Chronic pain is not associated with accelerated structural brain aging

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Introduction

Chronic pain is often associated with **changes in brain structure, brain function**, and cognitive and emotional processes. Although chronic pain is a highly prevalent and relevant health care issue, its **pathophysiology remains unclear**. In particular, the functional significance of gray and white matter changes in the brains of patients with chronic pain is still unresolved.
It has been noted that structural changes of the brain found in patients with chronic pain may resemble changes found in healthy aging and thus may represent **accelerated or premature aging of the brain** (Cruz-Almeida et al. 2019, Kuchinad et al. 2007, Moayedi et al. 2012).

Objective

To test the hypothesis that patients with chronic pain demonstrate accelerated brain aging compared with healthy pain-free control subjects.

Patients and Methods

Patients

Structural MRIs of **59 patients with chronic noncancer pain** (mean chronological age ± SD: 53.0 ± 9.0 years; 43 women) and **60 pain-free healthy controls** (52.6 ± 9.0 years; 44 women) were investigated.
Chronic pain was defined as persistent pain on most days of a month for at least 12 months of mild to severe intensity. **Pain duration** was 16 ± 11 years (minimum 1 year, maximum 50 years). Mean **pain intensity** on an 11-point numerical rating scale (0 representing "no pain" and 10 "worst pain imaginable") on the day of the measurement was 5 ± 2. The study was approved by the local Research Ethics Board and has been published recently (Sörös & Bantel 2020).

Magnetic resonance imaging

T1-weighted MR images of the entire brain were acquired on a Siemens MAGNETOM Prisma whole-body scanner (Siemens, Erlangen, Germany) at 3 Tesla with a 64-channel head/neck receive-array coil with a **high-resolution MPRAGE sequence**.

Brain age prediction

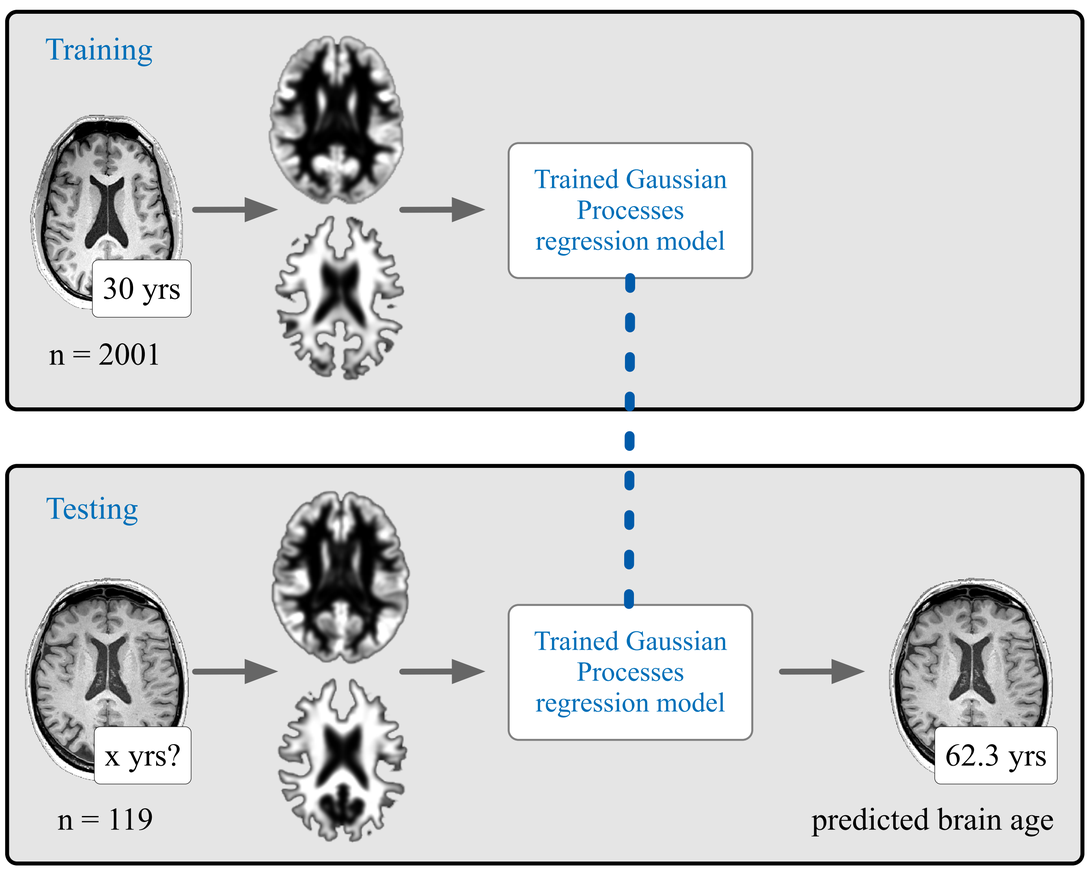

Figure 1: Schematic illustration of brain age prediction using brainageR. **Upper panel:** Structural MRIs of 2001 healthy individuals with known chronological age were segmented in gray and white matter and then used to train a Gaussian Processes regression model. **Lower panel:** This model was then used to predict the brain age of the 119 individuals included in this study.

Brain age was predicted using the software **brainageR version 1 (Figure 1)**. This software segments the individual T1-weighted structural MR images into gray and white matter and compares gray and white matter images with a large (n = 2001) training set of structural images, using machine learning (Cole et al. 2017, Cole et al. 2018). Finally, **brain age delta**, which is the predicted brain age minus chronological age, was calculated and compared across groups.

Results

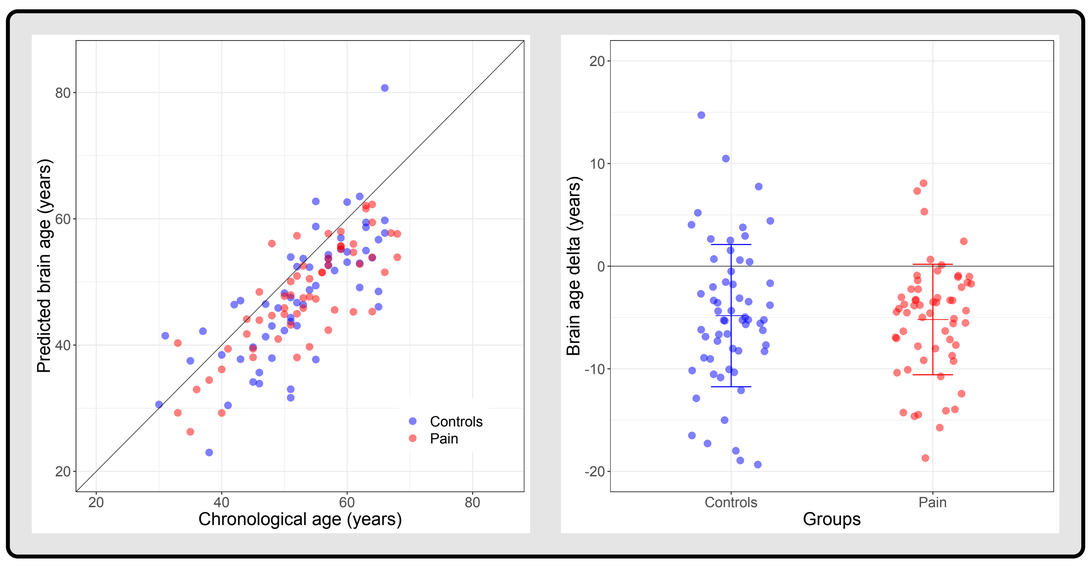

Figure 2: Left: Relationship between chronological age and predicted brain age. Blue circles represent pain-free control participants (n = 60), and red circles represent patients with chronic pain (n = 59). **Right:** Brain age delta (predicted brain age minus chronological age) for pain-free controls (blue) and patients with chronic pain (red). The error bars symbolize mean ± SD.

This study provided **no evidence for the hypothesis that chronic pain is associated with accelerated brain aging**. Brain age delta was -4.8 ± 6.9 years in the control group and -5.2 ± 5.4 years in the chronic pain group (Welch t-test, P = 0.74, Cohen's d = 0.061; **Figure 2**). A Bayesian independent-samples t-test indicated moderate evidence in favor of the null hypothesis (BF01 = 4.875, i.e., group means were equal).

Conclusions

Our results have important **implications for the pathogenesis of structural alterations of the brain and, ultimately, cognitive deficits in patients with chronic pain**.
Our results suggest that chronic pain does not induce widespread neural and glial degeneration, presumably the leading cause of age-related structural brain changes. Our results indirectly support recent alternative models of regional, **network-specific structural and functional brain alterations in chronic pain** (Cauda et al. 2014, Farmer et al. 2012).
These models also suggest that the frequently observed **cognitive deficits in chronic pain** are the direct consequence of persistent nociceptive input, mediated by the aforementioned network-specific structural and functional changes, rather than the result of generalized accelerated aging of the brain.

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