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Pain, aging, and the brain: new pieces to a complex puzzle

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Aging has a pronounced impact on the brain, changing its macroscopic structure as well as its cellular and molecular constituents. Aging also affects many other aspects of health, including co-morbidities such as chronic pain. Given that chronic pain is associated with brain alterations [2,3,6,8,9,14,16,20–22,24,25,27,31,36,38,39,41–43,45–47,50–52], the interplay of chronic pain, brain structure and aging is of considerable interest to scientists, clinicians and patients alike. In this issue of PAIN, Sörös and Bantel [44] tested whether chronic pain is associated with an older-appearing brain in chronic non-cancer pain patients (n=59) compared to healthy control subjects (n=60). The authors implemented a biomarker of brain aging, so-called 'brain age'. Brain age condenses brain-wide information from structural neuroimaging into a single number, using a supervised machine learning model of healthy aging, defined in an independent training dataset [12]. A key advantage of the brain-age paradigm is that by using machine learning, the model can learn from a wide range of different brain structures involved in healthy aging. Having an older-appearing brain has been previously associated with neurological and psychiatric diseases [10,11], cognitive performance and poorer health outcomes [12,23,49]. Our own work in community-dwelling older adults found that chronic pain was associated with poorer brain aging cross-sectionally [13]. In contrast, this latest study by Sörös and Bantel did not find any significant cross-sectional differences in brain aging between pain patients and matched-controls. At face value, these results appear contradictory, however, we can offer some alternative explanations that may serve as potential future avenues of inquiry.

First, Sörös and Bantel included only patients seeking treatment for pain, while we included older adults from the community. Further, we asked our generally healthy older-adult participants "*if they had received any treatments or tried any self-remedies (i.e., something they may have done at home) to relieve their worst pain during the past 3 months*". In those

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individuals with chronic pain (n=33), approximately half (n=19) reported having received pain treatments/ remedies during the past 3 months. Crucially, these individuals had significantly "younger" brains compared to those who did not report seeking pain treatments/ remedies (n=14)[13]. Older individuals not seeking treatments/ remedies during the past 3 months had brain ages that were significantly older (5.75±1.8 years) than those individuals reporting seeking treatments/remedies (−3.85±2.2 years, Bonferroni-corrected p=0.007) and no-pain controls (−3.90±1.7 years, Bonferroni-corrected p=0.001, Figure 1). In other words, our results are consistent with Sörös and Bantel's null findings, where all individuals with chronic non-cancer pain were recruited from specialized pain clinics seeking and receiving treatment for their pain. Further examination of our data shows that most individuals who experienced chronic pain and reported using treatments/ remedies in the past 3 months (18/19, ~94%) reported receiving complementary and/or performing self-care strategies to treat their pain (Table 1). These converging findings pose a key question: what may explain the lack of a brain-aging effect in persons reporting seeking treatments, when our other chronic pain participants do show older-appearing brains?

Potentially, the brain-age biomarker used by us [13] and by Sörös and Bantel, could be partially driven by volumetric changes in brain circuits related to complex behaviors like treatment seeking; a circuitry that can also be impacted by aging. For example, the mesolimbic reward network underlies reward-seeking and hedonic responses to positive stimuli, and has been implicated in pain chronification [5,27,32,48]. Indeed, a protective role of medication use against pain chronification has been shown in patients with low back pain when treatment was started early with findings suggesting that treatment outcome was contingent on medial prefrontal (mPFC)–nucleus accumbens (NAc) functional connectivity [5,48]. However, while NAc age-related changes are not well-understood; aging is generally associated with volumetric decreases in mPFC regions [18,19,26,40]. Other important players in the reward circuitry include the hippocampus and amygdala. Emerging evidence in animals and humans suggests decreases in hippocampal volume in chronic pain states [7,15,21,32,33,37,54] as well as in normal and pathological aging processes [4,53] where stressors such as debilitating chronic pain may play a significant role [29,30,53]. Similar although subtle age-related changes also occur in the amygdala [1,28] and emerging evidence implicates the amygdala in pain modulation [17,34,35]. Thus, the brain aging biomarker may be picking up abnormal brain aging signatures associated with treatment-seeking behaviors.

Alternatively, it is also possible that the association between brain age and seeking treatment per se may in fact be due to those patients successfully obtaining actual pain relief. This is consistent with our previous findings of a correlation between brain age and self-reported pain relief levels. As Sörös and Bantel did not have information about recent use of non-pharmacological treatments, nor degree of pain relief, this possibility still requires further replication. Further, other factors known to have a positive influence on brain aging like exercise and practicing meditation[10] will also need to be considered in future work and unfortunately were not available in the patients studied by Sörös and Bantel.

More work is needed to understand how the brain-age paradigm can be beneficial for the understanding of chronic pain and its treatments. These findings may suggest that the brain

aging biomarker is reflective of: a) reward neural circuitry; b) pain relief itself; c) pain relief specific to non-pharmacological treatments/self-remedies; or d) other non-specific, non-pain related brain circuitry, including findings due to random chance. Larger samples and wider range of study settings are needed to more rigorously test these different hypotheses. Nevertheless, we anticipate brain-age to play a role in the early identification of those at greater risk of functional decline and the evaluation of whether these trajectories can be improved by chronic pain treatment and relief.

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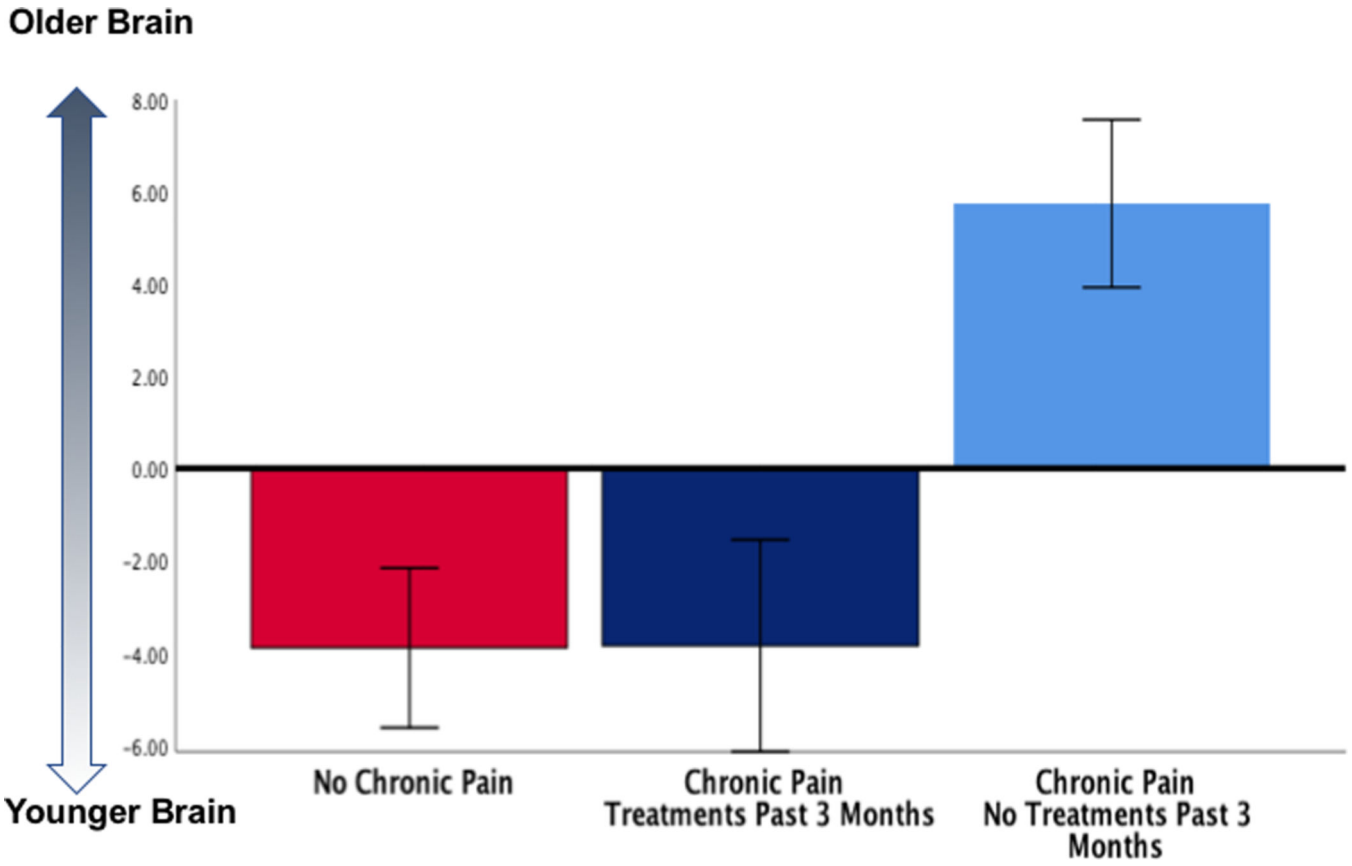

Figure 1.

Brain-PAD in pain participants who reported having any treatments or trying any self-remedies (i.e., something they may have done at home) to relieve their worst pain during the past 3 months (n=19) compared with those who did not (n=14) and no chronic pain controls (n=14).

Table 1.

Qualitative data as reported by our subset of older adults reporting treatments/self-remedies in the past 3 months (n=19).

Self-reported Pain Treatments/Remedies in the Past 3 Months (n=19)
Pain cream (n=1)
Weight lifting (n=1)
Exercise (n=1)
Exercise in water (n=1)
Heat (n=1)
Heating pad (n=3)
Icing and exercise (n=1)
Icing (n=1)
Exercise and knee massage (n=1)
Medication, icing and acupuncture (n=1)
Medication (n=1)
Salt bath and massaging (n=1)
Sitting and laying down (n=1)
Stretching and knee exercises (n=1)
Stretching and yoga (n=1)
Turmeric, ginger tea and diet change (n=1)
Walking, heating pad and TENS (n=1)