

Brain Predicted Age Difference Mediates the Impact of Pain Related Disability on Physical Performance in Community Dwelling Adults

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Highlights

- Brain-PAD was negatively associated with physical performance scores in sit-to-stand, walking, and total score, suggesting that ‘older’ brain age is related to worse physical function.
- Brain-PAD mediated the relationship between those with high impact knee pain and pain related severity and SPPB walking scores, and SPPB total scores.
- Brain aging may begin to explain the association between knee pain and physical performance, especially concerning walking.

ABSTRACT

The purpose of the study was to examine associations between physical performance and brain aging in individuals with knee pain and whether the association between pain and physical performance is mediated by brain aging. Participants (n=202) with low impact knee pain (n=111), high impact knee pain (n=60) and pain-free controls (n=31) completed self-reported pain, magnetic resonance imaging (MRI), and a Short Physical Performance Battery (SPPB) that included balance, walking, and sit to stand tasks. Brain predicted age difference, calculated using machine learning from MRI images, significantly mediated the relationships between walking and knee pain impact (CI: -0.124; -0.013), walking and pain-severity (CI: -0.008; -0.001), total SPPB score and knee pain impact (CI: -0.232; -0.025), and total SPPB scores and pain-severity (CI: -0.019; -0.001). Brain-aging begins to explain the association between pain and physical performance, especially walking. This study supports the idea that a brain aging prediction can be calculated from shorter duration MRI sequences and possibly implemented in a clinical setting to be used to identify individuals with pain who are at risk for accelerated brain atrophy and increased likelihood of disability.

Physical disability is a common concern in older community dwelling adults and musculoskeletal (MSK) conditions are thought to be the frequently reported underlying cause (1-4). The high prevalence of knee pain and radiographic diagnosis of knee osteoarthritis (KOA) suggests that issues involving the knee may be associated with physical performance limitations. KOA is a chronic degenerative MSK disorder characterized by pain upon movement and decreased physical function (e.g., decreased strength and range-of-motion in the knee joint). It is the leading cause of disability in older adults (5) affecting approximately 15% of people >55 years (6). Numerous studies have demonstrated an association between chronic pain and physical disability (7-16). Physical disability from KOA is complex and multifactorial involving interactions of disease severity (17), pain, comorbidities(18), and psychological, social, and environmental factors (19).

Our preliminary work (*submitted*) suggests that individuals with chronic musculoskeletal (MSK) pain have "age-like" brain atrophy with higher pain impact in persons with KOA. This supports our earlier work in older adults with and without chronic pain, where pain was associated with higher brain age (20). Early research indicates a bidirectional relationship between OA pain and brain structure, similar to that seen in other chronic pain conditions (21). Available studies related to mobility found that brain structure, obtained from magnetic resonance imaging (MRI) of the aging brain, has been limited to mostly gait (22) and this, to our knowledge, has not been explored in those with knee pain.

Machine learning models (23) have been used to predict brain age with findings of an older brain age than chronological age people with Alzheimer's Disease (24), mild cognitive impairment (25), HIV (26), and schizophrenia (27). Using this paradigm, brain-predicted age *difference* (brain-PAD; the difference between chronological age and brain-predicted age) has been examined in

disease and health research (28-31). Findings reflect an association between greater brain-PAD and declines in cognitive performance, increased chronic disease risk, and increased mortality (29-33). Those with older brain-PAD have greater pain intensity, sensitivity and inhibition in older adults with chronic MSK pain (20, 28). This is consistent with other research showing untreated pain was associated with added “age-like” brain atrophy (34-37).

As patients with knee pain tend to have increased functional limitations than those without knee pain, it is important to explore the causation of this association. Individuals with chronic pain have an older brain than those without pain and this in turn may lead to physical performance limitations in those with knee complaints. Using this rationale, we sought to 1) examine potential differences in physical performance between individuals with low impact pain KOA, high impact pain KOA, and a healthy pain-free control group, 2) identify associations between physical performance and brain age in individuals with KOA, and 3) examine whether the association between pain and physical performance is mediated by brain-PAD in individuals with KOA. Given our prior work showing that individuals with High Impact knee pain appear to have an ‘older’ brain compared to those with Low Impact knee pain, we hypothesized that High Impact knee pain may also be associated with physical performance limitations and mobility issues, and that differences in brain-predicted age may mediate this relationship.

METHODS

Participants

Participants were recruited as part of a larger multisite, observational study, aimed at elucidating the mechanisms underlying ethnic/race group differences in knee OA-related pain. Individuals with or at risk for knee osteoarthritis (OA), who were between the ages of 45-85 years, who spoke English as their primary language and identified as non-Hispanic Black and “Black/African

American” or “White/Caucasian/European”, were recruited from the community between August 2015 and May 2017. Multimedia recruitment strategies were used (e.g., posted fliers, radio/print media, and clinic referrals) to identify interested individuals. Exclusion criteria consisted of: 1) prosthetic knee replacement or other clinically significant surgery to the index knee; 2) cardiovascular disease; 3) history of acute myocardial infarction; 4) neurological disease (e.g., Parkinson’s, multiple sclerosis, and uncontrolled seizures); 5) hypertension (blood pressure > 150/95 mm Hg, uncontrolled); 6) peripheral neuropathy; 7) systemic rheumatic disorders (e.g., rheumatoid arthritis and fibromyalgia); 8) daily opioid use; 9) serious psychiatric illness; 10) pregnant; and 11) significantly greater body pain in a site other than the knee (KOA group only). All participants completed written informed consent prior to completing study procedures and were compensated.

Procedures

Full study procedures were approved by both the University of Florida (UF) and University of Alabama, Birmingham (UAB) Institutional Review Boards, and have been previously reported (38-40). Individuals first completed a telephone screening to determine initial eligibility (e.g., sex, age, ethnicity/race, and symptoms of knee OA). Eligible individuals were scheduled for a health assessment session (HAS), during which written informed consent was obtained and participants completed health and pain history questionnaires, and a physical exam to determine the most painful (i.e., index) knee. Radiographic imaging was also collected at the HAS to grade KOA severity according to the Kellgren-Lawrence (KL) classification (41). Approximately one week after the HAS, participants returned to the laboratory to complete quantitative sensory testing (QST) that consisted of thermal and mechanical pain sensitivity, temporal summation (TS), and

conditioned pain modulation (CPM) measures. Participants were asked to complete clinical pain measures online within 24 hours prior to the QST session or in-person immediately prior to beginning the QST session. At a third laboratory session approximately one week later, participants completed psychological questionnaires and a magnetic resonance imaging (MRI) session.

Measures

Self-reported pain

Graded Chronic Pain Scale (GCPS) (42). The GCPS is a commonly used and validated measure that assesses characteristic pain intensity and pain-related disability, and can be used to grade chronic pain impact. (42, 43). For this study, GCPS instructions were specific to pain and disability related to the knee. Participants rated 1) current knee pain, and 2) average and 3) worst knee pain over the past six months, and how much pain has interfered with 4) daily activities, 5) recreational/social/family activities, and 6) ability to work on a 0 (“no pain” or “no interference”) to 10 (“pain as bad as could be” or “unable to carry out activities”) numerical rating scale (NRS). Characteristic pain intensity was calculated as the mean of current, average, and worst pain ratings multiplied by 10, with scores ranging from 0-100. Pain-related disability was calculated similarly using items 4-6. One additional item asked participants to report how many days in the last six months that they have been kept from their usual activities due to pain. Higher scores indicate greater pain intensity and pain-related disability. *Disability points* were derived from the calculated GCPS pain-related disability score and number of disability days, accordingly: GCPS pain-related disability (score range: 0-29 = 0 points; 30-49 = 1 point; 50-69 = 2 points; ≥ 70 = 3 points), plus the total number of disability days (range: 0-6 days = 0 points; 7-14 days = 1 point; 15-30 days =

2 points; 31 days or more = 3 points). GCPS *characteristic pain intensity* and *disability points* were used to classify individuals into pain grades as follows: Grade 0 = no pain intensity; Grade 1 = disability points < 3 and GCPS characteristic pain intensity < 50; Grade 2 = disability points < 3 and characteristic pain intensity ≥ 50 ; Grade 3 = disability points 3-4 irrespective of characteristic pain intensity; Grade 4 = disability points 5-6 irrespective of characteristic pain intensity.(42) Knee Pain Impact Groups were operationalized as: Grade 0 = No chronic knee pain; Grades 1-2 = Low impact knee pain; Grades 3-4 = High impact knee pain.

Physical performance

Short Physical Performance Battery (SPPB) (44). The SPPB is a performance-based measure used to assess lower-extremity physical function. Participants are asked to complete three tasks (i.e., balance, gait speed, chair stand) and scored from 0-4, with higher scores representing increasing ability. Scores are summed for a total performance score ranging from 0-12. The SPPB was administered during the HAS visit.

Magnetic Resonance Imaging (MRI)

MRI data were acquired with a 3-Tesla Phillips Achieva whole body scanner (Best, Netherlands) using a 32-channel radio-frequency head coil at UF's McKnight Brain Institute (MBI), and an 8-channel radio-frequency head coil at UAB. Anatomical images were captured using a high-resolution 3D T1-weighted MP-RAGE sequence with the following parameters: repetition time (TR) = 7.0 ms, echo time (TE) = 3.2 ms, 176 slice acquisition in sagittal orientation, flip angle (α) = 8°, 1 mm³ isotropic voxels, field of view (FOV) = 240 × 240 × 176. Participants were instructed to not move their heads and cushioning was placed to minimize head movement.

Brain-Predicted Age Biomarker

We used a previously established brain-predicted age biomarker developed using machine-learning to accurately predict chronological age from neuroimaging data. Segmented and normalized T1-weighted structural MRI scans from a healthy training cohort ($n = 3,377$; mean age = 40.6 ± 21.4 years; age range = 18-92 years) (30) were used to predict chronological age in a Gaussian Processes regression model (R, *kermlab* package), using the *brainageR* software.¹ The model was tested for accuracy using randomly selected held-out test data that included 857 healthy adults (mean age 40.1 ± 21.8 years, age range = 18-90 years). Model performance was high, with a mean absolute error of 3.93 years and a correlation between chronological age and ‘brain-predicted’ age of $r = 0.97$, $R^2 = 0.95$. To further validate the model, it was tested on an entirely independent dataset ($n = 611$, age range = 18-90 years), and demonstrated a mean absolute error of 4.9 years, and a correlation with chronological age and ‘brain-predicted’ age of $r = 0.95$.

For the current study we applied the validated model to generate brain-predicted age values for our sample ($n = 202$). As in our prior work, we calculated a brain-predicted age difference (brain-PAD) variable by subtracting each participant’s chronological age from their brain-predicted age to be used for the current analysis (20).

Statistical Analysis

All data processing and analyses were conducted in SPSS v27.0 (Armonk, NY: IBM Corp). Prior to analysis, data were checked for distributional form and outliers. Descriptive statistics were used to obtain characteristics of the sample. One-way analysis of variance (ANOVA) was used to compare the mean values in continuous/discrete ordinal variables between Knee Pain Impact

¹ <https://github.com/james-cole/brainageR>

Groups, and χ^2 was used for comparison of nominal variables. Assumptions underlying each statistical test were examined. Physical performance (i.e., SPPB) was compared across Knee Pain Impact Groups using one-way analyses of covariance (ANCOVAs), with sex, ethnicity/race, chronological age, and study site, included as covariates. Partial correlations were used to examine associations between SPPB domains, brain-PAD, self-reported GCPS characteristic pain intensity and pain-related disability, controlling for sex, ethnicity/race, chronological age, and study site. Hierarchical linear regressions were performed to determine the association of Knee Pain Impact Group with physical performance (i.e., SPPB) and brain-PAD using three separate models (Model 1: Knee Pain Impact Group; Model 2: Model 1 *plus* sex, ethnicity/race, and study site, Model 3: Model 2 *plus* Age). Using the Hayes PROCESS macro (i.e., *Model 4*), separate mediation analyses were conducted to assess Knee Pain Impact Group, pain severity, and pain disability. We tested the direct and the total indirect effect of pain on balance, sit-to-stand, walking and total SPPB score mediated through brain-PAD (**figure 1**). The mediation analysis controlled for sex, race, age, and study site. To overcome potential unmet assumptions commonly found in mediation analysis, bootstrapping was employed for all analyses using 5,000 samples and reported as estimates (b) and standard errors (SE) or as 95% bootstrapped confidence intervals.

RESULTS

Our previous work demonstrated significant brain-PAD differences across Knee Pain Impact Groups (Johnson et al., *under review*). Therefore, the current analysis was focused on the differences in physical performance across Knee Pain Impact Groups and the mediating role of brain-PAD in the association between pain and physical performance.

Sample Characteristics

Of the 206 individuals who were eligible to receive an MRI as part of the larger parent study, 202 participants with complete pain, physical performance, and covariate data were included in the current analysis. The sample mean age was 58.04 ± 8.256 years, with 65.5% being female, and 55.4% identifying as non-Hispanic White (NHW). Pain Impact Groups are shown in **Table 1**. Self-reported GCPS characteristic pain intensity and GCPS pain-related disability measures differed significantly between pain impact groups ($p < 0.001$).

Knee Pain Impact Group and Physical Performance

Knee Pain Impact Group differences for SPPB balance, SPPB sit-to-stand, SPPB walking, and total SPPB scores, controlling for sex, ethnicity/race, chronological age and study site were calculated. Findings are presented in **Figure 3**. A significant main effect for Knee Pain Impact Group was found for SPPB balance ($F(2, 196) = 4.026$; $p=0.019$, $\eta_p^2 0.039$) and *Bonferroni post hoc* tests revealed that individuals classified as having High Impact knee pain scored lower (3.647 ± 0.067) than the Low Impact knee pain group (3.876 ± 0.048 ; $p = 0.021$) on SPPB balance.

Similarly, SPPB sit-to-stand scores differed significantly between Knee Pain Impact Groups, ($F(2, 196) = 8.799$; $p<0.001$, $\eta_p^2 0.084$), with individuals in the High Impact knee pain group scoring lower (1.887 ± 0.158) than the Low Impact knee pain group (2.490 ± 0.113 ; $p=0.007$), and pain-free controls (2.957 ± 0.213 ; $p<0.001$).

A significant main effect for Knee Pain Impact Group was found for SPPB walking scores ($F(2, 196) = 4.593$; $p=0.011$, $\eta_p^2 0.045$). *Post hoc* comparisons showed individuals with High Impact knee pain had lower walking scores (3.574 ± 0.073) than the control group (3.932 ± 0.100 ; $p=0.014$).

Overall, total SPPB scores differed significantly across the Knee Pain Impact Groups ($F(2, 196) = 13.732$; $p < 0.001$, $\eta_p^2 0.123$) whereby individuals with High Impact knee pain had lower total SPPB scores (9.127 ± 0.195) than Low Impact knee pain group (10.116 ± 0.142 ; $p < 0.001$), and pain-free controls (10.757 ± 0.268 ; $p < 0.001$).

Associations Between Pain, Physical Performance, and Brain-PAD

Partial correlations controlling for sex, ethnicity/race, chronological age, and study site suggested that brain-PAD was negatively associated with sit-to-stand ($r = -0.163$; $p = 0.022$) walking ($r = -0.227$; $p = 0.001$), and total SPPB scores ($r = -0.240$; $p < 0.001$). Brain-PAD was positively associated with GCPS pain-related disability scores ($r = 0.162$; $p = 0.023$) and approached statistical significance with GCPS characteristic pain intensity scores and Knee Pain Impact Group ($r = 0.129$; $p = 0.080$).

Hierarchical Linear Regression Analysis

Hierarchical regression analysis revealed Knee Pain Impact Group was significantly associated with brain-PAD, in the unadjusted model (i.e., Model 1), with pain group accounting for 2.2% of the variance ($\beta = 0.148$; $p = 0.036$), and 4.7% of the variance in the adjusted model (i.e., Model 2), which accounted for study site, sex, and ethnicity/race ($\beta = 0.137$; $p = 0.040$). GCPS characteristic pain intensity was not significantly associated with brain-PAD alone ($\beta = 0.130$; $p = 0.062$); however, when study site, sex, and ethnicity/race were included the model accounted for 15.8% of the variance ($\beta = 0.138$; $p = 0.038$). GCPS pain-related disability was significantly associated with brain-PAD in Model 1 ($\beta = 0.169$; $p = 0.015$), accounting for approximately 3% of the variance, and when study site, sex, and ethnicity/race were included (i.e., Model 2), 15% of the variance was accounted for in brain-PAD ($\beta = 0.178$; $p = 0.008$).

Brain-PAD was significantly associated with SPPB sit-to-stand scores ($\beta = -0.208$; $p = 0.002$), SPPB walking ($\beta = -0.208$; $p = 0.002$), and total SPPB ($\beta = -0.251$; $p < 0.001$) in the total sample, when study site, sex, ethnicity/race, and age were included in the model.

Mediation of Pain and Physical Performance by brain-PAD

To test the indirect effects of Knee Pain Impact Group, GCPS characteristic pain intensity, and GCPS pain-related disability on physical performance (i.e., SPPB scores) through brain-PAD, bootstrapped mediation analyses ($n=5000$) were performed while controlling for sex, age, ethnicity/race, and study site. As shown in Figure 1, we examined the direct effect of pain variables on physical performance (C' pathway) and the indirect effects of pain variables on physical performance through brain-PAD (mediated: a + b pathway). Brain-PAD significantly mediated the relationships between SPPB walking and Knee Pain Impact Group, SPPB walking and GCPS pain-related disability, total SPPB score and Knee Pain Impact Group, and total SPPB scores and GCPS pain-related disability. Mediation results are summarized in **Table 3**.

DISCUSSION

This study extends previous research, ours and others, investigating chronic pain conditions, physical function, and brain aging by providing evidence that individuals with higher impact knee pain have reduced physical performance scores in balance, sit-to-stand, walking, and overall physical function. Our recent work (Johnson et al., *under review*) showed that those with High Impact pain had an “older” appearing brain than those with Low Impact pain, and pain-free controls. A novel finding was that brain-predicted age difference (brain-PAD) positively correlated with pain-related disability, indicating an ‘older brain age’ was associated with greater levels of pain-related disability in persons with KOA. Also, we found that brain-PAD was negatively

associated with SPPB sit-to-stand, walking, and total scores, suggesting that ‘older’ brain age is related to worse physical function. Interestingly, brain-PAD mediated the relationship between Knee Pain Impact Groups and SPPB walking scores, and SPPB total scores. In addition, our results indicated that the relationship between GCPS pain-related disability and SPPB walking scores, as well as, overall physical performance. Taken together, these findings highlight the potential influence of age-related brain changes on physical function in persons with chronic pain.

The current study supports our previous work in a smaller subset of individuals from the same parent study examining pain and epigenetics (Peterson et al., *under review*), demonstrating that individuals with High Impact knee pain have reduced mobility scores compared to those with Low Impact knee pain, and adds to the evidence that KOA can lead to a reduction in physical function and limit mobility (7-16, 45-48). More individuals with arthritis (31%) are sedentary than people without arthritis (26%) (45). In individuals who do not have pain, total daily sedentary time has been shown to be negatively associated with mobility (49, 50). Pain is a commonly mentioned barrier to exercise in those with KOA and paradoxically, those who do not get enough exercise usually have exercise-related reductions in pain when they do begin to exercise (51). Individuals with more pain typically have less motivation to exercise than those with less or no pain. Those individuals, however, may have more pain on average because they exercise less thus leading to further disability. The directional causality of this phenomenon still needs investigation and longitudinal research will likely provide more insights.

Brain structure alters throughout life, and neuropathological influences may reveal inconsistencies from this typical brain ageing trajectory especially when examining brain atrophy for a given age. It is thought that chronic pain may act as a catalyst for aging the brain at a faster rate (52, 53). Using a brain age calculation, we were able to assess how chronic pain relates to

brain aging in those who have varying degrees of knee pain but are otherwise healthy. We found that those in the high impact pain group had an “older” appearing brain-age than those in the low impact pain group. The overall sample had a younger brain age compared to their chronological age, however those with high impact pain had an older brain relative to those with low impact pain and the pain free control group. Previous work has shown that older pain-free controls had a brain age that appeared 4 years younger than their chronological age while those with chronic pain had a brain that appeared 2 years older than their chronological age (52). Our sample did not have an older brain age than chronological age, regardless of pain impact status. This could be due to the age of our participants being younger than previous research samples and that other than pain status they did not display any other health discrepancy. However, we did see a significantly older brain in the high impact pain group compared to the low impact pain group and controls, which was comparable to other studies that had examined brain age and pain. Previous data in individuals with chronic back pain found that gray matter density was reduced in both the bilateral dorsolateral prefrontal cortex and right thalamus and were associated to pain characteristics (54). Similarly, in individuals with fibromyalgia, gray matter volumes of brain areas were related to pain-related areas and were significantly lower than controls (55). These findings demonstrate evidence that supports the association of chronic pain with accelerated gray matter atrophy. Early research indicates a bidirectional relationship between OA pain and brain structure, similar to that seen in other chronic pain conditions (21).

An aging brain has shown to reduce mobility and limit physical function in older individuals (56-58). We found that our brain aging variable correlated with pain related disability and was negatively associated with sit-to-stand scores, walking, and overall physical function. Furthermore, brain age mediated the relationship between walking and pain group, walking and

pain related disability, overall physical performance and pain group, and overall physical performance and pain related disability. Available studies related to disability found that white matter lesions, frequently found in magnetic resonance imaging (MRI) of the aging brain have shown to be associated with gait and balance impairment, (59, 60) cognitive impairment (61) and frequent falling (62). Global brain atrophy has been indicated as one of the risk factors for falls in older adults with mild cognitive disorders (63). While balance scores, a predictor of fall risk, was not associated with brain age; walking, sit to stand, and overall physical performance was associated with brain age and each of these performance variables relate to health related fitness muscular strength which is also a predictor of fall risk (64, 65). Additionally, declines in cerebral white matter volume (as seen in the aging brain) has been shown to be a possible contributor to the detrimental effect of musculoskeletal pain on gait speed which shows similarities to our findings (66). Based on our current and previous work, it is possible that age-related mobility impairments may be accelerated by having more pain and pain related disability whereby those with more severe pain have poor physical functioning and an older appearing brain than those with less pain, or no pain. Interventions that decrease pain impact and improve overall physical function may prevent or slow down accelerated brain-aging associated with performance deficits and chronic pain.

The study was cross-sectional and causality cannot be determined. It is very likely that the relationship between brain age and pain, pain related disability, walking and overall physical performance is bidirectional. Future longitudinal studies to understand the clinical significance of measuring brain aging, and using brain age outcomes to predict pain and pain related physical performance limitations is warranted. Third, screening criteria for the current study excluded those with clinical depression, moderate to severe cognitive impairment, and neurological diseases.

While this may limit the generalizability of our current findings, it also removed potential confounders as previous research has shown associations between brain age, cognitive impairment, and psychological function (29, 30). This study examined those with knee pain only, and therefore generalizability to other pain locations and conditions should be done with caution. Future studies, including individuals with other specific chronic pain conditions, are needed to further elucidate these associations and assist in the development of a brain biomarker specific to pain, pain related disability, and physical performance limitations.

Conclusion

Brain aging begins to explain the association between pain and physical performance, especially concerning walking. Biological aging, in this case brain aging, is not the same as chronological aging and it may be possible to slow biological aging and even reduce the possibility of suffering from age related diseases such as dementia despite increasing time spent on earth. By understanding the mechanism behind how the chronic pain impacts physical function, we can begin to identify therapeutic agents that can limit functional decline and disability in those with chronic pain, such as chronic knee pain. One particular intervention that has been demonstrated to be independently beneficial to chronic pain management, the aging brain, and physical function is regular physical activity. As such, future studies using exercise interventions to improve pain outcomes, slow brain aging and improve overall physical function in an aging population should be examined further. Furthermore, this study supports the idea that a brain aging biomarker can be calculated from shorter duration MRI sequences and implemented clinically to be used to identify individuals with pain who are at a greater risk of accelerated brain atrophy and increased likelihood of disability.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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