Research Paper

PAIN 164 (2023) 2822–2838

PAIN®

Brain-predicted age difference estimated using DeepBrainNet is significantly associated with pain and function—a multi-institutional and multiscanner study

Pedro A. Valdes-Hernandez[a,b,c], Chavier Laffitte Nodarse[a,b,c], Alisa J. Johnson[a,b], Soamy Montesino-Goicolea[a,b,c], Vishnu Bashyam[d,e], Christos Davatzikos[d], Julio A. Peraza[f], James H. Cole[g,h], Zhiguang Huo[i], Roger B. Fillingim[a], Yenisel Cruz-Almeida[a,b,c,j,*]

Abstract

Brain age predicted differences (brain-PAD: predicted brain age minus chronological age) have been reported to be significantly larger for individuals with chronic pain compared with those without. However, a debate remains after one article showed no significant differences. Using Gaussian Process Regression, an article provides evidence that these negative results might owe to the use of mixed samples by reporting a differential effect of chronic pain on brain-PAD across pain types. However, some remaining methodological issues regarding training sample size and sex-specific effects should be tackled before settling this controversy. Here, we explored differences in brain-PAD between musculoskeletal pain types and controls using a novel convolutional neural network for predicting brain-PADs, ie, DeepBrainNet. Based on a very large, multi-institutional, and heterogeneous training sample and requiring less magnetic resonance imaging preprocessing than other methods for brain age prediction, DeepBrainNet offers robust and reproducible brain-PADs, possibly highly sensitive to neuropathology. Controlling for scanner-related variability, we used a large sample (n = 660) with different scanners, ages (19-83 years), and musculoskeletal pain types (chronic low back [CBP] and osteoarthritis [OA] pain). Irrespective of sex, brain-PAD of OA pain participants was ~3 to 4.7 years higher than that of CBP and controls, whereas brain-PAD did not significantly differ among controls and CBP. Moreover, brain-PAD was significantly related to multiple variables underlying the multidimensional pain experience. This comprehensive work adds evidence of pain type–specific effects of chronic pain on brain age. This could help in the clarification of the debate around possible relationships between brain aging mechanisms and pain.

Keywords: Brain aging, Osteoarthritis, Back pain, Convolutional neural network

1. Introduction

Machine learning has enabled researchers to use high-dimensional magnetic resonance imaging (MRI) data sets to build predictive models of brain aging.[15] Given their high sensitivity, these brain age estimates may capture disease-related brain changes,[5,16–18,27,30,33,34] providing proxies to health states. Previously, we and others used Gaussian Process Regression to estimate brain-predicted age differences (brain-PAD) across several chronic pain samples,[20,35,36] providing evidence of accelerated brain aging in certain cohorts and pain types (ie, older adults, knee osteoarthritis [kOA], high-impact pain).[36,40] However, these associations are still debatable, with one investigation showing no difference in brain-PAD between 59 individuals with noncancer chronic pain and 60 controls.[52] Under

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

P. A. Valdes-Hernandez, C. Laffitte Nodarse contributed equally to this work.

[a] Department of Community Dentistry and Behavioral Science, University of Florida, Gainesville, FL, United States, [b] Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL, United States, [c] Center for Cognitive Aging and Memory, McKnight Brain Institute, University of Florida, Gainesville, FL, United States, [d] AI2D Center for AI and Data Science for Integrated Diagnostics, Center for Biomedical Image Computing & Analytics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [e] Artificial Intelligence in Biomedical Imaging Lab (AIBIL), Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [f] Department of Physics, Florida International University, Miami, FL, United States, [g] Centre for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom, [h] Dementia Research Centre, Queen Square Institute of Neurology, University College London, London, United Kingdom, [i] Department of Biostatistics, College of Public Health and Health Professions and College of Medicine, University of Florida, Gainesville, FL, United States, [j] Department of Neuroscience, College of Medicine, University of Florida, Gainesville, FL, United States

**Corresponding author. Community Dentistry and Behavioral Sciences/College of Dentistry/University of Florida 1329 SW 16th Street, Ste. 5180 Gainesville, FL 32608, United States. Tel.: +1 (352) 294-5845. Address: E-mail address: cryeni@ufl.edu (Y. Cruz-Almeida).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

http://dx.doi.org/10.1097/j.pain.0000000000002984

the premise that these negative results might owe to the use of a heterogeneous chronic pain sample, Hung et al.[35] recently compared patients vs controls separately for each chronic pain type and found that brain-PAD significantly differed between OA patients and controls, but not between patients with chronic back pain (CBP) and controls. These differences were significant in CBP female patients, but not in CBP male patients. However, the moderation by sex of these pain-related differences was not explicitly tested. Moreover, their brain age model was trained in a small sample of 812 healthy subjects, and their testing sample was relatively small, with 52 participants with OA and 50 participants with CBP. Therefore, replication is needed in larger and more heterogeneous samples.

Here, we implement a convolutional neural network (DeepBrainNet[5]) to investigate the differential association between different chronic musculoskeletal (MSK) pains and brain aging in a much larger (n = 660, 169 participants with OA and 170 participants with CBP) and more heterogeneous sample from different study sites and ages (ie, 20-83). Compared with other brain age prediction methods, DeepBrainNet is more suitable for our sample because it was trained on a significantly larger and more heterogeneous data set (n = 11,729) from 18 studies spanning different scanners, ages, and locations.

Based on the abovementioned findings where "older-appearing" brains were associated with the presence of pathologies,[5,16–18,27,30,33,34] including chronic pain,[20,35,36] we hypothesized that DeepBrainNet-based brain-PAD would be significantly greater in either participants with OA or CBP compared with controls. Under the premise that different neurobiological mechanisms underlie OA and CBP,[3] we hypothesize that brain-PAD would also differ among both groups. Moreover, based on the well-known differences in mechanisms of chronic pain among sexes,[4,26] specifically in the brain,[31] as well as the observed sex differences in brain-PAD,[10,21,50] we hypothesized that these differences would be moderated by sex (ie, women with MSK pain have significantly "older-appearing" brains compared with male patients or controls).

Finally, although the abovementioned, smaller sampled studies have reported significant associations between brain-PAD and some measures of psychological function,[20] experimental pain,[20] and clinical pain,[35] our larger and more heterogeneous sample furnishes a more comprehensive characterization of the relationship between brain age and the multidimensional experience of pain. We thus explored the association between brain-PAD and an expanded more complete set of clinical pain, sensory or functional variables, and their moderation by sex.

2. Materials and methods

2.1. Participants and magnetic resonance imaging scanners

This is a multicenter study combining 7 different MSK pain data sets from 8 different MRI scanners (encoded in the variable *scanner*).

2.1.1. University of Florida/University of Alabama-Birmingham data set

This was a subsample of a larger multisite observational study conducted at the University of Florida (UF) and at the University of Alabama-Birmingham (UAB) aimed at examining ethnic/race group differences in individuals (older than 45 years) with or at risk for kOA. The sample included participants with kOA and demographically matched controls. Magnetic resonance imaging data were collected at the McKnight Brain Institute at the University of Florida using a 3-Tesla Achieva Phillips (Best, the Netherlands) scanner using a 32-channel radio-frequency coil and at the University of Alabama, Birmingham, with the same MRI system but using an 8-channel head coil. Note that, although all experimental procedures were identical, and the MRI scanner was the same, each study used a different MRI coil. Therefore, the variable *scanner* took the values "UF Phillips" and "UAB Phillips." A high-resolution, T1-weighted (T1w) turbo field echo anatomical image was collected with TR = 7.0 milliseconds, TE = 3.2 milliseconds, 176 slices acquired in a sagittal orientation, flip angle = 8°, resolution = 1 mm^3. Head movement was minimized through cushions positioned inside the head coil.

The study was approved by the University of Florida and the University of Alabama Institutional Review Boards (IRBs) under the Common Rule, which requires the use of single IRB for United States–based institutions engaged in cooperative research. All participants provided verbal and written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

2.1.2. University of Florida only data set

This study included community-dwelling older adults (older than 60 years) and younger adults (18-30 years) as part of the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) project at the UF. Presence of MSK pain in this sample was determined after the participants completed a standardized pain history interview regarding the presence of pain across several body regions (ie, head/face, neck, shoulders, arms, hands, chest, stomach, upper and lower back, leg, knees, and feet) using a validated body manikin.[19] Our final sample included participants who reported kOA only, CBP only, and demographically matched pain-free individuals (controls). Part of the MRI data were obtained using the same Phillips scanner at UF described for the University of Florida/University of Alabama-Birmingham (UF/UAB) data set (the 32-channel configuration). The rest of the MRI data were acquired with a 3T Siemens MAGNETOM Prisma (AG, Erlangen, Germany) scanner (software version VE11C) at UF's McKnight Brain Institute, where a T1w 3D MPRAGE anatomical image was collected with PAT mode GRAPPA with Phase-Encoding (PE) acceleration factor = 2, 192 sagittal slices, Inversion Time (TI) = 900 milliseconds, Repetition Time (TR) = 2300 milliseconds, Echo Time (TE) = 2.96 milliseconds, flip angle = 9°, field of view (FOV) = 256 × 256 mm, and spatial resolution of 1 × 1 × 1 mm. Therefore, *scanner* took the values "UF Phillips" and "UF Siemens." The study was approved by the UF IRB and was conducted in accordance with the Declaration of Helsinki.

2.1.3. OpenPain data sets

We used data from 4 MRI studies with their data set available in the OpenPain Project database repository (www.openpain.org). These are data sets of different types of MSK pain. To ease their identification in the web site, we named them after their folder names in the repository.

2.1.3.1. OpenPain SALS data set (folder name: "subacute_longitudinal_study")

This data set included 70 participants with subacute back pain (SBP), 26 participants with CBP, and 26 controls at baseline.[57] This is a longitudinal study with up to 5 scanning time points after baseline (at 3.2, 10.4, 31.3, 57.7, and 154.2 weeks in average). For this study,

we used the data of the controls and participants with CBP of the first time point. In addition, we added some more participants with CBP as follows. Based on the criteria defined by Vachon-Presseau et al.,[57] we classified the participants with SBP into "recovered" if their reported severity of pain (based on a visual analog scale [VAS]) decreased 80% after 56 weeks from baseline. These participants were discarded from our study. Those who did not recover were classified as "persistent" and were deemed as participants with CBP after 56 weeks. Thus, their data (MRI and other variables) acquired during their last available time point beyond 56 weeks (time point 4 or 5) were used in our study. MPRAGE T1w images were collected at Northwestern University (NU) with a 3 T Siemens Trio, the standard radio-frequency head coil, and the following parameters: voxel size $= 1 \times 1 \times 1$ mm, repetition time = 2500 milliseconds, echo time = 3.36 milliseconds, flip angle = 9°, in-plane matrix resolution = 256 × 256; 160 slices, field of view = 256 mm.[57] Therefore, the variable *scanner* took the value "NU Trio."

2.1.3.2. OpenPain PPT (folder name: "placebo_predict_tetreault")

This data set included 56 participants with OA and 20 controls.[55] MPRAGE T1w images were also collected at Northwestern University with a 3T Siemens Trio using the MRI protocol of OpenPain SALS.[2,55] Therefore, the variable *scanner* also took the value "NU Trio." Note that 52 of the 56 participants with OA in this study were previously used by Hung et al.[35] to explore differential changes in brain-PAD associated with chronic pain.

2.1.3.3. OpenPain CBPR data set (folder name: "cbp_resting")

This data set included 34 participants with CBP and 34 matched controls. The MRI protocol for this data set is unavailable. We assumed they were acquired at Northwestern University using the same protocols of the SALS and PPT data set. However, because their brain images are only available in their skull-stripped version, we set the value of *scanner* to "NU Trio SS." The exceptions were the participants with IDs "healthy16" and "healthy17" who had whole brain MRIs and thus were assigned to *scanner* = "NU trio."

2.1.3.4. The OpenPain ACPS (folder name: "AccumbensChronicPainSignature")

This is a two-time-point study (median follow-up of 59.5 weeks), including 29 participants with CBP, 16 persistent SBP, 19 recovery SBP, and 33 controls.[41] Like with OpenPain SALS, recovered SBP participants were discarded and participants with persistent SBP were deemed CBP and their 56 weeks+ follow-up data used. MPRAGE T1w images were collected at Yale University using a Siemens 3-T Trio B magnet with a 32-channel head coil and TR = 1900 milliseconds, TE = 2.52 milliseconds, flip angle = 9°, and matrix 256 × 256 with 176 slices (1 mm thick). For this data set, images available in the OpenPain repository were already skull-stripped.[41] Thus, *scanner* = "YU Trio."

2.1.3.5. The OpenPain BNCM (folder name: "BrainNetworkChange_Mano")

This data set included 41 participants with CBP and 56 controls. Images were acquired using a 3-T MRI Scanner (3T Magnetom Trio with TIM system; Siemens, Erlangen, Germany) with a standard 12-channel phased array head coil either at Addenbrooke's hospital (Cambridge, United Kingdom) or CiNet (Osaka, Japan). A high-resolution three-dimensional T1w image was collected using a MPRAGE pulse sequence. For the participants in the United Kingdom, TR = 2300 milliseconds, TE = 2.98 milliseconds, time of inversion = 900 milliseconds, FA = 9°, BW = 240 Hz, FOV = 256 × 256 mm, 176 sagittal slices of 1-mm slice thickness with no interslice gap, acquisition matrix = 256 × 256. For the participants in Japan, TR = 2250 milliseconds, TE = 3.06 milliseconds, time of inversion = 900 milliseconds, FA = 9°, BW = 230 Hz, FOV = 256 × 256 mm, 208 sagittal slices of 1-mm slice thickness with no interslice gap, acquisition matrix = 256 × 256.[42] Therefore, *scanner* took the values "Addenbrooke Trio" for 17 patients with CBP and 17 controls and "CiNet Trio" for 24 patients with CBP and 39 controls. As reported in Ref. 35, the participants with CBP in this study were also used by Hung et al.[35] to explore differential changes in brain age difference associated with chronic pain.

2.2. DeepBrainNet-based brain age prediction

Developed by Bashyam et al.,[5] DeepBrainNet is a convolutional neural network–based brain age prediction method. It is built based on the *inception-resnet-v2* framework[54] and uses a 2D convolutional architecture. DeepBrainNet was trained using T1w MRI images from 11,729 individuals (ages 3-95 years) from a diverse range of geographic locations, scanners, acquisition protocols, and studies and tested in an independent sample of 2739 individuals. Features for the DeepBrainNet are calculated as follows. First, the T1w scan needs to be skull-stripped (ie, extracranial tissues must be removed using image preprocessing methods so that only gray and white matter, as well as CSF, are kept). Second, the skull-stripped image has to be spatially normalized to the 1-mm isotropic voxel FSL skull-stripped T1w template using a 12-parameter linear affine transformation. For training, each of the skull-stripped MRI image was divided into 80 2D slices (centered on the $z = 0$ plane in MNI coordinates) and considered as an independent sample, resulting in a training set of 1 million images. To obtain a final age prediction for a test sample, each of 80 slices of the test scan is input to the trained model independently and the median prediction is calculated as the subject's predicted brain age. To obtain skull-stripped images in our sample, we used *smriprep* (https://www.nipreps.org/smriprep/usage.html), the portion that processes the anatomical T1w images in *fmriprep*.[25] In brief, the T1w image was corrected for intensity nonuniformity using *N4BiasFieldCorrection*[56] distributed with ANTs 2.2.0 (Avants et al.,[1] RRID:SCR_004757) and skull-stripped with a Nipype implementation of the *antsBrainExtraction.sh* workflow from ANTs, using OASIS30ANTs as target template. The skull-stripping step was omitted for those images already available in their skull-stripped version (OpenPain CBR and OpenPain ACPS).

2.3. Measures characterizing experimental pain, function, and clinical pain

For each brain age prediction method, we explored the association between brain-PAD and several variables characterizing clinical pain, experimental pain (ie, quantitative sensory testing [QST]), and function (psychosocial, physical, and cognitive). These variables largely came from the UF and UAB participants, but some were also available from the OpenPain data sets. **Table 1** shows for which data sets each of these variables were measured.

2.3.1. Clinical pain variables

2.3.1.1. Number of pain locations

University of Florida/University of Alabama-Birmingham and UF participants were asked to indicate areas where they experienced pain, including head, neck, shoulders, chest, stomach, upper

back, lower back, arms, hands, knees, legs, and feet. The total number of pain locations was used for the analysis.

For the participants in OpenPain SALS, we used the radiculopathy scores that were quantified as the total of pain locations that patients had shaded in with pencil on the Short Form McGill Pain Questionnaire (SF-MPQ) form.[43] More details about how this questionnaire was administered in OpenPain SALS can be found elsewhere.[2,14]

2.3.1.2. Graded Chronic Pain Scale

The Graded Chronic Pain Scale (GCPS) is a 7-item scale that measures characteristic pain intensity and pain interference over the past 6 months. Participants are asked to rate their current, average, and worst pain on a 0 "no pain" to 10 "worst pain imaginable" numeric rating scale (NRS). Ratings were averaged and multiplied by 10 to calculate a characteristic pain intensity score (range: 0-100), with higher scores indicating greater pain intensity.[59] This was assessed in UF/UAB and UF participants.

2.3.1.3. Western Ontario and McMaster Universities Osteoarthritis Index—pain

The Western Ontario and McMaster Universities Osteoarthritis Index pain subscale assesses pain experienced in the lower limbs during various activities.[7] Items are rated on a 5-point scale, with higher scores indicating greater levels of pain during activities with scores ranging from 0 to 20. This was assessed in UAB/UF and UF studies.

2.3.1.4. The Pain Detect Questionnaire

The Pain Detect Questionnaire (PD-Q)[29] is a reliable screening tool with high sensitivity, specificity, and positive predictive accuracy to assess the likelihood of a neuropathic pain component in patients. Scores on the PD-Q range from 0 to 38, with a score of 12 and higher generally considered as neuropathic pain. This questionnaire was administered in the UAB/UF, UF, and OpenPain SALS studies.

2.3.1.5. Short Form McGill Pain Questionnaire–Revised

The SF-MPQ-2 is used to measure the quality and the intensity of pain.[23] It comprises Continuous pain, Intermittent pain, Neuropathic-type pain, and Affective experiences subscales. Each of 22 pain descriptors is rated on a 0 "no pain" to 10 "worst pain ever" scale within the past week, and a Total sum score is calculated for each subscale. This questionnaire was administered in the UF and UF/UAB studies, and the Continuous and Affective subscales were also available in the OpenPain SALS database.

2.3.1.6. Kellgren–Lawrence index

Radiographs were obtained for participants in the UF/UAB study only to determine degree of joint pathology according to the Kellgren–Lawrence (KL) criteria.[37] Grades range from 0 to 4 with higher grades indicating worse joint pathology.

2.3.1.7. Pain length and pain duration

University of Florida/University of Alabama-Birmingham participants were asked to report how long they had been experiencing knee pain (ie, Pain Length): (1) <6 months; (2) 6 months to 1 year; (3) 1 to 3 years; (4) 3 to 5 years; (5) >5 years. Participants from the UF, OpenPain CBPR, SALS, and ACPS data sets self-reported the number of years that they had experienced back pain (ie, Pain Duration). Thus, for these studies, years were also classified according to the Pain Length categories as in the UF/UAB data set.

2.3.1.8. Presence of musculoskeletal chronic pain

University of Alabama-Birmingham/University of Florida and UF only participants who self-reported pain for the past 3 months on most days with a GCPS pain intensity of 40 or higher in a 0 to 100 scale were deemed as chronic pain participants. For the

Table 1

Variables characterizing clinical pain, experimental pain, and function in the datasets.

	UF/UAB	UF	CBPR	SALS	ACPS	BNCM
Experimental pain/QST						
Heat pain (P.) TS index	✓					
Heat P. Sensitivity index	✓	✓				
Cold P. Rating index	✓	✓				
Punctate P. Sensitivity index	✓	✓				
Punctate P. TS index	✓	✓				
Pressure P. Index	✓	✓				
CPM during	✓					
CPM post	✓					
Psychosocial function						
CSQ-R Catastrophizing	✓	✓				
CSQ-R Coping	✓	✓				
CSQ-R Active coping	✓	✓				
CSQ-R Passive coping	✓	✓				
CSQ-R Distancing	✓	✓				
CSQ-R Ignoring	✓	✓				
CSQ-R Prayer	✓	✓				
CSQ-R Distraction	✓	✓				
IVC Active coping	✓					
IVC Passive coping	✓					
PANAS negative affect	✓	✓		✓		
PANAS positive affect	✓	✓		✓		
MSPSS	✓					
Somatization (PHQ-15)	✓					
PROMIS anxiety	✓					
PROMIS depression	✓					
PROMIS sleep	✓					
PSQI total		✓				
PSQI duration	✓					
Severity of insomnia	✓					
BDI			✓	✓	✓	✓
Physical and cognitive function						
SPPB Total score	✓	✓				
MoCA total score	✓	✓				
Clinical pain						
No. of pain sites	✓	✓				
GCPS pain intensity	✓	✓				
WOMAC pain	✓	✓				
PD-Q total	✓	✓		✓		
SF-MPQ-2-continuous	✓	✓				
SF-MPQ-2-intermittent	✓	✓				
SF-MPQ-2-neuropathic	✓	✓				
SF-MPQ-2 affective	✓	✓		✓		
SF-MPQ-2 total	✓	✓				
KL index	✓					
Pain length	✓	✓	✓	✓	✓	
Pain duration		✓	✓	✓	✓	✓

None of these variables were measured in OpenPain PPT.

BDI, Beck Depression Inventory; CPM, conditioned pain modulation; CSQ-R, Coping Strategies Questionnaire–Revised; GCPS, graded chronic pain scale; IVC, in vivo coping; KL, Kellgren-Lawrence; MoCA, Montreal cognitive assessment; MSPSS, multidimensional scale of perceived social support; PANAS, Positive and Negative Affect Scale; PD-Q, Pain Detect Questionnaire; PHQ-15, Patient Health Questionnaire Somatic Symptom Severity Scale Item 15; PROMIS, patient-reported outcomes measurement information system; PSQI, Pittsburgh sleep quality index; QST, quantitative sensory testing; SF-MPQ-2, Short Form McGill Pain Questionnaire–Revised; SPPB, short physical performance battery; TS, temporal summation; UF/UAB, University of Florida/University of Alabama-Birmingham; WOMAC pain, Western Ontario and McMaster Universities Osteoarthritis Index—Pain.

OpenPain data sets, classification of participants with chronic pain is provided in the metadata files found alongside the MRI data in the data set's repository. The criteria used to classify a participant as having chronic pain in each OpenPain data set is described in its corresponding paper(s),[41,42,55,57] including those participants with SBP at baseline who did not recover after 56 weeks ("persistent") who we classified as participants with CBP. In our analyses, we created the variable *MSK pain presence* taking the values "yes" or "no."

2.3.2. Experimental pain/quantitative sensory testing variables

The UF only and UF/UAB cohorts completed a multimodal QST session approximately 1 week before MRI data collection. Procedures were standardized and completed by trained research staff as follows.

2.3.2.1. Thermal pain

2.3.2.1.1. Heat temporal summation index

A contact heat-evoked potential stimulator thermode (Medoc Pathway; Ramat Yishai, Israel) was used to deliver 5 sequential heat pulses in 3 separate trials (ie, 44˚C, 46˚C, and 48˚C). Each trial began at a baseline temperature (35˚C) and rapidly increased (20˚C/second) to the target temperature. Participants were asked to rate their pain at the peak of each heat pulse on a 0 "no pain" to 100 "most intense pain imaginable" NRS. The trial was ended if the participant provided a pain rating of 100 or requested to stop. Temporal summation (TS) was calculated as follows: maximum pain rating—first pain rating within each trial. Temporal summation values were standardized and averaged across body sites and temperatures to create a heat temporal summation index, as in our previous work.[12] Higher values indicate greater heat TS.

2.3.2.1.2. Heat pain sensitivity index

University of Florida/University of Alabama-Birmingham data set: Heat stimuli were applied to the medial joint line of the most painful knee and on the ipsilateral ventral forearm using a 16 × 16 thermode (Medoc Pathway Thermal Sensory Analyzer; Ramat Yishai, Israel). Heat pain threshold was considered the first sensation of pain, and heat pain tolerance was the point at which pain could no longer be tolerated. Each trial began at a baseline temperature of 32˚C and gradually increased (0.5˚C/second) until ended by the participant pressing a button to stop the trial. Pain was rated after each trial of heat pain threshold and tolerance on a 0 "no pain" to 100 "most intense pain imaginable" NRS. The mean of 3 trials was used for analysis. Heat pain threshold, heat pain tolerance, and pain ratings from all heat TS pulse series (described above) at both body sites were standardized and averaged to compute a heat pain sensitivity index, with higher values indicating greater heat pain sensitivity.

University of Florida only data set: Heat stimuli were applied to the thenar eminence and first metatarsal using a 30 × 30 thermode (Medoc Pathway Thermal Sensory Analyzer; Ramat Yishai, Israel), with a starting temperature of 32˚C and gradually increasing at a rate of 1˚C/second until the participant reported the stimulus as first painful (heat pain threshold). Participants rated the pain intensity of each trial on a 0 to 100 NRS. Three trials were conducted at each body site and the average obtained for each test. Heat pain threshold and pain ratings were standardized and averaged to compute a heat pain sensitivity index, with higher values indicating greater heat pain sensitivity.

2.3.2.1.3. Cold pain rating index

University of Florida/University of Alabama-Birmingham: During a conditioned pain modulation trial, participants were asked to immerse their open hand, up to the wrist, into a 12˚C water bath (Neslab, Portsmouth, NH). Pain was assessed at 30 seconds on a 0 to 100 NRS. The procedure was repeated 2 times, separated by a 10-minute recovery period incorporating a heating pack for 1 minute. Pain ratings for both trials were standardized and averaged for an overall cold pain rating index, with higher values indicating greater cold pain sensitivity.

University of Florida only: Cold stimuli was delivered to the thenar eminence and the first metatarsal using a 30 × 30 thermode (Medoc Pathway Thermal Sensory Analyzer), with temperature starting at 32˚C and decreasing at a rate of 1˚C/second with a cut-off value of 0˚C. Participants were asked to indicate when the stimulus first became painful and rate the pain on a 0 to 100 NRS, for 3 trials at each body site. An average cold pain rating was computed across the 3 trials. Cold pain ratings were then standardized and averaged across testing sites for a cold pain rating index, with higher values indicating greater cold pain sensitivity.

2.3.2.2. Mechanical pain

2.3.2.2.1. Punctate mechanical pain

Mechanical punctate stimuli were applied using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300 g of pressure. Stimuli were applied to the patella of the most painful knee and the dorsal aspect of the ipsilateral hand (UF/UAB) and to the thenar eminence and first metatarsal (UF). Pain was assessed on a 0 to 100 NRS after a single contact and then after a series of 10 contacts, delivered at a rate of 1/second. Trials were repeated 2 times at each body site. Pain ratings from the single contacts from each body site and trial were standardized and averaged to calculate a punctate pain sensitivity index, with higher values indicating greater sensitivity.

2.3.2.2.2. Punctate pain temporal summation index

To calculate this index, pain ratings from the single contact were subtracted from pain ratings after the series of 10 contacts. Difference values were standardized and averaged across body sites and trials, with higher values indicating greater temporal summation.

2.3.2.2.3. Pressure pain index

Pressure pain threshold (PPT) was assessed at the medial and lateral joint lines of the most painful knee, the ipsilateral quadriceps, and trapezius muscle, with site order randomized, in the UF/UAB sample, and at the trapezius and the quadriceps in the UF sample using a handheld digital pressure algometer (AlgoMed, Medoc, Ramat Yishai, Israel). Participants were asked to press a button when the sensation first became painful. To maintain participant safety, a limit of 600 kPa (knee sites) and 1000 kPa (quadriceps and trapezius) was imposed. Three PPT values were averaged for each body site. These values were standardized and combined to calculate a pressure pain index for each sample. Values were reversed before combining so that greater scores represent more pain sensitivity.

2.3.2.3. Conditioned pain modulation

Conditioned pain modulation (CPM) was assessed using pressure pain applied to the left trapezius and cold-water

immersion (as described above). Pressure pain threshold was assessed at the trapezius, and then, the participant put their hand into the cold-water bath, submerged up to the wrist. At 30 seconds, cold pain was assessed followed by PPT. At 1 minute, the participant removed their hand from the cold-water bath and PPT was assessed immediately. After the first trial, a warm pack was placed on the participant's hand for 1 minute, and the trial was repeated after a 10-minute rest period. The difference between PPT preimmersion and PPT during immersion was averaged across both trials to calculate CPM During. The difference between PPT preimmersion and PPT postimmersion was averaged across both trials to calculate CPM Post. Positive values indicate a CPM response.

2.3.3. Psychosocial function variables

2.3.3.1. Coping Strategies Questionnaire–Revised

University of Florida only and UF/UAB cohorts completed the Coping Strategies Questionnaire–Revised (CSQ-R)[48,49] that assessed typical coping responses to pain using 27 items divided across 6 types of coping responses: (1) Catastrophizing, (2) Coping self-statements, (3) Distancing, (4) Ignoring, (5) Prayer, and (6) Distraction. Items are rated on a 7-point Likert-type scale from 0 "never do that" to 6 "always do that," with higher scores indicating greater use of that strategy. Active coping is computed as the mean scores of the Coping self-statements, Distancing, Ignoring, and Distraction subscales. Passive coping is computed as the mean scores of the Catastrophizing and Prayer subscales.

2.3.3.2. In vivo coping

University of Florida/University of Alabama-Birmingham participants completed the in vivo coping[24] to assess situational pain coping strategies after a QST battery, including passive (eg, pain catastrophizing; "I felt that if the pain got any worse, I wouldn't be able to tolerate it") and active (distraction; "I thought of other things to get my mind off of the pain") coping statements. Items were rated on a 1 "not at all" to 5 "very much" point scales. Active and passive coping subscale scores are the summed average of the items within each domain, with higher scores indicating greater use of that type of coping strategy.

2.3.3.3. Positive and Negative Affect Scale

The Positive and Negative Affect Scale (PANAS) comprises 20 items, 10 positive-valence (ie, interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, active) and 10 negative-valence (ie, distressed, upset, nervous, scared, hostile, irritable, ashamed, jittery, afraid, guilty). Items are rated on a 5-point scale ranging from 1 "very slightly or not at all" to 5 "extremely".[60] Higher scores on positive items indicate higher positive affect, while higher scores on negative items indicate higher negative affect (NA). Positive and Negative Affect Scale was assessed in the UF/UAB, UF, and OpenPain SALS studies.

2.3.3.4. Multidimensional scale of perceived social support

The multidimensional scale of perceived social support[63] is a brief measure of subjective social support rated on a 7-point scale asking individuals to rate the perceived adequacy of support they receive from family, friends, and significant other. Higher scores indicated greater perceived social support. This was assessed in the UF/UAB study only.

2.3.3.5. Patient Health Questionnaire Somatic Symptom Severity Scale Item 15

The Patient Health Questionnaire Somatic Symptom Severity Scale Item 15[39] assessed the degree to which participants are currently distressed about 15 common somatic symptoms. Higher scores indicated greater somatic sensitivity. Somatization was assessed in the UF/UAB study only.

2.3.3.6. Patient-reported outcomes measurement information system

The Depression Short Form (patient-reported outcomes measurement information system [PROMIS]-D-SF)[13] consists of 8 items to assess depressive symptomology, with higher scores indicating more depressive symptoms. The PROMIS Anxiety Short Form (PROMIS-A-SF) consists of 7 items rated on a 5-point scale. Higher scores indicate greater anxiety type symptoms. These measures were administered in the UF/UAB study only.

2.3.3.7. Sleep symptoms

University of Florida study participants completed the Pittsburgh Sleep Quality Index (PSQI)[11] scale which assessed sleep quality over a 1-month time interval. The instrument is used to measure the quality and patterns of sleep in 7 domains: (1) subjective sleep quality; (2) sleep latency (ie, the time it takes to fall asleep); (3) sleep duration (PSQI Duration in **Table 1**, encoded as >7 hours = 0, 6-7 hours = 1, 5-6 hours = 2, <5 hours = 3); (4) habitual sleep efficiency (the ratio of total sleep time to time in bed); (5) sleep disturbances; (6) the use of sleep-promoting medication (ie, prescribed or over the counter); and (7) daytime dysfunction over the last month. Each of the 7 domains is a rated on a 0 to 3 scale. The sum of the components produces a global score ranging from 0 to 21, where a higher score indicates worse sleep quality.[11]

University of Florida/University of Alabama-Birmingham study participants completed several questionnaires to assess sleep as follows: (1) The Severity of Insomnia questionnaire assessed difficulty falling asleep, staying asleep and problems waking up too early, and satisfaction with sleep pattern [0 (none/very satisfied) to 4 (very severe/very dissatisfied)], as well as others' perception of how sleep-related impairments affected their quality of life [0 (not noticeable) to 4 (very much noticeable)], worriedness/distress about sleep problems [0 (none) to 4 (very much)], and sleep-related interference with daily functioning [0 (none) to 4 (very much)]. Higher scores (range: 0-28) indicated greater insomnia symptoms. (2) The PSQI Duration subscale. (3) The PROMIS Sleep-Related Impairment scale[47,62] consisted of 8 items which assessed self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems and impaired alertness over the past 7 days. Higher scores indicate greater sleep impairment.

2.3.3.8. Beck Depression Inventory

The Beck Depression Inventory is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression.[6] This inventory was available for the OpenPain CBR, SALS, and ACPS databases.

2.3.4. Physical and cognitive function variables

2.3.4.1. Short physical performance battery

The short physical performance battery[32] consists of 3 measures of lower-extremity function: standing balance

(side-by-side, semitandem, and tandem stance), 4-m walking speed, and ability to rise from a chair. Each task is rated on a 0 to 4 scale, with increasing scores indicating better physical performance. Total scores range from 0 to 12. This was assessed in UF/UAB study and UF participants.

2.3.4.2. Montreal cognitive assessment

The Montreal cognitive assessment (MoCA)[38] was administered to assess global cognitive abilities including short-term memory, orientation, executive function, language abilities, animal naming, abstraction, attention, and clock-drawing test. Scores on the MoCA range from 0 to 30, with a score of 26 and higher generally considered normal global cognition.[38] This was assessed in UF/UAB and UF study participants.

2.4. Statistical analysis

Missing data were treated using pairwise elimination. Statistical significance was set to $\alpha = 0.05$ after correcting *P*-values using the false discovery rate.[8] To ensure normality, for every model (which entailed a specific subset of the whole data set), we applied a rank-based inverse normal transformation to the dependent variable (brain-PAD) using the "Blom" method with parameter $c = 3/8$.[22] After fitting the models, we applied the Shapiro–Wilk test of composite normality (with unspecified mean and variance) on the residuals (for Platykurtic distributions; while the Shapiro–Francia test was used for Leptokurtic distributions) to test whether the normality assumption required for linear models was fulfilled.[51]

Given the multisite and multiscanner nature of our sample, previous to testing our proposed hypotheses, we considered informative to report the extent to which this heterogeneity could affect the estimation of the brain-PAD. Moreover, we wanted to evaluate whether the pain-related differences were consistent across scanners, ie, if there was not significant interaction between *MSK pain presence* and *scanner*. To that end we tested whether there was a significant effect of *scanner* on MSK pain controls] differences in brain-PAD and we fitted the linear model, in Wilkinson notation, *brain-PAD* ~ *MSK pain presence* × *scanner* + *sex* + *age*, where *sex* took the values "male" and "female," and *age* is the chronological age. This analysis would also inform about the need to add terms accounting for pain-by-scanner interactions in the subsequent analyses.

We hypothesized that brain-PAD would be significantly different among participants with OA and participants with CBP and that it would be greater in participants with OA or CBP compared with controls (H_{type}). We also hypothesized that these differences would be moderated by sex ($H_{type\text{-}by\text{-}sex}$). To test these hypotheses, we fitted a linear mixed model *brain-PAD* ~ *pain type* × *sex* + *age* + *(1* | *scanner)*, where *pain type* was a categorical variable taking the values "control," "oa," and "cbp" (ie, an ANCOVA with random effects). Note that race was not included as a covariate in any of these models because it was not available for the OpenPain ACPS, OpenPain CBPR, and OpenPain PPT databases. After fitting this model, we were first interested in evaluating whether the interaction effect *pain type*: *sex* was significant ($H_{type\text{-}by\text{-}sex}$). In case of a significant interaction, we were then interested in evaluating a set of contrasts of interest to understand the direction of the effects, ie, simple effects of *pain type* at the levels of *sex* (H_{type}, by sex) and simple effects of *sex* at the level of *pain type*. Also using the coefficients of this model, we were also interested in replicating the above-mentioned reports by Hung et al.[35] of a differential effect of pain among MSK pain types, ie, the effects of *pain type* after averaging across the levels of *sex* (H_{type}, but marginalizing sex). In the case of no significant interaction, we fitted the reduced model without interaction *brain-PAD* ~ *pain type* + *sex* + *age* + *(1* | *scanner)* instead and evaluated the effect of *pain type* (H_{type}).

We were also interested in replicating the difference in brain-PAD between MSK pain (irrespective of type, namely H_{MSK}) and controls we previously observed in a smaller sample.[20] Leveraging the abovementioned linear mixed model, we tested this by evaluating the statistical significance of the average of the marginal means of the brain-PAD across OA and CBP minus the marginal mean of the brain-PAD of the controls.

We were also interested in exploring the association between brain-PAD and a set of clinical pain, sensory, or functional variables (H_{var}) and whether they would be moderated by sex ($H_{var\text{-}by\text{-}sex}$) (Note that this is equivalent to testing whether sex differences in brain-PAD are moderated by the clinical pain, sensory, or functional variables). Similar to the testing of H_{type} and H $H_{type\text{-}by\text{-}sex}$, a general framework to explore these associations is to fit the linear mixed model *brain-PAD* ~ *variable of interest* × *sex* + *age* + *race* + *(variable of interest* | *scanner)*, where *variable of interest* is each of the clinical pain or function variable. Note that we added the categorical variable *race*, taking the values "African American," "Caucasian," "Hispanic," "Asian," and "Pacific Islander" because the variables of interest were only present in samples for which race information was available. The only exceptions were for Pain Duration and the Beck Depression Inventory because they were available in OpenPain ACPS and OpenPain CBPR, which had no race information. Also note that we modeled a random intercept and random effects of *variable of interest* per study site (*scanner* can be used to encode study site) and the latter to account for possible differences in the way these variables were acquired at different studies. We first tested the significance of the interaction term (*variable of interest*: *sex*), ie, $H_{var\text{-}by\text{-}sex}$, and then, in case of significance, we tested the simple effects of *variable of interest* at level of *sex* (H_{var}). In case the interaction term was not significant, we tested the effect of *variable of interest* (H_{var}) in a simple model not including the interaction term. For the experimental pain and function variables, the regressions were performed using the whole sample, while for the clinical pain, the regressions were performed for only those participants having MSK pain. Note that, while a moderation-by-sex analysis allows to compare the slopes of the associations across sexes, a comparison of the correlation would allow to compare how different is the strength of the association between the variable of interest and brain-PAD. Thus, we also report the partial correlations between each *variable of interest* and *brain-PAD* for each sex and their comparison using the z-test for the comparison between correlations.

Effects sizes were reported using the Cohen f^2, which measures the relative variance explained by the effect when added to the regression model ($0.1^2 \leq f^2 < 0.25^2$ for small effects, $0.25^2 \leq f^2 < 0.4^2$ for medium effects, and $f^2 > 0.4^2$ for large effects). For pairwise comparisons, we additionally reported the difference in marginal means, namely ΔPAD, and its SE.

Mixed models were fitted by maximizing their likelihood using the "Quasi-Newton" optimizer, tolerance of 1e-16, step size tolerance of 1e-12, and maximum 10,000 iterations. All analyses were rerun after removing those measurements deemed outliers, based on their Cook distance being 3 times higher than their sample average,[45] and their results are presented in the Supplemental Materials (available at http://links.lww.com/PAIN/B875).

3. Results

3.1. Final sample size and participants demographics

All preprocessed MRI images were submitted to a careful quality control procedure. All raw images, segmented, brain masked, and normalized images were visually inspected. Those having poor signal-to-noise, inaccurate brain extraction, or poor spatial normalization were discarded from the study (see Table S1 in the Supplemental Materials for details, available at http://links.lww.com/PAIN/B875). This led to a final sample of 321 controls and 339 participants with MSK pain, of which 169 had OA and 170 had CBP, for a total of 660 individuals across 3 groups. Detailed demographic information is shown in **Tables 2 and 3**. There were no significant differences in sex distribution by group (χ^2 test = 2.37, $P = 0.31$), but there was a significant difference in sex by scanner ($\chi^2 = 22.3, P = 0.0022$). There were also no significant age differences between MSK pain presence and controls. However, because OA predominantly manifests in middle-aged and older adults, the minimum age of the participants with OA was 45 years, while it was 19 and 18 years for the controls and participants with CBP ($P <$ 1e-20, Welch ANOVA effect of *pain type* on *age*). Also, female participants were slightly older than male participants in our sample (mean ages 51.6 and 48.1 years, respectively, $P = 0.0045$) because of male participants having an age distribution slightly more negatively skewed than that of female participants (ie, fewer female participants in the 20-40 year range and fewer male participants in the 50-70 year range).

The average severity of clinical pain (scaled from 1 to 100) in the total MSK pain sample, as reported using a visual analog scale for all studies except the UF study which used a NRS and the OpenPain PPT that did not have any available, was 45.7, and distributed according to a minimum, 25 percentile, median, 75 percentile, and maximum of 0, 44, 58.2, 73.3 and 100, respectively. **Table 4** summarizes other pain characteristics of the sample.

3.2. Brain age predictions

In the prediction of brain age, the DeepBrainNet model yielded a mean absolute error ($MAE_{controls}$) = 6.69, 95% confidence interval (CI) [6.16, 7.25] years for the controls (n = 321), and MAE_{MSK} = 6.19, 95% CI [5.68, 6.75] years for the MSK pain participants (n = 339). In addition, the correlations between the chronological and predicted brain ages were high and highly significant (ie, $r = 0.88$ with $P <$ 1e-20 for controls and $r = 0.79$ with $P <$ 1e-20 for MSK pain participants; **Fig. 1**). For the complete data set (n = 660), $MAE_{total} = 6.43$, 95% CI [6.07, 6.82] and $r = 0.86$ with $P <$ 1e-20. An independent sample t test revealed that the difference $MAE_{MSK} - MAE_{controls} = -0.5$ years was not significantly different from zero, with a 95% CI (obtained with 10,000 bootstraps) of [−0.26, 1.26] years.

3.3. Brain-predicted age difference by scanner

We explored the effect of this important confounder by fitting the linear model *brain-PAD ~ MSK pain presence × scanner + sex + age*. We found that the *MSK pain presence*:*scanner* interaction term was not significant ($P = 0.69$). On the other hand, the effect of *scanner* was very significant (P = 3.55e-20, Cohen $f^2 = 0.18 > 0.4^2$), while the effect of *MSK pain presence* was also significant ($P = 0.00073$, $0.1^2 \leq$ Cohen $f^2 = 0.017 < 0.25^2$, with difference in the marginal means of brain-PAD [ΔPAD] between MSK individuals and controls of 1.7 years and SE of 0.5 years), revealing that it would be impossible to detect any difference in brain-PAD between MSK individuals and controls without removing the confounding effect of *scanner*. These can be appreciated in **Figure 2**.

3.4. Pain-related differences in brain-predicted age

The interaction term *pain type*:*sex* (corresponding to the hypothesis $H_{type\text{-}by\text{-}sex}$) was not statistically significant ($P > 0.05$) in the model *brain-PAD ~ pain type × sex + scanner + age + (1|scanner)*. We thus fitted the model without an interaction term (H_{type}) and found a significant main effect of *pain type* (P = 1.0e-5) with a small effect size (Cohen $f^2 = 0.04 \leq 0.25^2$). Post hoc pairwise differences revealed that brain-PAD of participants with OA was significantly higher than that of participants with CBP

Table 2

Distribution of participants by pain type, sex, race, and study sites/scanners.

	Pain type				Sex		Race		
	Control	OA	CBP	MSK (OA + CBP)	M	F	AA	C	H/O
Scanner									
NU Trio	42	54	48	102	70	74	28*	28*	12*
NU Trio SS	32	0	30	30	33	29	n/a	n/a	n/a
Yale Trio	33	0	40	40	37	36	n/a	n/a	n/a
UF Achieva	121	68	11	79	69	127	54	131	11
UAB Achieva	32	47	0	47	28	51	43	36	0
UF Prisma	13	0	2	2	8	5	1	12	3
Adden. Trio	37	0	22	22	35	24	n/a	n/a	n/a
CiNET Trio	17	0	17	17	11	23	n/a	n/a	n/a
Total	321	169	170	339	291	369	126	204	26
Sex									
Male	148	66	77	143			50	77	13
Female	173	103	93	196			76	127	13
Race									
AA	32	70	24	94	76	50			
C	132	45	27	72	115	89			
H/O	16	0	10	10	13	13			

Race category "Other" included 3 Asian and 3 Pacific Islanders.

* Race information is not available for OpenPain CBPR, PPT, and BNCM data sets.

AA, African American; Adden, Addenbrook; C, Caucasian; CBP, chronic back pain; F, female; H/O, Hispanic or other; M, male; MSK, musculoskeletal pain; n/a, not available; NU, Northwestern University; OA, osteoarthritis pain; OP, OpenPain; UAB, University of Alabama-Birmingham; UF, University of Florida.

Table 3

Distribution of age across pain types and sex.

Statistics	Pain type				Sex	
	Control	OA	CBP	MSK (OA + CBP)	Male	Female
Mean age	48.9	57.4	44.8	51.1	48.1	51.6
SD age	17.3	7.5	13.7	12.7	16.0	14.3
Minimum age	19.0	44.0	18.0	18.0	18.0	18.0
Maximum age	82.9	83.0	85.3	85.3	85.3	83.0
Effect of grouping variable		Pain type		MSK pain presence		Sex
P		$P < 1e-20$		$P = 0.063$		$P = 0.0045$

Owing to heteroscedasticity, Welch ANOVA was used to estimate the effect of *pain type*. For the rest of the comparisons, both Welch ANOVA and ANOVA led to almost identical results.
CBP, chronic back pain; MSK, musculoskeletal pain; OA, osteoarthritis pain.

($P = 0.0022$ with ΔPAD [SE] = 2.7 [0.79] years) and controls ($P = 5.5e-6$ with ΔPAD [SE] = 3.1 [0.64] years). There was no significant difference between CBP participants and controls. Finally, using the contrast comparing OA + CBP and controls, we found that brain-PAD was significantly higher in the whole group of MSK pain participants compared with the controls (H_{MSK}; $P = 0.00048$ with ΔPAD [SE] = 1.75 [0.5]). This is all summarized in **Figure 3**. The figure also shows that, after discarding outliers, the effect size of *pain type* became large (Cohen $f^2 = 0.1 \geq 0.25^2$), with stronger evidence for all effects (eg, OA vs CBP: $P = 6.5e-7$ with ΔPAD [SE] = 3.56 [0.68] years, OA vs control: $P = 9.0e-11$ with ΔPAD [SE] = 3.69 [0.55] years). For all models, rejection of composite normality failed after correcting for multiple comparisons ($P > 0.05$).

With the goal of replicating the reports by Hung et al.,[35] we also evaluated the differences between each MSK type and controls for each sex subsample (ie, H_{type} for each sex). For a more complete analysis, we also included the OA vs CBP comparison for each sex. After Bonferroni correction across pairs, we found a significant difference between the OA and control groups for female participants ($P = 0.0046$ ΔPAD [SE] = 2.62 [0.82] years) and for male participants ($P = 0.00061$ ΔPAD [SE] = 3.79 [1.01] years), as well as a significant difference between the OA and CBP groups for male participants ($P = 0.0049$ ΔPAD [SE] = 3.77 [1.19] years), but not for female participants. When removing outliers, we found larger and more significant differences for all 4 comparisons, that is, between the OA and control groups for female participants ($P = 0.00018$ ΔPAD [SE] = 2.99 [0.74] years) and for male participants ($P = 6.6e-6$ ΔPAD [SE] = 4.16 [0.86] years), as well as between the OA and CBP groups for male participants ($P = 2.2e-5$ ΔPAD [SE] = 4.69 [1.02] years) and this time also for female participants ($P = 0.0081$ ΔPAD [SE] = 2.88 [0.95] years).

3.5. Associations between brain-predicted age differences derived by DeepBrainNet with measures of pain and function

We found no significant *variable of interest*-by-*sex* interaction ($H_{var\text{-}by\text{-}sex}$) in the model *brain-PAD* ~ *variable of interest* × *sex* + *scanner* + *age* + *(variable of interest* | *scanner)* for any clinical pain, QST, or function variable of interest. We found, however, significant associations between brain-PAD and several clinical pain, QST, and function variables (H_{var}) in the model without interaction, *brain-PAD* ~ *variable of interest* + *sex* + *scanner* + *age* + *(variable of interest* | *scanner)*, which are depicted in **Figures 4 and 5**. Effect sizes and *P*-values for these associations are summarized in **Tables 5 and 6**. This was replicated after removing outliers (see Figures S1 and S2 and Tables S2 and S3 of the Supplemental Materials, available at http://links.lww.com/PAIN/B875). In all linear models, rejection of composite normality of the residuals failed after correcting for multiple comparisons ($P > 0.05$).

Tables 7 and 8 also report the partial correlations between each *variable of interest* and *brain-PAD* for each sex and their comparison using the z-test for the comparison between correlations. Both tables show significant correlations for a subset of the variables in **Table 5** (and **Fig. 4**) and **Table 6** (and **Fig. 5**), respectively, with the same sign of the associations.

4. Discussion

This is the first investigation on how brain age, predicted by a CNN method (DeepBrainNet), relates to MSK pain, using MRI scans from different cohorts, scanners, ages (ie, 19-83), and MSK pain types (ie, OA and CBP pain). To the best of our knowledge, this is the largest and most heterogeneous sample ever used to relate brain aging to chronic pain. As a consequence of this heterogeneity, we found a significant variability in brain age prediction across MRI scanners that, if not accounted for, would have hindered the ability to detect chronic pain–brain aging associations.

Irrespective of sex, individuals with chronic OA pain had approximately 3 to 4.7 years older-appearing brains compared with controls and CBP. This aligns with our previous work where older individuals with chronic pain had older brains compared with matched healthy controls.[20] They are also partially in agreement with the reports by Hung et al.[35] Like in their work (we refer to their **Fig. 2A**), we found that OA, but not individuals with CBP, had significantly older-appearing brains compared with controls. We also replicated their result that OA participants had older-appearing brains than controls for each sex (their **Fig. 2B**). However, we did not replicate their significant (though weak) difference between CBP and controls in female participants (their **Fig. 2B**). This could owe to several methodological differences, such as differences in sample size and etiologies

Table 4

Pain characteristics in the total sample.

Pain characteristic	Mean ± SD	Min-Max	Studies where measured
Clinical pain severity	57.6 ± 21.6	0-100	All studies except OP PPT
No. of pain locations	4.9 ± 3.5	1-21	UF/UAB, UF and OP SALS
GCPS pain intensity	62.95 ± 16.4	40-100	UF/UAB and UF
WOMAC pain	8.0 ± 4.3	1-20	UF/UAB and UF
Pain duration (y)	9.5 ± 9.6	<1-56	UF/UAB and UF

GCPS, Graded Chronic Pain Scale; OP, OpenPain; PPT, pressure pain threshold; UF/UAB, University of Florida/University of Alabama-Birmingham; WOMAC pain, Western Ontario and McMaster Universities Osteoarthritis Index—pain.

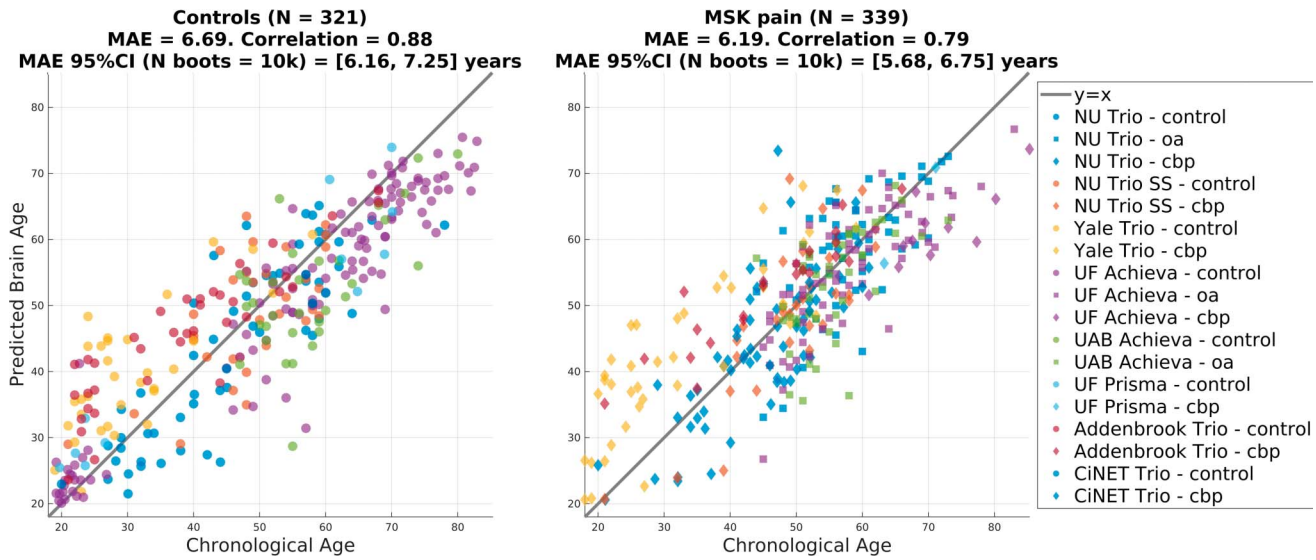

Figure 1. Brain age predictions for controls and MSK pain participants. Circles, diamonds, and squares correspond to controls, participants with OA, and participants with CBP, respectively. CBP, chronic back pain; MAE, mean absolute error; MSK, musculoskeletal; NU, Northwestern University; OA, osteoarthritis; UAB, University of Alabama-Birmingham; UF, University of Florida.

within the back pain groups. Note that despite having selected their participants with OA and participants with back pain from different studies, their controls for both conditions came from a third common study, which possibly precluded controlling for the effect of study, rendering difficult to determine whether their observed differences were pain-related or scanner-related. In addition, Hung et al.[35] assessed group differences separately for each sex, which does not allow for the determination of sex-related effects on the group differences. We explicitly answered this question for the first time by testing the actual sex differences in these differential effects of chronic pain using the moderation analysis and found no significant results.

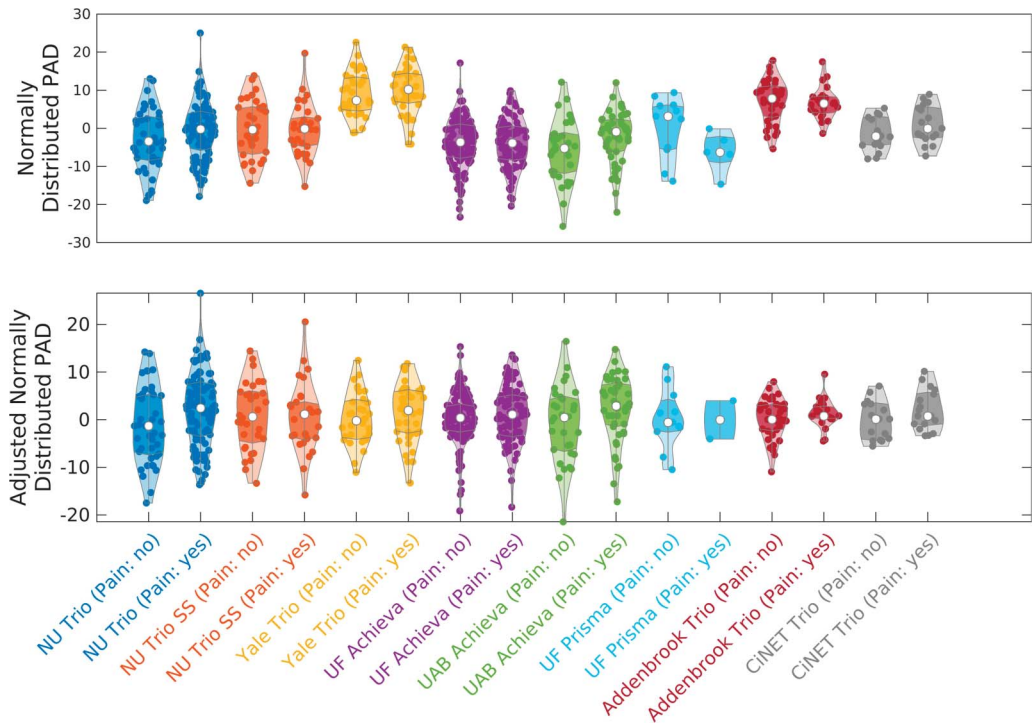

Figure 2. Distribution of the predicted age difference (brain-PAD) predicted by DeepBrainNet distributed across *MSK pain presence* and *scanner*. In the top panel, the significant large main effect of *scanner* ($P = 5.10e\text{-}21$ with Cohen $f^2 = 0.19 > 0.4^2$; modeled in *brain-PAD* ~ *MSK pain presence* × *scanner* + *sex* + *age*) is visually appreciated in the great variability in the brain-PAD among scanners. The bottom panel depicts the distribution of brain-PAD values after correcting for the main effect of *scanner*, *sex*, and *age*, allowing to depict a significant (but small) effect of *MSK pain presence* ($P = 0.0018$, $0.1^2 \leq$ Cohen $f^2 = 0.015 < 0.25^2$, and ΔPAD [SE] = 3.1 [0.2] years) that was recovered after the correction. There was no significant *MSK pain presence* by *scanner* interaction in this model ($P = 0.69$ for the *MSK pain presence:scanner* interaction effect). MSK, musculoskeletal; NU, Northwestern University; UAB, University of Alabama-Birmingham; UF, University of Florida.

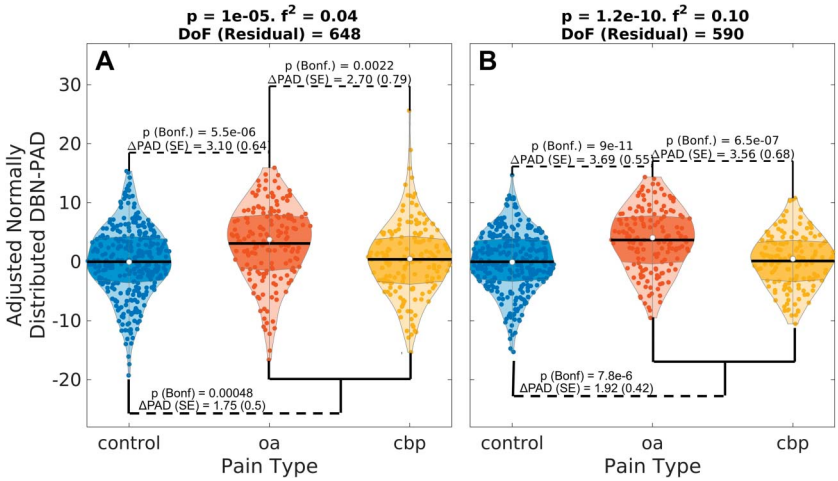

Figure 3. Effect of pain on brain-PAD. Panel (A) Plotted brain-PAD values were adjusted for the effects of all independent variables in the mixed model *brain-PAD* ~ *pain type* + *scanner* + *sex* + *age* + *(1|scanner)* except *pain type*. The figure depicts the Bonferroni corrected p-values of all contrasts of interest, ie, the differences among groups, as well as pain versus no pain (ie, the marginal main effect of *MSK pain presence*). Panel (B) same results after removing outliers. Within the violin plots, the shaded area is the interquartile region, the white dot indicates the median and the black horizontal line is the mean. DoF, degrees of freedom; △PAD (in years), difference in brain-PAD across groups; SE (in years), standard error.

The fact that accelerated brain age seem to only manifest in OA is intriguing. However, it is not surprising that brain age happens to be different between OA and CBP pains because their brain morphological signatures have been reported to be significantly different.[3] Moreover, although brain structure is significantly different between CBP and healthy controls,[3] they could possibly have similar brain age estimates given the many-to-one nature of the MRI-to-brain age map. Novel spatially distributed brain age prediction methods, eg, that based on the U-Net architecture,[46] could help to determine more specific

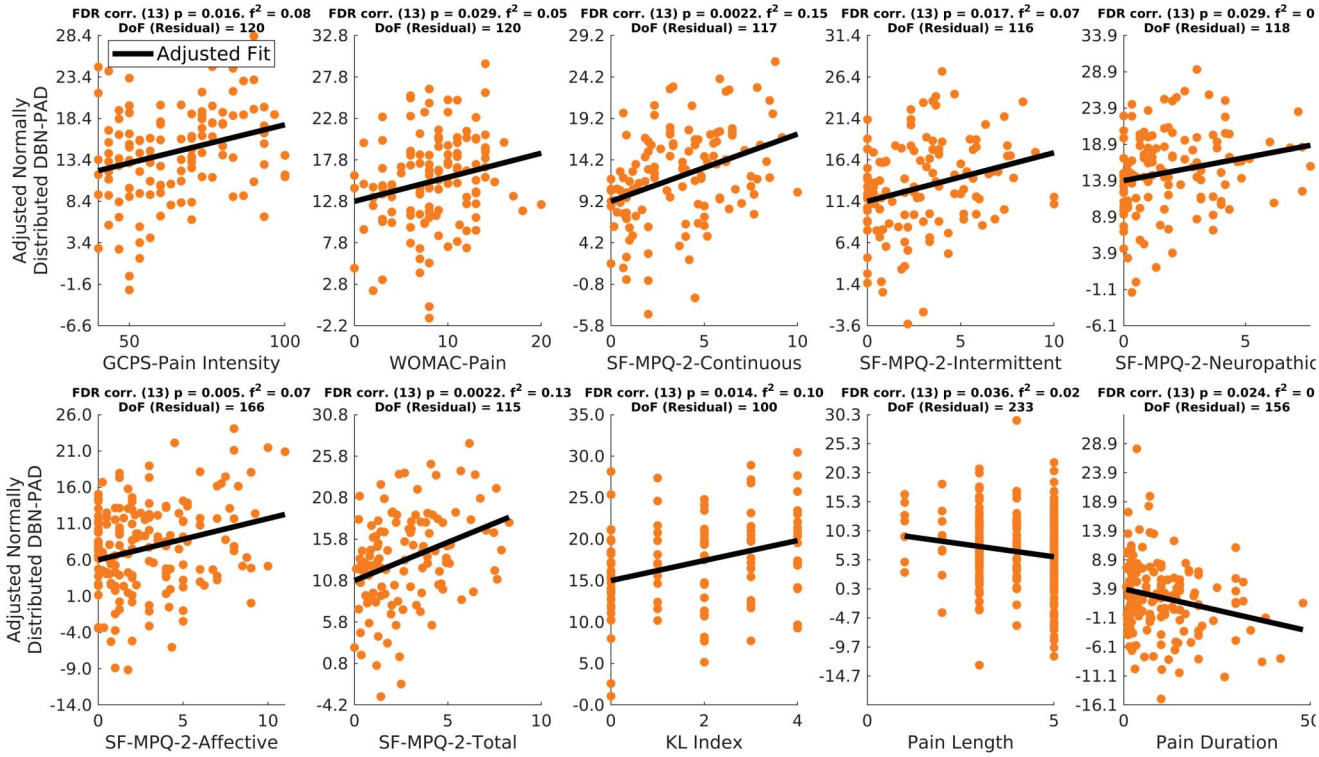

Figure 4. Linear mixed regression on clinical pain variables in the musculoskeletal (MSK) pain only sample. Significant (corrected $P < 0.05$) associations between variables characterizing clinical pain and the adjusted normalized brain-PAD are shown, restricted to the participants having MSK pain. *P*-values (indicated in the title of each subplot) were corrected using FDR correction across the 13 clinical pain variables tested. Pairwise deletion was used for missing data. The resulting degrees of freedom (DoF) is specified in the title of each subplot. DBN, DeepBrainNet; FDR, false discovery rate; GCPS, Graded Chronic Pain Scale; KL, Kellgren-Lawrence; PAD, predicted age difference; SF-MPQ, Short Form McGill Pain Questionnaire; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

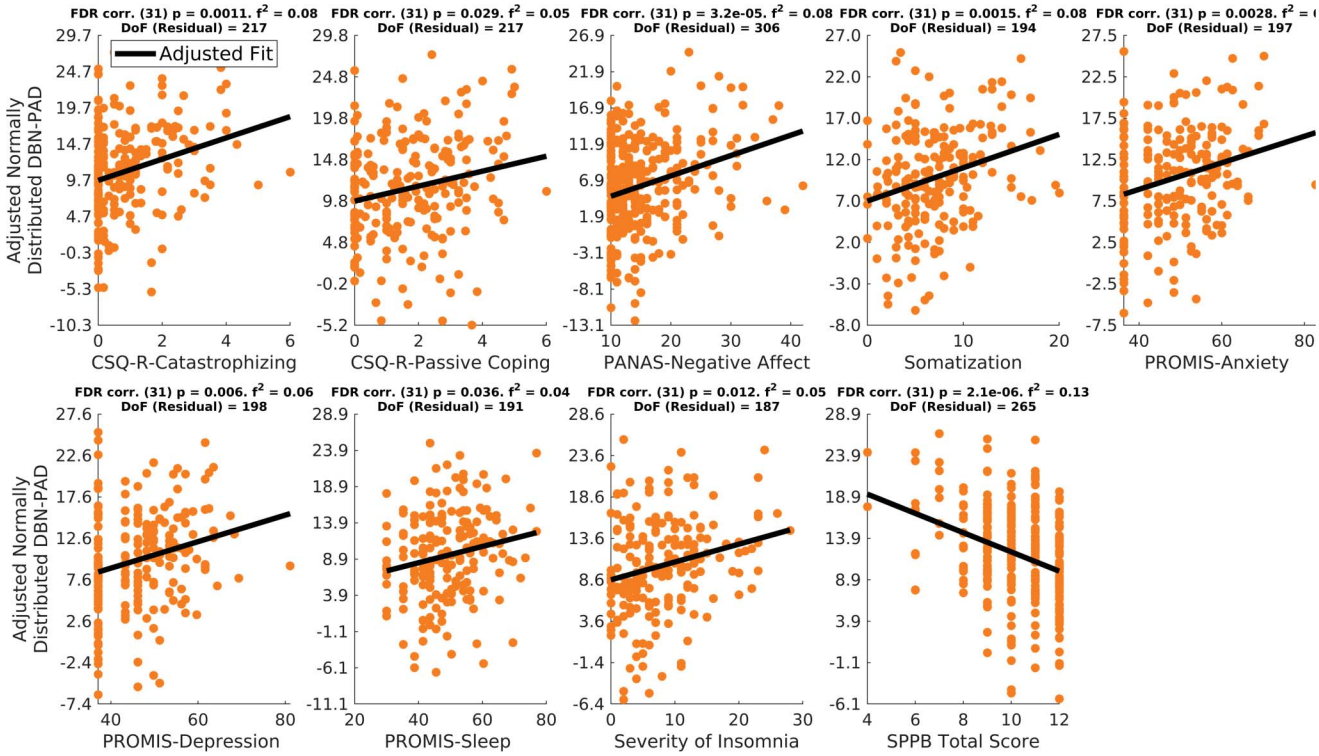

Figure 5. Linear mixed regression on function variables in the whole Sample. Significant (corrected *P*-value < 0.05) associations between variables characterizing experimental pain and function and the adjusted normalized brain-PAD are shown (values adjusted for effects of all independent variables in the mixed model *brain-PAD* ~ *variable of interest* + *scanner* + *sex* + *age* + [*variable of interest* | *scanner*] except *variable of interest*). *P*-values (indicated in the title of each subplot) were corrected using FDR correction across the 30 variables tested. Pairwise deletion was used for missing data. CSQ-R, Coping Strategies Questionnaire–Revised; DBN, DeepBrainNet; DoF, degrees of freedom; FDR, false discovery rate; PAD, predicted age difference; PANAS, Positive and Negative Affect Scale; PROMIS, patient-reported outcomes measurement information system; SPPB, short physical performance battery.

spatial brain age signatures of different MSK pain. On the other hand, the lack of sex-related effects is unexpected, given the increased pain sensitivity and risk for clinical pain commonly being observed among women attributed to a variety of mechanisms.[4,26,31] Again, sex-related differences in accelerated brain aging might only be observable at the local level, as recent reports suggest.[50,61]

Contrary to a previous report by Sörös and Bantel,[52] we did find a significant difference between all MSK pain participants and controls. Hung et al.[35] had hypothesized that the lack of a significant MSK pain control difference reported by Sörös and Bantel[52] owed to the fact that this difference differed among pain types, and thus, pain effects could not be detected by merging all MSK pain participants. Our differential MSK control differences

Table 5

Results of the linear mixed model regression of the brain-predicted age difference on the variables characterizing clinical pain, restricted to those participants having musculoskeletal pain.

Variable	Cohen f^2	FDR-corrected *P*	Bonferroni-corrected *P*	DoF
GCPS pain intensity	0.08[m]	0.016		120
WOMAC pain	0.05[s]	0.029		120
SF-MPQ-2-continuous	0.15[m]	0.0022	0.0024	117
SF-MPQ-2-intermittent	0.07[m]	0.017		116
SF-MPQ-2-neuropathic	0.05[s]	0.029		118
SF-MPQ-2-affective	0.07[m]	0.005	0.015	166
SF-MPQ-2-total	0.13[m]	0.0022	0.0044	115
KL index	0.10[m]	0.014		100
Pain length	0.02[s]	0.036		233
Pain duration	0.05[s]	0.024		156

P-values were corrected for multiple comparisons (using FDR and Bonferroni corrections) across all 13 clinical pain variables. Not significant corrected *P*-values (*P* > 0.05) are not shown. Superscripts "s", "m", and "l" indicate small ($0.1^2 \leq f^2 < 0.25^2$) and medium ($0.25^2 \leq f^2 < 0.4^2$) and "large" ($f^2 > 0.4^2$) effect sizes, respectively.

DoF, degrees of freedom; FDR, false discovery rate; GCPS, Graded Chronic Pain Scale; KL, Kellgren-Lawrence; SF-MPQ, Short Form McGill Pain Questionnaire; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

Table 6

Results of the linear mixed model regression of the brain-predicted age difference on the variables characterizing experimental pain and function using the whole sample.

Variable	Cohen f^2	FDR-corrected *P*	Bonferroni-corrected *P*	DoF
CSQ-R Catastrophizing	0.08[m]	0.0011	0.0033	217
CSQ-R Passive coping	0.05[s]	0.029		217
PANAS negative affect	0.08[m]	3.2e-05	6.3e-05	306
Somatization	0.08[m]	0.0015	0.006	194
PROMIS-anxiety	0.07[m]	0.0028	0.014	197
PROMIS depression	0.06 [s]	0.006	0.036	198
PROMIS sleep	0.04 [s]	0.036		191
Severity of insomnia	0.05[s]	0.012		187
SPPB total score	0.13[m]	2.1e-06	2.1e-06	265

P-values were corrected for multiple comparisons (using FDR and Bonferroni corrections) across all 31 variables tested. Not significant corrected *P*-values ($P > 0.05$) are not shown. Superscripts "s", "m", and "l" indicate small ($0.1^2 \leq f^2 < 0.25^2$) and medium ($0.25^2 \leq f^2 < 0.4^2$) and "large" ($f^2 > 0.4^2$) effect sizes, respectively.

CSQ-R, Coping Strategies Questionnaire–Revised; DoF, degrees of freedom; FDR, false discovery rate; PANAS, Positive and Negative Affect Scale; PROMIS, patient-reported outcomes measurement information system; SPPB, short physical performance battery.

among pain types is evidence for this hypothesis, but our bigger sample size could have also allowed brain age values from the OA group to drive towards a significant MSK control difference.

We also found that older-appearing brains were associated with greater intensity of pain, greater severity of the sensory (continuous, intermittent, and neuropathic), and affective dimensions of pain, greater pain-related interference with daily activities, and greater radiographic severity of knee joint pathology in participants with knee OA pain. Overall, this suggest that accelerated brain aging could be linked to structural aberrations associated with pain severity. Moreover, after controlling for age, older-appearing brains were associated with shorter pain durations, replicating the result by Hung et al.,[35] using the smaller OpenPain BNCM sample. This association suggests that provided that pain severity is accounted for, MSK groups with longer pain durations will have younger-appearing brains, which will thus differ less from those of control groups. This further supports the plausibility of the significant difference in brain aging between MSK pain and controls in older adults found by our group[20] that could not be replicated by Sörös and Bantel[52] because pain durations were shorter in the former sample compared with the latter (6.3 ± 8.8 years vs 15.9 ± 11 years, respectively), although pain severity in both samples was similar (5.2 ± 1.9 vs 5 ± 2, respectively). Although seemingly counterintuitive, a negative pain duration–brain aging association after controlling for age may reflect that those individuals of a given age with more recent chronic pain onsets (who were older at onset) suffer in ways that are associated with more deleterious brain changes compared with those with longer pains (who were younger at onset). Figure S5 (available at http://links.lww.com/PAIN/B875) illustrates this. Recently, we have also reported this type of behavior between pain durations and brain functional connectivity.[58]

Accelerated brain aging was not generally significantly associated with any experimental pain measure, suggesting that brain alterations associated with accelerated brain aging might not occur in primary areas implicated in experimental pain sensitivity. Conversely, older-appearing brains were associated with greater pain catastrophizing, passive coping, NA, depressive symptomology, anxiety, sleep impairments, severity of insomnia, and worse physical function, suggesting that accelerated brain aging could owe to alterations in areas implicated in the person's general functioning, in tandem with his/her clinical pain characterization. These results also resemble others in the literature. For

Table 7

Partial regressions between variables characterizing clinical pain and brain-predicted age difference for each sex and their comparison, restricted to those participants having musculoskeletal pain.

Variable	DoF: Correlation (*P*)			*P* of sex difference
	Female participants	Male participants	Both	
GCPS-pain intensity	66: **0.28 (0.022)**	32: 0.21 (0.47)	113: **0.22 (0.027)**	0.77
WOMAC pain	66: **0.25 (0.032)**	32: 0.17 (0.57)	113: **0.2 (0.038)**	0.77
SF-MPQ-2-continuous	83: **0.23 (0.032)**	52: −0.081 (0.66)	150: 0.12 (0.16)	0.42
SF-MPQ-2-intermittent	64: **0.42 (0.00075)**	31: 0.21 (0.47)	110: 0.**31 (0.004)**	0.57
SF-MPQ-2-neuropathic	63: **0.31 (0.015)**	31: 0.22 (0.47)	109: **0.27 (0.0074)**	0.77
SF-MPQ-2-affective	65: **0.3 (0.015**)	31: 0.11 (0.66)	111: **0.21 (0.035)**	0.57
SF-MPQ-2-total	89: **0.39 (0.00075)**	56: 0.057 (0.66)	160: **0.24 (0.005)**	0.42
KL index	63: **0.41 (0.0009)**	30: 0.22 (0.47)	108: **0.31 (0.004)**	0.57

P-values were corrected for multiple comparisons using FDR correction across all 13 variables tested. Significant correlations in bold font.

DoF, degrees of freedom; FDR, false discovery rate; GCPS, Graded Chronic Pain Scale; SF-MPQ-2, Short Form McGill Pain Questionnaire–Revised; WOMAC pain, Western Ontario and McMaster Universities Osteoarthritis Index—pain.

Table 8

Partial regressions between variables characterizing experimental pain and function and brain-predicted age difference for each sex and their comparison, for the whole sample.

Variable	DoF: Correlation (*P*)			*P* of sex difference
	Female participants	Male participants	Both	
Pressure index	155: −0.17 (0.1)	80: −0.12 (0.53)	250: **−0.2 (0.005)**	0.96
CSQ-R Catastrophizing	130: **0.29 (0.0052)**	66: 0.18 (0.43)	211: **0.25 (0.0016)**	0.96
PANAS negative affect	178: **0.28 (0.0031)**	109: 0.24 (0.1)	302: **0.25 (9.6e-05)**	0.96
Somatization	118: **0.31 (0.0031)**	52: 0.16 (0.53)	185: **0.22 (0.0097)**	0.96
PROMIS-anxiety	118: **0.26 (0.02)**	55: 0.23 (0.36)	188: **0.24 (0.005)**	0.96
PROMIS depression	119: **0.25 (0.021)**	55: 0.19 (0.43)	189: **0.23 (0.005)**	0.96
Severity of insomnia	113: 0.22 (0.057)	50: 0.21 (0.43)	178: **0.21 (0.014)**	0.97
SPPB total score	161: **−0.28 (0.0031)**	84: **−0.32 (0.048)**	260: **−0.29 (5.2e-05)**	0.96

P-values were corrected for multiple comparisons using FDR correction across all 31 variables tested. Significant correlations in bold font.
CSQ-R, Coping Strategies Questionnaire–Revised; DoF, degrees of freedom; FDR, false discovery rate; PANAS, Positive and Negative Affect Scale; PROMIS, patient-reported outcomes measurement information system; SPPB, short physical performance battery.

example, using a different brain age predicting method based on Gaussian Process Regression,[15] we reported that older-appearing brains were associated with lower positive affect in older adults[20] and higher NA, more in vivo coping strategies, and pain catastrophizing.[36] This confirms that the results are consistent across different brain age methodologies.

The association between brain age and either clinical pain or function was not moderated by sex. Provided that brain aging is a proxy of health outcomes, this aligns with a report that sex did not moderate the association between pain (or pain-related health outcomes) and several psychological factors in a large sample of participants with chronic pain.[53] On the other hand, the correlations between brain age and either clinical pain or function were only significant for female participants. However, because none of these correlations significantly differed among sexes, we have no concluding evidence of sex effects on these associations because these differences in significance could simply owe to the fact the subsamples of female participants were larger than those of male participants and thus more powered. More sex-balanced samples should be used to explore these differences.

Our study has several limitations. First, because this is a cross-sectional study, we are only testing associations and not causal relationships. In addition, most measures were only available in the UF/UAB studies. This consistent lack of measures limits controlling for the effect of important confounders such as depressive symptoms and medications. In addition, the age distribution in the OA group significantly differed from the controls and CBP group, owing to OA predominantly manifesting in middle and older ages. However, this should not be of concern. First, our independent variable is age-independent: Theoretically, because brain-PAD is an age-independent deviation from chronological age by design and in practice because we removed the effects of chronological age by including it as a covariate. Second, by including *scanner* as a covariate, each pain group is compared with its own age-matched control group in a pooled error model. Nevertheless, to address doubts about a possible age-related sample selection bias, we repeated the analysis only using participants older than 44 years and found similar results (see Figure S3, available at http://links.lww.com/PAIN/B875)—coincidently, this subsampling also eliminated the sex-related unbalance in age distributions, also helping to clear out any additional concern related to this issue (see Figure S4, available at http://links.lww.com/PAIN/B875). Finally, we did not investigate which specific brain areas may be experiencing accelerated aging. Future measures of local contributions to brain age (eg, using explanation maps[61]) may be more sensitive to different chronic pain conditions.

5. Conclusions

Using DeepBrainNet to predict brain age, and a large multicenter sample, we found that participants with OA have older-appearing brains compared with controls and participants with CBP, whereas no significant difference was observed between participants with CBP and controls. We also found significant associations between the predicted brain age difference and several measures of severity and comorbidities of chronic pain. Our results hint that more sophisticated MRI-based brain-age algorithms (eg, local brain age predictions) may provide simplistic, clinically accessible and easily implementable biomarkers of chronic pain. Because several modifiable lifestyle risk factors,[9,28] including body mass index, waist-to-hip ratio, smoking, and drinking,[44] may be related to brain age, these biomarkers may also be used to monitor treatment outcomes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

The authors are grateful to our volunteers for their participation and the UF/UAB and UF study teams, as well the creators of the OpenPain data set.

This work was supported by NIH/NIA grants R01AG059809, R01AG067757 and K01AG048259 (Y.C.-A.), and R37AG033906 (R.B.F.). A portion of this work's data set was performed in the McKnight Brain Institute at the National High Magnetic Field Laboratory's Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility, which is supported by National Science Foundation Cooperative Agreement No. DMR-1644779 and DMR-1157490 and the State of Florida.

CRediT author statement: P.A.V.-H.: conceptualization, methodology, software, formal analysis, data curation, writing—original draft, visualization. C.L.N.: software, formal analysis, data curation, writing—review & editing. A.J.J.: data curation,

writing—review & editing. S.M.-G.: data curation, writing—review & editing. V.B.: software, writing—review & editing. C.D.: software, writing—review & editing. J.A.P.: software, writing—review & editing. J.H.C.: conceptualization, writing—review & editing. R.B.F.: supervision, writing—review & editing. Y.C.-A: conceptualization, methodology, resources, writing—review & editing, supervision, project administration, funding acquisition.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B875.

Article history:
Received 28 September 2022
Received in revised form 19 May 2023
Accepted 31 May 2023
Available online 25 July 2023

References

[1] Avants BB, Tustison N, Song G. Advanced normalization tools (ANTS). Insight J 2009;2:1–35.
[2] Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15:1117–9.
[3] Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. PLoS One 2011;6:e26010.
[4] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth 2013;111:52–8.
[5] Bashyam VM, Erus G, Doshi J, Habes M, Nasrallah IM, Truelove-Hill M, Srinivasan D, Mamourian L, Pomponio R, Fan Y, Launer LJ, Masters CL, Maruff P, Zhuo C, Völzke H, Johnson SC, Fripp J, Koutsouleris N, Satterthwaite TD, Wolf D, Gur RE, Gur RC, Morris J, Albert MS, Grabe HJ, Resnick S, Bryan RN, Wolk DA, Shou H, Davatzikos C. MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. Brain 2020;143:2312–24.
[6] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[7] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
[8] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 1995;57:289–300.
[9] Bittner N, Jockwitz C, Franke K, Gaser C, Moebus S, Bayen UJ, Amunts K, Caspers S. When your brain looks older than expected: combined lifestyle risk and BrainAGE. Brain Struct Funct 2021;226:621–45.
[10] Boyle R, Jollans L, Rueda-Delgado LM, Rizzo R, Yener GG, McMorrow JP, Knight SP, Carey D, Robertson IH, Emek-Savaş DD, Stern Y, Kenny RA, Whelan R. Brain-predicted age difference score is related to specific cognitive functions: a multi-site replication analysis. Brain Imaging Behav 2021;15:327–45.
[11] Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1988;28:193–213.
[12] Cardoso JS, Riley JL, Glover T, Sibille KT, Bartley EJ, Goodin BR, Bulls HW, Herbert M, Addison AS, Staud R, Redden DT, Bradley LA, Fillingim RB, Cruz-Almeida Y. Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis. PAIN 2016;157:2104–14.
[13] Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, DeVellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai J-S, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays R; PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol 2010;63:1179–94.
[14] Chanda ML, Alvin MD, Schnitzer TJ, Apkarian AV. Pain characteristic differences between subacute and chronic back pain. J Pain 2011;12:792–800.
[15] Cole JH, Franke K. Predicting age using neuroimaging: innovative brain ageing biomarkers. Trends Neurosci 2017;40:681–90.
[16] Cole JH, Poudel RPK, Tsagkrasoulis D, Caan MWA, Steves C, Spector TD, Montana G. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. Neuroimage 2017;163:115–24.
[17] Cole JH, Underwood J, Caan MWA, De Francesco D, van Zoest RA, Leech R, Wit FWNM, Portegies P, Geurtsen GJ, Schmand BA, Schim van der Loeff MF, Franceschi C, Sabin CA, Majoie CBLM, Winston A, Reiss P, Sharp DJ. Increased brain-predicted aging in treated HIV disease. Neurology 2017;88:1349–57.
[18] Cole JH, Ritchie SJ, Bastin ME, Valdés Hernández MC, Muñoz Maniega S, Royle N, Corley J, Pattie A, Harris SE, Zhang Q, Wray NR, Redmond P, Marioni RE, Starr JM, Cox SR, Wardlaw JM, Sharp DJ, Deary IJ. Brain age predicts mortality. Mol Psychiatry 2018;23:1385–92.
[19] Cruz-Almeida Y, Martinez-Arizala A, Widerstrm-Noga EG. Chronicity of pain associated with spinal cord injury: a longitudinal analysis. J Rehabil Res Dev 2005;42:585–94.
[20] Cruz-Almeida Y, Fillingim RB, Riley JL, Woods AJ, Porges E, Cohen R, Cole J. Chronic pain is associated with a brain aging biomarker in community-dwelling older adults. PAIN 2019;160:1119–30.
[21] Cumplido-Mayoral I, García-Prat M, Operto G, Falcon C, Shekari M, Cacciaglia R, Milà-Alomà M, Lorenzini L, Ingala S, Wink AM, Mutsaerts HJ, Minguillón C, Fauria K, Molinuevo JL, Haller S, Chetelat G, Waldman A, Schwarz A, Barkhof F, Suridjan I, Kollmorgen G, Bayfield A, Zetterberg H, Blennow K, Suárez-Calvet M, Vilaplana V, Gispert JD, study A, study E, study A, study O. Biological brain age prediction using machine learning on structural neuroimaging data: Multi-cohort validation against biomarkers of Alzheimer's disease and neurodegeneration stratified by sex. eLife 2023;12:e81067.
[22] Downton F, Blom G. Statistical estimates and transformed beta-variables. By G. Blom. Pp.176. 40s. 1958. (Almqvist and Wiksell: John Wiley and Sons: chapman and Hall). Math Gaz 1961;45:369.
[23] Dworkin RH, Turk DC, Trudeau JJ, Benson C, Biondi DM, Katz NP, Kim M. Validation of the short-form McGill pain questionnaire-2 (SF-MPQ-2) in acute low back pain. J Pain 2015;16:357–66.
[24] Edwards RR, Campbell CM, Fillingim RB. Catastrophizing and experimental pain sensitivity: only in vivo reports of catastrophic cognitions correlate with pain responses. J Pain 2005;6:338–9.
[25] Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, Kent JD, Goncalves M, DuPre E, Snyder M, Oya H, Ghosh SS, Wright J, Durnez J, Poldrack RA, Gorgolewski KJ. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods 2019;16:111–6.
[26] Fillingim RB. Biopsychosocial contributions to sex differences in pain. BJOG 2015;122:769.
[27] Franke K, Gaser C, Manor B, Novak V. Advanced BrainAGE in older adults with type 2 diabetes mellitus. Front Aging Neurosci 2013;5:90.
[28] Franz CE, Hatton SN, Elman JA, Warren T, Gillespie NA, Whitsel NA, Puckett OK, Dale AM, Eyler LT, Fennema-Notestine C, Hagler DJ, Hauger RL, McKenzie R, Neale MC, Panizzon MS, Pearce RC, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Williams M, Xian H, Lyons MJ, Kremen WS. Lifestyle and the aging brain: interactive effects of modifiable lifestyle behaviors and cognitive ability in men from midlife to old age. Neurobiol Aging 2021;108:80–9.
[29] Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911–20.
[30] Gaser C, Franke K, Klöppel S, Koutsouleris N, Sauer H; Alzheimer's Disease Neuroimaging Initiative. BrainAGE in mild cognitive impaired patients: predicting the conversion to alzheimer's disease. PLoS One 2013;8:e67346.
[31] Gupta A, Mayer EA, Fling C, Labus JS, Naliboff BD, Hong JY, Kilpatrick LA. Sex-based differences in brain alterations across chronic pain conditions. J Neurosci Res 2017;95:604–16.
[32] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.
[33] Habes M, Janowitz D, Erus G, Toledo JB, Resnick SM, Doshi J, Van Der Auwera S, Wittfeld K, Hegenscheid K, Hosten N, Biffar R, Homuth G, Völzke H, Grabe HJ, Hoffmann W, Davatzikos C. Advanced brain aging: relationship with epidemiologic and genetic risk factors, and overlap with Alzheimer disease atrophy patterns. Transl Psychiatry 2016;6:e775.
[34] Hajek T, Franke K, Kolenic M, Capkova J, Matejka M, Propper L, Uher R, Stopkova P, Novak T, Paus T, Kopecek M, Spaniel F, Alda M. Brain age in early stages of bipolar disorders or schizophrenia. Schizophrenia Bull 2019;45:190–8.

[35] Hung PS-P, Zhang JY, Noorani A, Walker MR, Huang M, Zhang JW, Laperriere N, Rudzicz F, Hodaie M. Differential expression of a brain aging biomarker across discrete chronic pain disorders. PAIN 2022;163: 1468–78.
[36] Johnson AJ, Buchanan T, Laffitte Nodarse C, Valdes Hernandez PA, Huo Z, Cole JH, Buford TW, Fillingim RB, Cruz-Almeida Y. Cross-sectional brain-predicted age differences in community-dwelling middle-aged and older adults with high impact knee pain. J Pain Res 2022;15:3575–87.
[37] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
[38] Koski L. Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. Cerebrovasc Dis 2013; 36:6–18.
[39] Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic Med 2002;64:258–66.
[40] Lysne P, Cohen R, Hoyos L, Fillingim RB, Riley JL, Cruz-Almeida Y. Age and pain differences in non-verbal fluency performance: associations with cortical thickness and subcortical volumes. Exp Gerontol 2019;126: 110708.
[41] Makary MM, Polosecki P, Cecchi GA, DeAraujo IE, Barron DS, Constable TR, Whang PG, Thomas DA, Mowafi H, Small DM, Geha P. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain. Proc Natl Acad Sci USA 2020;117: 10015–23.
[42] Mano H, Kotecha G, Leibnitz K, Matsubara T, Nakae A, Shenker N, Shibata M, Voon V, Yoshida W, Lee M, Yanagida T, Kawato M, Rosa MJ, Seymour B. Classification and characterisation of brain network changes in chronic back pain: a multicenter study. Wellcome Open Res 2018;3: 19.
[43] Melzack R. The short-form McGill pain questionnaire. PAIN 1987;30: 191–7.
[44] Mouches P, Wilms M, Bannister JJ, Aulakh A, Langner S, Forkert ND. An exploratory causal analysis of the relationships between the brain age gap and cardiovascular risk factors. Front Aging Neurosci 2022;14:941864.
[45] Neter J, Kutner MH, Nachtsheim CJ, Wasserman W. Applied Linear Statistical Models. 4th ed. Chicago: Irwin, 1990
[46] Popescu SG, Glocker B, Sharp DJ, Cole JH. Local brain-age: a U-net model. Front Aging Neurosci 2021;13:761954.
[47] PROMIS Health Organization PROMIS Cooperative Group. Measure development & research, 2020.
[48] Riley JL, Robinson ME. CSQ: five factors or fiction? Clin J Pain 1997;13: 156–62.
[49] Riley JL III, Robinson ME, Geisser ME. Empirical subgroups of the coping strategies questionnaire-revised: a multisample study. Clin J Pain 1999; 15:111–6.
[50] Sanford N, Ge R, Antoniades M, Modabbernia A, Haas SS, Whalley HC, Galea L, Popescu SG, Cole JH, Frangou S. Sex differences in predictors and regional patterns of brain age gap estimates. Hum Brain Mapp 2022; 43:4689–98.
[51] Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52:591–611.
[52] Sörös P, Bantel C. Chronic noncancer pain is not associated with accelerated brain aging as assessed by structural magnetic resonance imaging in patients treated in specialized outpatient clinics. PAIN 2020; 161:641–50.
[53] Suso-Ribera C, Martínez-Borba V, Martín-Brufau R, Suso-Vergara S, García-Palacios A. Individual differences and health in chronic pain: are sex-differences relevant? Health Qual Life Outcomes 2019;17: 128.
[54] Szegedy C, Ioffe S, Vanhoucke V, Alemi AA. Inception-v4, inception-ResNet and the impact of residual connections on learning. Proceedings of the Thirty-First AAAI Conference on Artificial Intelligence. AAAI'17. AAAI Press, 2017. p. 4278–84.
[55] Tétreault P, Mansour A, Vachon-Presseau E, Schnitzer TJ, Apkarian AV, Baliki MN. Brain connectivity predicts placebo response across chronic pain clinical trials. PLoS Biol 2016;14:e1002570.
[56] Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC. N4ITK: improved N3 bias correction. IEEE Trans Med Imaging 2010; 29:1310–20.
[57] Vachon-Presseau E, Tétreault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, Comasco E, Schnitzer TJ, Baliki MN, Apkarian AV. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain 2016;139:1958–70.
[58] Valdes-Hernandez PA, Montesino-Goicolea S, Hoyos L, Porges EC, Huo Z, Ebner NC, Woods AJ, Cohen R, Riley JL III, Fillingim RB, Cruz-Almeida Y. Resting-state functional connectivity patterns are associated with worst pain duration in community-dwelling older adults. Pain Reports 2021;6:e978.
[59] Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. PAIN 1992;50:133–49.
[60] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Personal Social Psychol 1988;54:1063–70.
[61] Yin C, Imms P, Cheng M, Amgalan A, Chowdhury NF, Massett RJ, Chaudhari NN, Chen X, Thompson PM, Bogdan P, Irimia A, Alzheimer's Disease Neuroimaging Initiative, Aisen P, Petersen R, Weiner MW, Aisen P, Petersen R, Jack CR, Jagust W, Trojanowki JQ, Toga AW, Beckett L, Green RC, Saykin AJ, Morris JC, Perrin RJ, Shaw LM, Khachaturian Z, Carrillo M, Potter W, Barnes L, Bernard M, González H, Ho C, Hsiao JK, Jackson J, Masliah E, Masterman D, Okonkwo O, Perrin R, Ryan L, Silverberg N, Fleisher A, Lilly E, Weiner MW, Truran Sacrey D, Fockler J, Conti C, Veitch D, Neuhaus J, Jin C, Nosheny R, Ashford M, Flenniken D, Kormos A, Green RC, Montine T, Conti C, Petersen R, Aisen P, Rafii M, Raman R, Jimenez G, Donohue M, Gessert D, Salazar J, Zimmerman C, Cabrera Y, Walter S, Miller G, Coker G, Clanton T, Hergesheimer L, Smith S, Adegoke O, Mahboubi P, Moore S, Pizzola J, Shaffer E, Sloan B, Beckett L, Harvey D, Donohue M, Jack CR, Forghanian-Arani A, Borowski B, Ward C, Schwarz C, Jones D, Gunter J, Kantarci K, Senjem M, Vemuri P, Reid R, Fox NC, Malone I, Thompson P, Thomopoulos SI, Nir TM, Jahanshad N, DeCarli C, Knaack A, Fletcher E, Harvey D, Tosun-Turgut D, Chen SR, Choe M, Crawford K, Yushkevich PA, Das S, Jagust W, Koeppe RA, Reiman EM, Chen K, Mathis C, Landau S, Morris JC, Perrin R, Cairns NJ, Householder E, Franklin E, Bernhardt H, Taylor-Reinwald L, Shaw LM, Trojanowki JQ, Korecka M, Figurski M, Toga AW, Crawford K, Neu S, Saykin AJ, Nho K, Risacher SL, Apostolova LG, Shen L, Foroud TM, Nudelman K, Faber K, Wilmes K, Weiner MW, Thal L, Khachaturian Z, Hsiao JK, Silbert LC, Lind B, Crissey R, Kaye JA, Carter R, Dolen S, Quinn J, Schneider LS, Pawluczyk S, Becerra M, Teodoro L, Dagerman K, Spann BM, Brewer J, Vanderswag H, Fleisher A, Ziolkowski J, Heidebrink JL, Zbizek-Nulph L, Lord JL, Zbizek-Nulph L, Petersen R, Mason SS, Albers CS, Knopman D, Johnson K, Villanueva-Meyer J, Pavlik V, Pacini N, Lamb A, Kass JS, Doody RS, Shibley V, Chowdhury M, Rountree S, Dang M, Stern Y, Honig LS, Mintz A, Ances B, Morris JC, Winkfield D, Carroll M, Stobbs-Cucchi G, Oliver A, Creech ML, Mintun MA, Schneider S, Geldmacher D, Natelson Love M, Griffith R, Clark D, Brockington J, Marson D, Grossman H, Goldstein MA, Greenberg J, Mitsis E, Shah RC, Lamar M, Samuels P, Duara R, Greig-Custo MT, Rodriguez R, Albert M, Onyike C, Farrington L, Rudow S, Brichko R, Kielb S, Smith A, Raj BA, Fargher K, Sadowski M, Wisniewski T, Shulman M, Faustin A, Rao J, Castro KM, Ulysse A, Chen S, Sheikh MO, Singleton-Garvin J, Doraiswamy PM, Petrella JR, James O, Wong TZ, Borges-Neto S, Karlawish JH, Wolk DA, Vaishnavi S, Clark CM, Arnold SE, Smith CD, Jicha GA, El Khouli R, Raslau FD, Lopez OL, Oakley M, Simpson DM, Porsteinsson AP, Martin K, Kowalski N, Keltz M, Goldstein BS, Makino KM, Ismail MS, Brand C, Thai G, Pierce A, Yanez B, Sosa E, Witbracht M, Kelley B, Nguyen T, Womack K, Mathews D, Quiceno M, Levey AI, Lah JJ, Hajjar I, Cellar JS, Burns JM, Swerdlow RH, Brooks WM, Silverman DH, Kremen S, Apostolova L, Tingus K, Lu PH, Bartzokis G, Woo E, Teng E, Graff-Radford NR, Parfitt F, Poki-Walker K, Farlow MR, Hake AM, Matthews BR, Brosch JR, Herring S, van Dyck CH, Mecca AP, MacAvoy MG, Carson RE, Varma P, Chertkow H, Vaitekunis S, Hosein C, Black S, Stefanovic B, Heyn CC, Hsiung GYR, Kim E, Mudge B, Sossi V, Feldman H, Assaly M, Finger E, Pasternak S, Rachinsky I, Kertesz A, Drost D, Rogers J, Grant I, Muse B, Rogalski E, Robson J, Mesulam MM, Kerwin D, Wu CK, Johnson N, Lipowski K, Weintraub S, Bonakdarpour B, Pomara N, Hernando R, Sarrael A, Rosen HJ, Miller BL, Perry D, Turner RS, Johnson K, Reynolds B, MCCann K, Poe J, Sperling RA, Johnson KA, Marshall GA, Yesavage J, Taylor JL, Chao S, Coleman J, White JD, Lane B, Rosen A, Tinklenberg J, Belden CM, Spann BM, Clark KA, Zamrini E, Sabbagh M, Killiany R, Stern R, Mez J, Kowall N, Budson AE, Obisesan TO, Ntekim OE, Wolday S, Khan JI, Nwulia E, Nadarajah S, Lerner A, Ogrocki P, Tatsuoka C, Fatica P, Fletcher E, Maillard P, Olichney J, DeCarli C, Carmichael O, Bates V, Capote H, Rainka M, Borrie M, Lee TY, Bartha DR, Johnson S, Asthana S, Carlsson CM, Perrin A, Burke A, Scharre DW, Kataki M, Tarawneh R, Kelley B, Hart D, Zimmerman EA, Celmins D, Miller DD, Boles Ponto LL, Smith KE, Koleva H, Shim H, Nam KW, Schultz SK, Williamson JD, Craft S, Cleveland J, Yang M, Sink KM, Ott BR, Drake J, Tremont G, Daiello LA, Drake JD, Sabbagh M, Ritter A, Bernick C, Munic D, Mintz A, O'Connelll A, Mintzer J, Wiliams A, Masdeu J, Shi J, Garcia A, Sabbagh M, Newhouse P, Potkin S, Salloway S, Malloy P, Correia S, Kittur S, Pearlson GD, Blank K, Anderson K, Flashman LA, Seltzer M, Hynes ML, Santulli RB, Relkin N, Chiang G, Lee A, Lin M, Ravdin L, Weiner MW, Aisen P, Petersen R, Weiner MW, Aisen P, Petersen R, Green RC, Harvey D, Jack CR Jr, Jagust W, Morris JC, Saykin AJ, Shaw LM, Toga AW, Trojanowki JQ, Neylan T, Grafman J, Green RC, Montine T, Aisen P, Jimenez G,

Donohue M, Gessert D, Salazar J, Zimmerman C, Walter S, Adegoke O, Mahboubi P, Danowski S, Coker G, Clanton T, Pizzola J, Shaffer E, Nguyen-Barrera C, Neylan T, Hayes J, Finley S, Harvey D, Donohue M, Jack CR Jr, Bernstein M, Borowski B, Gunter J, Senjem M, Kantarci K, Ward C, Tosun-Turgut D, Rossi Chen S, Landau S, Koeppe RA, Foster N, Reiman EM, Chen K, Morris JC, Perrin RJ, Franklin E, Shaw LM, Trojanowki JQ, Korecka M, Figurski M, Toga AW, Crawford K, Neu S, Saykin AJ, Foroud TM, Potkin S, Shen L, Faber K, Kim S, Nho K, Wilmes K, Schneider LS, Pawluczyk S, Becerra M, Teodoro L, Dagerman K, Spann BM, Brewer J, Vanderswag H, Fleisher A, Stern Y, Honig LS, Mintz A, Shah RC, Sood A, Blanchard KS, Fleischman D, Arfanakis K, Duara DR, Varon DD, Greig MT, Doraiswamy PM, Petrella JR, James O, Borges-Neto S, Wong TZ, Porsteinsson AP, Martin KS, Thai G, Pierce A, Reist C, Yanez B, Sosa E, Witbracht M, Sadowsky C, Martinez W, Villena T, Rosen H, Perry D, Turner RS, Johnson K, Reynolds B, MCCann K, Poe J, Sperling RA, Johnson KA, Marshall G, Belden CM, Spann BM, Clark KA, Zamrini E, Sabbagh M, Obisesan TO, Ntekim OE, Nwulia E, Nadarajah S, Asthana S, Carlsson CM, Peskind ER, Petrie EC, Li G, Yesavage J, Taylor JL, Chao S, Coleman J, White JD, Lane B, Rosen A, Tinklenberg J, Lin M, Chiang G, Ravdin L, Relkin N, O'Connelll A, Mintzer J, Wiliams A, Mackin S, Aisen P, Raman R, Jimenez-Maggiora G, Donohue M, Gessert D, Salazar J, Zimmerman C, Walter S, Adegoke O, Mahboubi P, Mackin S, Weiner MW, Aisen P, Raman R, Jack CR Jr, Landau S, Saykin AJ, Toga AW, DeCarli C, Koeppe RA, Green RC, Drake E, Weiner MW, Aisen P, Raman R, Donohue M, Mackin S, Nelson C, Bickford D, Butters M, Zmuda M, Jack CR Jr, Bernstein M, Borowski B, Gunter J, Senjem M, Kantarci K, Ward C, Reyes D, Koeppe RA, Landau S, Toga AW, Crawford K, Neu S, Saykin AJ, Foroud TM, Faber KM, Nho K, Nudelman KN, Mackin S, Rosen H, Nelson C, Bickford D, Au YH, Scherer K, Catalinotto D, Stark S, Ong E, Fernandez D, Butters M, Zmuda M, Lopez OL, Oakley M, Simpson DM. Anatomically interpretable deep learning of brain age captures domain-specific cognitive impairment. Proc Natl Acad Sci USA 2023;120:e2214634120.

[62] Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, Johnston KL, Pilkonis PA. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. Behav Sleep Med 2012;10:6–24.

[63] Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the multidimensional scale of perceived social support. J Personal Assess 1990;55:610–7.