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# Thermal Psychophysics and Associated Brain Activation Patterns Along a Continuum of Healthy Aging

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## Abstract

**Objective.** To examine psychophysical and brain activation patterns to innocuous and painful thermal stimulation along a continuum of healthy older adults. **Design.** Single center, cross-sectional, within-subjects design. **Methods.** Thermal perceptual psychophysics (warmth, mild, and moderate pain) were tested in 37 healthy older adults (65–97 years, median = 73 years). Percept thresholds (°C) and unpleasantness ratings (0–20 scale) were obtained and then applied during functional magnetic resonance imaging scanning. General linear modeling assessed effects of age on psychophysical results. Multiple linear regressions were used to test the main and interaction effects of brain activation against age and psychophysical reports. Specifically, differential age effects were examined by comparing percent-signal change slopes between those above/below age 73 (a median split). **Results.** Advancing age was associated with greater thresholds for thermal perception ($z = 2.09$, $P = 0.037$), which was driven by age and warmth detection correlation ($r = 0.33$, $P = 0.048$). Greater warmth detection thresholds were associated with reduced hippocampal activation in "older" vs "younger" individuals (>/<73 years; $beta < 0.40$, $P < 0.01$). Advancing age, in general, was correlated with greater activation of the middle cingulate gyrus ($beta > 0.44$, $P < 0.01$) during mild pain. Differential age effects were found for prefrontal activation during moderate pain. In "older" individuals, higher moderate pain thresholds and greater degrees of moderate pain unpleasantness correlated with lesser prefrontal activation (anterolateral prefrontal cortex and middle–frontal operculum; $beta < -0.39$, $P < 0.009$); the opposite pattern was found in "younger" individuals. **Conclusions.** Advancing age may lead to altered thermal sensation and (in some circumstances) altered pain perception secondary to age-related changes in attention/novelty detection and cognitive functions.

**Key Words:** Magnetic Resonance Imaging (MRI); Geriatric; Older Adults; Perception

## Introduction

Pain in aging is a growing problem, with painful conditions increasingly prevalent in older populations [1–3]. Seventy percent of older adults have some level of pain, and 38% have pain that interferes with daily living [4]. Untreated pain has significant effects on quality of life (e.g., sleep disturbances, anxiety, depression, decreased socialization) [5]. Unfortunately, up to 60% of those in the community and 80% of institutionalized older adults experience untreated pain (reviewed in Herr and Garand [6]). Whether this high clinical pain prevalence in older adults is related to age-related changes in central nervous system pain processing pathways remains unclear. The effects of aging on pain processing in the context of

experimental evoked pain stimuli seem to be psychophysically (e.g., threshold, suprathreshold, tolerance) and modality (e.g., pressure, thermal, electrical) dependent [7]. However, a recent meta-analysis concluded that the best evidence for altered pain perception with aging relates to increased thresholds for low-level pain in the setting of thermal modalities [8]. Focused examination of associated neural correlates of altered pain processing in aging has been minimally explored and merits further investigation.

Dampening of somatosensation and low-level pain thresholds has been proposed to signify a kind of "presbyalgos," akin to visual ("presbyopia") and auditory ("presbycusis") deficits associated with older age [9]. Although many of the changes leading to dampening of other sensations have a predominantly peripheral pathophysiology [10,11], this does not appear to be the case for altered pain in aging. Indeed, although older age is associated with reduced thinly myelinated Aδ fiber activity, there is no parallel reduction in unmyelinated C-fibers, the nociceptive fibers underlying thermal evoked pain responses and most clinical chronic pain conditions [12–16]. It is thus likely that central processes are involved in age-related changes of thermal pain perception. A supraspinal etiology in particular seems feasible given findings of reduced cold pressor modulation of heat pain in older adults, suggesting reduced endogenous pain modulation as age increases [17,18]. The latter could suggest a deficit in frontal, top-down pain modulation. However, placebo analgesia, which is thought to be mediated by frontal mechanisms, appears to remain intact in comparisons of young and old individuals [19,20].

Pain is conceptualized as a multidimensional phenomenon consisting of an unpleasant sensory (intensity) and affective (unpleasantness) experience that may or may not be associated with actual tissue damage [21,22]. Although many brain regions appear to work in concert to facilitate the neural signature of pain [23], the pain literature frequently refers to a core set of pathways and regions collectively deemed the "pain matrix." The lateral pathway is associated with perceiving the location, intensity, and quality of pain; it includes the primary (S1) and secondary somatosensory (S2) cortices and posterior insular cortex (pINS) [24–26]. The medial pathway, which includes anterior insula (aINS), anterior/mid cingulate cortex (A/MCC), and lateral prefrontal cortices (PFC), is associated with pain-related affect and motivation [27–29]. The prefrontal components of the medial pathway in particular are active in the cognitive–evaluative aspects of pain [30–32], leading to top-down pain modulation [33,34]. Pain-related affective states, such as anxiety, and novelty detection, are mediated via limbic activity in the amygdala (AMY) and hippocampus (HIPPO) [35–37].

Experimental work examining neural correlates of altered pain processing in aging has implicated age-related structural changes in multiple central pain processing regions [38,39]; these include generalized atrophy [19,40,41] and more focal volume loss of the insula [42] and somatosensory regions [43]. Data on pain-relevant, age-related functional changes are more limited. A pilot study by Quinton and colleagues [44] found that, in comparison with young adults, older adults demonstrate reduced activation to thermal pain in the aINS, S1, and supplementary motor regions. A more recent thermal pain study [45] found that decreased pain intensity and "sharpness" in older subjects was associated with reduced activation in the contralateral mid-INS and S1. These two studies' results argue for a decrement of lateral/sensory pain-related function with increased age and provide a logical correlate for psychophysical results suggesting reduced somatosensation and low-level pain intensity. However, it is unclear how to reconcile behavioral findings of reduced pain processing with increased age with some studies indicating increased pain unpleasantness with advancing age. For example, Cole and colleagues [46], using mechanical stimuli, found that more intensely rated pressure pain in older subjects was associated with reduced activation of the contralateral striatum; they posited that these results reflected age-induced impairment of striatum-mediated pain modulation. It thus remains possible that multiple supraspinal mechanisms may also be involved in altered pain processing in the elderly.

Age-associated alterations in the structure and function of various pain systems may lead to reduced ability to manage pain effectively, perhaps by reduced perception of early, less intense, nociceptive signals that limit early intervention. For example, if one is less sensitive to lower levels of a noxious stimulus, then one is less likely to seek care for painful conditions associated with progressive tissue damage (e.g., osteoarthritis) or conditions in which ongoing activity may potentially further damage tissue (e.g., after injury). In concert with possibly reduced integrity of pain modulation, these changes could lead to increased pain-related disability and suffering. Given the paucity of combined psychophysical and neuroimaging studies, drawing definitive conclusions about pain in aging is not yet possible. The primary aim of this study was to examine thermal pain psychophysics and associated functional magnetic resonance imaging (fMRI) brain activation patterns along a continuum of healthy, pain-free older adults (age range = 65–97 years). We hypothesized that the aging process leads to increased thermal pain thresholds through reduced overall pain matrix activation, namely in sensory structures. Our first prediction (psychophysics) was that increasing age would be associated with decreased pain sensitivity (increased thermal thresholds) but no changes in reports of pain unpleasantness. Our second prediction (fMRI) was that increasing age would be associated with reduced activation patterns primarily in sensory pain structures (e.g., S1, S2, and pINS). However, given some prior findings of reduced pain tolerance and impaired pain modulation in older

individuals, we posited that altered activation in additional medial/pain modulatory regions may also be seen.

## Methods

The current study was a single-center cross-sectional investigation of only healthy aged subjects participating in multiple prior studies; detailed recruitment, psychophysical, and fMRI methodology may be found elsewhere [47–49]. The Vanderbilt University Institutional Review Board approved all experimental procedures, and each participant provided written informed consent before enrollment. We implemented the STROBE guidelines for reporting cross-sectional data. As specific methodological details are published elsewhere, a brief summary is provided below.

### Subjects

The 37 subjects included in this study resided in metropolitan Nashville, Tennessee. General study inclusion criteria were age >64 years and generally healthy status. Exclusion criteria were claustrophobia, inability to pass MRI screening, chronic pain or daily use of analgesic medications, or cognitive impairment (Mini-Mental State Exam [MMSE] score ≤27). Extended exclusion criteria included history of stroke, cancer, neuropathy, Raynaud's disease, diabetes, or current major depression. These criteria resulted in a healthy sample of older adults. As experimental pain thresholds have been shown to be associated with hormone replacement therapy (HRT) [50], we collected HRT status in females.

### Assessments

All participants were instructed to avoid caffeine for at least four hours before scanning and to not use any pain medication (opioid or nonopioid) for at least 24 hours before all data collection procedures. Participants were reimbursed $100.00 (USD) for their time. Data collection occurred over two days. Day 1 procedures took place at the subject's residence and included screening and enrollment procedures including review of current medications, assessment of socioeconomic status (SES) using the Hollingshead four-factor socioeconomic status test [51], MRI safety clearance, and cognitive screening using the MMSE [52]. Day 2 procedures were conducted at the Vanderbilt University School of Nursing and Vanderbilt University Institute of Imaging Science; they consisted of administering various assessment scales, psychophysical testing, and functional neuroimaging. MRI safety screening was confirmed before multiple other assessments including the Brief Pain Inventory Short-Form (BPI-SF) [53], Geriatric Depression Scale Short-Form (GDS-SF) [54], and Spielberger State-Trait Anxiety Inventory (STAI) [55]. Subjects then participated in psychophysical and MRI procedures.

### Thermal Stimulation Protocol (Psychophysics)

In an experiment room adjacent to the scanner, pain psychophysics were assessed using the Medoc Pathway Pain and Sensory Evaluation System [56]. The Medoc thermode (30×30 cm) was attached to the palm of the right hand and programmed to deliver heat increasing at a rate of 1°C/second for each of the individually defined percepts (warmth, mild pain, moderate pain). The baseline temperature was set at 30°C, which was previously identified as a neutral temperature [57]. Participants were asked to stop the heat stimulus by clicking a mouse button when the perception of warmth, mild pain, and moderate pain occurred. Immediately after threshold detection, participants were asked to rate the unpleasantness associated with each percept using a 0–20 unpleasantness scale (0 = neutral, 20 = extremely intolerable) [58]. Each trial was completed three times, with average temperature and unpleasantness ratings subsequently calculated.

### Functional MRI

After basic psychophysical testing, the Medoc was programmed with each individual's average temperature eliciting percepts of warmth, mild pain, and moderate pain. Using a standard block design, participants completed four functional runs consisting of six thermal stimulation periods (two at each intensity, duration 16 seconds per stimulus, ramp rate 8°C/sec), followed by a 24-second baseline with no stimuli. During each functional run, lights remained on and participants were instructed to stay awake with eyes open.

### Brain Imaging Acquisition: Structural and Functional

Imaging was performed with a Philips 3T Achieva MRI scanner (Philips Healthcare Inc., Best, the Netherlands). Briefly, a standard whole-brain 3D anatomical T1-weighted/TFE (with SENSE coil) scan was acquired for alignment and display of fMRI activation maps. In each 264-second-duration functional run, 28-field echo EPI scans were acquired (132 dynamics, 4.40-mm slice thickness with 0.45-mm gap, two seconds of TR, 35-ms TE, 79° flip angle, FOV = 240, matrix = 128×128).

### Image Processing

Slice timing correction and motion correction were conducted using standard SPM8 approaches. Intrascan fMRI volumes were co-registered using standard rigid body registration in SPM8. Using the first image volume from each scan, volumes were co-registered to structural T1-weighted volumes. Images were spatially smoothed with an 8-mm full-width half-maximum (FWHM) Gaussian kernel. Structural data were registered to Montreal Neuroimaging (MNI) space, and the resulting transformation matrix was applied to the fMRI data.

### Analysis of Head Motion

To address the potential confound of head motion during pain delivery and throughout scanning procedures, the robust weighted least squares approach [59] was used to motion-correct during standard preprocessing with SPM8. Outliers were defined as any subject with mean motion >1 mm across the x, y, z, pitch, roll, yaw coordinates.

### General and Psychophysical Analyses

Demographic standardized measure scores and all key study variables were summarized using median and 25th to 75th percentile interquartile ranges (IQRs; continuous data) and numbers (percentages; categorical data). Continuous data were transformed as necessary to meet statistical assumptions of modeling approaches used in the analyses and to generate appropriately centered interaction variables. General linear modeling that adjusted the standard errors for the clustered (repeated) nature of the data was used to assess the main and interaction effects of age and thermal percept level (warmth, mild, and moderate pain) on psychophysical data (temperature thresholds and unpleasantness). Unless otherwise noted, an unadjusted $P < 0.05$ was used for determining statistical significance. STATA, version 14, and SPSS, version 24, were used for these analyses.

### fMRI Activation, Head Motion, Multiple Comparisons

Whole-brain fMRI activation at the single-subject level was modeled as the contrast of warmth > baseline, mild pain > baseline, moderate pain > baseline. As each subject's individual temperatures were used in the collection of fMRI data, ramp upward and ramp downward times were controlled in the general linear model (GLM) as covariates of no interest. These resulting subject-specific contrast maps were used in higher-level analyses for within-group analysis in SPM8 to compare warmth and pain (mild and moderate) with baseline. These analyses generated an activation map of T-statistics that were used to identify brain regions indicating statistically significant activation. Analysis of head motion found that no subjects exceeded the predetermined movement >1-mm artifact criterion. Before group analysis, differences in brain volume were controlled using a standardized residual of total gray matter volume to total intracranial volume, calculated from the T1 images (in the same space as the BOLD images). This residual was used a control variable in the group-level analysis. To account for voxelwise-multiple comparisons, statistical thresholds for these higher-level analyses were corrected using the intrinsic smoothness of the data [60] and Monte Carlo simulations in 3dClustSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) at 10,000 iterations to produce family-wise error-corrected data ($P \leq 0.05$) based on whole-brain analysis with a cluster size of 2,568 voxels for significance. After generating whole-brain statistically significant clusters for each contrast using Marsbar [61], 5-mm spherical Region of Interest (ROI)s were created around the peak MNI coordinates in each cluster. Next, the average percent signal change (PSC) was extracted to test for the association of brain signal changes and psychophysical measures and those clusters demonstrating significant associations with age, psychophysics, or an age*psychophysics interaction based on comparing "young" old individuals (<73 years) with "older" old individuals (>73). Multiple linear regressions were used to test the main and interaction effects of age and psychophysical reports on brain activation data from each of the specific ROI contrasts. Interaction effects were illustrated by displaying fit lines for the upper and lower portions of the age distributions (above and below the centered value, 73 years). These results were then subjected to Bonferroni correction for multiple comparisons based on the number of unique regressions per region (five total: age, sensory threshold, affective rating, age*temperature interaction, and age*affect interaction) for a final significance threshold of $P \leq 0.01$. Primary findings of interest in this analysis pertained to answering the following question: What changes in brain function underlie differences in psychophysical responses seen with aging?

## Results

### Sample

The median age of the sample (N = 37) was 68.0 years (min = 65, max = 97), with similar proportions of females and males (51.4% and 48.6%, respectively). Most had at least a high school education (N = 34, 92%), and many (N = 14, 38%) had an advanced degree. The sample had normative MMSE scores (IQR = 29–30, min = 27), and most were not experiencing any pain at the time of the fMRI acquisition (Table 1). State anxiety and depression-related scores were minimal.

### Psychophysics

Summaries of the temperature at which warmth, mild pain, and moderate pain thresholds were reported are shown in Table 2, as are the unpleasantness ratings at each respective percept level. Statistically significant increases in both temperature intensity and unpleasantness were reported at each of the increasing threshold levels ($P < 0.001$).

A statistically significant interaction effect of age on thermal percept threshold was found ($z = 2.09$, $P = 0.037$). As shown in Table 2, increasing age was significantly correlated with an increase in temperature threshold (i.e., decreased sensitivity) for the perception of warmth ($r = 0.33$, $P = 0.048$). Age was not significantly associated with sensation at the other thresholds or with

**Table 1.** Demographic and clinical summaries (N = 37)

| Demographics | Median [IQR] or No. (%) |
|---|---|
| Age | 68.0 [66–81] |
| Race | |
| Caucasian | 32 (86.5) |
| African American | 4 (10.8) |
| Asian | 1 (2.7) |
| Gender | |
| Female | 19 (51.4) |
| Male | 18 (48.6) |
| Marital status | |
| Married | 22 (59.5) |
| Not married | 15 (40.5) |
| Marital occupational status | |
| One spouse gainfully employed | 21 (56.8) |
| Both spouses gainfully employed | 16 (43.2) |
| Level of school completed (N = 36) | |
| <High school | 3 (8.3) |
| High school graduate | 2 (5.6) |
| Technical/some college | 7 (19.4) |
| College graduate | 10 (27.8) |
| Advanced degree | 14 (37.9) |
| Standardized measures | |
| BMI | 25.6 [23–29] |
| Total SES score* | 58.0 [44–65] |
| MMSE score† | 30.0 [29–30] |
| BPI-SF average pain‡ | 1.0 [0–2] |
| BPI-SF pain right now‡ | 0.0 [0–0]^ |
| GDS-SF score§ | 0.0 [0–1] |
| STAI state score¶ | 48.0 [45–51] |
| STAI trait score¶ | 47.0 [44–50] |

BMI = body mass index; BPI-SF = Brief Pain Inventory Short-Form; IQR = interquartile range; MMSE = Mini-Mental State Examination; SES = socioeconomic status; STAI = State or Trait Anxiety Inventory.

*Hollingshead Four-Factor Measure of Socioeconomic Status (range = 8–66; 8 = lowest SES, 66 = highest SES). This scale takes into account prior employment status of retired persons.

†MMSE-Folstein Mini-Mental State Examination (range = 0–30; 0 = completely cognitively impaired, 30 = completely cognitively intact).

‡BPI-SF-Brief Pain Inventory Short Form (range = 0–10; 0 = no pain, 10 = most pain);^Max value was 3.

§GDS-SF-Geriatric Depression Scale Short Form (range = 0–15; 0 = no indication of depression, 15 = high possibility of depression).

¶STAI-Spielberger State or Trait Anxiety Inventory (range = 20–80; 20 = indicates increased anxiety, 80 = indicates least amount of anxiety).

reports of unpleasantness of the sensation at any threshold ($r \leq \pm 0.22$).

## fMRI

Results from the one-sample T-test maps showing brain regions activated during each level of thermal stimulation—warmth > baseline, mild pain > baseline, and moderate pain > baseline—are shown in Figure 1. Results reflect a GLM with age included as a covariate of interest in order to examine how increasing age was associated with activation patters across each thermal contrast. Significant clusters labeled in Figure 1 ($P < 0.05$) are further visualized in the Supplementary Data. These were subjected to further analyses examining the association between, activation, age, and psychophysical responses (discussed below).

**Table 2.** Summary of psychophysical results for sensory thresholds and affective ratings (N = 37)

| Variables | Min | Max | Median | IQR | *r* (Age) |
|---|---|---|---|---|---|
| Sensory threshold, °C | | | | | |
| Warmth | 31 | 38 | 32.0 | 32–34 | **0.33*** |
| Mild pain | 33 | 47 | 36.0 | 34–39 | 0.12 |
| Moderate pain | 34 | 48 | 40.0 | 38–45 | –0.06 |
| Unpleasantness (0–20 scale) | | | | | |
| Warmth | 0 | 6 | 0.0 | 0–2 | –0.06 |
| Mild pain | 0 | 16 | 3.0 | 0–5 | –0.16 |
| Moderate pain | 0 | 19 | 6.0 | 5–9 | –0.22 |

Sensory threshold (°C) = temperature in which the percept variable was obtained. Unpleasantness determined via 0–20 rating scale for each percept (0 = neural, 20 = extremely intolerable). Statistically significant increases in both sensory and affective thresholds were reported at each of the increasing threshold levels ($P < 0.001$). A statistically significant age*threshold interaction effect was found for sensory thresholds ($z = 2.09$, $P = 0.037$) but not for affective ratings ($z = 1.70$, $P = 0.089$).

IQR = interquartile range.

*Statistically significant correlation between age and warmth detection ($P = 0.048$).

## Age, Psychophysics, and fMRI

Table 3 displays summaries of the significant associations between psychophysical reports with peak cluster PSC that met Bonferroni correction for multiple comparisons ($P \leq 0.01$). In Table 3, PSC across significant clusters were placed in two separate GLMs with regressors including subject age, psychophysical response (sensory perceptual thresholds or affective ratings), and age*psychophysical response. Each column thus represents the effect of an individual covariate of interest (e.g., age) on activation, adjusted for the effect of the other variables in the model (e.g., percept threshold temperature). An age*psychophysics interaction effect was indicative of a scenario in which the correlation of a psychophysical response (i.e., percept threshold temperature or affect) with thermal activation significantly differed based on the age of the respondent. In our study, participant age was mean-centered at 73 years. Therefore, an interaction effect indicated a statistically significant difference for the correlation between psychophysical responses with PSC for participants below vs above 73 years. Peak regions in Table 3 are organized by the main effect of age on activation, as seen in Figure 1. Significant effects were considered based on a Bonferroni-corrected threshold of $P \leq 0.01$ (arrived at via the total number of unique response effects tested, five total).

## Warmth > Baseline Contrast

Warmth-induced activation in the HIPPO was negatively associated with age (T = –3.54) (Figure 1) and remained so after adjustment for effects of affective warmth ratings but not sensory percept thresholds (affective: *beta* = –0.44, $P = 0.008$; sensory: beta= –0.37, $P = 0.018$). There was a significant interaction effect of age*temp for warmth detection threshold (beta = –0.40, $P = 0.01$). Figure 2 illustrates this interaction effect: Specifically in "older" subjects (≥73 years), as temperature thresholds eliciting a sensation of warmth increased, there was a

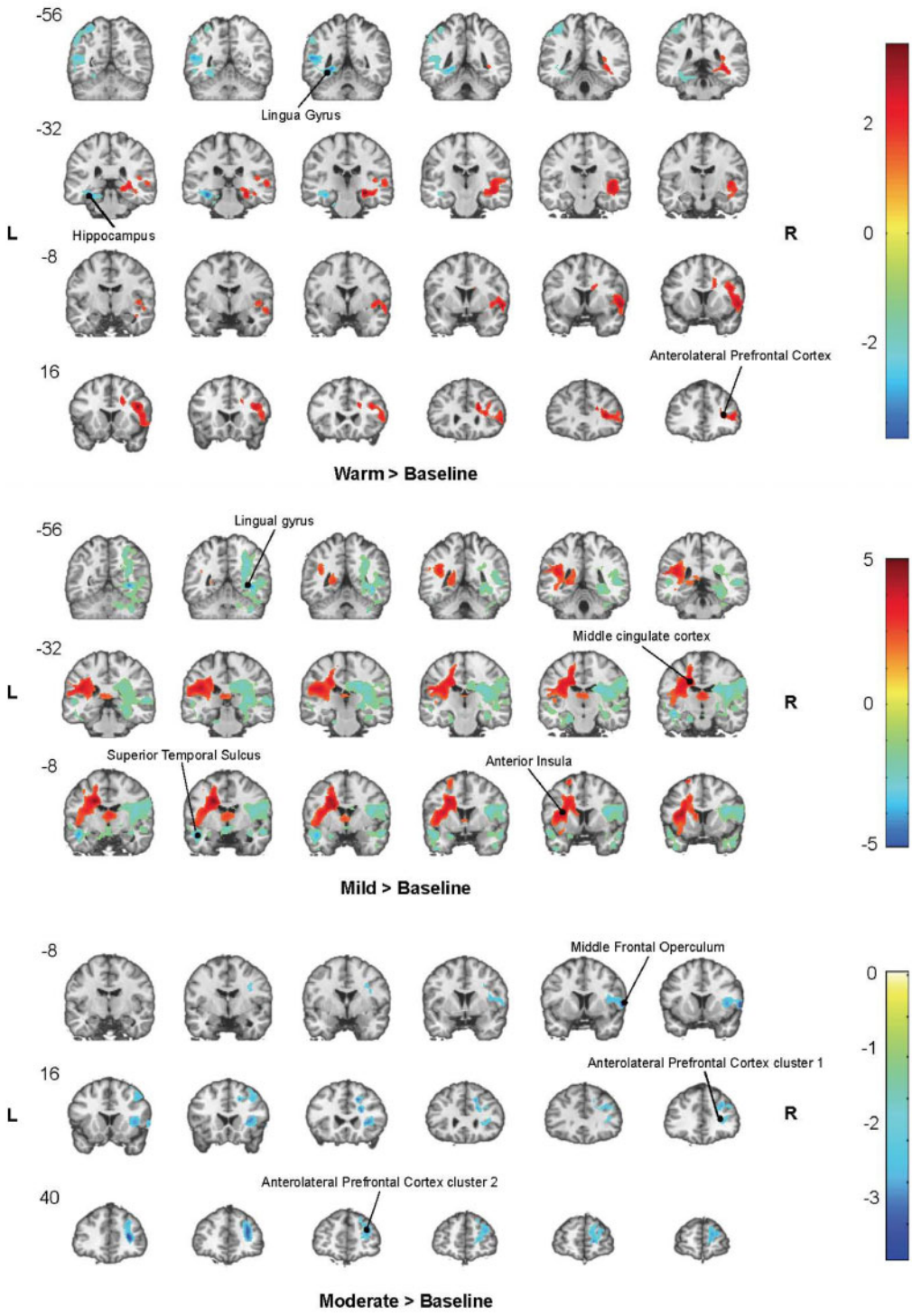


**Figure 1.** Regression results examining the association of age with brain activation during thermal stimulation (N = 37, df = 30). Significant clusters were defined as those having a voxel level of $P < 0.05$, cluster volume of 2,568 voxels, familywise error corrected (FWE) $P < 0.05$. The upper and middle sections of the figure display brain activation (positive association with age) and deactivation (negative association with age) to the contrasts of [warmth baseline] and [mild pain baseline], respectively. The bottom portion of the figure displays deactivation only to the contrast of [moderate pain baseline]. Numbers next to the first image in each row indicate slice position relative to the AC/PC midline. Axial spacing = 4 mm. The color bar represents the T-score intensity for each contrast.

**Table 3.** Thermal brain activations (percent signal change) with significant age and psychophysical response effects

| Region | MNI Coord [X, Y, Z] | T | Sensory Threshold | | | Affect Rating | | |
|---|---|---|---|---|---|---|---|---|
| | | | $beta_{(age)}$ (*P*) | $beta_{(temp)}$ (*P*) | $beta_{(age*tmp)}$ (*P*) | $beta_{(age)}$ (*P*) | $beta_{(affect)}$ (*P*) | $beta_{(age*affct)}$ (*P*) |
| Warmth > Baseline | | | | | | | | |
| (L) HIPPO | –32, –30, –14 | 3.54 | –0.37 (0.018) | –0.11 (0.454) | **–0.40 (0.010)** | **–0.44 (0.008)** | –0.03 (0.827) | –0.13 (0.416) |
| Mild > Baseline | | | | | | | | |
| (L) MCC (BA 24) | –9, –12, +34 | 5.00 | **0.44 (0.006)** | –0.18 (0.203) | 0.29 (0.060) | **0.48 (0.003)** | –0.21 (0.155) | 0.05 (0.752) |
| Moderate > Baseline | | | | | | | | |
| (R) alPFC (BA 10) – cluster 1 | +30, +42, +12 | 3.43 | **–0.39 (0.007)** | 0.12 (0.394) | **–0.44 (0.002)** | **–0.51 (0.001)** | –0.01 (0.939) | –0.37 (0.013) |
| (R) alPFC (BA 10) – cluster 2 | +32, +46, +22 | 3.27 | –0.31 (0.035) | 0.23 (0.113) | **–0.41 (0.006)** | **–0.45 (0.004)** | –0.03 (0.849) | **–0.43 (0.005)** |
| (R) mFO (BA 44) | +60, +10, +4 | 3.19 | –0.12 (0.395) | 0.17 (0.213) | **–0.58 (<0.001)** | –0.28 (0.083) | –0.03 (0.843) | **–0.43 (0.009)** |

Sensory threshold refers to temperature (temp, °C) in which the percept variable (warmth, mild and moderate pain) was obtained. Affect rating refers to percept unpleasantness as rated by a 0–20 scale. Bold indicates meeting Bonferroni correction for multiple comparisons ($P \leq 0.01$).

alPFC = anterolateral prefrontal cortex; BA = Brodmann Area; HIPPO = hippocampus; L = left; MCC = middle cingulate cortex; MNI = Montreal Neurologic Institute; mFO = middle frontal operculum; R = right; T = T-statistic.

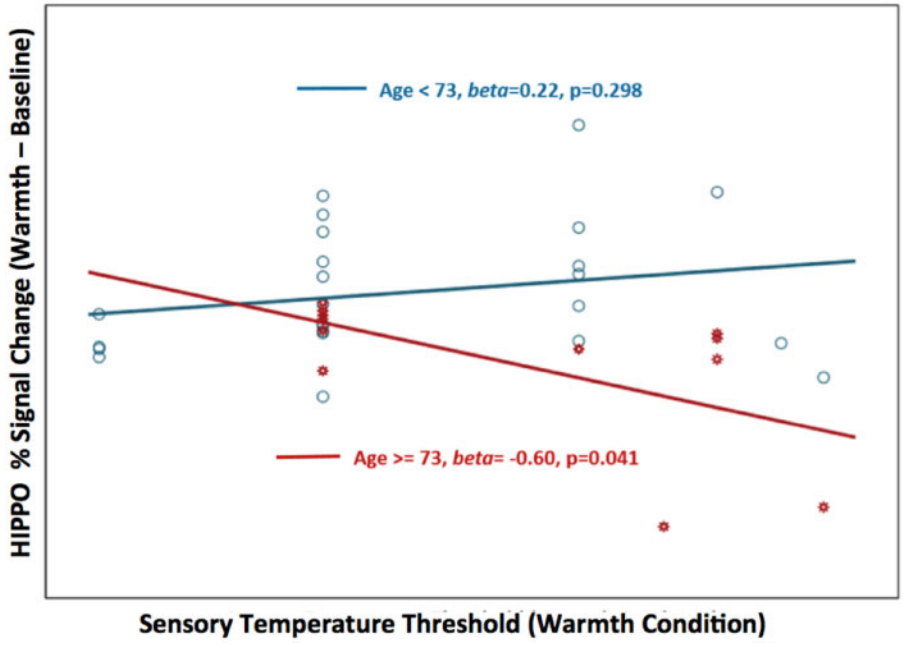


**Figure 2.** Qualitative view of significant interaction effect between age*temperature of warmth detection for warmth-associated hippocampal (HIPPO) activation. This interaction was driven by individuals >73 years of age (red line), who showed a significant tendency for reduced activation with higher warmth detection thresholds. The opposite pattern tended to occur in those <73 years (blue line).

corresponding decrease in activation in the HIPPO (*beta* = –0.60, $P = 0.041$). This effect was not borne out in younger subjects (*beta* = 0.22, $P = 0.298$).

## Mild Pain > Baseline Contrast

Increasing age was associated with greater left MCC activation during the perception of mild thermal pain (T = 5.0) (Figure 1). This effect of age on MCC activation during mild pain remained after adjusting the perception of mild pain sensory threshold and affective ratings (sensory: *beta* = 0.44, $P = 0.006$; affective: *beta* = 0.48, $P = 0.003$).

## Moderate Pain > Baseline Contrast

Moderate pain–induced activation of two anterolateral prefrontal cortex (alPFC) clusters in BA 10 (cluster 1 and 2) decreased as a function of age (T = –3.43 and 3.27) (Figure 1 bottom). This relationship persisted with adjustment for sensory percept thresholds and affective ratings for cluster 1 (sensory: *beta* = –0.39, $P = 0.007$; affective: *beta* –0.51, $P = 0.001$), whereas cluster 2 showed this pattern only for affective ratings correction (*beta* = –0.45, $P = 0.004$). There were also significant interaction effects for each cluster with respect to age*sensory percept of moderate pain for cluster 1 (age*sensory: *beta* = –0.44, $P = 0.002$). Cluster 2

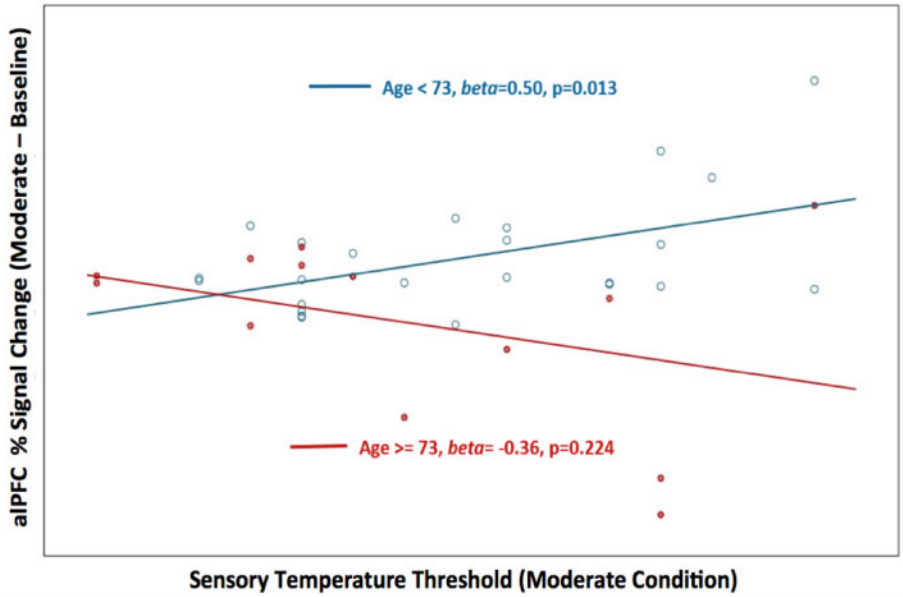


**Figure 3.** Qualitative view of significant interaction effect between age*temperature of moderate heat pain for associated activation of one cluster in the anterolateral prefrontal cortex (alPFC). This interaction was driven by individuals >73 years of age (red line), who showed a significant tendency for reduced activation with higher warmth detection thresholds. The opposite pattern tended to occur in those <73 years (blue line).

additionally had interaction effects for age*sensory percept and age*affective ratings of moderate pain (age*sensory: *beta* = –0.41, $P = 0.006$; age*affective ratings: *beta* = –0.43, $P = 0.005$). The significant interaction effect for the sensory domain at alPFC cluster 1 was driven by "younger" old subjects (<73 years old: age*sensory *beta* = 0.50, $P = 0.013$; >73 years old: age*sensory *beta* = –0.36, $P = 0.227$) (Figure 3). In contrast to "older" subjects, "younger" individuals showed increased activation associated with the perception of moderate pain sensory thresholds. "Older" subjects additionally drove interactions for cluster 2 (sensory interaction: <73 years old: age*sensory *beta* = 0.60, $P = 0.002$; >73 years old: age*sensory *beta* = –0.24, $P = 0.427$; affective interaction: <73 years old: age*affective rating *beta* = 0.39, $P = 0.058$; >73 years old: age*affective rating *beta* = –0.48, $P = 0.096$).

Moderate pain–induced right middle frontal operculum (mFO, BA 44) activation was also reduced with increasing age (T = –3.19) (Figure 1 bottom). Here, while adjustments for psychophysical responses led to loss of main effects of age, there were significant interaction effects for age*sensory percept threshold (*beta* = –0.58, $P < 0.001$) and age*affective ratings of moderate pain (*beta* = –0.43, $P < 0.009$). Although the age*sensory interaction effect was driven primarily by increased activation in "younger" old (<73 years) subjects (*beta* = 0.55, $P = 0.005$) (Figure 4A), the age*affective rating interaction was seemingly driven by general slope differences between "younger" and "older" individuals ($P > 0.05$ for both groups) (Figure 4B).

## Discussion

The increasing prevalence of older individuals makes an understanding of age-associated changes in pain perception crucial. Here, in a sample of healthy older persons, we examined psychophysical and fMRI-associated responses to innocuous and painful thermal stimuli. We predicted that increasing age would be associated with decreased pain sensitivity (increased thermal thresholds) but no change in pain unpleasantness. This prediction was partly supported. We found a significant age*sensory threshold interaction driven by greater warmth detection threshold temperatures as age advanced. There were no significant correlations specifically for age and pain-related percept thresholds, nor between age and affective ratings of warmth and thermal pain.

A number of prior psychophysical studies comparing younger and older subjects have found evidence of age-related effects on sensory detection [62], pain thresholds, mild/moderate pain intensity ratings, and pain tolerance for thermal [45,63,64], mechanical [46,65], and electrical or laser pain stimulus modalities [17,66]. Here we found a general sensory threshold and age interaction effect driven by increased warmth detection thresholds in relatively older individuals. It is possible that a lack of "pain-specific" age effects was secondary to examining psychophysics in the setting of a continuum of older age, rather than comparing young and old adults. We also did not collect pain intensity ratings related to the percept-driven nature of our sensory stimuli in our study design; doing so may have added to the pain-specific findings.

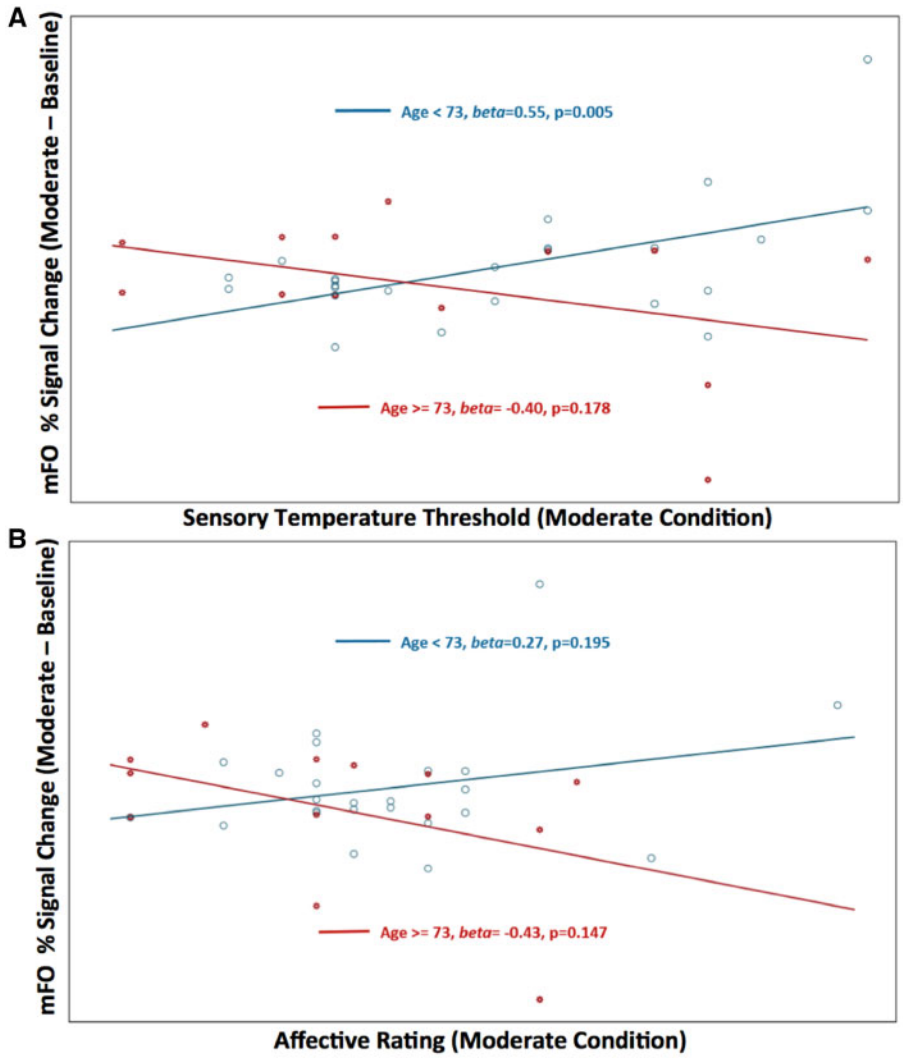


**Figure 4.** Qualitative view of significant interaction effects between age*temperature (A) and age*affective ratings (B) of moderate heat pain for associated activation in the medial frontal operculum (mFO). The age*temperature effect was driven primarily by increased activation in "young" old (<73 years) subjects (beta = 0.55, $P = 0.005$); the age*affective rating effect was seemingly driven by general slope differences between "young" and "old" old individuals ($P > 0.05$ for both groups).

Nevertheless, our psychophysical results do fit well with a recent systematic meta-analysis showing that the most consistent age-related effect on pain pertains to low-intensity stimuli using thermal modalities [8]. A quarter of our sample was >80 years of age (max = 97); thus, our results extend prior findings to the "oldest old," who have seldom been included in pain studies.

Based on prior psychophysical studies and our own results, our second prediction (fMRI) was that increased thermal sensory threshold temperatures, in conjunction with advancing age, would be associated with reduced activation among lateral pain pathway structures (S1, S2, pINS). Given (albeit less frequent) prior findings suggestive of reduced pain tolerance and pain modulation in older age, we also posited that altered activation patterns of medial pain-related regions might be found. These predictions were partly supported. Notably, no relationships were found between activation in lateral pain structures and age for any tested percept. We did, however, find a number of medial pathway-related regions displaying age-associated alterations of activation. First, activation of the contralateral HIPPO during warmth perception generally lessened as age increased, a pattern generally independent of psychophysical responses. However, there was a differential age effect between "younger" (<73 years) and "older" (>73 years) individuals with respect HIPPO activation during warmth perception. In "younger" old individuals, contralateral HIPPO activation tended to be positively correlated with warmth perception; the opposite pattern occurred in "older" individuals. With respect to somatosensation and pain, the HIPPO is implicated in novelty detection, pain-related anxiety, and aversion [36,37], with deactivations predominating during low-level pain, at least in younger

samples [67]. Large cross-sectional studies suggest that the HIPPO has pronounced volume loss and reduced large-scale network connectivity with healthy aging [39,68]. Similarly, aging is associated with reduced novelty-related processing in the HIPPO [69]. Reduced functional and structural integrity of this region as part of advanced aging may thus impair novelty-related somatosensation detection, leading to greater innocuous warmth thresholds.

Our primary psychophysical finding was that of increased warmth detection threshold with increased older age; thus, we found no "pain-specific" age-related psychophysical changes. Nevertheless, we did find altered activation patterns as a function of age during pain. First, we found that, in the contralateral (left) MCC, advancing age (adjusted for psychophysical responses) was generally associated with increased activation during mild thermal pain. The MCC is a key hub within the medial pain system, implicated in cognitive control and affect-related visceral (e.g., cardiac) and somatomotor (e.g., facial expression) responses to salient stimuli [70,71]. Prior studies of pain in aging have found similar MCC activation during pain perception in young and older individuals [44–46]. Further, gray matter volume reductions are not commonly reported in this region. Thus pain-related structure and function in the MCC appears to be relatively preserved even in advanced old age, at least for mild thermal pain. This preservation may help explain a lack of correlations between age and affective responses to thermal stimuli here.

Moderate thermal pain was associated with age-related activation changes in two prefrontal regions, the mFO and alPFC. Activation in these regions during moderate pain was generally correlated negatively with age. Closer inspection of these results again revealed differential activation patterns between "younger" and "older" old adults; activation in these frontal regions in "younger" old tended to be positively correlated with moderate pain threshold and affective ratings, whereas "older" old adults tended to show the opposite pattern. The mFO and neighboring aINS frequently co-activate during salient internal and external stimuli, promoting outward, goal-directed or inward, introspective processing, respectively [72,73]. With respect to pain, the mFO and alPFC are active during encoding and evaluation of pain intensity [74]. The mFO in particular is thought to be involved in active attention and working memory related to a salient stimulus [75]. Meanwhile, the alPFC is implicated in cognitive reappraisal processes [76,77], including the cognitive modulation of pain. Cognitive control and emotional regulation are known to be impaired with older age [78], with associated reductions in prefrontal gray matter volume and activation of prefrontal networks involving mFO and alPFC during reappraisal tasks [45,79,80]. However, as our current findings and other work show, older adults still recruit prefrontal and cingulate activation in the context of affective stimuli, as well as during deliberate emotion regulation [81]. Behavioral studies indicate that altered emotional regulation in older age manifests through reduced attention to negative affective stimuli [82]; the latter behavioral effect may be secondary to, for example, reduced mFO activation in advancing age.

In contrast to more sensory-specific changes with age, age-related changes in the pain-related affect have been neither strong nor consistent among prior studies [8]. However, prior analyses have considered potential age-related changes in pain affect secondary to impaired pain modulation in the elderly [17,18]. An age-associated reduction in prefrontal activation fits well with prior work suggesting impaired top-down pain modulation or increased pain unpleasantness in elderly individuals [17,18]. Intriguingly, expectation-based (placebo) analgesia, which requires intact frontal function, is intact in healthy older adults [19,20]. It may be that older adults rely on compensatory, or context-dependent, affect regulation pathways. Our data suggest that, at least with respect to thermal pain, prefrontal activation processes are altered in advanced age in a manner that may place these individuals at higher risk for greater disability and suffering.

Several caveats must be kept in mind with respect to this study. First, we examined pain psychophysics and activation in the context of an older age continuum; this may help explain, compared with prior work, our finding fewer "pain-specific" changes in age-related psychophysical responses and brain activation. Our results apply only to comparisons of relatively "older" vs relatively "younger" older individuals, a comparison rarely studied in prior work. Further, use of suprathreshold pain stimuli beyond moderate pain may have also led to alternative, possibly more robust, psychophysical and activation-based findings. With respect to imaging findings, we did not perform partial volume corrections in processing activation maps, which could have affected signal-to-noise ratios and spatial extent of significant clusters [82]. However, use of more conservative multiple comparison correction methods likely limited the extent of false-positive results. Our use of a median split procedure to examine differential aging effects is a somewhat arbitrary, though useful, means for examining these effects in a single sample design. An additional limitation pertains to our demographics, which reflected participants who were predominantly Caucasian with relatively elevated socioeconomic status. Finally, to better answer the question of how age alone affects pain perception and processing, we took care to exclude any individuals with frequent or chronic pain; it would thus be interesting in a future study to perhaps see how age-related changes are different in a population afflicted by daily pain.

Relative strengths of this study pertain to our analyses of data from a relatively large number of "older old" subjects (80–90 years), who are not frequently included in pain studies. Our use of standardized psychophysical

methods and thermal stimuli was also beneficial; this modality has provided the most consistent behavioral results across multiple studies [8]. Future work in this regard should be extended to examine both effective (pain-induced) and resting-state functional connectivity in healthy older adults to obtain a network-based perspective on pain-related changes. Examining neural correlates of additional pain modalities, as well as quantitative sensory testing, would also be useful.

This study examined patterns of altered psychophysical responses and associated brain activations along a continuum of older adult aging. We found that advancing age was associated with greater thresholds for warmth perception (i.e., decreased warmth perception), possibly facilitated by less HIPPO-mediated novelty detection. Thresholds for mild pain and associated affective ratings were unaltered by increasingly older age, which was, however, associated with intact cingulate (medial pain) activation. Moderate thermal pain was associated with less activation in "older" old adults in prefrontal pain modulatory regions, which could relate to a trend reported in prior studies toward greater pain-related unpleasantness in older individuals. Our understanding of pain in the aged will benefit from future studies examining the effects of suprathreshold pain levels as well as pain-related functional connectivity measures across the lifespan.

## Authors' Contributions

All authors have read and agree with the contents of the manuscript and take full responsibility for the data presented. PB synthesized data interpretation, helped produce figures and tables, and wrote the manuscript. RC assisted with conceptualization of the project, planning/design of MRI-related tasks, and manuscript drafting and editing. MD conducted all statistical analyses outside neuroimaging and produced initial drafts of tables and graphical figures. SB designed psychophysical procedures, trained subjects on procedures, and assisted in manuscript drafting. SA analyzed imaging data and contributed to manuscript drafting. JG assisted with conceptual MRI and associated task development. TM conceptualized the project and assisted with all levels of manuscript development.

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## Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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