$, $p = 0.001$, $\eta_p^2 = 0.180$), with older adults displaying higher VDT at the foot and hand compared to young adults, indicating a loss of somatosensory function in older adults (mean difference (*SE*) by age = 7.767 (3.232); [Tables 2 and 3](#); [Figure 1](#)).

Brain Volume Associations With Somatosensory Function in Older Adults

Brain volume associations with QST measures were tested employing general linear models (GLMs), while controlling for sex, EHI, and estimated total intracranial volume (cluster-wise probability < 0.05). In older participants, higher cold detection thresholds, heat pain threshold ratings, and MDTs were associated with volume variations across multiple brain regions using threshold-free cluster enhancement approaches. Higher cold detection threshold at the metatarsal was associated with increased volume in the inferior occipital gyrus and sulcus. Increased heat pain threshold rating at the thenar eminence was associated with increased volume of the pericallosal sulcus (S of corpus callosum). Also, a higher MDT at the thenar eminence was associated with reduced brain volume in the lateral aspect of the superior temporal gyrus and increased brain volume in the middle occipital sulcus and lunatus sulcus. These results are presented in [Table 4](#) and [Figure 2](#).

Discussion and Implications

This study examined the impact of age and anatomical testing site on somatosensory function in healthy young and older adults employing a multimodal QST battery to both innocuous and noxious stimuli, similar to the protocol used by the German Research Network on Neuropathic Pain (7). A novel component of this study was our examination of brain structure associations with QST measures that were significantly different between the age groups, providing further support for the role of central neural mechanisms in age-related changes in somatosensory processing.

Table 2. Unadjusted and Adjusted Mean ± SD Raw QST Values by Age and Testing Site

QST	Unadjusted		Partially Adjusted 1		Partially Adjusted 2		Fully Adjusted	
	Younger Adults, M ± SD	Older Adults, M ± SD	Younger Adults, M ± SD	Older Adults, M ± SD	Younger Adults, M ± SD	Older Adults, M ± SD	Younger Adults, M ± SD	Older Adults, M ± SD
CDT								
Th	31.08 ± 0.31	30.24 ± 0.98	31.08 ± 0.31	30.24 ± 0.98	31.09 ± 0.32	30.17 ± 1.03	31.09 ± .32	30.17 ± 1.03
Meta	28.06 ± 1.66	22.96 ± 5.65	28.06 ± 1.66	22.96 ± 5.65	28.01 ± 1.33	22.76 ± 6.04	28.01 ± 1.33	22.76 ± 6.04
CPT								
Th	11.33 ± 7.60	10.79 ± 7.22	11.33 ± 7.60	10.79 ± 7.22	11.29 ± 7.51	10.65 ± 7.51	11.29 ± 7.51	10.65 ± 7.51
Meta	8.56 ± 8.23	10.53 ± 9.41	8.56 ± 8.23	10.53 ± 9.41	9.44 ± 8.52	10.19 ± 9.41	9.44 ± 8.53	10.19 ± 9.41
CPR								
Th	14.02 ± 18.76	30.87 ± 25.48	14.03 ± 18.76	30.87 ± 25.49	14.50 ± 19.89	31.01 ± 24.02	14.50 ± 19.89	31.01 ± 24.09
Meta	15.76 ± 22.16	23.94 ± 24.50	15.76 ± 22.15	23.94 ± 24.51	16.72 ± 23.67	25.09 ± 23.86	16.72 ± 23.67	25.90 ± 23.86
WDT								
Th	32.97 ± 0.28	33.59 ± 1.00	32.97 ± 0.28	33.59 ± 1.00	32.96 ± 0.28	33.61 ± 1.06	32.96 ± 0.28	33.61 ± 1.06
Meta	35.27 ± 1.73	42.26 ± 4.09	35.27 ± 1.73	42.26 ± 4.09	35.46 ± 1.78	42.23 ± 4.15	35.46 ± 0.78	42.24 ± 4.15
HPT								
Th	44.55 ± 4.07	43.90 ± 4.64	44.55 ± 4.08	43.90 ± 4.64	44.37 ± 4.17	44.14 ± 4.61	44.37 ± 4.17	44.14 ± 4.61
Meta	44.38 ± 3.12	46.67 ± 2.41	44.38 ± 3.11	46.67 ± 2.41	44.06 ± 3.19	46.70 ± 2.40	44.06 ± 3.19	46.70 ± 2.40
HPR								
Th	18.05 ± 22.39	36.55 ± 28.17	18.05 ± 22.39	36.55 ± 28.17	18.94 ± 23.78	37.85 ± 27.08	18.94 ± 23.78	37.85 ± 27.08
Meta	19.78 ± 23.16	36.64 ± 27.91	19.78 ± 23.16	36.64 ± 26.90	20.69 ± 24.49	38.72 ± 27.77	20.69 ± 24.95	38.72 ± 27.77
MDT								
Th	2.55 ± 0.34	3.15 ± 0.47	2.55 ± 0.34	3.15 ± 0.47	2.55 ± 0.38	3.18 ± 0.49	2.55 ± 0.38	3.16 ± 0.50
Meta	3.15 ± 0.48	3.86 ± 0.44	3.15 ± 0.48	3.86 ± 0.44	3.16 ± 0.50	3.86 ± 0.44	3.17 ± 0.49	3.86 ± 0.44
PPT								
Quad	640.56 ± 269.39	481.91 ± 242.66	640.56 ± 269.39	481.91 ± 242.66	614.37 ± 264.29	487.99 ± 260.41	614.37 ± 264.29	487.99 ± 260.41
Trap	344.73 ± 21.71	336.44 ± 176.97	344.73 ± 217.72	336.44 ± 176.97	330.24 ± 235.13	335.81 ± 175.99	330.24 ± 235.13	335.81 ± 175.99
MTS								
Th	5.73 ± 6.90	11.62 ± 15.75	5.70 ± 6.90	11.62 ± 15.75	6.53 ± 7.09	11.69 ± 16.49	6.54 ± 7.09	11.69 ± 16.49
Meta	8.20 ± 11.09	16.02 ± 16.08	8.20 ± 11.08	16.01 ± 16.08	9.38 ± 11.49	16.79 ± 16.12	9.38 ± 11.49	16.74 ± 16.12
VDT								
Th	0.53 ± 0.20	1.14 ± 0.89	0.53 ± 0.20	1.14 ± 0.89	0.52 ± 0.20	1.16 ± 0.93	0.51 ± 0.20	1.16 ± 0.93
Meta	0.81 ± 0.30	11.97 ± 19.71	0.81 ± 0.30	11.97 ± 19.71	0.78 ± 0.31	13.23 ± 21.29	0.78 ± 0.31	13.23 ± 21.28

Notes: QST = quantitative sensory testing; Th = thenar (hand); Meta = metatarsal (first metatarsal head of the foot); Quad = quadriceps; Trap = trapezius; CDT = cold detection threshold; CPT = cold pain threshold; CPR = cold pain ratings; WDT = warm detection threshold; HPT = heat pain threshold; HPR = heat pain rating; MDT = mechanical detection threshold; PPT = pressure pain threshold; MTS = mechanical temporal summation; VDT = vibratory detection threshold. Unadjusted = no covariates; partially adjusted 1 = included ethnicity/race covariate; partially adjusted 2 = included ethnicity/race and affect covariates; fully adjusted = included ethnicity/race, affect, and cognitive function covariates.

Table 3. QST Age × Test Site Interactions and Main Effects

Variable		Unadjusted	Partially Adjusted 1	Partially Adjusted 2	Fully Adjusted
CDT	Age × Test site	.791	.785	.892	.875
	Age	<.001	<.001	.001	.002
	Test site	.967	.124	.252	.158
CPT	Age × Test site	.270	.271	.434	.581
	Age	.847	.847	.636	.801
	Test site	.215	.051	.939	.525
CPR	Age × Test site	.150	.153	.272	.099
	Age	.078	.802	.303	.208
	Test site	.254	.716	.679	.070
WDT	Age × Test site	.005	.004	.017	.018
	Age	<.001	<.001	<.001	<.001
	Test site	.169	.026	.020	.439
HPT	Age × Test site	.001	.001	.005	.014
	Age	.199	.202	.151	.213
	Test site	.043	.078	.044	.500
HPR	Age × Test site	.672	.675	.709	.928
	Age	.029	.303	.113	.238
	Test site	.355	.837	.812	.289
MDT	Age × Test site	.628	.635	.872	.812
	Age	<.001	<.001	<.001	<.001
	Test site	.900	.929	.823	.694
PPT	Age × Test site	.040	.044	.120	.217
	Age	.205	.453	.292	.430
	Test site	.083	.980	.982	.199
MTS	Age × Test site	.759	.762	.750	.625
	Age	.066	.062	.901	.091
	Test site	.954	.142	.790	.397
VDT	Age × Test site	.914	.918	.933	.958
	Age	.002	.002	.002	.001
	Test site	.664	.386	.496	.980

Notes: QST = quantitative sensory testing; CDT = cold detection threshold; CPT = cold pain threshold; CPR = cold pain rating; WDT = warm detection threshold; HPT = heat pain threshold; HPR = heat pain rating; MDT = mechanical detection threshold; PPT = pressure pain threshold; MTS = mechanical temporal summation; VDT = vibratory detection threshold. Unadjusted = no covariates; partially adjusted 1 = included ethnicity/race covariate; partially adjusted 2 = included ethnicity/race and affect covariates; fully adjusted = included ethnicity/race, affect, and cognitive function covariates. Bold values indicate statistical significance at $\alpha = 0.05$.

Overall, the sample of young and older adults was very healthy with low depressive symptoms and other age-related comorbidities. Older adults displayed higher state PA (PANAS-PA) and lower trait NA (PANAS-NA) scores compared to younger adults. This finding is in line with the “positivity effect” previously demonstrated in a meta-analysis of over 100 research studies (36), suggesting that older adults have the tendency to prioritize achieving emotional gratification and therefore tend to show a positive bias, particularly in the absence of other comorbid conditions (37). Trait PA scores were high, and state NA scores were very low, in both age groups. Thus, the lack of age-related differences seen in these measures may be the result of ceiling and floor effects, reflecting the overall physical and psychological health of the current sample. As expected, cognitive function (ie, 3MS) was lower in older adults compared to young adults (38); while this difference

was statistically significant, it was relatively small in magnitude and in line with the existing literature.

Thermal Somatosensory Function

A decline in thermal sensitivity is one of the most consistently demonstrated age-related changes in somatosensation (13,33). Our findings support previous literature as older adults required a lower (ie, colder) temperature for *cold detection* compared to younger adults, at both testing sites (ie, hand and foot). However, in contrast to previous research (33), we did not find age or test site differences in *cold pain* thresholds. This may be due in part to differences in categorization of “older” adults as we set our “older adult” minimum at 60 years old, while Rolke et al. (33) categorized older adults as individuals aged 40 years and older. However, it would be expected that a larger age gap (as in

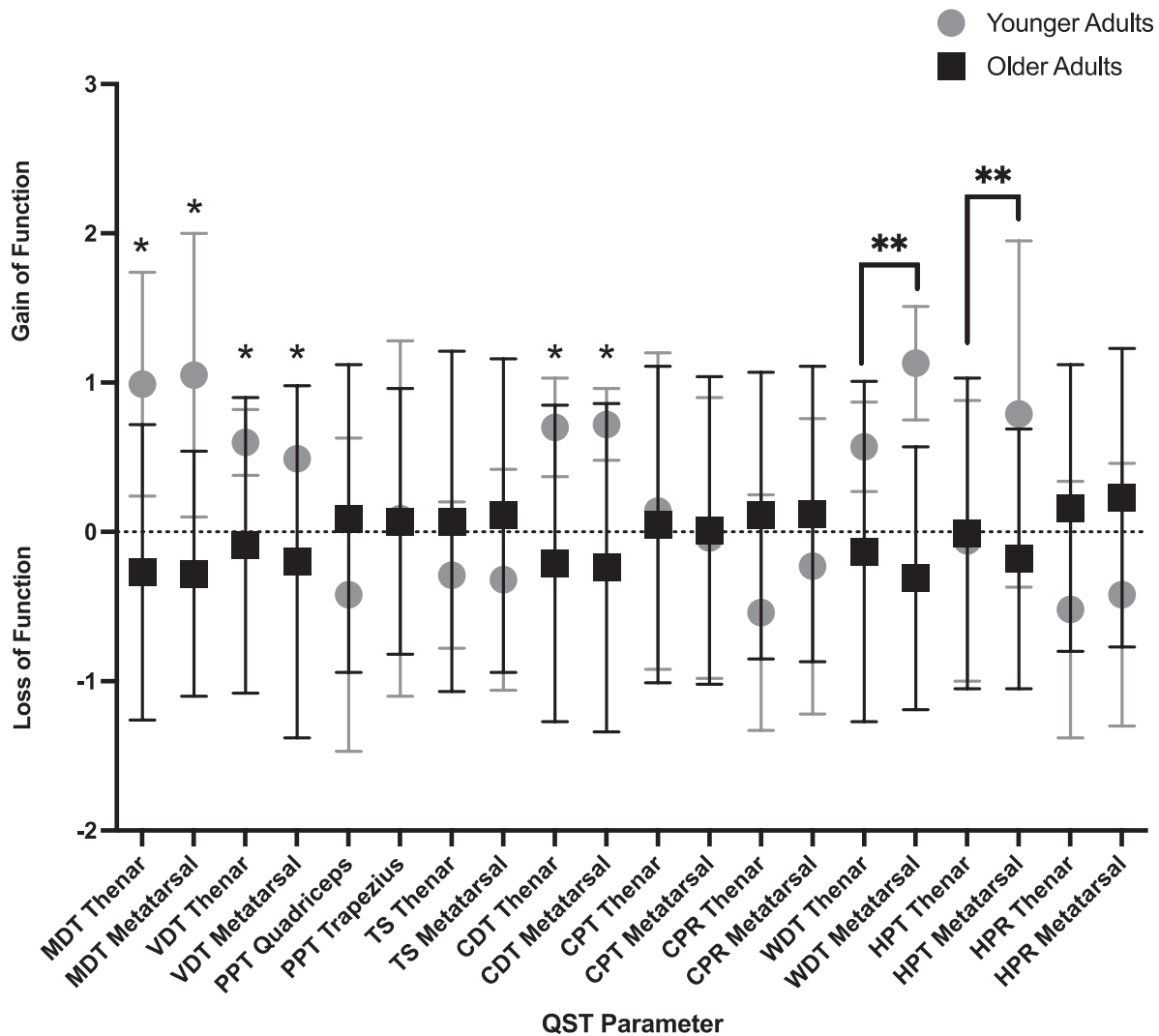


Figure 1. Standardized quantitative sensory testing (QST) scores by age and test site, fully adjusted for all covariates (ethnicity/race, affect, and cognitive function). *Note:* MDT = mechanical detection threshold; VDT = vibratory detection threshold; PPT = pressure pain threshold; TS = temporal summation; CDT = cold detection threshold; CPT = cold pain threshold; CPR = cold pain rating; WDT = warmth detection threshold; HPT = heat pain threshold; HPR = heat pain rating; Thenar = hand; Metatarsal = first metatarsal of foot; values are presented as Z-scores and error bars represent standard deviation (SD); **p* < .05 for main effect of age; ***p* < .05 for Age x Test site interaction effects.

Table 4. General Linear Model Whole Surface Vertex-Wise Brain Volume Associations With QST in Older Adults

Null-Z	QST	Annotation Max Vertex	MNI Coordinates Max Vertex			Size (mm ²)	CWP
			x	y	z		
Right hemisphere	MDT thenar	Temporal superior lateral	57.9	-0.0	-4.7	817.49	.0002
	MDT thenar	Occipital middle and lunata	27.9	-87.1	2.8	489.24	.015
	CDT metatarsal	Occipital	32.8	-86.9	-13.7	403.06	.044
Left hemisphere	HPR thenar	Pericallosum	-3.2	26.7	-2.3	641.14	.001

Notes: QST = quantitative sensory testing; CWP = cluster-wise probability; MDT = mechanical detection threshold; CDT = cold detection threshold; HPR = heat pain rating. Bold values indicate statistical significance at $\alpha = 0.05$.

our study) would more readily reveal age effects on pain detection (39). Also, the sample size reported by Rolke et al. (33) was small in an overall larger sample than the current study. Therefore, this difference in study findings requires

more investigation and may represent a more complex relationship between aging and somatosensory function than originally thought. While not statistically significant, *cold pain ratings* did show variation by age group, with older

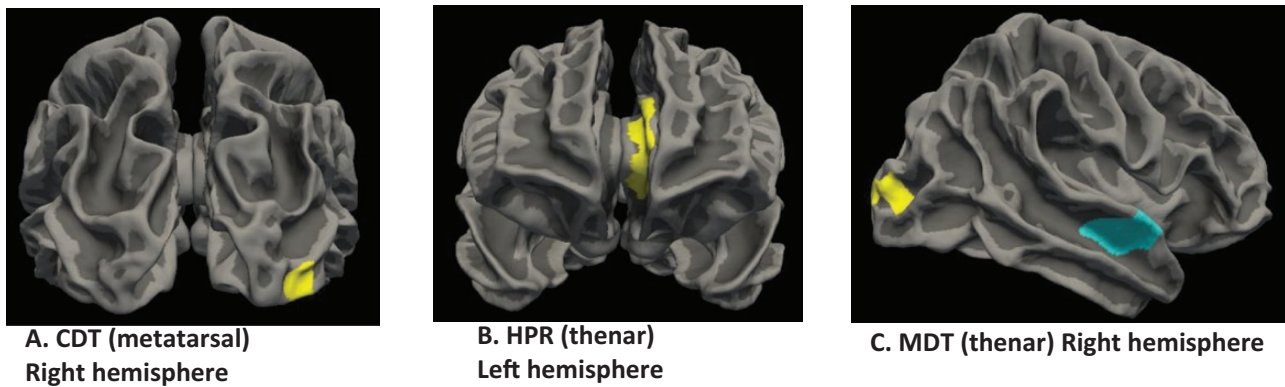


Figure 2. Brain volume associations with quantitative sensory testing measures showing age-related differences in older adults: (A) Significant relationship between inferior occipital gyrus and sulcus and cold detection threshold; (B) significant relationship between pericallosal sulcus and heat pain ratings; (C) significant relationship between superior temporal gyrus and middle occipital sulcus and lunatus sulcus with mechanical detection thresholds. *Note:* CDT = cold detection threshold; HPR = heat pain rating; MDT = mechanical detection threshold; metatarsal = first metatarsal of foot; thenar = hand.

adults rating cold pain higher at both the hand and foot. Given that *cold pain detection* temperatures did not differ between age groups, indicating older adults maintained an intact suprathreshold cold detection capacity, it is interesting that older adults rated more pain upon pain detection, indicating an enhanced subjective response.

We also found *warmth detection threshold* and *heat pain threshold* effects were dependent on age and test site in this sample of healthy adults, consistent with previously published results (16,33,40,41). Older adults in the current sample required more heat stimulation to perceive warmth at both the hand and foot, with effects most pronounced at the foot. *Heat pain thresholds* were only different between age groups at the foot, again demonstrating decreased somatosensory function in the lower extremities of older adults, but preserved suprathreshold detection at the hand. These findings are in line with Riley et al. (16), which demonstrated older adults may be less sensitive to thermal stimuli detection, particularly in the lower body (eg, knee). Stevens and Choo (41) also found thermal sensitivity declines with age with the greatest differences being observed at the foot. Interestingly, as with cold pain ratings, *heat pain ratings* were also higher among older adults compared to younger adults at both testing sites. While these differences were no longer statistically significant after controlling for race, affect, and cognitive function, they are worth noting as they may help to explain compensatory processes at a neural level that occur with aging. Prior research demonstrates a tendency for older adults to rate pain higher in response to thermal stimuli compared to younger adults (42) and shows a reduced thermal pain range (ie, the difference between threshold and tolerance values) (16,39), which may place older adults at a greater risk for injury (15). Furthermore, these findings may suggest selective degradation of cutaneous A-delta nociceptors, resulting in the loss of early warning functions (eg, thermal detection thresholds) to thermal stimuli, with C fiber function (ie, nociception) remaining intact (43,44).

Mechanical Somatosensory Function

In our sample of healthy community-dwelling younger and older adults, age was significantly associated with *MDT* at both sites such that older adults required more force to perceive mechanical stimuli. This is in line with previous research demonstrating that healthy older adults displayed increased MDTs compared to younger adults (45), suggesting a loss of tactile sensitivity with aging. We also observed a significant age \times test site interaction for *PPT* in the crude and partially adjusted (ie, race) models, which indicate that *PPT* may decrease in distal (eg, quadriceps) compared to proximal (eg, trapezius) body sites in older adults. However, this effect did not remain significant when controlling for affect, suggesting mood may also influence somatosensory function in older adults (24). As with other noxious (eg, thermal) stimuli, data regarding age effects on *PPT* are inconsistent, with some studies showing age-related declines (20,46), increases (47), or no differences (7).

Deterioration of the somatosensory system presumably occurs across all levels of the somatosensory system, including both the peripheral and central nervous systems. (48–51) Recent research indicates that changes in cutaneous receptors, including density, size, and distribution of Meissner's corpuscles and Merkel's cells, may contribute to declines in tactile acuity and mechanoreception in older adults (51), as well as changes in the skin (52,53). For example, in a recent investigation, García-Piqueras et al. (51) found that in older adults (ie, aged 60–90 years), in approximately 70% of examined Meissner's corpuscles, their size was reduced, the structure had changed to round instead of elongated, and they were no longer located inside of the dermal papillae, but were found behind rete pegs. Furthermore, there was reduced evidence for protein synthesis and the axon was difficult to distinguish. This was in stark contrast to corpuscles in younger and middle-aged adults, which were elongated, always localized in the dermal

papillae, demonstrated strong protein immunoreactivity, and had easily identifiable axons (51). Also, Merkel's cells were only found in isolation in older adults, compared to clusters of 4 in younger adults. However, no differences were observed in Pacinian corpuscles based on age. Interestingly, Piezo2 positivity in Meissner's corpuscles was reduced, as was the density of Piezo2-positive Merkel's cells in older adults compared to young and middle-aged adults. Taken together, these findings suggest a strong role for peripheral sensory structures in age-dependent changes in somatosensation. Future studies are needed to pinpoint the localization of epidermal changes in relation to non-uniform age-related changes in somatosensory processes to confirm peripheral involvement.

As QST assesses function across the entire sensory neuraxis, dysfunction in peripheral nerves, as well as the central nervous system, may contribute to alterations in somatosensory function. Pathways from the periphery to the cerebral cortex, by which mechanical stimulation is transferred into electrical energy and interpreted, are likely implicated in age-related sensory losses. Structural and functional changes in the somatosensory cortex, anterior cingulate cortex, and prefrontal cortex have also been associated with *PPT* (53), and cold pain threshold (48), in older adults, which suggests a brain-related component may underlie typical age-related sensory changes (54).

Multiple QST modalities can be used to induce temporal summation of cutaneous pain in humans, including thermal (55), mechanical (7), and electrical (56). In this study, we employed mechanical stimulation to provoke a wind-up response of cutaneous pain. Consistent with previous research using the same type of testing stimulus, we did not find age or testing site differences in temporal summation (7,33). However, these findings contrast with a recent meta-analysis showing temporal summation is enhanced in older adults compared to younger adults. Interestingly, the magnitude of differences observed seems to depend on the stimulus type, with thermal-induced temporal summation showing the largest pooled effect size (57). This may explain why we did not observe age-related differences in this study. Previous literature has reported signs of both "hypofunction" (slowing and atypical fibers) and "hyperfunction" (spontaneous activity, sensitization) in C-fibers of healthy older adults (58). These contrasting alterations observed in C-fibers may also be the result of compensatory molecular processes in the peripheral nervous system (59).

VDT appears to be a key somatosensory test that distinguishes older and younger adults. We observed age-related differences in this study, such that older adults required more stimuli to detect vibration at both testing sites. Previous research indicates that VDT at the foot doubles in the 7th decade of life (45), and better vibratory detection is associated with a "younger" brain (50). Furthermore, higher VDTs have been associated with an older epigenetic age (19), which may be an important consideration for

identifying individuals at a greater risk of functional decline. Vibrotactile acuity appears to decline with aging (60), particularly in the lower extremities, placing older adults at a greater risk for falls and loss of mobility (61). Given the availability and ease of use, vibratory thresholds may provide objective measures of sensory nerve function in clinical settings that promote early detection of adults at risk for mobility limitations, allowing for early intervention.

Brain Volume Associations With Somatosensory Outcomes

Age-related brain changes are well documented. Reductions in brain volume have been associated with changes in mobility (62,63) and cognitive function (64–66), which are both inextricably related to somatosensory function (67). Older adults also demonstrate different patterns of brain activation compared to younger adults (68,69). Research has also indicated that age-related changes in brain structure and function are associated with pain perception (50,70). However, the relationship between central neural plasticity and age-related somatosensory decline is not fully understood.

In this study, we found that among older adults, higher cold detection threshold (indicating less sensory detection capacity) at the foot was associated with increased volume in the inferior occipital gyrus and sulcus. This association may represent a type of compensatory function whereby the decline of one sensory modality (thermal detection in the lower extremity) is offset through other senses (eg, vision) (71). Also, increased heat pain rating at the thenar eminence was associated with increased volume of the pericallosal sulcus (S of corpus callosum), which may indicate white matter alterations help to maintain detection of ecologically meaningful events (eg, pain) in aging, helping to overcome declines in other sensory processes. Additionally, a higher MDT at the hand (ie, less tactile sensitivity) was associated with reduced brain volume in the lateral aspect of the superior temporal gyrus and increased brain volume in the middle occipital sulcus and lunatus sulcus. This supports other research findings indicating that cross-modal audiotactile effects are especially relevant for individuals with other sensory declines (72) and the neurophysiological correlates of multisensory integration (73). While these findings are preliminary, they point to potential compensatory brain alterations in response to a loss of somatosensory function in older age and the role of multisensory integration for healthy aging.

Limitations

Our findings must be considered in light of some study limitations. First, the NEPAL cohort was relatively small and restrictive to healthy individuals excluding those with any signs of cognitive impairments. Therefore, these findings may not generalize to larger populations of older adults

with multiple common health conditions. However, the use of a healthy sample allowed for comparisons across age groups not confounded by comorbid conditions. Future studies including participants with more severe pain and/or health conditions may improve our understanding of the complex nature of somatosensory decline among older adults in the population. Also, consideration of older adults with depression and other mood disorders, in relation to somatosensory function, may help to further identify risk profiles for mobility loss and poor health outcomes. Second, the current analysis is cross-sectional and does not allow for determination of predictive relationships between brain structure and somatosensory processing. Also, the standard deviations were quite large across the various somatosensory measures, particularly at the metatarsal. Therefore, despite using a conservative approach (ie, Cluster-wise Correction for Multiple Comparisons), the correlations demonstrated between somatosensory variables and brain structure must be interpreted with caution. Clearly, causality and directionality cannot be inferred from the current study findings and definitive conclusions about what processes (ie, peripheral, central, or both) are driving nonuniform changes in somatosensory function in older adults. Future studies using longitudinal data are needed in order to elucidate the trajectories of brain changes in relation to somatosensory function in older adults, and how they relate to mobility and health outcomes. Finally, the sample of older adults was relatively homogenous in regard to education and ethnicity/race. Future studies exploring these relationships in diverse community samples are warranted.

Conclusions

In summary, our study supports the specific factor theory of sensory loss, demonstrating that somatosensory alterations are not global, but rather specific to sensory modalities. Our findings demonstrate that there are age-related declines in somatosensory function, even in very healthy adults, but that these effects vary across individuals. Also, our findings suggest that somatosensory dysfunction in older adults is associated with changes in both the peripheral and central nervous systems, and that compensatory brain processes may occur that help individuals overcome sensory deficits. Thus, declines in one sensory modality (eg, mechanoreception) do not imply global impairment across other sensory modalities (eg, thermoreception), which may have important assessment and treatment implications. However, more research on both the peripheral and central processes associated with somatosensory loss is needed to better understand their involvement. Future studies would benefit from comprehensively evaluating somatosensory function in various clinical populations and effects on mobility, the peripheral nervous system structure, brain structure and connectivity, and health outcomes.

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Conflict of Interest

None declared.

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