






# Cross-Sectional Brain-Predicted Age Differences in Community-Dwelling Middle-Aged and Older Adults with High Impact Knee Pain

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**Purpose:** Knee OA-related pain varies in impact across individuals and may relate to central nervous system alterations like accelerated brain aging processes. We previously reported that older adults with chronic musculoskeletal pain had a significantly greater brain-predicted age, compared to pain-free controls, indicating an “older” appearing brain. Yet this association is not well understood. This cross-sectional study examines brain-predicted age differences associated with chronic knee osteoarthritis pain, in a larger, more demographically diverse sample with consideration for pain’s impact.

**Patients and Methods:** Participants (mean age = 57.8 ± 8.0 years) with/without knee OA-related pain were classified according to pain’s impact on daily function (ie, impact): low-impact (n=111), and high-impact (n=60) pain, and pain-free controls (n=31). Participants completed demographic, pain, and psychosocial assessments, and T1-weighted magnetic resonance imaging. Brain-predicted age difference (brain-PAD) was compared across groups using analysis of covariance. Partial correlations examined associations of brain-PAD with pain and psychosocial variables.

**Results:** Individuals with high-impact chronic knee pain had significantly “older” brains for their age compared to individuals with low-impact knee pain ( $p < 0.05$ ). Brain-PAD was also significantly associated with clinical pain, negative affect, passive coping, and pain catastrophizing ( $p$ 's<0.05).

**Conclusion:** Our findings suggest that high impact chronic knee pain is associated with an older appearing brain on MRI. Future studies are needed to determine the impact of pain-related interference and pain management on somatosensory processing and brain aging biomarkers for high-risk populations and effective intervention strategies.

**Keywords:** knee osteoarthritis, high impact chronic pain, brain aging, experimental pain, psychosocial

## Introduction

Knee osteoarthritis (OA) is a leading cause of chronic pain among middle-aged and older adults, and contributes to significant physical disability and global disease burden.<sup>1,2</sup> However, the impact of knee OA-related pain is variable,<sup>3,4</sup> and the factors contributing to this heterogeneity are poorly understood.<sup>5,6</sup> Recent evidence indicates that factors beyond OA radiographic pathology underlie pain in knee OA,<sup>7</sup> including systemic factors (eg, inflammation, gut microbiome, nervous system).<sup>8–10</sup> Specifically, structural and functional brain changes have been demonstrated in those with chronic knee OA-related pain,<sup>11,12</sup> including gray matter decline in the primary motor cortex, left temporal lobe, and precuneus

cortex,<sup>13</sup> similar to changes observed in aging.<sup>14,15</sup> Given the overlap in pain- and age-related changes in brain structure, it is possible that chronic pain may exacerbate typical age-related brain atrophy, and increase the risk for poor health outcomes.<sup>16</sup>

Technological advances have led to the development of brain aging biomarkers, which are able to detect deviations from healthy brain aging patterns, allowing for the investigation of accelerated biological aging specific to the brain.<sup>17–19</sup> Brain aging biomarkers are estimated by training machine-learning algorithms using large structural magnetic resonance imaging (MRI) datasets from thousands of healthy individuals across a wide age span (eg, 18–90 years).<sup>20</sup> In our prior work, we investigated an established brain aging biomarker,<sup>17,20</sup> and found that older adults reporting chronic musculoskeletal (MSK) pain (ie, pain on most days during activities in the past 3 months) had an “older” appearing brain compared to pain-free age-matched controls.<sup>21</sup> Furthermore, we found that an older appearing brain was associated with greater pain intensity, pain sensitivity and inhibition, and positive affect and other personality traits in our sample of older adults.<sup>21,22</sup> These findings are consistent with previous research demonstrating sustained untreated pain was associated with added “age-like” brain atrophy.<sup>23,24</sup> Furthermore, individuals with chronic pain who also experience daily pain-related limitations (ie, disability) may be at an even greater risk for brain atrophy due to restrictions in activities, decreased social engagement, and greater mental health and cognitive impairments.<sup>25</sup>

However, the role of brain aging in chronic pain is not clear. In a subsequent study,<sup>26</sup> Soros et al did not find evidence of accelerated brain aging in a younger cohort of non-cancer chronic pain patients receiving pain treatment from several pain and rheumatology clinics and the emergency room.<sup>26</sup> It is possible that these contrasting findings are due to differences in study population characteristics, including type of pain (eg, pain with and without physical limitation and location), cohort age, and other non-specific factors (eg, treatment seeking, pain relief). However, a recent study found that across three different pain conditions, individuals with osteoarthritis pain and trigeminal neuralgia showed significantly older appearing brains.<sup>27</sup> Despite these findings, there has been limited examination of the global brain aging patterns in persons with chronic pain. Given that brain aging as measured employing brain aging biomarkers has been associated with worse cognitive performance, increased likelihood for chronic disease (eg, cardiovascular diseases), and increased mortality,<sup>17,28–30</sup> it is imperative to elucidate the relationship between chronic pain and brain aging to identify adults at greater risk for cognitive and physical function decline.<sup>22,31</sup>

Therefore, we hypothesized that adults reporting chronic knee OA-related pain with high-impact chronic pain (ie, pain limiting daily function) would present with an older-appearing brain compared to those with less limiting pain, or those with no pain. We further hypothesized that brain aging would be associated with experimental pain sensitivity and psychosocial factors previously associated with knee OA pain, in line with the biopsychosocial model of chronic pain. The purpose of this study was to examine brain predicted age differences in the largest sample studied to date, including a more demographically diverse cohort of middle-aged and older adults with a specific chronic pain condition (ie, chronic knee pain), presenting with variable levels of pain-related disability.<sup>25,32</sup> The present study furthers our understanding of the association between chronic pain and brain aging patterns by examining these associations in pain-free individuals and those with low impact and high impact chronic knee pain.

## Materials and Methods

### Participants

The current study sample was recruited as part of a multisite observational study aimed at examining ethnic/race group differences in individuals with or at risk for knee osteoarthritis (OA). The larger parent study was conducted at the University of Florida (UF) and the University of Alabama, Birmingham. The study was approved by the University of Florida (UF) and University of Alabama, Birmingham (UAB) Institutional Review Boards (IRB#201400209), under the Common Rule which requires the use of single IRB for US based institutions engaged in cooperative research. UF served as the Institutional Review Board of Record, providing regulatory and ethical oversight of the research. The study was carried out in accordance with the Declaration of Helsinki. Power calculations were conducted a priori to examine brain-PAD group differences ( $1-\beta = 0.80$ , two-sided  $\alpha = 0.05$ ) to detect a medium-sized effect ( $\eta_p^2 = 0.06$  and Cohen's  $f=0.25$ ). Individuals aged 45–85 years, who spoke English and self-identified as non-Hispanic, and “Black/

African American” or “White/Caucasian/European” were recruited from the communities surrounding UF and UAB, between August 2015 and May 2017, using posted fliers, radio/print media, clinic and word-of-mouth referrals. All enrolled participants completed written informed consent and were compensated for their involvement. Individuals were excluded based on the following: 1) prosthetic knee replacement or other clinically significant surgery to the index (arthritic) knee; 2) heart disease, congestive heart failure, or history of acute myocardial infarction; 3) uncontrolled hypertension (blood pressure >150/95 mm Hg); 4) peripheral neuropathy; 5) systemic rheumatic disorders (ie, rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia); 6) chronic daily opioid use; 7) hospitalization within the preceding year for psychiatric illness; 8) neurological diseases (ie, Parkinson’s, multiple sclerosis, stroke with loss of sensory or motor function, or uncontrolled seizures); 10) pregnant or nursing; and 11) significantly greater body pain in a site other than the knee. Individuals with and without clinical knee OA criteria were included in the parent study.<sup>33</sup>

## Procedures

Following an initial phone screening, during which sociodemographic (eg, sex, age, ethnicity/race), and health information (eg, brief health history and symptoms of knee OA) were collected, individuals were scheduled for a baseline health assessment session (HAS). The HAS consisted of a health and pain history, and physical examination to determine the most painful (ie, index) knee. Radiographs were collected and graded by the study’s rheumatologist according to the Kellgren–Lawrence (KL) classification.<sup>34</sup> Quantitative sensory testing (QST) occurred approximately 1 week later. Magnetic resonance imaging (MRI) was completed approximately 1 week after the QST session. Participants completed clinical pain measures within 24 hours of the QST session, and psychosocial questionnaires were completed within 24 hours of the MRI.

## Measures

### Clinical Pain Measures

#### Graded Chronic Pain Scale (GCPS)

The *GCPS*, a validated and reliable measure, was used to assess pain intensity and pain-related disability.<sup>35</sup> Participants were asked to rate on a 0 (“no pain”) to 10 (“pain as bad as could be”) numerical rating scale (NRS) their current, average, and worst pain in the past 6 months. Similarly, pain-related disability items (ie, how much pain has interfered with daily activities, recreational/social/family activities, and ability to work) on average, over the past 6 months, were rated on a 0 (“no interference”) to 10 (“unable to carry out activities”) scale. Ratings were averaged and multiplied by 10 to yield a 0–100 score for each domain, with higher scores indicating greater pain intensity and pain-related disability. Another item asked “How many days in the last six months have you been kept from your usual activities because of pain?” Pain-related disability points were calculated from 1) the averaged ratings (ie, 0–29 = 0 points; 30–49 = 1 point; 50–69 = 2 points;  $\geq 70$  = 3 points) and 2) total number of disability days (ie, 0–6 days = 0 points; 7–14 days = 1 point; 15–30 days = 2 points; 31 days or more = 3 points). Disability points were summed. GCPS pain intensity and disability point scores were then combined as follows: Grade 0 = no reported pain intensity; Grade 1 = low pain intensity (ie, <50) and low disability (ie, <3 disability points); Grade 2 = high pain intensity (ie,  $\geq 50$ ) and low disability; Grade 3 = high disability-moderately limiting (ie, 3–4 disability points), regardless of pain intensity; Grade 4 = high disability-severely limiting (ie, 5–6 disability points), regardless of pain intensity.<sup>35</sup> Consistent with the recommendations from the Task Force for the Classification of Chronic Pain consensus for the 11th version of the International Classification of Diseases (ICD-11) of the World Health Organization (WHO),<sup>32</sup> and the Graded Chronic Pain Scale-Revised,<sup>36</sup> *Pain Grades* were used to classify individuals without (ie, Grade 0), or with (ie, Grades 1–4) chronic pain, and as low-impact (ie, Grades 1–2), and high-impact (ie, Grades 3–4) chronic knee pain.

#### Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The *WOMAC* pain subscale assessed lower extremity pain related to arthritis over the past 48 hours on a 5-point scale, with higher scores indicating greater pain severity.<sup>37</sup>

### MRI Pain Ratings

Participants were asked to rate their current knee pain on a 0 (“no pain”) to 100 (“worst pain imaginable”) NRS immediately prior to MRI scanning.

### Psychosocial Measures

#### In vivo Coping (IVC)

The *IVC scale* consists of 10 items which assess Passive (eg, “I felt that if the pain got any worse I wouldn’t be able to tolerate it.”), and Active (eg, “I thought of other things to get my mind off the pain.”) situational pain coping. Items were rated from 1 (“not at all”) to 5 (“very much”), with totals computed as the sum of items from each domain (ie, Passive and Active).<sup>38</sup> The IVC was administered following quantitative sensory testing (QST) to provide a measure of in vivo coping during experimental pain.

#### Positive and Negative Affect Scale (PANAS)

The *PANAS* consists of 20 words used to describe positive (PA) and negative (NA) affect. Participants were asked to rate how they “generally feel” on a 5-point Likert-type scale, with higher scores indicating greater PA or NA.<sup>39</sup>

#### Pain Catastrophizing

Pain catastrophizing was assessed using the Coping Strategies Questionnaire-Revised (CSQ-R) catastrophizing subscale,<sup>40</sup> which consists of six items that assess the helplessness dimension of pain catastrophizing, with higher scores representing greater catastrophizing.

### Experimental Pain Measures

Multimodal Quantitative Sensory Testing (QST) was used to assess experimental pain sensitivity using a standardized protocol, as previously reported.<sup>41</sup> All QST procedures were performed by trained study staff in a quiet room, with participants comfortably seated. The experimenter played recorded instructions prior to each test and participant understanding was checked.

#### Heat Pain

A Medoc Pathway Thermal Sensory Analyzer (Ramat Yishai, Israel) delivered heat stimuli to the medial joint line of the index knee (ie, most painful or randomly assigned for pain-free controls) and ipsilateral forearm to assess *heat pain threshold* (ie, first sensation of pain; HPTh), and *heat pain tolerance* (ie, point at which pain could no longer be tolerated; HPTol). Each trial began at a baseline temperature of 32°C and temperature gradually increased at a rate of 0.5°C/second until the participant ended the trial by pressing a button. The mean or trimmed mean of three trials within 3°C for each detection measure was used in the analysis. Participants also rated pain on a 0–100 NRS following a train of five heat pulses delivered at 44°C, 46°C, and 48°C successively to both testing sites in random order. Heat pain after sensations were also rated at 15 and 30 seconds after the last stimulus for each temperature and testing site. Heat pain threshold, tolerance and pain ratings were averaged separately for each temperature and testing site and standardized.<sup>42</sup> Heat pain threshold and heat pain tolerance values were reversed, and all standardized values were combined to calculate a *heat pain sensitivity index*.

#### Mechanical Pain

A handheld digital pressure algometer (Algomed, Medoc, Ramat Yishai, Israel) assessed pressure pain threshold (PPT) at the medial and lateral joint line of the index knee, the ipsilateral quadriceps, and trapezius. A constant rate of pressure (30 kPa/second) was applied to each site, and ended when the participant pressed a button indicating their first experience of pain. Maximum pressure levels (600 kPa for knee sites, 1000 kPa for quadriceps and trapezius) were predetermined to maintain participant safety. The means or trimmed means of three trials within 40 kPa were calculated for each testing site and standardized (*z*-scored), reversed, and averaged to create an overall pressure pain sensitivity index.

### Punctate Temporal Summation (TS)

Punctate TS was determined by using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300g applied to the index patella and back of the ipsilateral hand. Order of testing site was randomized across participants. Pain was rated (0–100 NRS) after a single, and a series of 10 contact(s). The procedure was repeated twice at each testing site. Difference scores of the average pain rating following a single stimulus and the average pain rating following 10 stimuli were computed for each test site, standardized, and combined to create a punctate temporal summation score used in the analysis.

### Conditioned Pain Modulation (CPM)

Pressure pain threshold (PPT), as described above, was delivered to left trapezius as the test stimulus. Participants then placed their right hand, up to the wrist, into a cold-water bath (ie, conditioning stimulus) maintained at 12°C (Neslab refrigeration unit, Portsmouth, NH, USA). After 30 seconds, PPT was assessed again. CPM was calculated as follows:  $[(\text{prePPT} - \text{duringPPT})/\text{prePPT}] \times 100$ , with negative values indicating pain inhibition. CPM served as a proxy measure of endogenous pain inhibition.

## Neuroimaging

MRI data was collected at the University of Florida using a 3-tesla Phillips (Best, the Netherlands) scanner using a 32-channel radio-frequency coil, and an 8-channel head coil at the University of Alabama – Birmingham. A high-resolution, T1-weighted turbo field echo anatomical scan was collected using the following parameters: TR = 7.0 ms, TE = 3.2 ms, 176 slices acquired in a sagittal orientation, flip angle = 8 degrees, resolution = 1 mm<sup>3</sup>. Head movement was minimized via cushions positioned inside the head coil and instructions to participants.

### Brain Aging Biomarker

The brain aging biomarker used here was derived using a previously established “brain-age” framework.<sup>20</sup> This involved training a machine-learning model to accurately predict chronological age from neuroimaging data in a training cohort comprised 3377 healthy individuals (age mean = 40.6 ± 21.4 years; age range = 18–92 years) and a testing cohort of 857 healthy adults (mean age 40.1 ± 21.8 years, age range = 18–90 years) amalgamated from seven public datasets. Thus, the training and testing cohorts were independent, but derived from the same scanning sites. The training datasets were screened according to local study protocols to ensure that they were free of neurological and psychiatric disorders, had no history of head trauma and other major medical conditions.<sup>17</sup> Ethical approval for each initial study and subsequent data sharing was verified for each data repository. Models used segmented and spatially normalized T1-weighted MRI scans as the predictor variables in a Gaussian process regression, with chronological age as the outcome variable. Model accuracy based on the held-out test data (using random assignment to training and test) was high, with a mean absolute error of 3.93 years and a correlation between chronological age and “brain-predicted” age of  $r = 0.97$ ,  $R^2 = 0.95$ . Then, using the regression model trained on the full independent dataset ( $n = 3377$ ), brain-predicted age values were generated for the  $n = 202$  participants in the current study. Consistent with our prior work,<sup>21</sup> the individual participants’ chronological age was subtracted from the brain-predicted age value to generate the brain-predicted age difference (brain-PAD) used for the current analysis.

## Data Analysis

Data were checked for normality, outliers, and conformance to assumptions. One-way analysis of variance (ANOVA) and  $\chi^2$  were used to test for group differences for continuous/discrete ordinal and nominal variables, respectively. One-way analysis of covariance (ANCOVA) was conducted accounting for sex, race, age, and study site similar to our previous work,<sup>21</sup> to compare brain-PAD between pain impact groups. These covariates were chosen based on prior literature,<sup>43</sup> and differences between pain impact groups in the current sample. Additionally, we investigated the potential role of radiographic pathology (ie, KL grade) on the relationship between pain impact and brain-PAD, adjusting for the same covariates. A probability less than 0.05 was considered statistically significant. Bonferroni post hoc comparisons were conducted. Pearson partial correlations were used to assess associations between brain-PAD with clinical and

experimental pain and psychological variables, accounting for age, sex, race, and study site in the total sample. Bootstrapping procedures with 5000 samples were employed for all analyses and reported as 95% Bias-corrected and accelerated (BCa) bootstrapped confidence intervals. For the analyses examining associations of brain-PAD with self-reported and experimental pain, as well as psychological function, we report both uncorrected (ie,  $p =$ ) and corrected probability values (ie, corrected  $p =$ ) adjusting for multiple comparisons applying the Holm–Bonferroni method,<sup>44</sup> using the calculator by Gaetano.<sup>45</sup> Data analyses were performed using IBM SPSS 27 software.

## Results

### Demographic Characteristics

Two-hundred and two individuals (mean age =  $58.2 \pm 8.2$ ; 65.5% female) completed all study measures. Demographic and clinical characteristics by pain impact groups are presented in Table 1. There was a significant difference in race ( $p < 0.05$ ), pain severity and pain-related disability ( $p$ 's  $< 0.001$ ), across pain impact groups, such that non-Hispanic Blacks were overrepresented in the High Impact Chronic Pain (HICP) group, and those in the HICP group reported greater pain and pain-related disability.

### Brain-PAD Differences Between Pain Impact Groups

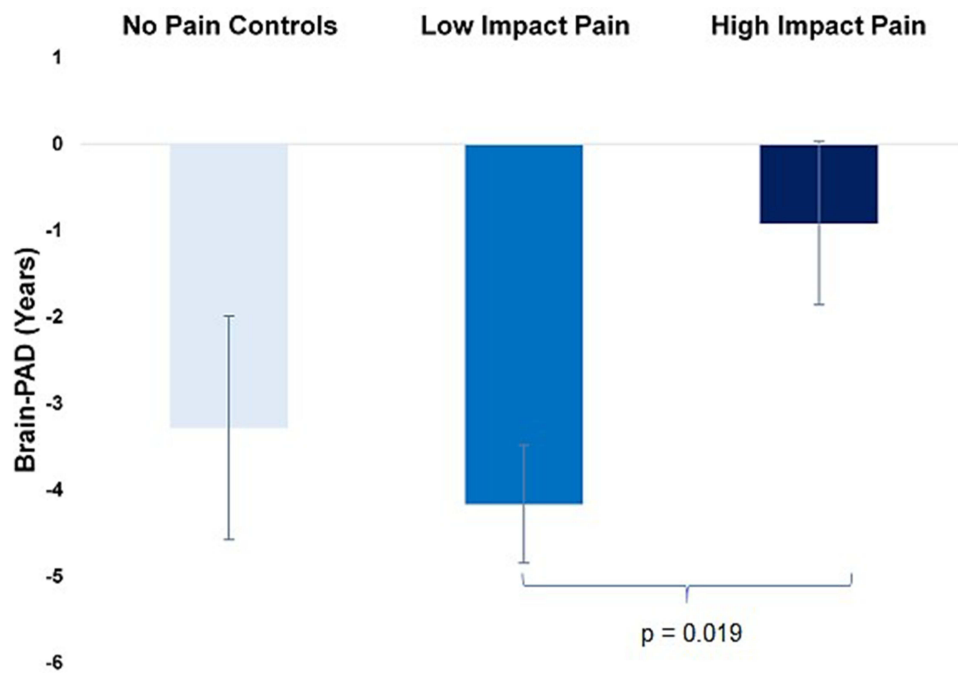
The results from an ANCOVA comparing brain-PAD between Pain Impact Groups showed significant differences in brain-PAD ( $F(2195) = 3.82$ ,  $p = 0.024$ ,  $\eta_p^2 = 0.04$ , Figure 1). Post-hoc tests revealed those with High Impact Chronic knee pain had a significantly “older” brain age pattern than those with Low Impact Chronic knee pain (mean difference =  $3.25 \pm 1.2$ , Bonferroni corrected  $p = 0.019$ , BCa 95% CI: 1.15, 5.32). Pain impact groups also differed significantly on brain-PAD even when including KL grade in the analysis ( $F(2189) = 3.43$ ,  $p = 0.034$ ,  $\eta_p^2 = 0.04$ ).

**Table 1** Demographic and Clinical Characteristics Across Pain Impact Groups

Variable, M $\pm$ SD, or no. (%)	No Chronic Pain (n = 31)	Low-Impact Pain (n = 111)	High-Impact Pain (n = 60)	p-value
Chronological Age (years)	60.1 $\pm$ 9.9	58.7 $\pm$ 8.1	56.2 $\pm$ 7.2	0.052
Predicted Brain Age (years)	56.7 $\pm$ 12.4	54.6 $\pm$ 10.7	55.3 $\pm$ 10.0	0.627
Sex				0.650
Male	9 (29.1)	37 (33.3)	23 (38.3)	
Female	22 (70.9)	74 (66.7)	37 (61.7)	
Race				<b>0.026</b>
Non-Hispanic Black	13 (41.9)	43 (38.7)	36 (60.0)	
Non-Hispanic White	18 (58.1)	68 (61.3)	24 (40.0)	
Site				0.756
UF	21 (67.7)	68 (61.3)	36 (60.0)	
UAB	10 (32.3)	43 (38.7)	24 (40.0)	
KL Grade*				0.335
0	16 (51.6)	34 (30.6)	17 (28.3)	
1	5 (16.1)	20 (18.0)	8 (13.3)	
2	6 (19.4)	25 (22.5)	11 (18.3)	
3	2 (6.5)	16 (14.4)	11 (18.3)	
4	2 (6.5)	13 (11.7)	11 (18.3)	
GPCS Pain Intensity	0 $\pm$ 0.0	38.6 $\pm$ 22.4	68.9 $\pm$ 18.4	<b>&lt;0.001</b>
GPCS Pain Disability	0.4 $\pm$ 2.4	20.5 $\pm$ 19.9	69.9 $\pm$ 22.6	<b>&lt;0.001</b>
GPCS Disability Points	0 $\pm$ 0.0	0.5 $\pm$ 0.8	4.2 $\pm$ 1.1	<b>&lt;0.001</b>
WOMAC-Pain	0.1 $\pm$ 0.4	4.5 $\pm$ 3.8	9.9 $\pm$ 4.0	<b>&lt;0.001</b>
Pain at Neuroimaging	0.3 $\pm$ 1.8	8.0 $\pm$ 15.3	23.6 $\pm$ 24.0	<b>&lt;0.001</b>

**Notes:** \*denotes missing data. Bolded values indicate statistical significance at  $\alpha = 0.05$ .

**Abbreviations:** UF, University of Florida; UAB, University of Alabama, Birmingham; KL, Kellgren–Lawrence; GPCS, Graded Chronic Pain Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index, NRS, numerical rating scale.



**Figure 1** Brain-PAD in years across pain impact groups. Values above the origin indicate an increase in brain-PAD, calculated as brain-predicted age minus chronological age. Covariates include age, sex, race, and study site. Error bars represent  $\pm 2$  standard errors.

## Brain-PAD Associations with Self-Reported Pain

Adjusted partial correlations suggested that brain-PAD was significantly correlated with average GCPS pain intensity ( $r = 0.15$ ,  $p = 0.039$ , corrected  $p = 0.273$ , BCa 95% CI: 0.02, 0.28), clinical pain at the MRI session ( $r = 0.20$ ,  $p = 0.006$ , corrected  $p = 0.072$ , BCa 95% CI: 0.08, 0.31), and WOMAC pain ratings ( $r = 0.14$ ,  $p = 0.044$ , corrected  $p = 0.273$ , BCa 95% CI: 0.01, 0.27), [Figure 2](#).

## Brain-PAD Associations with Experimental Pain

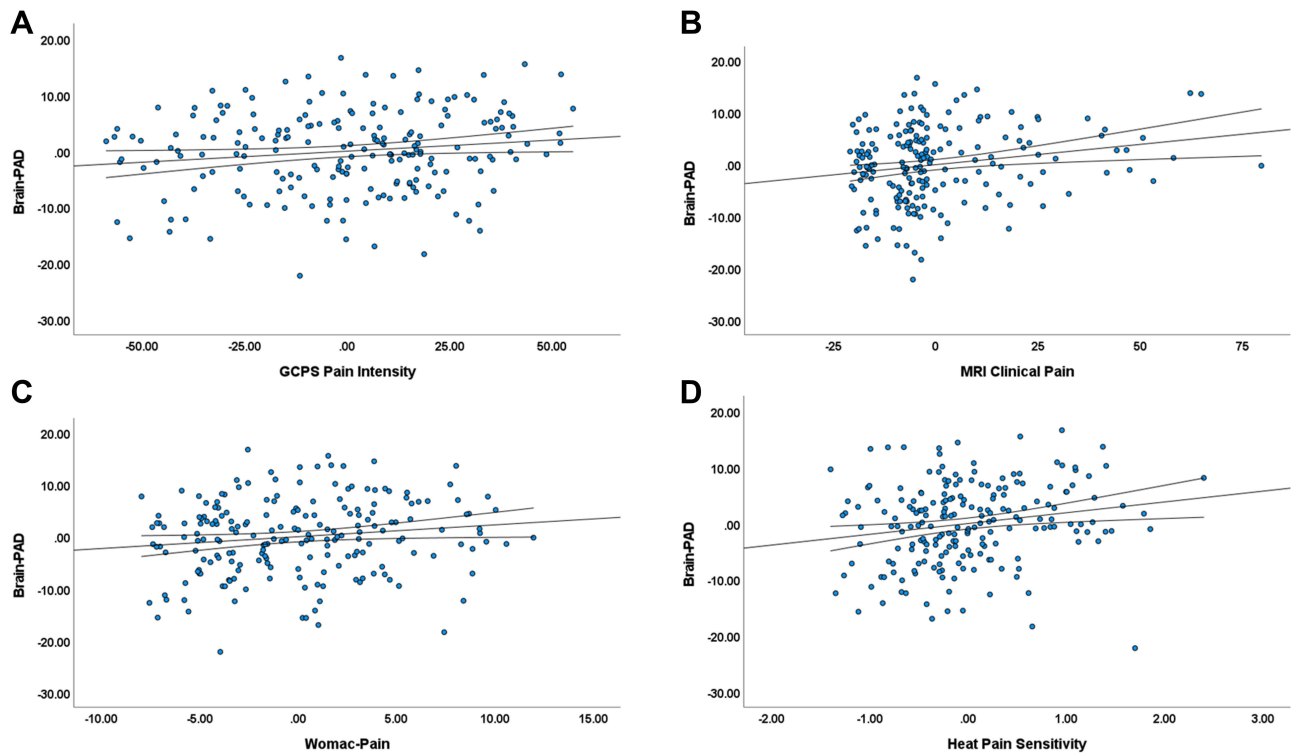
Adjusted partial correlations controlling for sex, race, age, and study site suggested that brain-PAD was significantly associated with experimental heat pain sensitivity ( $r = 0.19$ ,  $p = 0.008$ , corrected  $p = 0.072$ , BCa 95% CI: 0.03, 0.34), [Figure 2](#). There were no significant associations between brain-PAD with endogenous pain inhibition ( $r = -0.02$ ,  $p = 0.848$ , corrected  $p = 1.0$ ), punctate temporal summation ( $r = 0.07$ ,  $p = 0.327$ , corrected  $p = 1.0$ ), or pressure pain sensitivity ( $r = 0.01$ ,  $p = 0.844$ , corrected  $p = 1.0$ ).

## Brain-PAD Associations with Psychosocial Factors

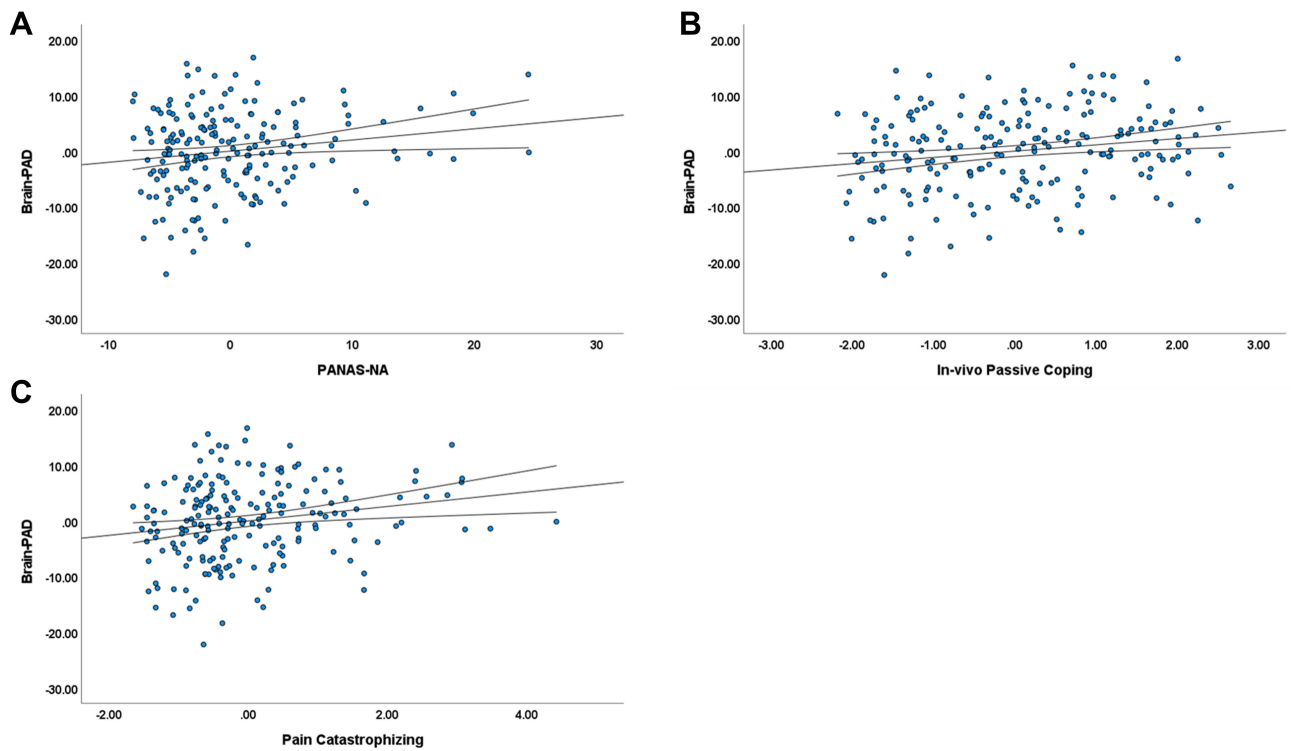
Brain-PAD was significantly associated with PANAS-Negative Affect ( $r = 0.17$ ,  $p = 0.023$ , corrected  $p = 0.184$ , BCa 95% CI: 0.03, 0.29), IVC-Passive ( $r = 0.19$ ,  $p = 0.007$ , corrected  $p = 0.072$ , BCa 95% CI: 0.06, 0.32), and Pain Catastrophizing ( $r = 0.19$ ,  $p = 0.006$ , corrected  $p = 0.072$ , BCa 95% CI: 0.08, 0.31), adjusting for age, sex, race, and study site ([Figure 3](#)).

## Discussion

To our knowledge, this is the first study to examine predicted brain age differences in chronic pain with consideration for the impact of both pain intensity and its daily interference (ie, pain impact). Our main hypothesis was supported, as there were significant differences in brain-predicted age differences (brain-PAD) between individuals with high- and low-impact chronic knee pain. Specifically, those with high-impact chronic knee pain (ie, chronic pain with severe physical limitations) had “older” appearing brains compared to individuals with low-impact chronic knee pain, regardless of age, sex, race, and study site. This finding did not change with consideration for radiographic joint



**Figure 2** Partial correlations between brain-PAD and (A) GCPS pain intensity, (B) Clinical knee pain at MRI, and (C) WOMAC-Pain, and (D) Heat pain sensitivity, adjusting for age, sex, race, and study site.



**Figure 3** Partial correlations between brain-PAD and (A) Positive and Negative Affect Schedule – Negative Affect (PANAS-NA), (B) In vivo Passive Coping, and (C) CSQ-R Pain Catastrophizing, adjusting for age, sex, race, and study site.



degeneration, and is in line with our prior work demonstrating advanced brain aging among older individuals reporting chronic pain experienced during daily activities.<sup>21</sup> High-impact chronic pain (HICP) is a relatively new pain classification conceptualized by the US National Pain Strategy, and was developed to overcome the limitations in previous definitions of chronic pain that relied solely on pain symptom duration.<sup>46,47</sup> Population-based studies indicate that HICP places individuals at increased odds of severe pain, physical disability, and cognitive impairment.<sup>25,48</sup> While the effects of HICP are just beginning to be examined, the relationship with brain aging is similar to that seen with other debilitating chronic diseases,<sup>17,18</sup> and may indicate that those with HICP are at an increased risk for accelerated biological aging.

In line with our previous findings, predicted brain age was positively associated with clinical knee pain and pain reported at the MRI session, with “older” predicted brain age related to greater clinical pain.<sup>21</sup> We found a significant positive association between predicted brain age differences and heat pain sensitivity in the current sample, with greater sensitivity associated with an “older” appearing brain. Although these findings did not survive multiple comparison corrections, the pattern of associations between clinical pain and brain-PAD indicates a positive relationship between brain aging and greater pain that warrants further examination. Also, variability in associations of brain aging with different measures of pain sensitivity may be related to stimuli-specific pain mechanisms. Future studies are needed to elucidate whether there are associations between QST measures and brain aging and further, to determine if QST may provide additional predictive value to biological aging biomarkers such as brain-predicted age.

Brain aging was also associated with passive coping, negative affect, and pain catastrophizing, indicating an “older” brain age was related to greater psychosocial distress in our participants; however, these associations were no longer significant after correction for multiple comparisons. In our previous study, we found associations between a “younger” brain age and positive affect in persons with chronic MSK pain, with no associations with negative affect.<sup>21</sup> The significantly younger age of the present sample (mean age ~58 years) compared to our previous study in older adults (mean age ~71 years),<sup>21</sup> may have contributed to differences in study findings. Specifically, older adults compared to younger individuals attend to, and remember more positive than negative information (ie, the “positivity effect”),<sup>49</sup> which may help to explain why the relationship between positive affect and less brain aging was evident in our prior study, but not in the current sample. Nonetheless, our findings appear consistent with the idea that affective disorders, such as major depressive disorder, characterized by chronic negative affect, may impact brain aging processes as evidenced by the brain-PAD biomarker.<sup>50</sup> Our findings are also supported by prior research demonstrating an apparent role for the corticolimbic circuitry, which is implicated in the emotional processing of pain, in pain chronification.<sup>23,51,52</sup> While the brain aging algorithm used in the current study does not provide a specific location where the brain aging occurs, it does recognize that there are multiple signatures of “healthy” brain aging, and that deviations from “normal” brain aging patterns can vary. Indeed, our findings are consistent with maladaptive psychosocial characteristics associated with reductions in grey matter,<sup>53–55</sup> and point to the importance of pain’s psychosocial impact on brain aging patterns.

A greater understanding of brain aging in relation to chronic pain holds substantial clinical utility for several reasons. First, brain aging biomarkers are clinically accessible, and can be easily calculated from routine structural MRI sequences that do not require large amounts of time to acquire or interpret. Second, brain aging biomarkers have the potential to evaluate potential treatments to improve health span in our aging population. For example, treatments such as exercise and joint replacement have reported grey matter increases comparable to changes in clinical pain.<sup>56–59</sup> While conservative non-pharmacological interventions (eg, dry needling, manual therapy) show promise for reducing pain in knee OA,<sup>60–62</sup> future prospective studies are needed to test whether various pharmacological and non-pharmacological pain interventions can modulate brain aging biomarkers to further understand the influence of different pain management strategies on brain aging. Third, brain age biomarkers may be used to identify individuals with chronic pain who are at a greater risk for accelerated biological aging, allowing for earlier intervention strategies and the prevention of detrimental health challenges.

## Limitations

Several limitations must be considered when interpreting these results. While the current sample was diverse and included middle-aged and older adults, a larger sample would have enabled us to stratify by age group and directly compare predicted brain age differences across the lifespan. In addition, our groups were very diverse regarding pain impact, which may have contributed to the small effect sizes in the current study compared with our previous study showing larger effects among community-dwelling older adults with/without chronic pain. However, by including individuals with high- and low-impact chronic knee pain, compared to pain-free age-matched controls, we were able to examine brain aging in accordance with the biopsychosocial model of pain.<sup>63</sup> Second, the study was cross-sectional and causality cannot be determined. It is likely that the relationship between predicted brain aging and pain is bidirectional and future longitudinal studies aimed at understanding the clinical significance of predicted brain aging differences, and its ability to predict treatment outcomes in pain are warranted. Third, screening criteria for the current study excluded those with clinical depression, cognitive impairment, and neurological diseases. While this may limit the generalizability of our current findings, it also removed potential confounders as previous research has shown associations between predicted brain age differences, cognitive impairment, and psychological function.<sup>17,28</sup> Also, as our study focused on persons with chronic knee pain related to knee OA, generalizability to other chronic pain conditions is limited. Future studies, including participants with other specific chronic pain conditions are needed to further elucidate the association between brain age and chronic pain impact.

## Conclusion

This study provides initial evidence of the effects of pain impact on predicted brain age differences in middle-aged and older adults, and provides additional evidence for an increased neurobiological burden in persons with high-impact chronic knee pain. Further, the results from this larger cohort study indicate that a brain aging biomarker is associated with pain impact regardless of chronological age or sex, and is related to clinical pain, and psychosocial factors. Applying biological aging biomarkers represents one valuable way for overcoming challenges with identifying biomarkers at the individual level and could assist in the development of targeted interventions for persons with debilitating chronic pain. Further, brain aging biomarkers can be derived from routine, short MRI sequences that can be easily implemented clinically; thus, it may be a useful, simple biomarker for identifying those individuals with pain who are at a greater risk of accelerated brain atrophy and poor health outcomes.

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## Disclosure

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