UNIVERSITY of MARYLAND
SCHOOL OF NURSING
PLACEBO BEYOND OPINIONS CENTER

Mechanisms of Placebo Effects in Chronic Pain

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PiNeuro Seminar Series

Overview

Outline the taxonomy of placebo effects

Discuss the relationship between placebo effects and in chronic pain

Identify potential prediction mechanisms for placebo formation.

Why does this matter?

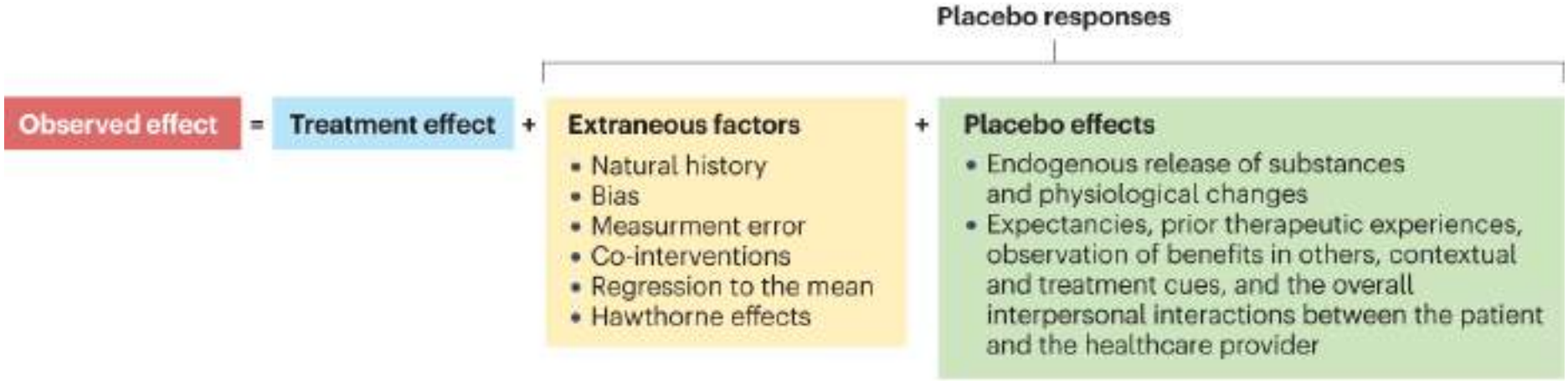
In depression studies, **50% of placebo-controlled randomized controlled trials (RCTs) fail** to show the active drug is superior to a placebo, largely due to high placebo response rates

The placebo response has been estimated to account for roughly 82% of the total drug response observed in some analyses of FDA data

Similar to depression, pain is a subjective and highly placebo-responsive condition.

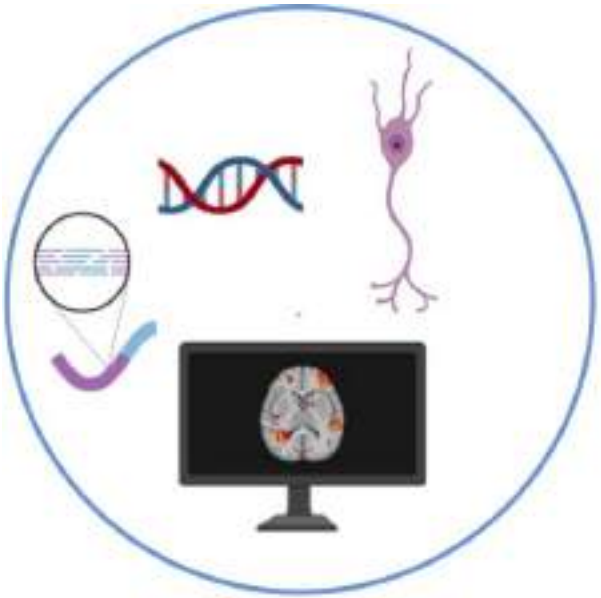
Colloca and Barsky, NEJM, 2019

Treatment effects, placebo responses and placebo effects

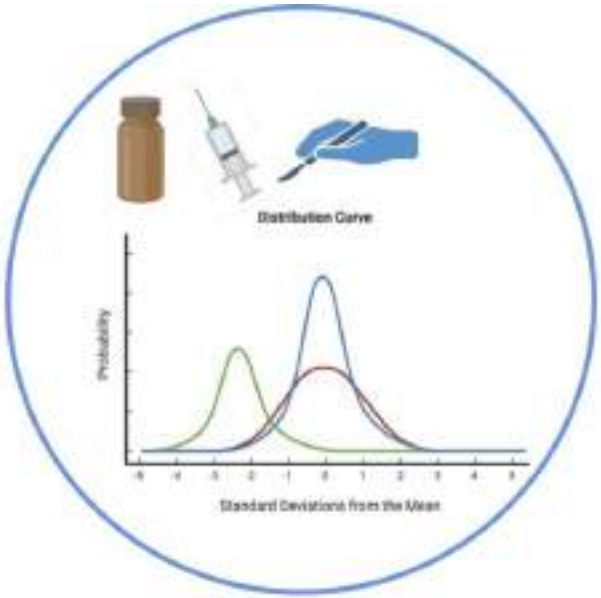


Neogi and Colloca, Nat Rev Rheumatol. 2023

Milestones in pain and placebo research



Basic and translational neuroscience of placebo and nocebo effects

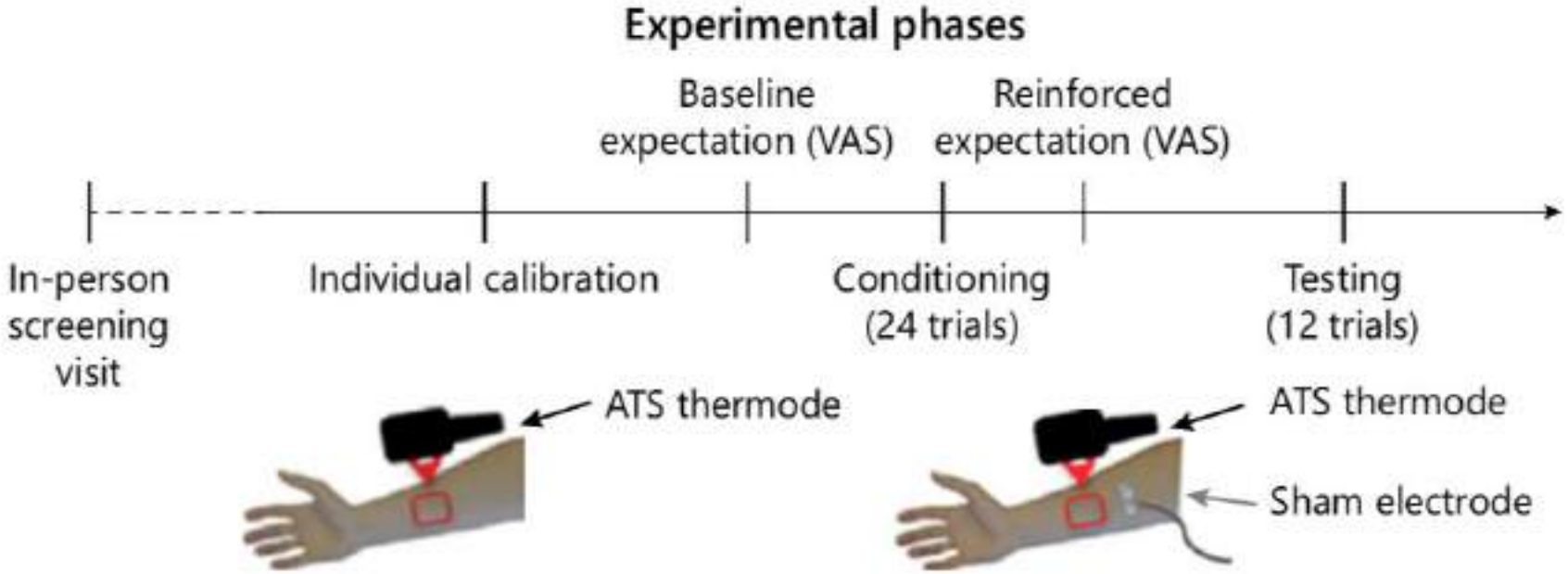


Understanding of the dynamics of expectation updates

Neuromodulation

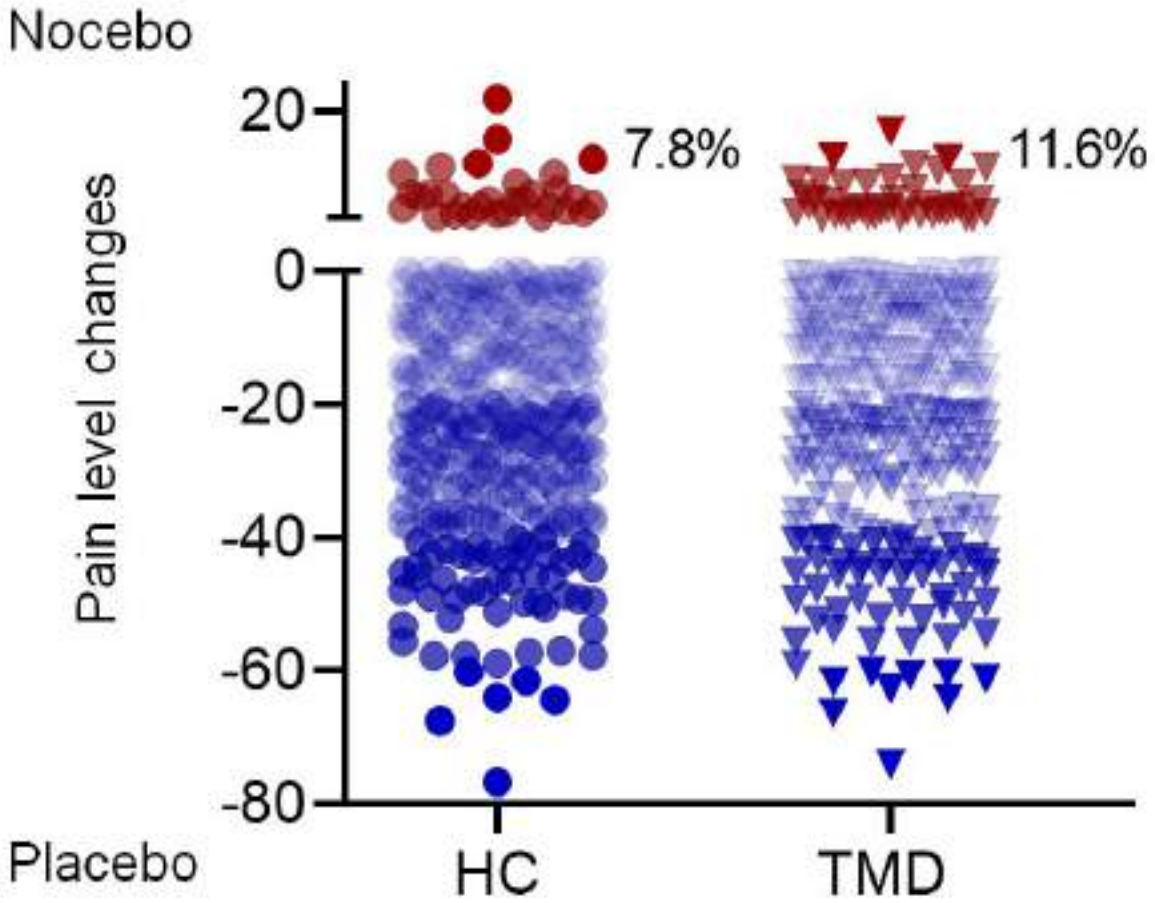
Rodrigues, Raghuraman et al. PAIN 2025

Placebo effects: A translational lab model



Colloca et al. Psychother Psychosom 2020

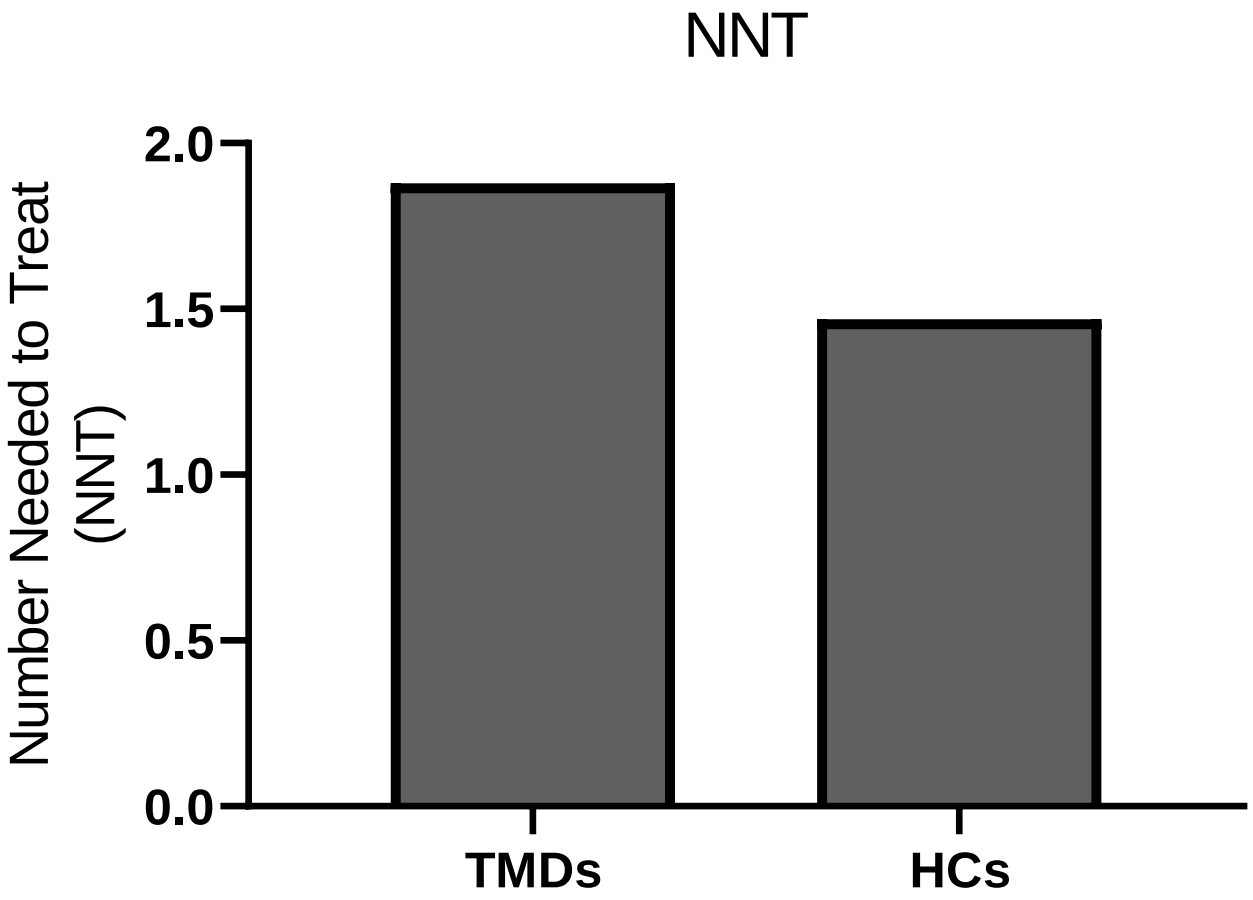
Distribution of individual placebo effects



TMD = 384 temporomandibular disorder, HC = 384 Healthy controls

Colloca et al. Psychother Psychosom. 2020
Colloca Ann Review Toxicol and Pharmacology 2024

Placebo effects: Magnitude and number to treat

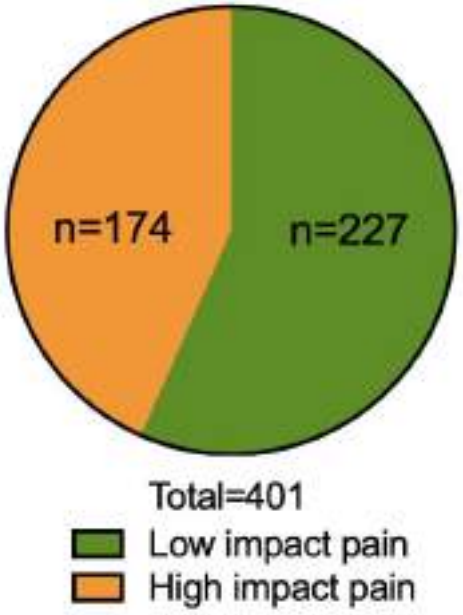


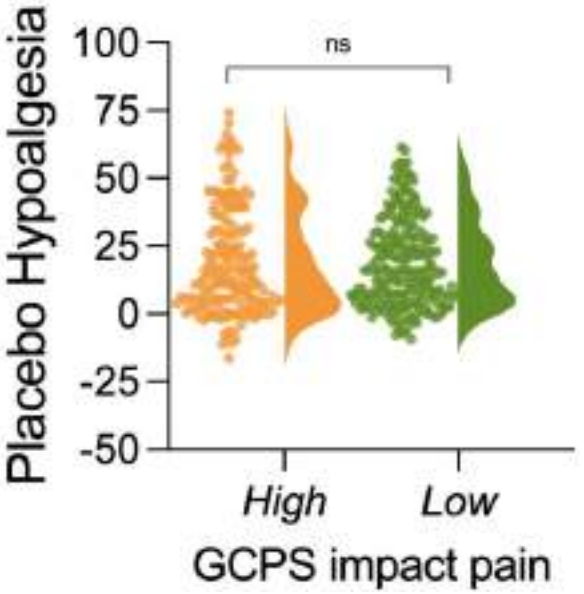
TMD = temporomandibular disorder; HC = Healthy controls

Colloca et al. Psychother Psychosom. 2020.
Lynch et al. Pain Res Manag. 2006.

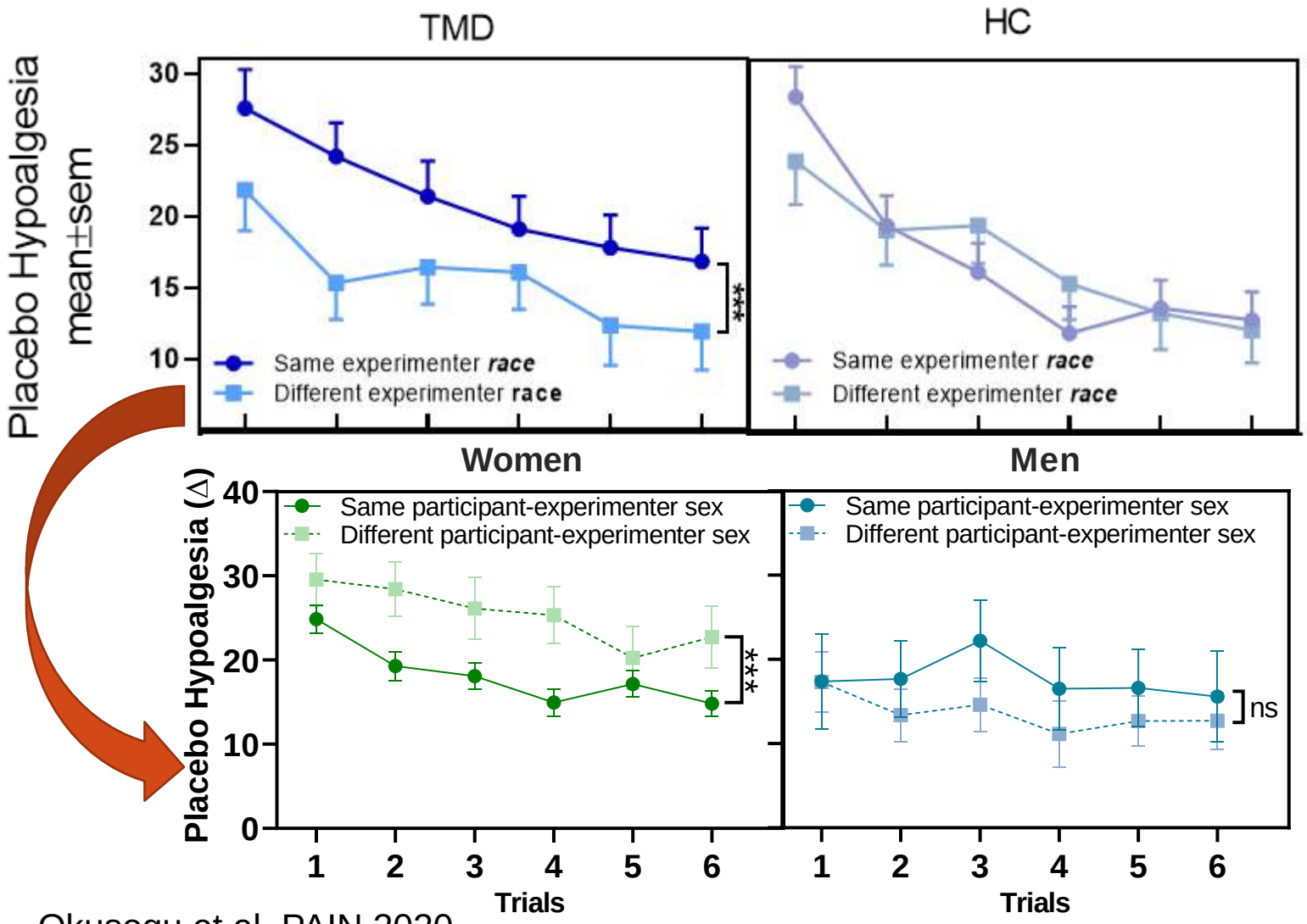
Number Needed to Treat
anticonvulsants and opioids
NNT = 1.7 to 3

PE magnitude is independent of pain severity



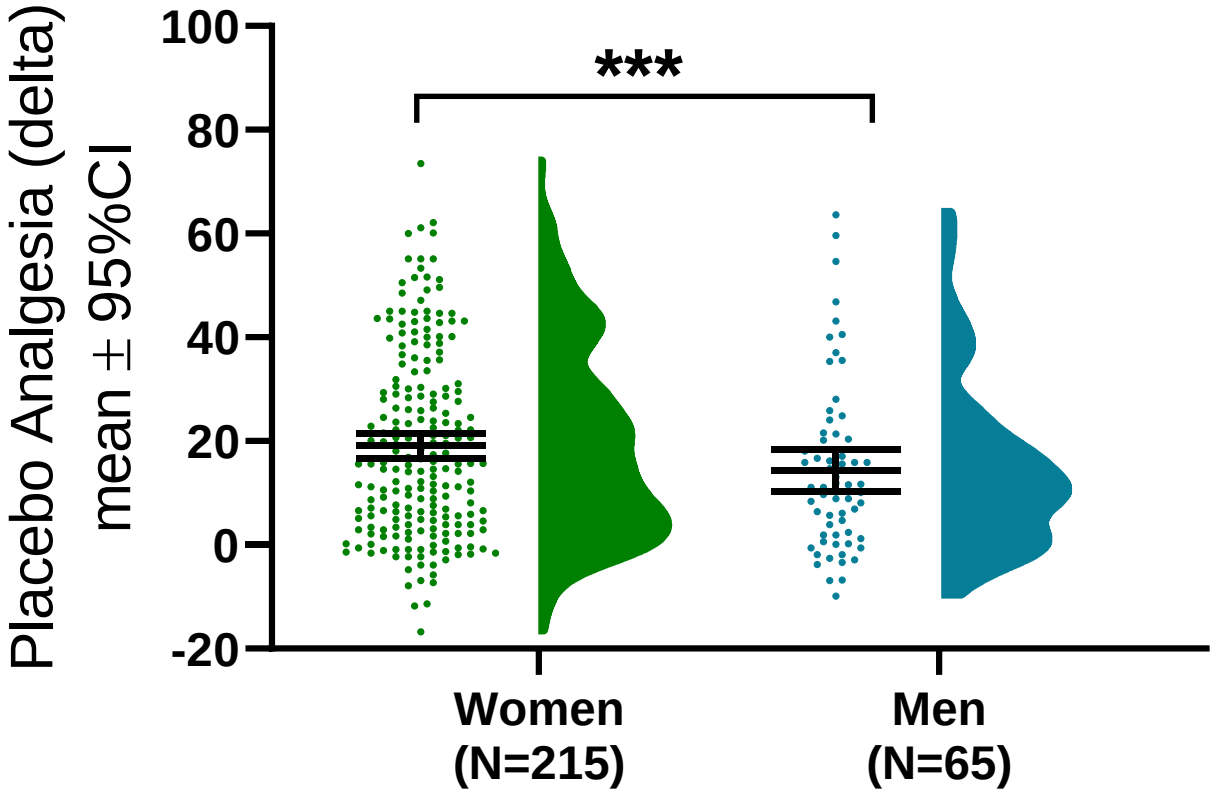


Participant-experimenter race/ethnicity and sex



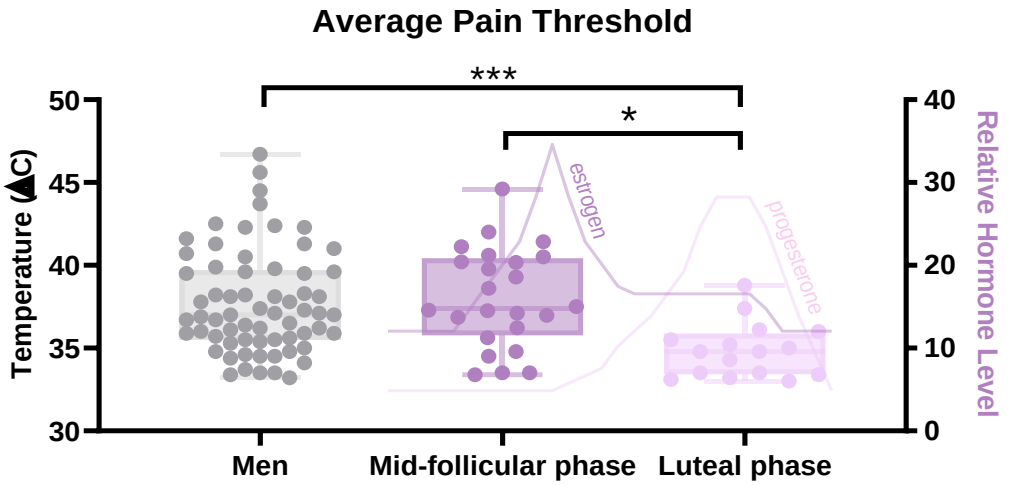
Okusogu et al. PAIN 2020
Olson et al. PAIN 2021

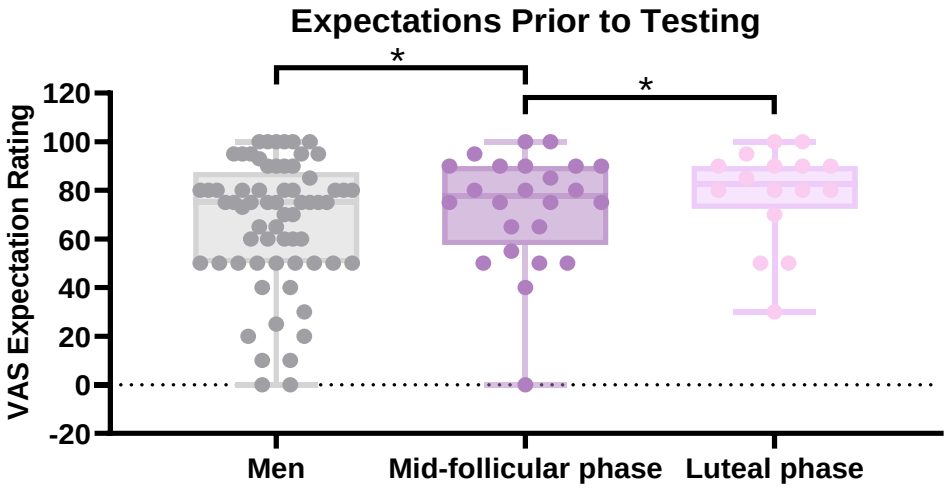
Sex differences in placebo in chronic pain



Olson et al. Pain 2021

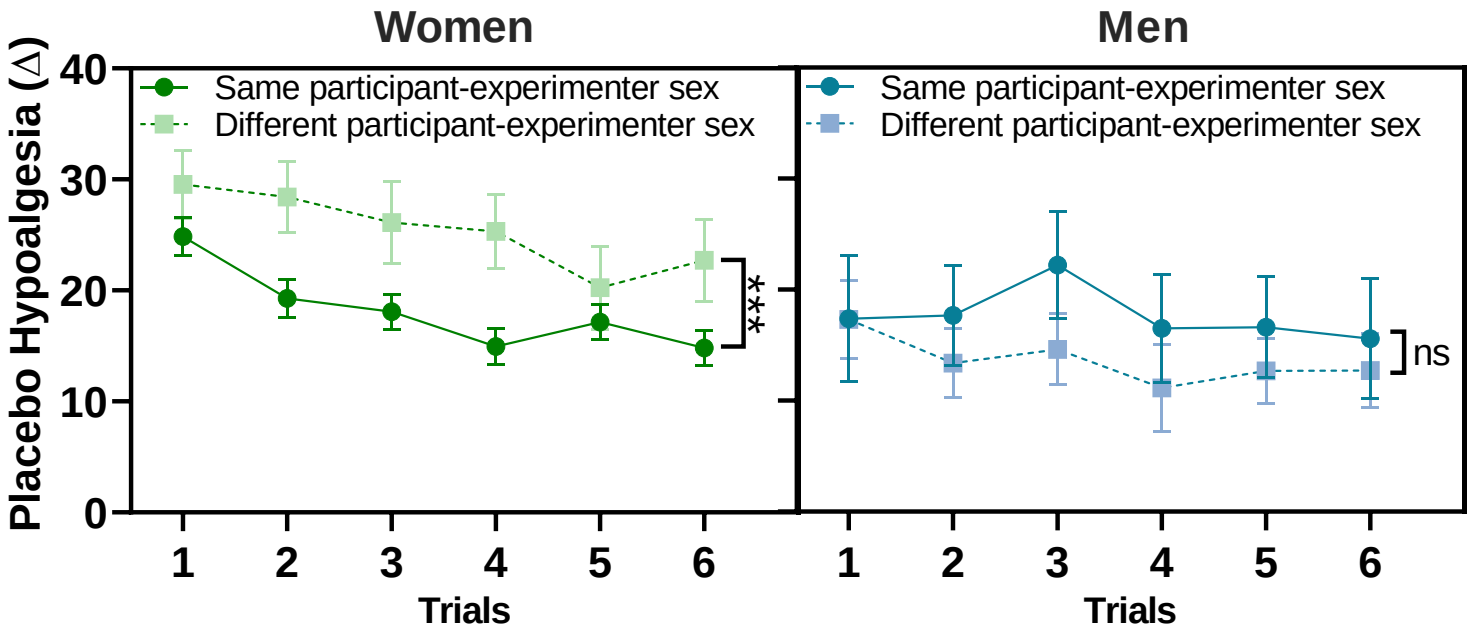
Sex effects in pain tolerance and expectations





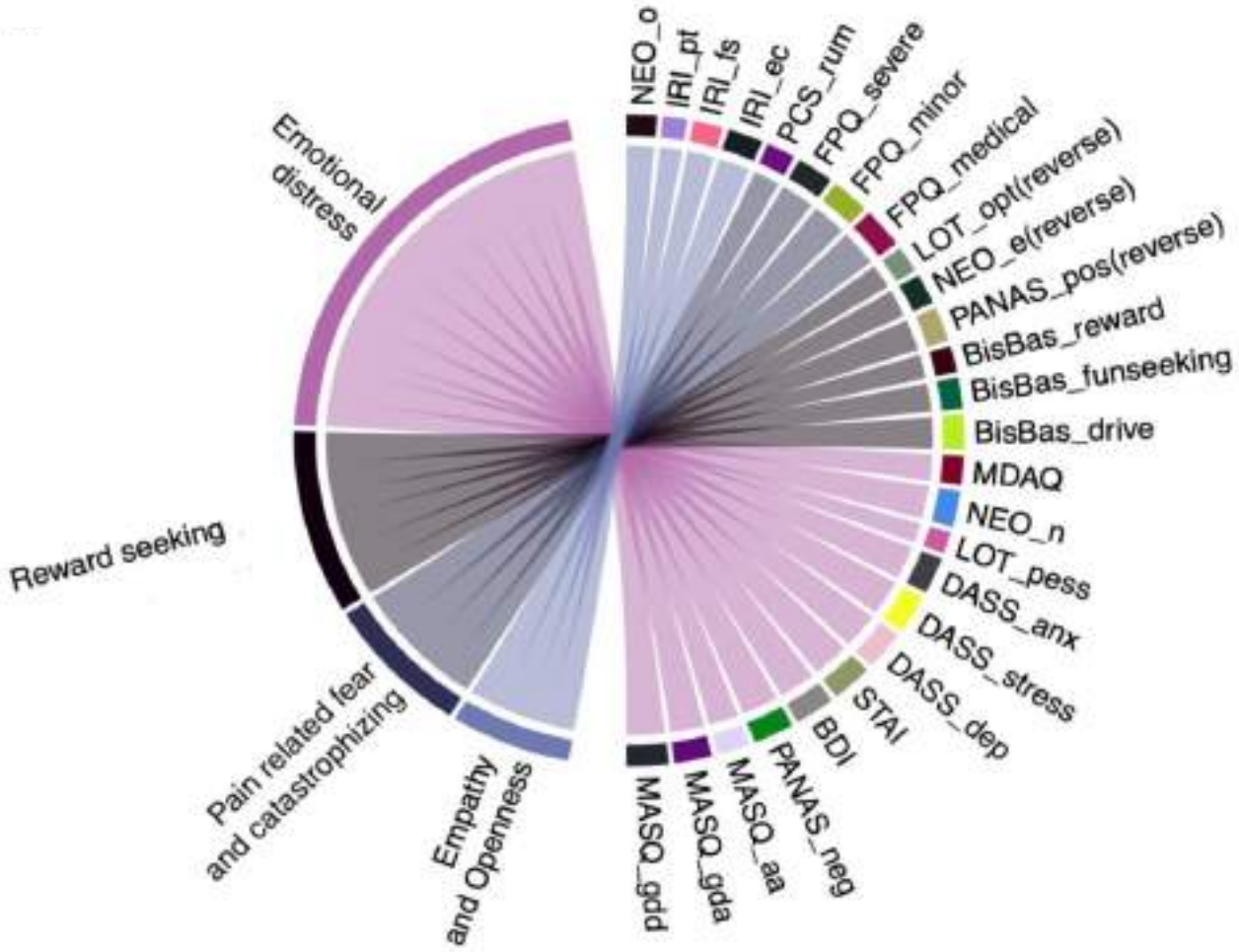
Olson et al. PAIN 2021

Participant-experimenter sex concordance



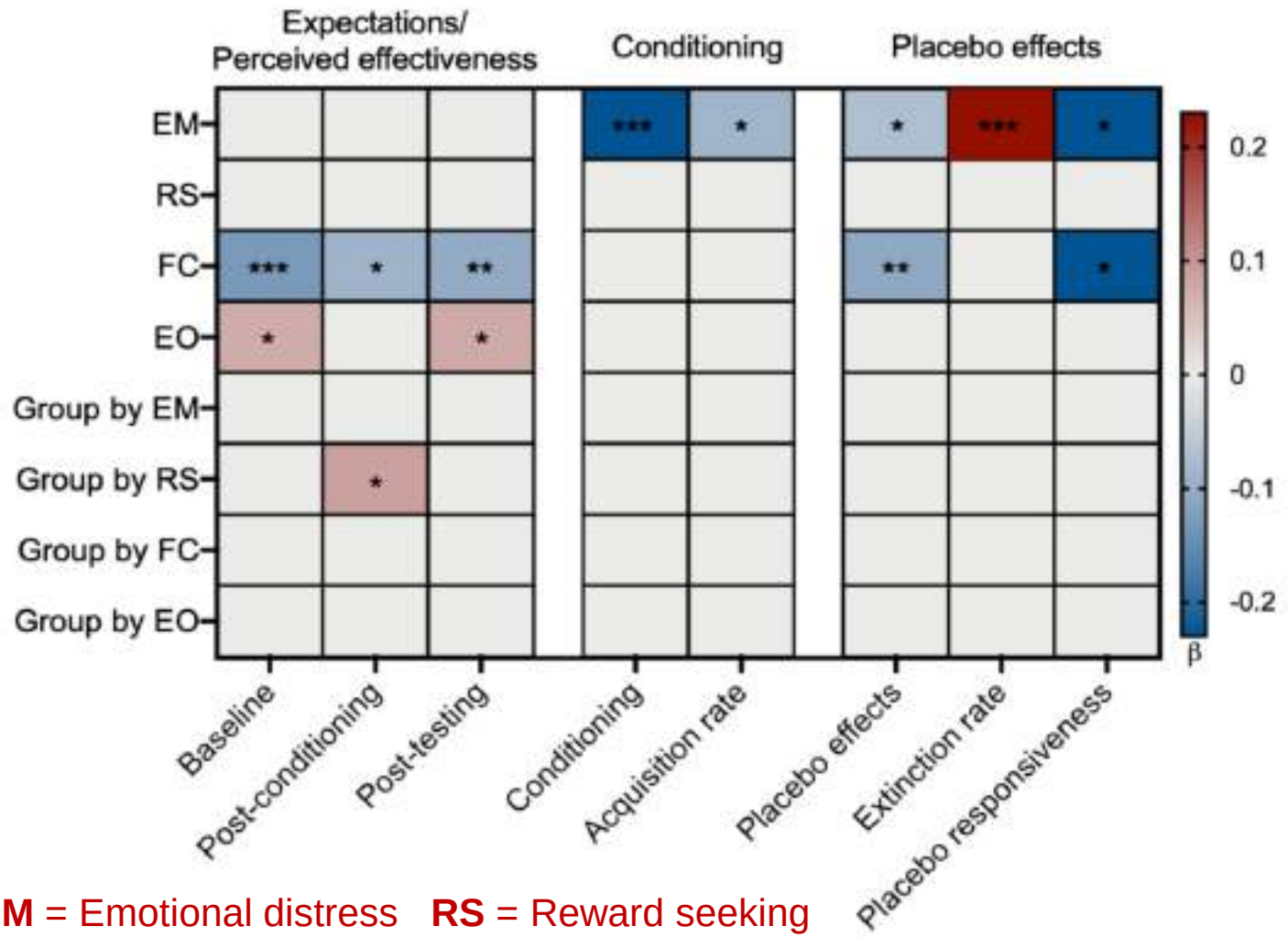
Olson et al. PAIN 2021

Psychological factors as predictors of PE



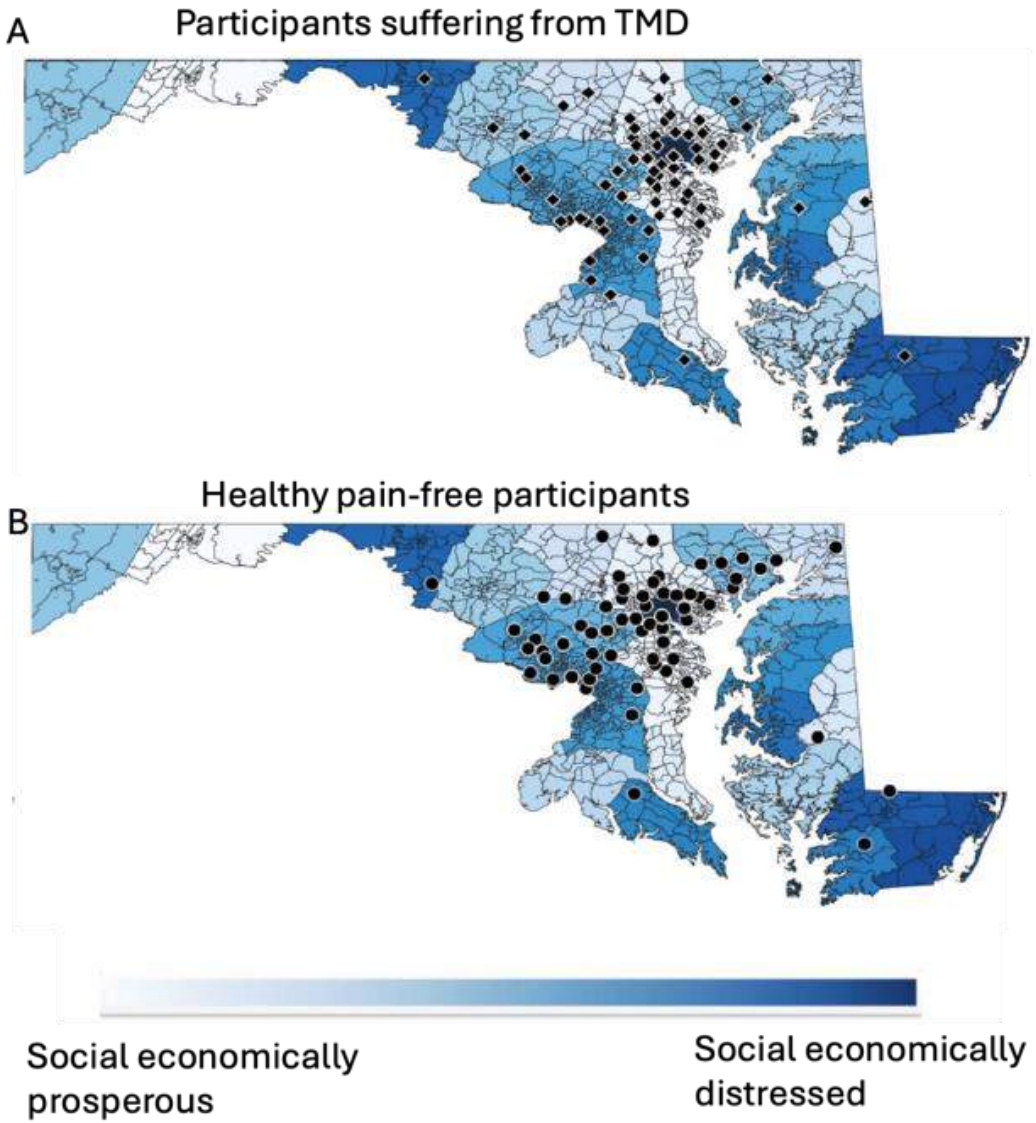
Wang et al. PAIN 2021

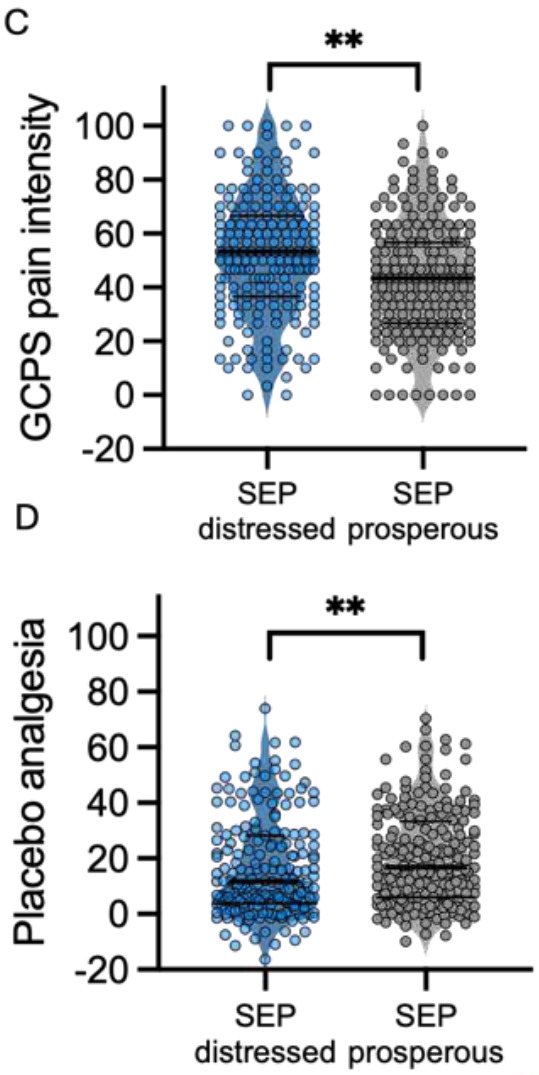
Smaller placebo effects with emotionally distress and catastrophizing



EM = Emotional distress **RS** = Reward seeking
FC = Pain related fear and catastrophizing **EO** = Empathy and openness

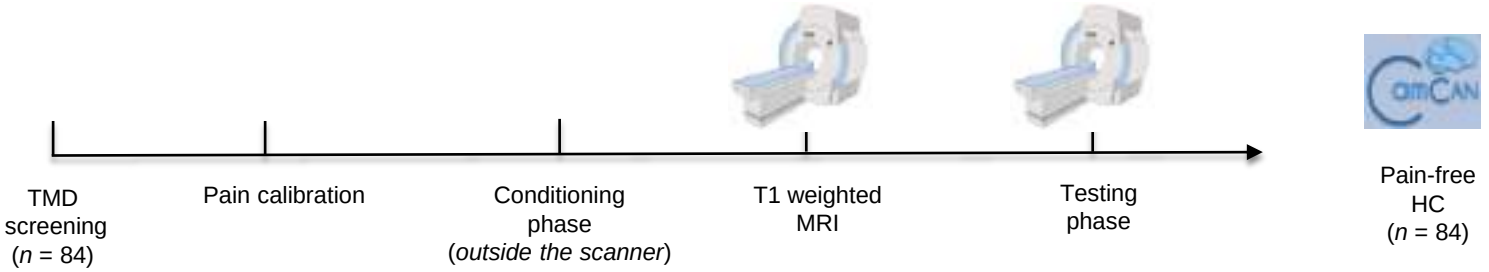
Smaller placebo effects in poor neighbors

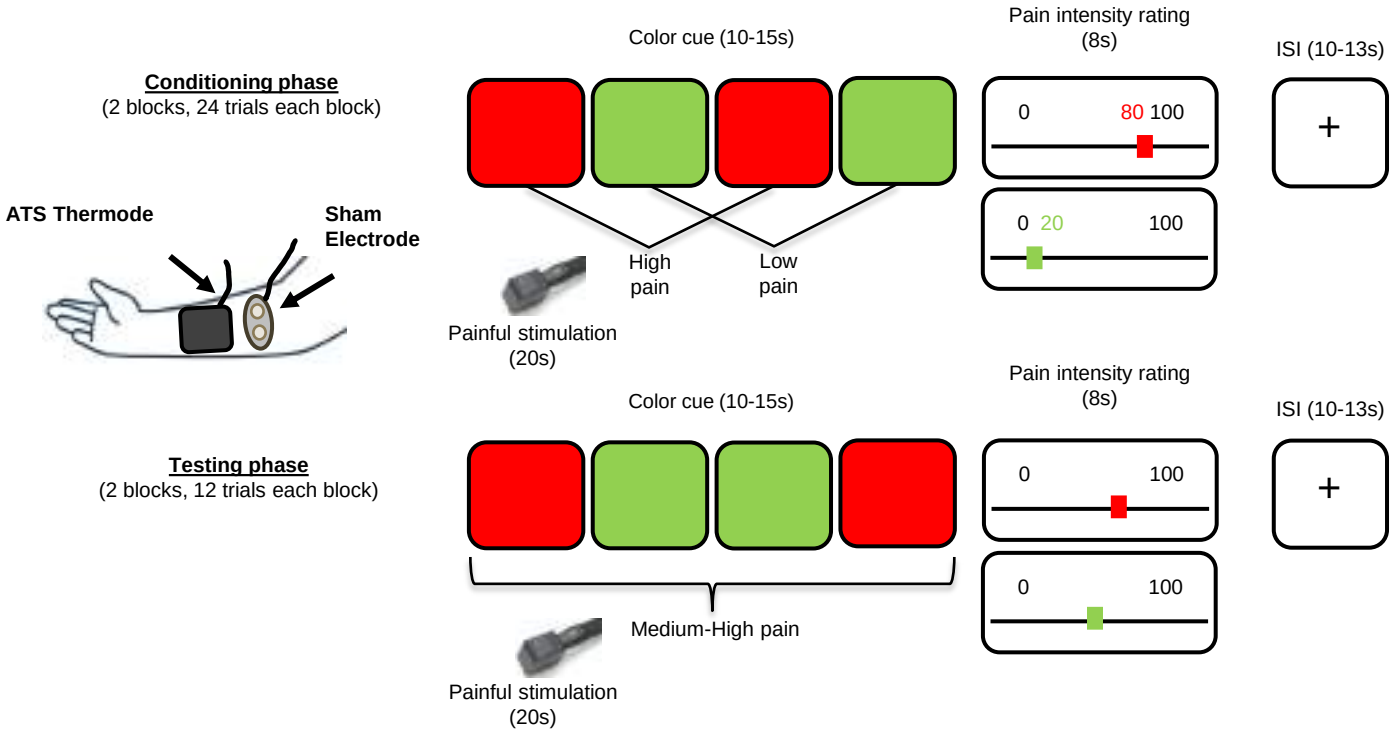




Raghuraman et al., J of Pain 2025

Biomarkers of placebo effects





Cundiff-O'Sullivan et al. PAIN *in press*

Brain Ageing and Chronic Pain

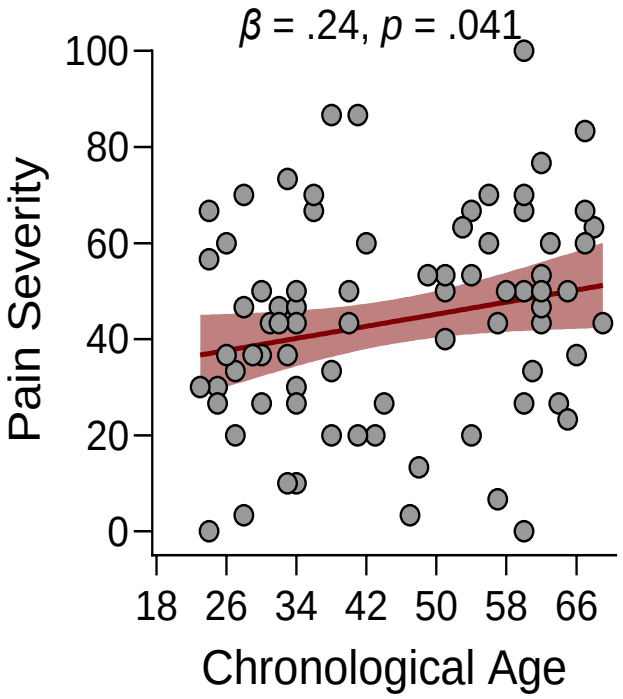
- Reduced gray matter volume
- Increased white matter hyperintensities
- Older brain-predicted age vs. pain-free controls
- Affected regions: insula, ACC/PCC, thalamus, hippocampus

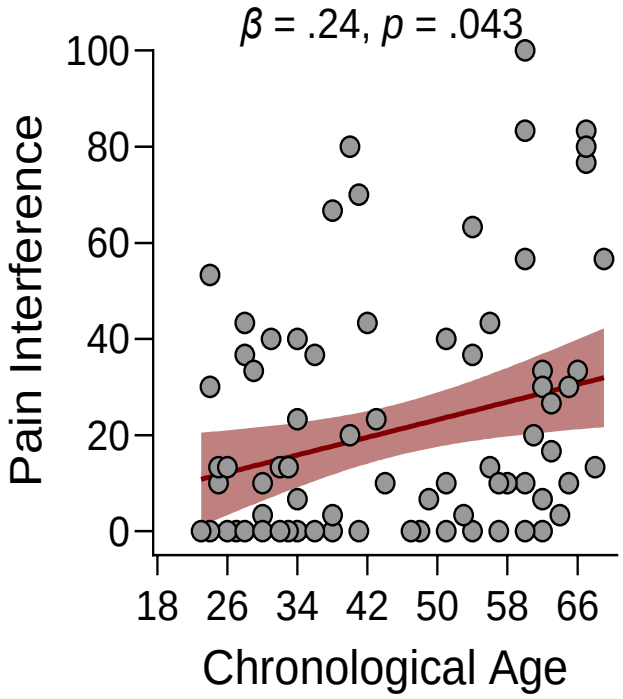
Pain-modulatory networks decline with age

- Reduced functional connectivity among PAG–ACC–insula–amygdala
- Linked to impaired endogenous analgesia and higher chronic pain risk
- Availability of data-driven machine learning techniques to estimate an age based on structural MRI data

Donovan et al. Nature Neuroscience. 2025; Zhao L et al. Trends in Cognitive Sciences. 2025; Sadlon A, et al. Annals of Neurology. 2023

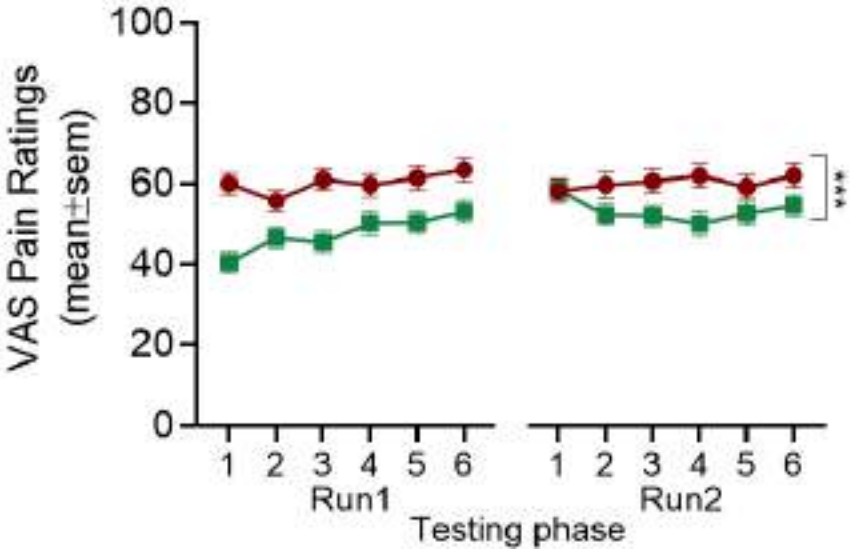
Older chronological age is associated with higher pain disability

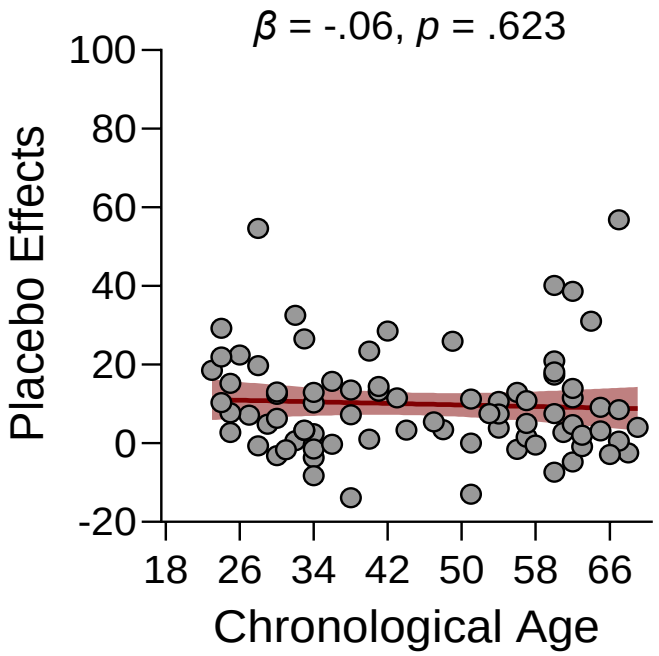




Cundiff-O'Sullivan et al. PAIN *in press*

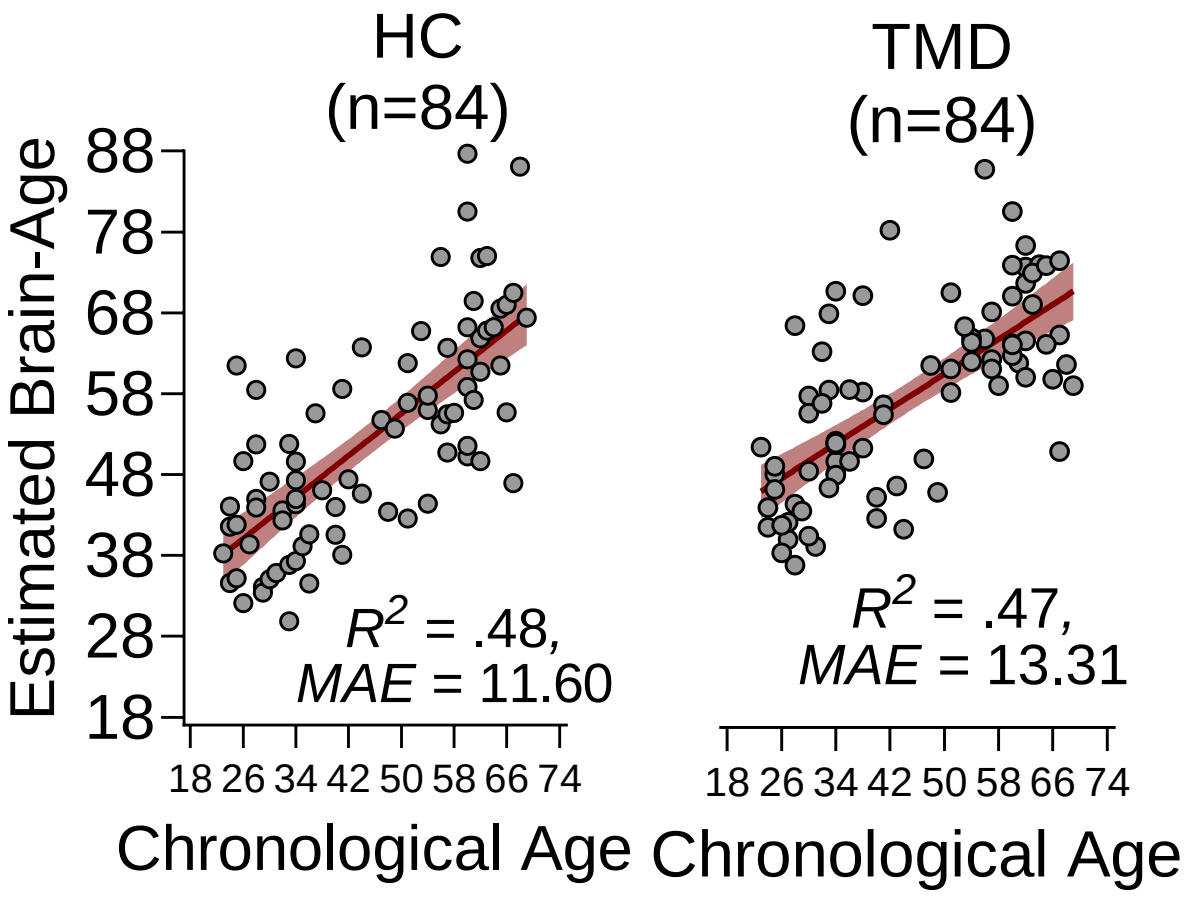
Older chronological age is NOT associated with chronological age in adults





Cundiff-O'Sullivan et al. PAIN *in press*

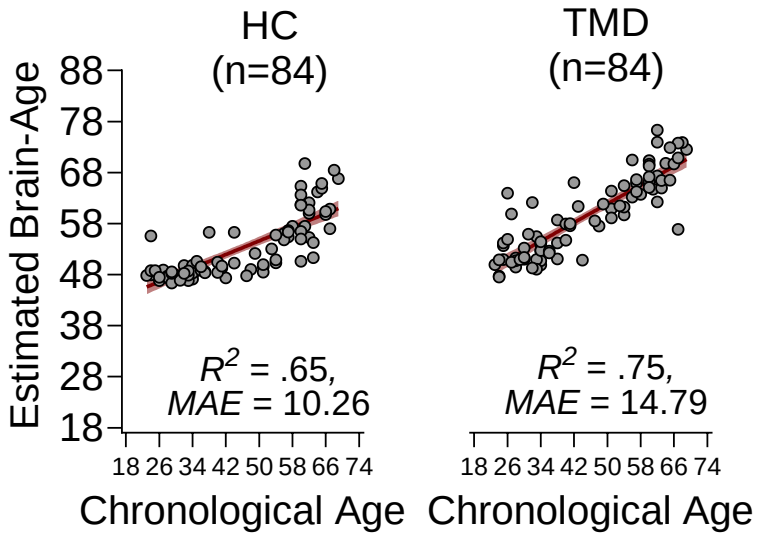
Estimated brain-age explains 48% and 47% variance in chronological age using GPR approach

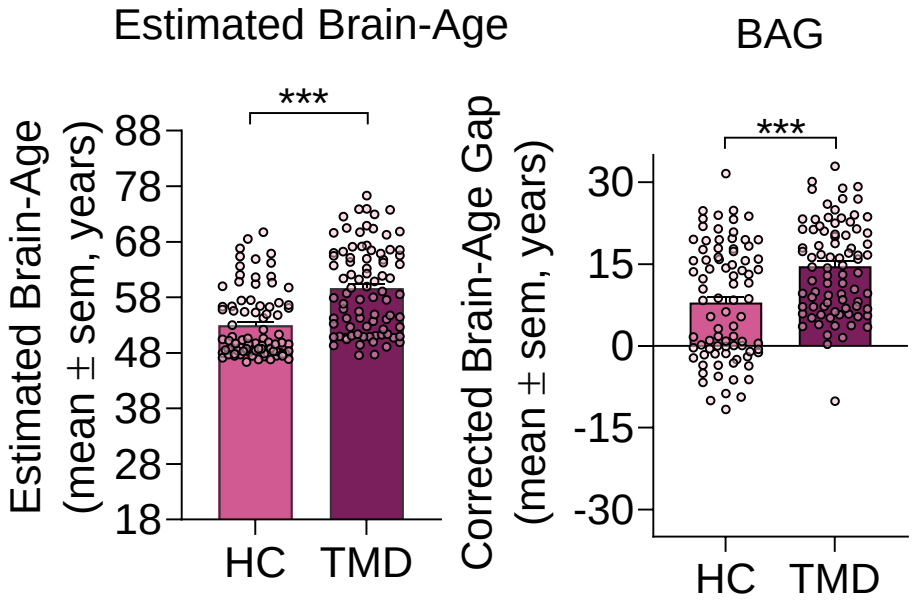


GPR=**Gaussian process regression**

Cundiff-O'Sullivan et al. PAIN *in press*

Estimated brain-age explains 65% and 75% variance in chronological age using CNN approach



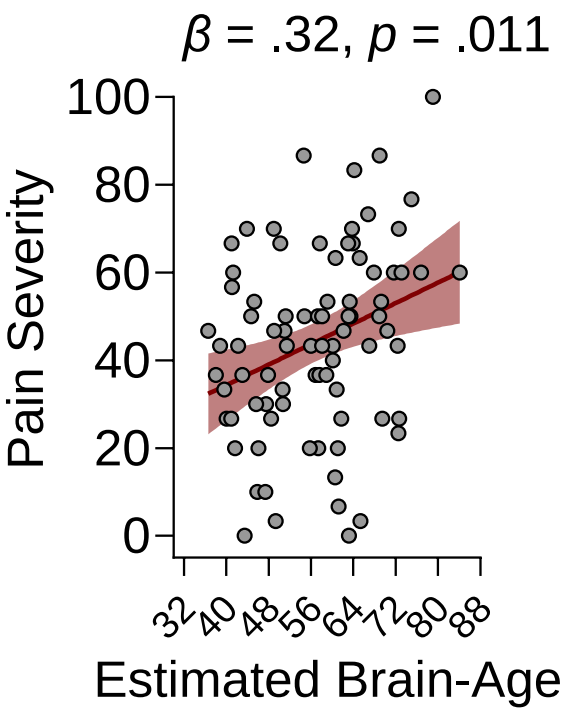


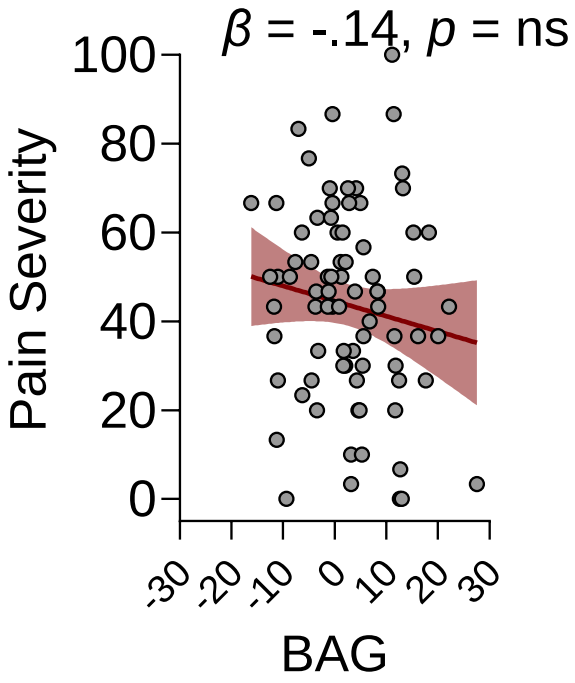
BAG= **brain-age gap**

CNN=**Convolutional neural network**

Cundiff-O'Sullivan et al. PAIN *in press*

Relationships between brain-age and pain severity (GPR)





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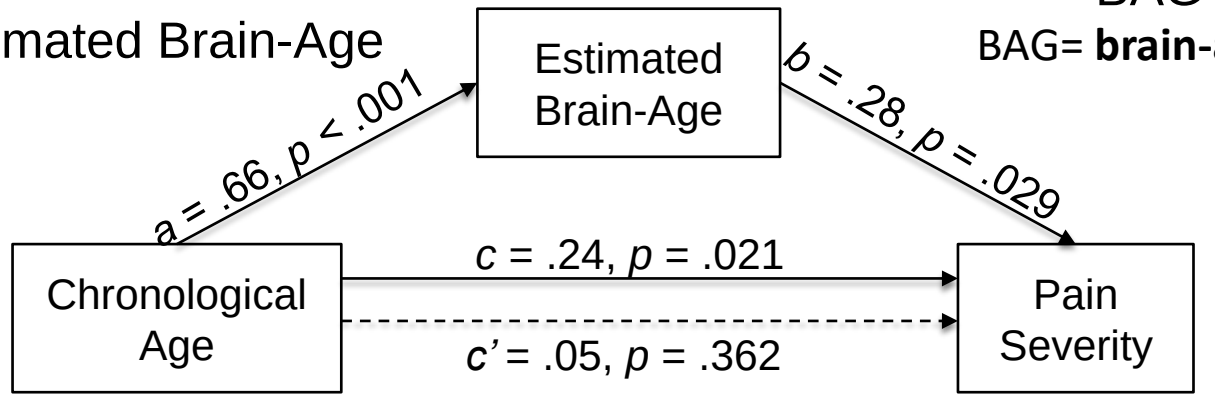
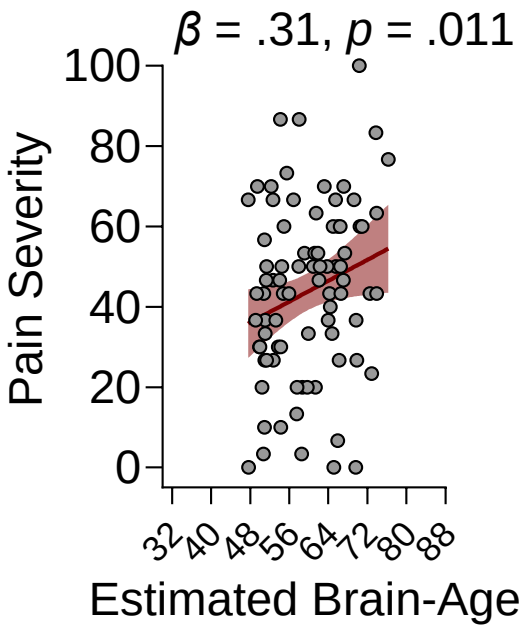


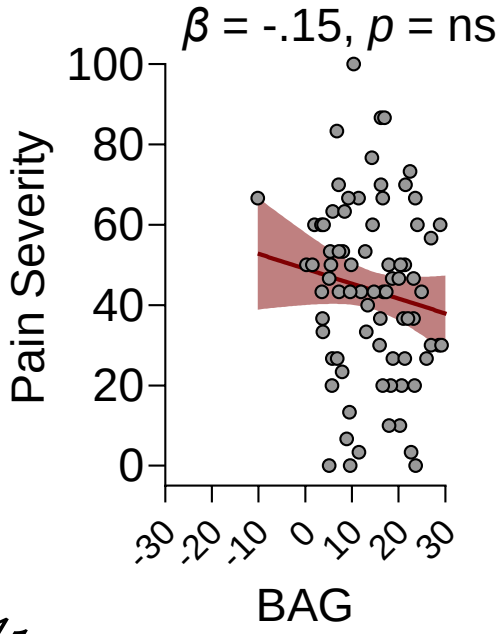
Indirect effects: *a*b* = .26, *90% BCI* = [.01, .37]

Cundiff-O'Sullivan et al. PAIN *in press*

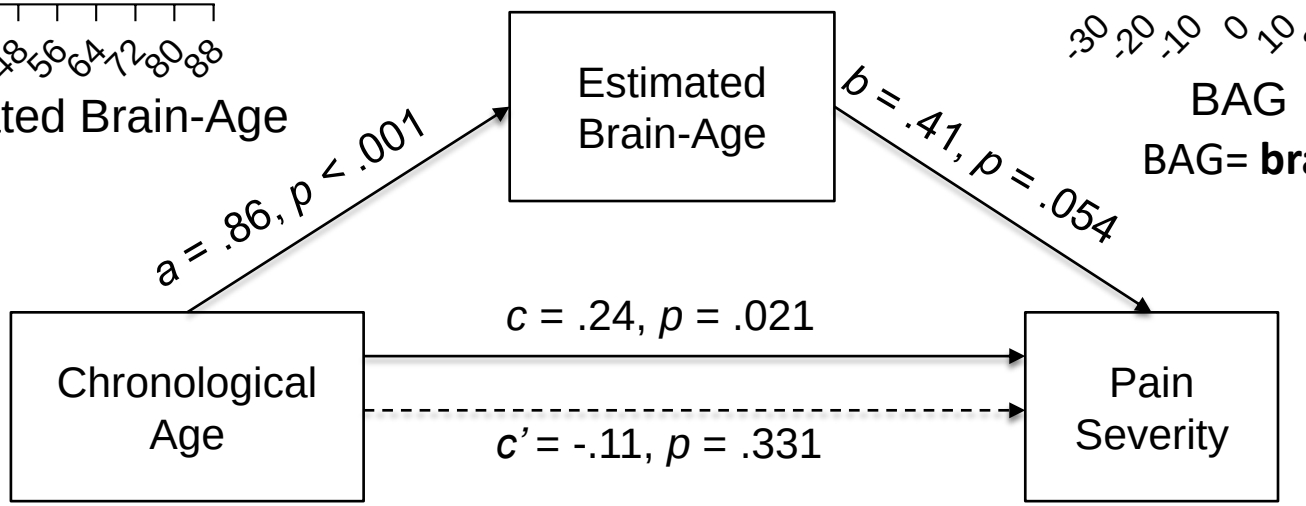
GPR=**Gaussian process regression**

Relationships between brain-age and pain severity (CNN)





BAG= **brain-age gap**

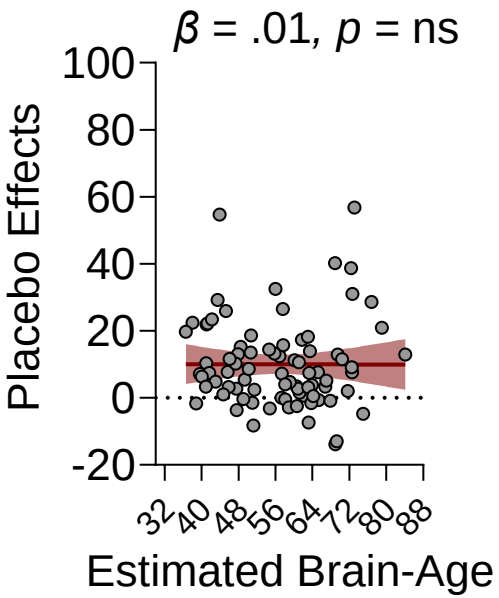


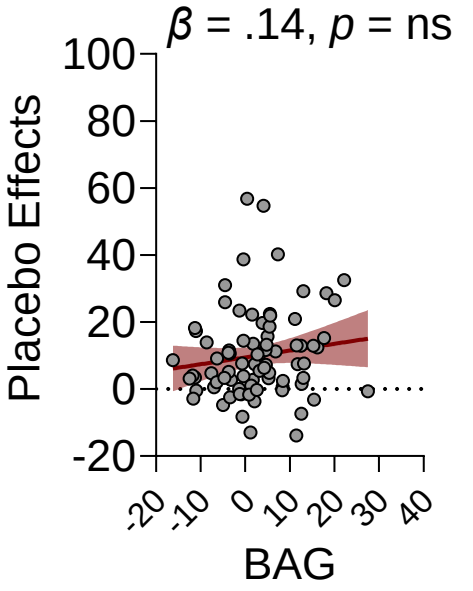
Indirect effects: *a*b* = .35, *90% BCI* = [.02, .74]

Cundiff-O'Sullivan et al. PAIN *in press*

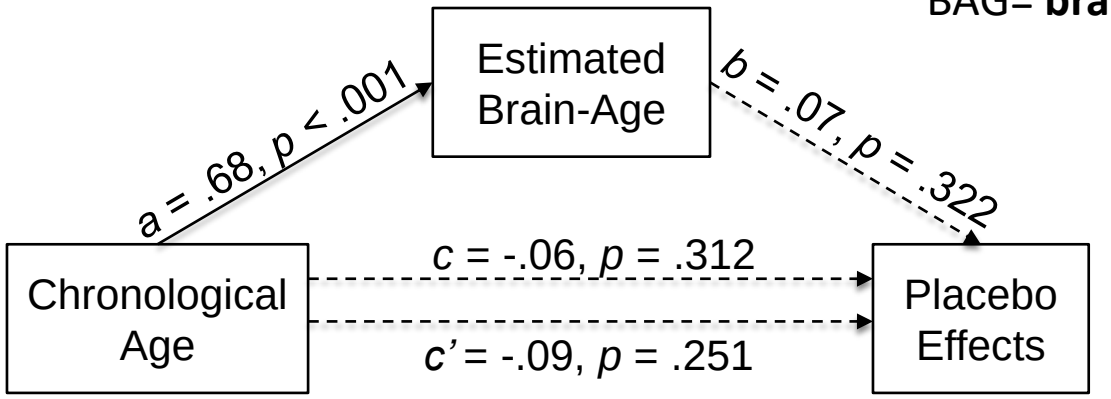
CNN=**Convolutional neural network**

Relationship between brain-age and placebo effects (GPR)





BAG= **brain-age gap**

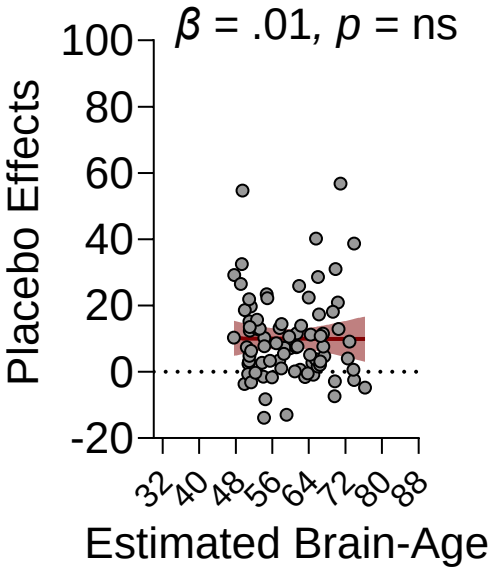


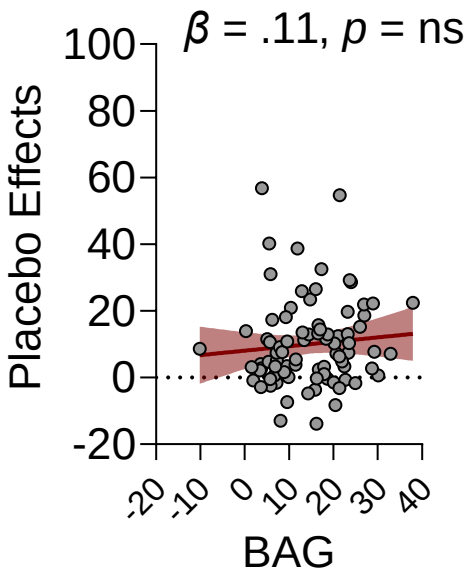
Indirect effects: *a*b* = .05, *90% BCI* = [-.12, .23]

Cundiff-O'Sullivan et al. PAIN *in press*

GPR=**Gaussian process regression**

Relationship between brain-age and placebo effects (CNN)





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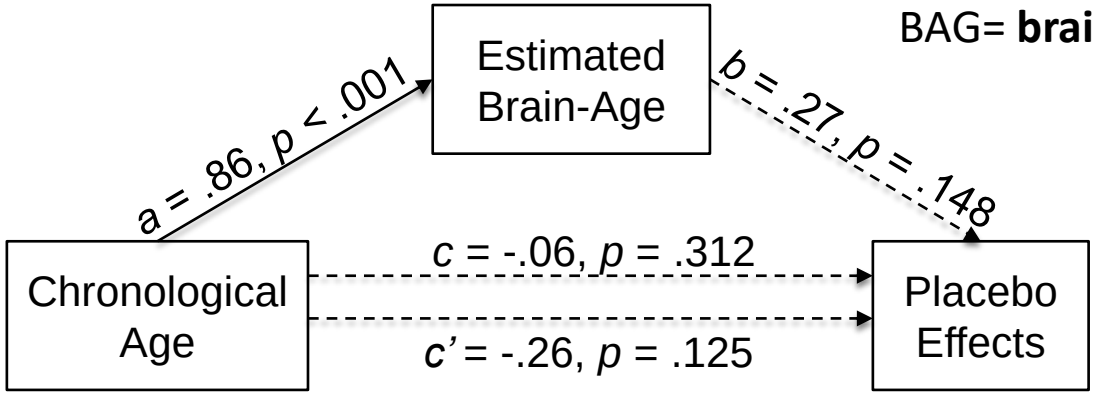
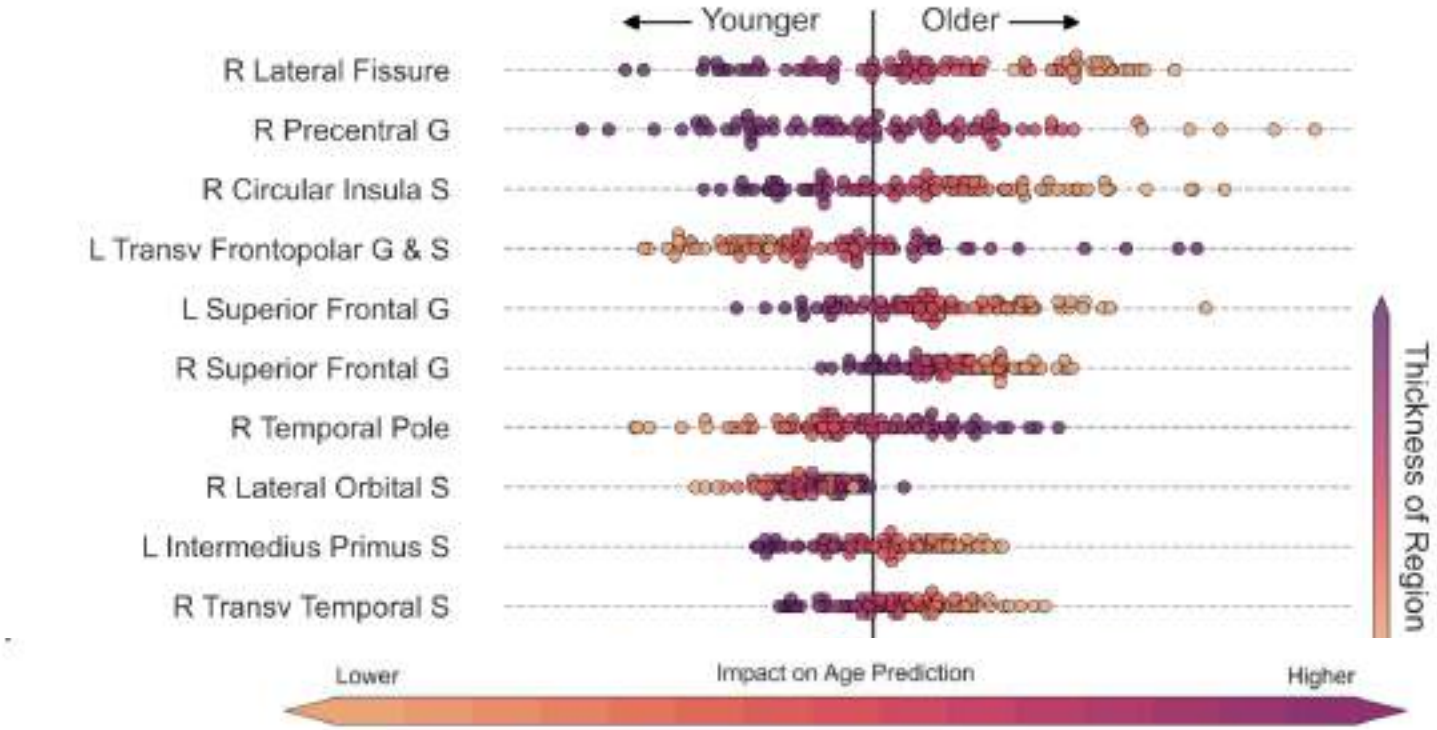


Indirect effects: *a*b* = .23, *90% BCI* = [-.10, .59]

Cundiff-O'Sullivan et al. PAIN *in press*

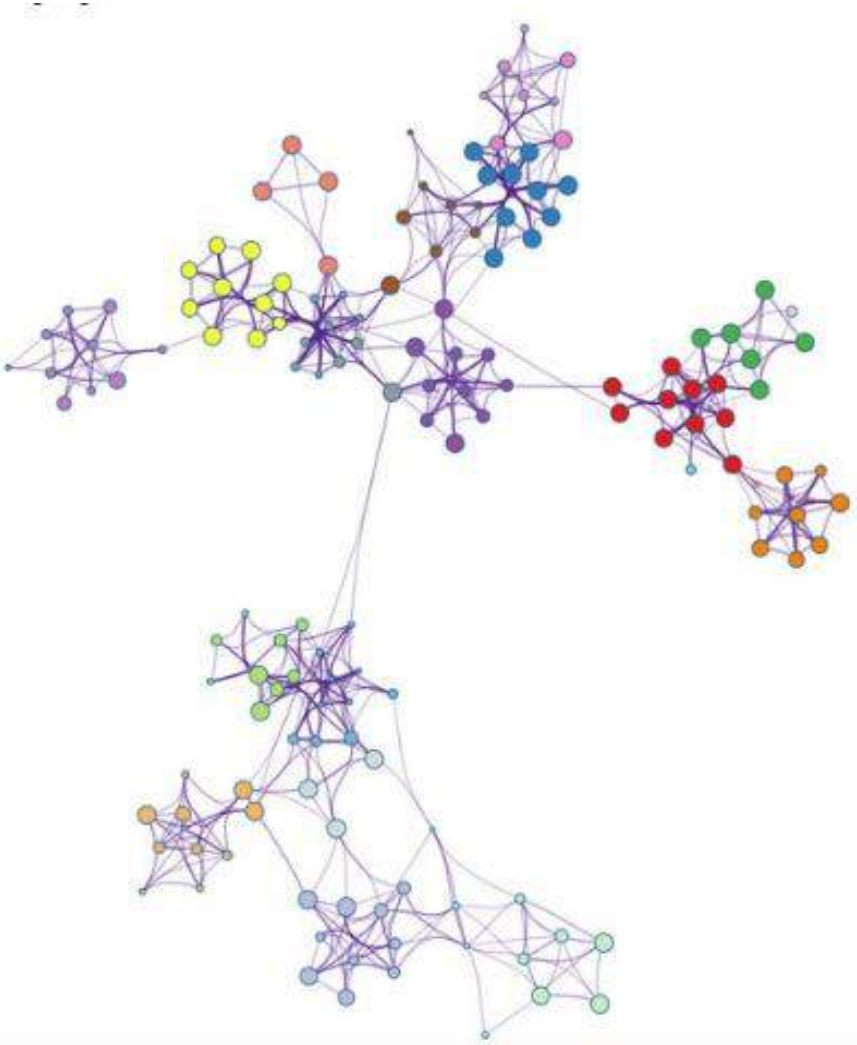
CNN=**Convolutional neural network**

Thickness of the top 15 contributing brain regions in relation to estimated brain age



Cundiff-O'Sullivan et al. PAIN *in press*

Omics as predictors of placebo effects



- Regulation of expression of SLITs and ROBOs
- Huntington disease
- Ribosome biogenesis
- Cellular response to chemical stress
- Mitochondrial translational initiation
- mRNA Splicing
- Transcriptional Regulation by TP53
- Cristae formation
- HIV infection
- TRBP containing complex
- Detoxification of Reactive Oxygen Species
- DNA repair
- Autophagy
- Membrane trafficking
- Positive regulation of intrinsic apoptosis
- Membrane organization

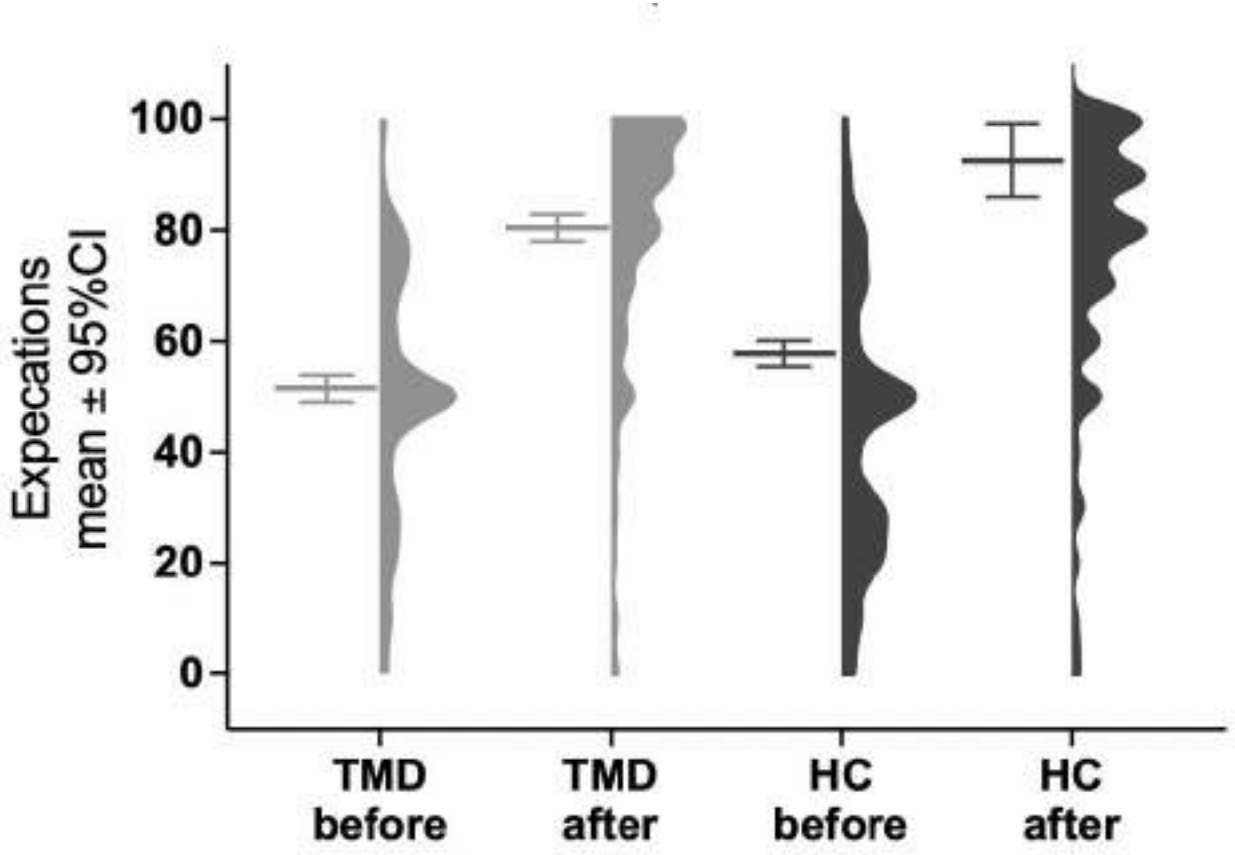
Colloca et al Clin Pharmacol Ther. 2024

Is there a simple tool to estimate placebo responses and effects?

Questionnaires for **expectations**?

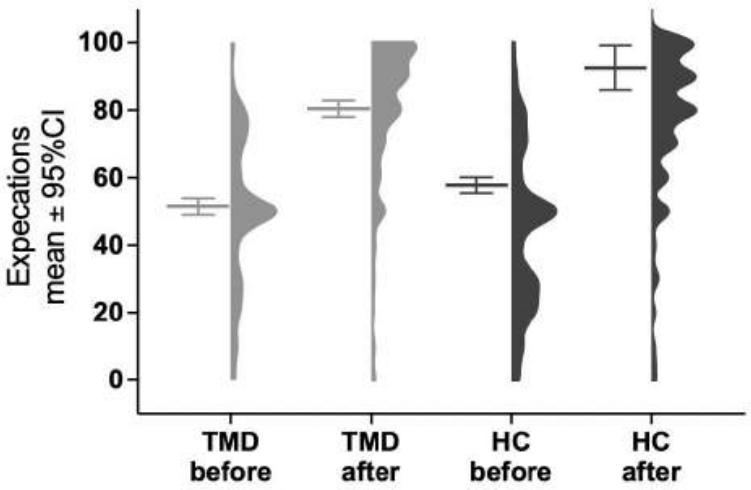
- Pain Self-Efficacy Questionnaire (PSEQ)
- Expectation for Treatment Scale (ETS)
- Treatment Expectation Questionnaire (TEX-Q)
- Visual Analog Scale for Expectation of Pain Reduction

Baseline and post-treatment expectations

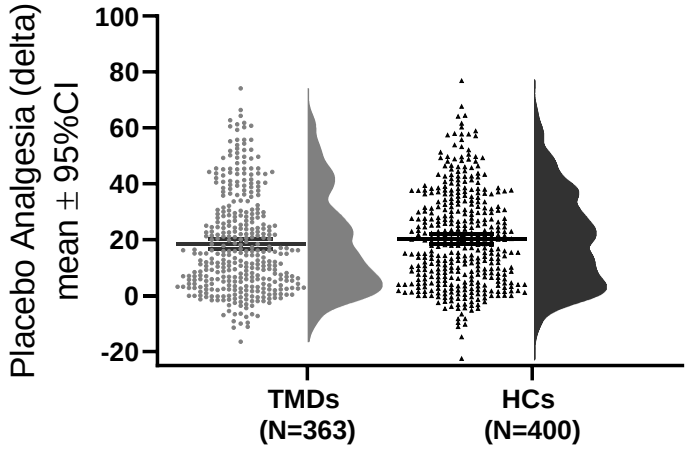


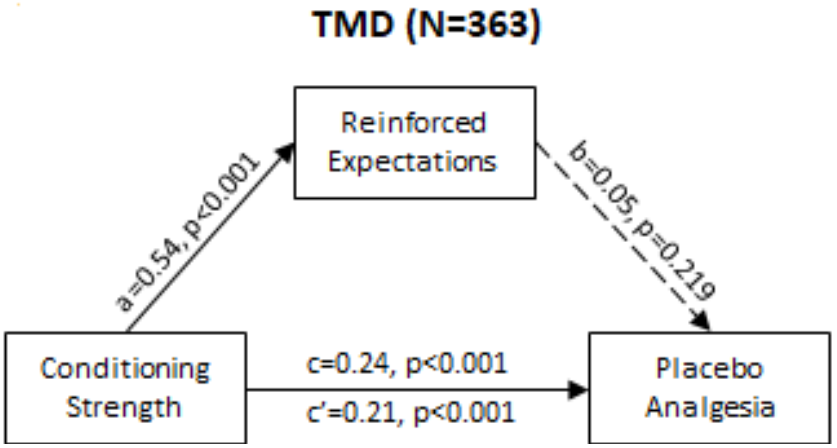
Colloca, …, & Wang. Psychotherapy and Psychosomatics, 2020

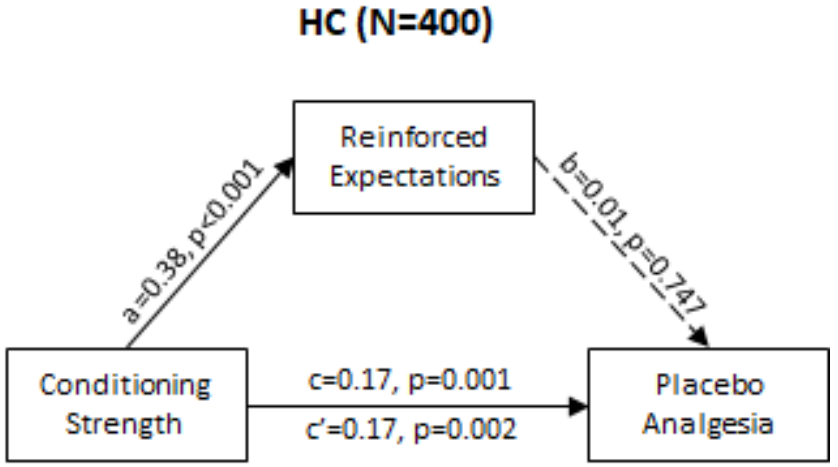
Expectations and placebo effects



Placebo Analgesia

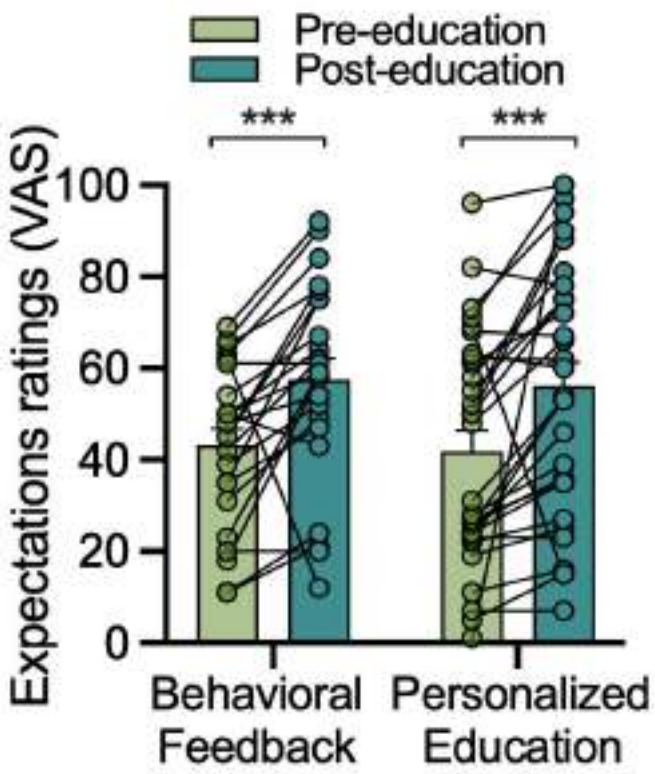


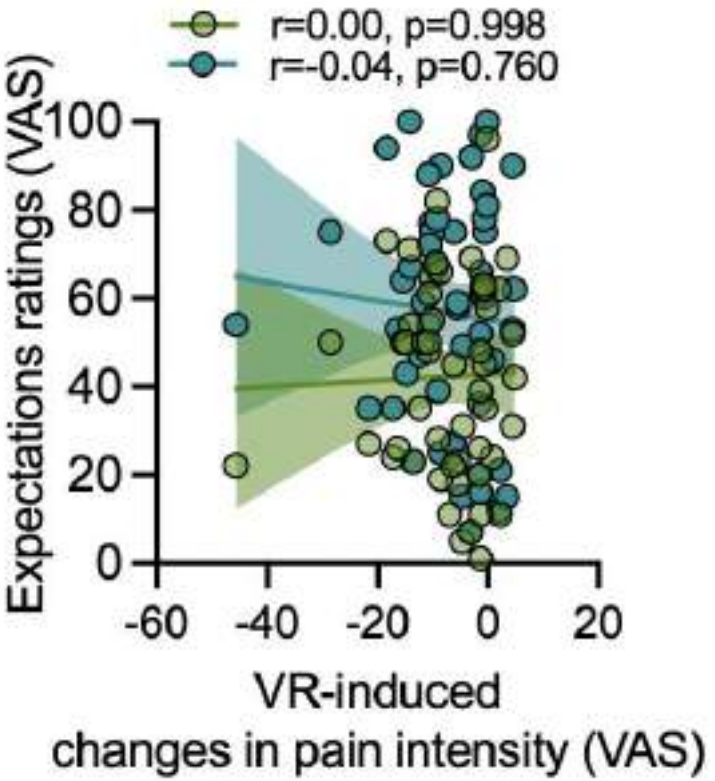




Colloca, …, & Wang. Psychotherapy and Psychosomatics, 2020

VR effects were independent of expectations





Colloca et al. Nature Digit Med. 2025

Overall take-home messages

In adults with orofacial pain, male sex, higher neighborhood distress, catastrophizing, and psychological distress were associated with a reduced magnitude of placebo effects.

In terms of brain ageing, neither estimated brain age nor brain age gap was associated with placebo responsiveness. This suggests that age-related brain changes may not explain alterations in placebo effects in chronic pain conditions.

The preservation of placebo effects despite brain ageing and chronic pain raises intriguing questions about the brain's "inner pharmacy" and its resilience to psychiatric and neurodegenerative processes, such as schizophrenia, Parkinson's disease, and Alzheimer's disease.

Funding agencies

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