Jewel N. White
Curriculum Vitae
University of Maryland, Baltimore
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EDUCATION

University of Maryland, School of Medicine	Baltimore, MD
Doctor of Philosophy in Neuroscience	Conferred: 7/2024
University of Virginia, College of Arts and Sciences	Charlottesville, VA
Bachelors in Biology, Psychology minor	Conferred: 5/2019

PROFESSIONAL APPOINTMENTS

Graduate Research Assistant, University of Maryland School of Medicine	8/2020-7/2024
Collaborative Teaching Fellow, Johns Hopkins University	8/2022-5/2023
Postbaccalaureate Research Education Intern, University of Georgia	7/2019-7/2020
Teaching Intern, Curry School of Education, University of Virginia	1/2019-5/2019
Undergraduate Research Assistant, University of Virginia	8/2017-5/2019
NIH Bridges to the Baccalaureate Intern, Virginia Commonwealth University	Summer 2017

PUBLICATIONS

Colloca, L, Mocci, E, Wang, Y, Massalee, R, Chen, S, **White, J**, Johnson, K, Patron Fidalgo, G, Wilson, G, Goldman, D, Dorsey, G. Transcriptomic profiles associated with experimental placebo effects in orofacial pain. *Clinical Pharmacology & Therapeutics, 2024.*

Raghuraman, N., **White, JN**, Watson, L, Bellei-Rodriguez, CE, Shafir, R, Wang, Y, Colloca, L. Neuropsychological mechanisms of social learning in human placebo effects. *Psychopharmacology, 2024*.

White, JN, Bellei-Rodriguez, CE, Wang, Y, Watson, L, Heagerty, JM, Li, S, Brown, B, Varshney, A, Shafir, R, Colloca, L. Effects of state empathy on socially induced hypoalgesia using immersive virtual reality. In submission.

GRANTS AND FELLOWSHIPS

National Institute of Dental and Craniofacial Research (NIDCR) Helping to End Addiction Long- term (HEAL) Initiative Diversity Supplement – 1R21 DE032532-01. Award term: 2/2023-7/2024

IMSD/Meyerhoff Fellowship, University of Maryland, Baltimore

Award term: 8/2020-7/2024

HONORS & AWARDS

Poster semi-finalist, Canadian Pain Society annual scientific meeting	4/2024
Travel award – International Association for the Study of Pain	3/2024
Baltimore Brain Series Award	3/2024
American Association for the Advancement of Science Membership	2/2024
IMSD/Meyerhoff Fellowship, University of Maryland, Baltimore	8/2020-7/2024
Magna Cum Laude, Thomas Nelson Community College (TNCC)	5/2017
TRiO Student of the Year, TNCC	5/2017
All-Virginia Academic Scholar, Phi Theta Kappa Honor Society	5/2017
Dean's List, TNCC	5/2015-5/2017

INVITED TALKS AND PRESENTATIONS

Invited Seminar Speaker, NIDA Baltimore Brain Series	5/2024
Invited Sponsored Presenter, 2024 NIH Pain Consortium Symposium	5/2024
Invited Speaker, Science in Society Conference, Glenelg High School	2/2024
Invited Speaker, Germanna Community College First-Generation Day	8/2022
Keynote Speaker, Virginia Community College System (VCCS)	5/2017

ORAL PRESENTATIONS

White, J. (2024, April) Nocebo: Impact, Mechanisms, and Future Perspectives. Oral presentation delivered at the Canadian Pain Society 44th Annual Scientific Meeting, Ottawa, Canada

White, J.N., Brown, K., Preston, C., Wagner, J. (2020, July) Cellular Mechanisms of Learning and Memory are Altered by Cocaine-Conditioning in Mice. Research presentation presented at the University of Georgia Postbaccalaureate Research Program (PREP) Symposium, Athens, GA

ABSTRACTS AND POSTER PRESENTATIONS

White, J., Bellei-Rodriguez, C., Wang, Y., Watson, L., Heagerty, JM., Li, S., Brown, B., Varshney, A., Shafir, R., Colloca, L. (2024, April) Virtual Reality Experiences and Neural Responses: Unraveling the Dynamics of Empathy and Placebo Effects. Poster pitch delivered at the Canadian Pain Society 44th Annual Scientific Meeting, Ottawa, Canada

White, J., Bellei-Rodriguez, C., Wang, Y., Watson, L., Heagerty, JM., Li, S., Brown, B., Varshney, A., Shafir, R., Colloca, L. (2024, March) Avatar versus human in pain: effects of state empathy on socially induced hypoalgesia using immersive virtual reality. Abstract accepted for the Society for Social Neuroscience Annual Meeting, Tsukuba, Japan.

White, J.N., Wang, Y., Massalee, R. Colloca, L. (2023, May) Brain Structural

Signatures in Placebo Responders with Temporomandibular Disorders. Poster presented at the Society for Interdisciplinary Placebo Studies 4th International Conference, Duisburg, Germany

White, J.N., Wang, Y., Massalee, R. Colloca, L. (2022, September) Brain-Power & Placebo: Structural Brain Differences among High and Low Placebo Responders with Temporomandibular Disorders. Poster presented at the Greater Baltimore Society for Neuroscience Scientific Meeting 2022, Baltimore, MD

White, J.N., Wang, Y., Massalee, R. Colloca, L. (2022, September) Brain-Power & Placebo: Structural Brain Differences among High and Low Placebo Responders with Temporomandibular Disorders. Poster presented at the International Association for the Study of Pain World Congress 2022, Toronto, Canada

White, J.N., Thomas, N., Adkins, A., Salvatore, J.E. (2018, June) Association Between AVPR1A Genotype, Social Behavior, and Alcohol Consumption in a College Sample. Poster presented at the 41st Annual Research Society on Alcoholism Scientific Meeting, San Diego, CA

White, J.N., Thomas, N., Adkins, A., Salvatore, J.E. (2017, August) Association Between AVPR1A Genotype, Social Behavior, and Alcohol Consumption in a College Sample. Poster presented at the Virginia Commonwealth University Bridges to the Baccalaureate Program (NIH-R25GM102795) Symposium, Richmond, VA

CO-AUTHOR PRESENTATIONS

Belleï-Rodriguez, C.-É., Raghuraman, N., **White, J. N.**, Watson, L., Shafir, R., Wang, Y., Colloca, L. (2024, March) Implicit racial bias moderates the impact of self-reported race/ethnicity on socially induced placebo analgesic effects. Poster to be Presented at the Society for Social Neuroscience Annual Meeting, Tsukuba, Japan.

Van Eron, L., **White, J.N.**, Wang, Y, Colloca, L. (2023, August) Effects of Gonadal Hormones, Sex and Psychological Traits on Placebo Hypoalgesia in Individuals with Temporomandibular Disorders. Poster Presented at the University of Maryland Scholars Symposium, Baltimore, MD

Abase, J., Shafir, R. **White, J.N.**, Wang, Y., Colloca, L. (2023, August) Neuromarkers of Pain Sensitivity and Modulation: A Peak-alpha Frequency Study. Poster Presented at the University of Maryland Scholars Symposium, Baltimore, MD

TEACHING EXPERIENCE

Notre Dame of Maryland University 8/2022-5/2023
(Collaborative Teaching Fellows Program (CTFP))

Role: Teaching Fellow.
Learned the tenets of teaching pedagogy as well as effective teaching practices.

Baltimore Underground Science Space (CTFP) 8/2022-5/2023
Role: Teaching Assistant, Teaching Fellow, Research Assistant for the BUGSS Open Insulin Project.
Teaching assistant for the BUGSS Build-a-Genome course which taught members of the Baltimore community the basics of genomics. Taught a lecture on bioinformatics and led multiple lab sessions where students learned basic lab skills such as pipetting and plating, induced the Scramble system with synthetic yeast chromosomes, grew yeast colonies on selective conditions, and sent their results for sequencing.

Teaching internship (University of Virginia Curry School of Education) 1/2019-5/2019
Role: Teaching intern
Completed a semester-long teaching internship at the elementary grade school level.

MENTORSHIP EXPERIENCE

VanguardSTEM Guerilla Mentoring Event 1/31/2024
Role: Mentor for underrepresented women and non-binary people in STEM

University of Maryland, Baltimore (Research Scholars Program) 8/2023-7/2024
Role: Mentor and Primary Research Advisor for High School Research Scholar in Dr. Luana Colloca's Lab

University of Maryland, Baltimore (UM Scholars Summer Program) Summer 2023
Role: Mentor and Primary Research Advisor for Undergraduate Research Scholar in Dr. Luana Colloca's lab

STEM coach for Kindergarten-3rd grade ExploraVision contest, STEMcx 9/2022-5/2023
Duties: Co-lead a project for the elementary level ExploraVision science invention project with STEMcx

Peer mentor, Thomas Nelson Community College TRiO Program 8/2016-5/2017

RESEARCH EXPERIENCE

University of Maryland, Baltimore (UMB) (School of Nursing) 4/2022-7/2024
Graduate Research Assistant: *Department of Pain and Translational Symptom Science*.
Lab interest: Neural mechanisms of social learning & pain modulation.
- Conducted clinical and translational pain and placebo research
- Assessed the social, psychological, and biological contributions to health outcomes

Administered psychological assessments approved for clinical use in adults with chronic pain
Performed brain imaging (EEG, MRI)
Operated virtual reality systems (Unity game engine)

University of Georgia (College of Veterinary Medicine) 8/2019-8/2020
NIH PREP Scholar, Research Assistant: Department of Physiology and Pharmacology. Lab interest: Neurophysiology of the hippocampus, cellular mechanisms of learning and memory, neuropharmacology of drugs of abuse and rodent models of addiction.

Performed behavioral assays on mice using cocaine conditioned place preference model.
Performed mouse brain extraction, dissection, and slicing.
Performed extracellular field recordings on mouse brain slices using electrophysiology.

University of Virginia (Center for Public Health Genomics) 8/2017-5/2019
Research Assistant, Department of Biomedical Engineering. Lab interest: genetics of cardiovascular and metabolic diseases.

Performed mammalian cell culture (cell splitting/counting/freezing, transfection (lipofectamine), adenovirus.)
Performed RNA and protein isolation and quantification using Nanodrop and colorimetric assays.
Managed mouse colony: weaning, genotyping of mice; quantified body fat of genetically-engineered mice using echoMRI.

University of Virginia (Curry School of Education) 1/2018-5/2019
Research Assistant, Department of Education. Lab interest: educational disparities of minority STEM students.

Interviewed service providers, student organization leaders, and focus groups.
Analyzed and coded interview data.
Co-created protocols for research project.

Virginia Commonwealth University (NIH-R25GM102795) 5/2017-7/2017
1. *Research Assistant, Department of Biology;* 2. *Research Assistant and Primary Author on Scientific Poster, Department of Psychology.* Lab interest: genetic and environmental factors involved in human alcohol consumption.

Performed ELISA test, cultured microorganisms, performed PCR, SDS-PAGE, DNA isolation, and bacterial transformation.
Reviewed primary literature for a research study.
Ran descriptive statistics, regression analyses, and meta-analyses using SPSS software to examine association between genotype and multiple variables; designed tables, figures, charts and graphs to illustrate analytic findings.

Thomas Nelson Community College (In conjunction with the College of William and Mary/Howard Hughes Medical Institute and John Hopkins University for Phage Research for Tuberculosis Bacteriophage) 8/2016-5/2017

Research Assistant, Department of Biology. Lab interest: Bacteriophage isolation.
Isolated bacteriophages using plating techniques, DNA and RNA extraction, and gel electrophoresis.
Annotated genomes using DNAMaster and Serial Cloner software.

EXTRACURRICULAR UNIVERSITY SERVICE

Executive Board, UMB IMSD/Meyerhoff Program	8/2022-7/2024
Diversity Committee Member, UMB Program in Neuroscience	8/2020-7/2024
Executive Board Secretary, Phi Theta Kappa Honor Society	8/2016-5/2017
Chair of Five Star Committee, Phi Theta Kappa Honor Society	8/2016-5/2017

RELATED PROFESSIONAL SKILLSET

CITI human research training
HIPAA, Good Clinical Practice, Human Research Protections, Bloodborne Pathogens

Translational research
• REDCap • Qualtrics • SurveyMonkey • Psychological and mood assessments • Clinical questionnaires • Interviews • Behavioral instrument administration • Quantitative Sensory Testing (QST) • Virtual reality operation (Unity game engine)

Neuroimaging
MRI • Electroencephalography (EEG) • FSL • FreeSurfer • General linear model (GLM)

Statistics
• SPSS • R

Microsoft office

PROFESSIONAL MEMBERSHIPS

Member, American Association for the Advancement of Science	Since 2/2024
Member, Society for Social Neuroscience	Since 1/2024
Member, Canadian Pain Society	Since 11/2023
Member, Placebo Beyond Opinions Center, UMB	Since 11/2023
Member, International Association for the Study of Pain (IASP)	Since 6/2022
Member, Society for Neuroscience DC Metro Area Chapter	Since 4/2022
Member, Association for Women in Science, Baltimore Chapter	Since 1/2022
Member, Black in Neuro	Since 8/2020
Member, Phi Theta Kappa Honor Society	Since 5/2016

Abstract

Title of Dissertation: A Biopsychosocial Model to Study Interindividual Differences in Placebo Effects: Translational Approaches for Acute and Chronic Pain Management

Jewel N. White, Doctor of Philosophy, 2024

Dissertation Directed by: Luana Colloca, MD, PhD, MS, Professor, Pain and Translational Symptom Science

To date, chronic pain is among the most prevalent and economically burdensome chronic diseases, affecting nearly one in five individuals worldwide and costing $635 billion per year in the United States alone. Current treatments for chronic pain are limited or mildly efficacious, and some may produce adverse side effects and conditions such as drug-induced hyperalgesia or substance use disorder. Limitations of pharmacological treatments urge the development of nonpharmacological therapies for pain.

Placebo effects engage the descending modulatory neural systems to induce analgesia and present a promising opportunity to study the effectiveness of nonpharmacological and noninvasive interventions for improving pain symptoms. However, not everyone will respond to a placebo treatment. Biopsychosocial factors that vary between individuals, including culture, environment, sex, and neural characteristics, may influence individual response to placebo. Therefore, understanding the mechanisms underlying the effects of biopsychosocial factors on interindividual differences in placebo effects is critical for the development of translational approaches for pain management. Here, two well-established social learning and classical conditioning paradigms were used to test the hypothesis that social, sex, and neural traits would contribute to the generation of placebo

effects. The main findings of this work are threefold. First, cognitive state empathy was greater for a human demonstrator in pain compared to an avatar, and this socially induced empathy mediated subsequently induced placebo effects. Second, women exhibited larger expectations and placebo effects compared to men, and gonadal hormone levels were associated with conditioning strength, expectations, and placebo hypoalgesia. Testosterone levels were negatively associated with chronic pain severity in women, and estradiol levels in individuals with chronic pain and pain-free individuals mediated the impact of sex on expectations assessed after conditioning. These expectations mediated the impact of sex on placebo effects in individuals with chronic pain. Third, cortical morphology was positively correlated with placebo response in individuals with chronic pain. This work provides support for the careful consideration of the effects of biopsychosocial factors in the analysis and interpretation of placebo hypoalgesia studies. Importantly, these findings suggest that empathy, sex hormone, and morphological measurements can be important factors to leverage for translational and clinical approaches for chronic pain management.

A Biopsychosocial Model to Study Interindividual Differences in Placebo Effects: Translational Approaches for Acute and Chronic Pain Management

by
Jewel N. White

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2024

For Miles.

Acknowledgements

It is my greatest honor to dedicate these acknowledgements to each individual who has played an invaluable part in this work.

To Dr. Luana Colloca, I thank you for not only directing this work, but for your unwavering commitment to my mentorship. Your brilliant insights, constructive criticism, and steadfast encouragement have always been positively received and have helped to mold me into the scientist that I am today. Your enthusiasm for research and dedication to scientific rigor has motivated me to strive for nothing less than the very best as a scientist and individual, and I will carry this with me throughout the rest of my career.

To Drs. Chen, Renn, Teixeira Da Silva, and Waddell, thank you for your time and dedication to the development and completion of this work. Each piece of advice or suggestion contributed immensely to this product, and I am grateful to have had the opportunity to learn from such outstanding scientists who were invested in my success.

To all my mentors, thank you for always being a text, call or email away long after I graduated from college or finished an internship. To Dr. Mete Civelek, Dr. Merci Best, Dr. Erin Dolan and all the leaders of PREP@UGA, and the leaders of VCU Bridges – where my scientific journey began – thank you for your honest advice, uplifting encouragement, and countless letters of recommendation.

To all of my friends, you have supported me throughout each facet of graduate school and have become so much more than friends; you are forever my family. To Catherine. Chimdiya, Gautam, and Meghann, may we always stay true to true crime. To Garis, Ruchael, and Shanaliz, I miss our coffee dates, lunches, happy hours, hangouts, talks, tears, and laughs already.

To my family, I would not be who I am today without you. My commitment to science reflects the values of hard work, determination, and grit that you instilled in me from an early age. I am proud to be your daughter, sister, and aunt; this work is an endless thank you to always being there for me.

To Miles, you are my greatest reason why. I began this journey as you kicked and rolled in my womb, and when you were born, you became the reason behind each late night, each experiment, and the resilience and perseverance that led me – us – to this very moment. My hope is that you read this work someday and know that each milestone leading to its completion was motivated by becoming a role model to you. I love you and I am endlessly proud of you. “You are me and more.”

To Alex, you are the love of my life and my very best friend. Your unconditional love and support of all my endeavors has strengthened me in ways that show throughout the pages of this work. Truly, I could not have, nor would I have wanted, to do this without you.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
AI	Artificial Intelligence
BAI	Beck Anxiety Inventory
BDI	Beck's Depression Inventory
BES	Basic Empathy Scale
cLBP	Chronic Low Back Pain
CNS	Central Nervous System
CS	Central Sensitization
CTh	Cortical Thickness
DEG	Differentially Expressed Gene
dlPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
GCPS	Graded Chronic Pain Scale
GMV	Grey Matter Volume
IASP	International Association for the Study of Pain
IRI	Interpersonal Reactivity Index
IBS	Irritable Bowel Syndrome
LMM	Linear Mixed Model
ML	Machine Learning
MRI	Magnetic Resonance Imaging
NAc	Nucleus Accumbens

NIH	National Institutes of Health
OBC	Oral Behavior Checklist
OLP	Open Label Placebo
OUD	Opioid Use Disorder
PAF	Peak Alpha Frequency
PAG	Periaqueductal Gray
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHG	Parahippocampal Gyrus
PNS	Peripheral Nervous System
RVM	Rostral Ventral Medulla
SABV	Sex as a Biological Variable
SC	Spinal Cord
STAI	State Trait Anxiety Index
TMD	Temporomandibular Disorder
TRP	Transient Receptor Potential
VAS	Visual Analogue Scale
vmPFC	Ventromedial Prefrontal Cortex
VR	Virtual Reality
VS	Ventral Stratum/Striatal
QST	Quantitative Sensory Testing

Chapter I: Background and Significance

A. Individual variations in pain

Theories and definition

Pain is as old as consciousness itself. In ancient civilizations, pain was attributed to bodily invasion by spirits of the deceased or emotions centered in the heart (Dallenbach, 1939, Linton, 2005, Doleys et al., 2014). In the Middle Ages, pain was a sign of punishment from the gods (Rey et al., 1993). During the rebirth of science in the Renaissance era, Leonardo da Vinci proposed that pain was related to tubular nerves thought to convey sensations to the brain via the spinal cord (Doleys et al., 2014). In the 17th century, Rene Descartes developed his Cartesian mind-and-body model in which he described the body as a machine governed by the mind, and that pain was a disturbance passed down along nerve fibers to the brain via one pain pathway (Melzack and Katz 2004, Linton, 2005) (see Fig.1). Descartes's pain theory was not disparate from modern theories of pain. However, rather than by a direct pathway, as illustrated in *Treaties of Man*, pain processing occurs at multiple brain regions with various functions that modulate nociceptive signals, or signals that encode and process noxious (i.e., tissue-damaging, or potentially tissue-damaging) stimuli (Dubin and Patapoutian, 2010, Tracey Jr. et al., 2017, Armstrong et al., 2023). One of the most influential modern pain theories to date is Melzack and Wall's Gate Control Theory of Pain, which posits that a gate control system modulates excitatory and inhibitory sensory input before evoking conscious pain perception and associated responses (Melzack and Wall 1965, Doleys et al., 2014, Mendell et al., 2014).

Figure 1: Descartes' pain pathway, Treatise of Man (published posth., 1664).

Theories of pain have shifted considerably since the days of ancient Egypt and Greece. Once regarded as punishment, transient or acute pain is now regarded by some as a "detect and protect" mechanism (Julius et al., 2001, St John Smith et al., 2018), although others consider acute pain a failure of avoidant behavior (Baliki and Apkarian, 2015). Since 1964, the official definition of pain from the International Association for the Study of Pain (IASP) has changed in slight but significant ways to reflect the advances of pain research and the understanding of individual experiences of pain. The IASP currently defines pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (IASP 2020). Accompanying this definition are key notes providing further context regarding the experience of pain: Pain is different from nociception; is always subjective and should be respected as such; and is influenced by biological, psychological, and social (biopsychosocial) factors.

B. Mechanisms of pain

Nociception

Nociception is the mechanism which protects an organism from injury (Woodworth and Sherrington, 1904, Dubin and Patapoutian, 2010, Baliki and Apkarian, 2015, Sneddon, 2017, Tracey Jr. et al., 2017). Nociception is distinct from pain and refers to the process of encoding and processing noxious stimuli via nociceptors – a specialized class of neurons that are preferentially sensitive to noxious stimuli and are found on the skin, joints, viscera, and muscles (McMahon et al., 2013). Nociceptors in the peripheral nervous system (PNS) typically respond to noxious thermal, mechanical, and chemical stimuli and relay information to the central nervous system (CNS) regarding stimuli location and intensity (Julius et al., 2001, Riedel et al., 2001). Many nociceptors are polymodal, meaning they respond to multiple types of stimuli, and others have specialized response properties for perceiving burning or itch sensations (Julius et al., 2001, Smith et al., 2018, McMahon et al., 2013). Some nociceptors in the joint are classified as silent nociceptors, meaning they are normally dormant and unresponsive to stimuli unless tissue damage causes release of inflammatory molecules, in which case they may become mechanosensitive (Julius et al., 2001, Kendroud et al., 2022). Nociceptors are further subclassified into unmyelinated C-fibers or lightly myelinated A-delta fibers (Julius et al., 2001, Kendroud et al., 2022, McMahon et al., 2013). Nociceptors in the periphery are the first to detect noxious stimuli from the environment and are thus classified as primary afferent, or first order sensory neurons, which are found in the dorsal root ganglion and trigeminal ganglia (Kendroud et al., 2022, McMahon et al., 2013). Nociceptive stimuli activate transient receptor potential (TRP) channels on nerve endings, causing primary afferents to depolarize and fire action potentials, the frequency of which determines the intensity of the stimulus (Kendroud et al., 2022).

Tissue damage from noxious stimuli results in the release of inflammatory mediators such as bradykinin, which can activate or sensitize nociceptors to natural stimuli (McMahon et al., 2013). Nociceptive information is then carried from peripheral nerves to the brain in the ascending pain pathway. In this pathway, peripheral A-delta nerve fibers release glutamate onto second-order neurons, also called interneurons, in the dorsal horn of the spinal cord (SC) and transmit the 'first-pain' signals that induce sensations immediately felt after the noxious stimulus is applied (Yam et al., 2018, McMahon et al., 2013). Peripheral C fibers release neuropeptide neurotransmitters such as substance P onto interneurons and transmit 'second-pain' signals that induce delayed dull, aching, burning, and throbbing pain (Yam et al., 2018, McMahon et al., 2013). SC interneurons then modulate and transmit nociceptive signals to the rostral ventral medulla (RVM) and periaqueductal gray (PAG) in the brainstem, where the signals are then transmitted to third order neurons in the thalamus, and eventually are relayed to the cerebral cortex of the brain within the spinothalamic tracts, where they are perceived as pain (McMahon et al., 2013).

In addition to playing an afferent role in pain signaling by sending sensory information to the CNS, nociceptors also act as efferents (i.e., carrying motor information away from the CNS to the muscles and glands) that release vasoactive substances such as substance P through the peripheral endings of nociceptors that act on blood vessels and immune cells, initiating neurogenic inflammation (Pierau et al., 2001, Dubin et al., 2010).

Once nociceptive signals from the ascending pathway reach the somatosensory cortex, it triggers the descending pain pathway to suppress pain signals (Sneddon et al., 2017, Kendroud et al., 2022). Descending pain modulation is mediated through projections to

the PAG, which receives inputs from the hypothalamus and other subcortical structures and relays nociceptive information to the RVM (Waselus et al., 2011, Sneddon et al., 2017). The RVM then sends descending projections to the SC (McMahon et al., 2013). At the level of the SC, G-protein-coupled receptors, such as mu, delta, and kappa opioid receptors on the presynaptic ends of nociceptors, are activated by endogenous opioid ligands, causing cell hyperpolarization and inhibition of substance P, ultimately blocking nociceptive transmission from C-fibers (Kendroud et al., 2022).

Multidimensional and individual experiences of pain

One of critical roles of the nervous system is to provide information about injury or the threat thereof (McMahon et al., 2013). The aversive sensation of pain contributes to this role, as it involves a conscious signaling of nocifensive failure to protect the body from injury (Apkarian et al., 2018, Apkarian et al., 2019). However, the experience of pain transcends physical sensation – pain is an individual, multidimensional experience including sensory, emotional, affective, and discriminative components (Melzack and Casey, 1968). Modern research supports the theory that pain is a biopsychosocial phenomenon influenced by neural traits, sex, genetics, age, culture, and environment (Fillingim, 2017). Because of this, sensitivity to pain considerably varies across individuals. Kim et al. observed profound variability in the pain ratings of 500 participants who received an identical noxious heat pain stimulus of 49 degrees Celsius; the ratings ranged from 5 to 95 on a scale of zero (no pain) to 100 (maximum tolerable pain). Fillingim et al. reported similar results in their study using an experimental stimulus delivered at a standardized intensity. Over 300 individuals were asked to report

their pain ratings on a scale of zero to 100 after receiving a heat stimulus of 48 degrees Celsius. While the mean pain rating was around 72 out of 100, there was a wide range of variability in pain ratings among the individuals (Fillingim, 2017). Even when stimuli aren't identical, between-subject individual differences account for 60% of the total variance in pain ratings (Nielsen et al., 2009). Individual, subjective pain ratings such as these are essential for pain diagnosis and treatment. However, individual differences in pain sensitivity complicate treatment (Fillingim, 2017). Therefore, understanding the components of pain perception is critical for elucidating the mechanisms contributing to individual differences in pain experience and, ultimately, developing effective treatments for pain.

Pain perception occurs by the activation of cortical networks involved in pain processing, such as the primary somatosensory cortex, primary motor and supplementary motor cortices, secondary somatosensory cortex, insular cortex, anterior cingulate cortex (ACC), thalamus, as well as regions within the prefrontal and parietal cortices, the amygdala, the hippocampus, and the subcortical structures including the basal ganglia (Martucci and Mackey, 2018) Changes in activity (Jensen et al., 2014) or morphology (Kotikalapudi et al., 2023) are shown to predict individual sensitivity to pain. Thus, pain perception can occur without nociceptive input, and the experience of pain can occur by direct brain stimulation (Martucci and Mackey, 2018).

Beyond the brain, psychosocial mechanisms are also shown to influence pain. 'Psychosocial mechanisms' refer to mechanisms or pathways through which the social environment influences psychological health (Mama et al., 2016), including but not limited to social norms, healthcare access, and gender (Sorenson et al., 2003), past

experiences, context, and cognitive and emotional input (Martucci and Mackey, 2018) and perceived stress (Garey et al., 2015). For example, studies on surgical pain (e.g., Granot et al., 2005; Masselin-Dubois et al., 2013; Theunissen et al., 2012) demonstrate that pre-surgical anxiety and pain catastrophizing, referring to the magnification and rumination of pain-related information, (Pavlin et al., 2005; Pinto et al., 2012; Burns et al., 2015) are associated with greater post-surgical pain. Conversely, expectancies regarding positive surgical outcomes have been associated with lower immediate post-surgical pain (Powell et al., 2012; Pinto et al., 2013; Ronaldson et al., 2014).

In addition to highlighting the effects on transient, or acute pain, these studies also showed that psychosocial mechanisms can influence a phenomenon not only related to post-operative pain, but various other pain states: the transition from acute pain to chronic pain.

Acute to chronic pain transition

Acute pain is the primary reason for doctor visits, and many patients experience acute pain during their hospital stay (Castroman et al., 2022). Acute tissue insults from noxious stimuli trigger acute inflammation and the transmission of nociceptive impulses from the PNS to the CNS in the ascending pain pathway, which triggers inhibition of nociceptive input by the CNS in the descending pain pathway (Feizerfan and Sheh, 2015). Acute pain is typically associated with an identified injury or tissue-damaging event and is short-term, lasting three to six months or less before the pain resolves (Amaechi et al., 2021). Therapy for acute pain aims to treat an underlying cause and to interrupt nociceptive signals (Grichnik and Ferrante, 1991).

Termination of acute nociception and full recovery of tissue would restore normal homeostasis and end pain (Feizerfan and Sheh, 2015). However, continuous or repetitive nociceptive stimulation leads to pathophysiological changes in pain processing that result in persistent pain that may become chronic (Feizerfan and Sheh, 2015).

As opposed to transient, acute pain, chronic pain is a debilitating disease characterized by persistent and pathological pain that may arise from psychological states, serves no biological purpose, and may or may not be associated with an identified injury or tissue-damaging event or have an identified cause (Grichnik and Ferrante, 1991). An important component of chronic pain is visceral pain, for example, stress-induced abdominal pain in irritable bowel syndrome (IBS) (Moloney et al., 2015) or pain in the absence of injury (Grundy et al., 2019). Typically, chronic pain is long term, lasting longer than three to six months and possibly permanently (Whitten and Cristobal, 2005, Dydyk and Conermann, 2024). To date, chronic pain is the most common and economically burdensome chronic disease, costing $560-635 billion per year in the United States in treatment-related costs (Gaskin and Richard, 2012, Chang et al., 2015).

In nearly all chronic pain states, amplified pain by CNS mechanisms leads to widespread pain and primary hyperalgesia, referring to the leftward shift of the stimulus response curve where the threshold for pain is lowered, eliciting an exaggerated pain response (Meyer et al., 2005, Hsieh et al., 2015), and central sensitization (CS), or amplified pain by CNS mechanisms (Harte et al., 2018). CS may evoke multisite, secondary hyperalgesia – increased pain sensitivity felt away from the injury site (Treede et al., 2015) or allodynia – pain from non-noxious stimuli (Jensen and Finnerup, 2014, He and Kim, 2023). CS is thought to be caused by abnormal increases in peripheral nociceptive

signal transmission and decreased inhibitory input or increased excitatory input at the spinal cord, brainstem, and cortical levels. CS contributes to neuropathic pain (Latremoliere and Woolf, 2009), temporal summation of pain in individuals with, for example, fibromyalgia syndrome (Staud et al., 2008), and dysesthesia (Finnerup et al., 2001) among other symptoms often reported by patients with chronic pain.

Chronification of pain may be caused by changes in pain-responsive regions such as the prefrontal cortex (PFC), including changes in neurotransmitters, neuronal plasticity, gene expression, glial cells, and neuroinflammation that result in alterations to its structure, activity, and connectivity (Basbaum et al., 2009, Ong et al., 2019). The medial PFC in particular may induce pain chronification via its corticostriatal projection, possibly depending on the level of dopamine receptor activation in the ventral tegmental area-nucleus accumbens reward pathway (Ong et al., 2019).

One of the most important ways to reduce the occurrence of chronic pain is to prevent the incidence of acute pain. If acute pain presents itself, prompt and effective treatment of acute pain may interrupt chronification of pain (Mills et al., 2019).

Current treatments and new approaches for acute and chronic pain management

Despite the prevalence of acute pain symptoms and chronic pain diseases, current treatments for either are limited (Castroman et al., 2022), mildly efficacious (Reinecke et al., 2015) or present adverse safety profiles (Martel et al., 2015). Drug development for analgesics remains an arduous task because there is no single target for the various factors that influence pain, such as modifiable factors like substance use or the pain itself, or non-modifiable factors like age and sex (Hecke et al., 2013). Further, while some

patients are mildly affected by clinical pain, others suffer from debilitating pain symptoms. For example, acute postsurgical pain occurs in about 80% of surgery patients, and some of these patients develop chronic postsurgical pain (Castroman et al., 2022). For patients with acute mild to moderate pain, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line, nonopioid treatment options (Amaechi et al., 2021), while strategies for chronic pain management have primarily included pharmacological treatments that dampen ascending neurotransmission, and opioid-receptor mediated therapies (Colloca 2019). However, chronic opioid use presents high risk of adverse effects and disorders such as opioid-induced hyperalgesia (Stoicea et. al, 2015) and opioid use disorder (OUD) (Nalamachu, 2013, Volkow and Blanco, 2021). As a result, pharmacological intervention alone may not prevent processes related to the transition from acute to chronic pain and may even produce negative side effects (Dydyk and Conermann, 2024). The emergence of the opioid epidemic in the United States remains one of the most devastating consequences of the increased rate of opioid prescriptions (Volkow and Blanco, 2021). In order to minimize harm and maximize treatment benefit, pain therapies should rely on multidisciplinary approaches and should involve more than one therapeutic modality (Grichnik and Ferrante, 1991), including noninvasive and nonpharmacologic treatment (Qaseem et al., 2017). Further, pain management should be safe, effective, and tailored for each patient, including a review of treatment expectancies (Volkow and Blanco, 2021, Amaechi et. al, 2021), referring to the anticipated future outcomes of an intervention (Colloca, 2019).

In both experimental and clinical settings, pain perception and treatment outcomes are modulated by placebo and nocebo effects, which are due to positive and negative

expectancies, respectively, regarding health outcomes (Colloca, 2019). These effects are of particular interest in pain research due to the potential of placebo as a non-pharmacological option to induce analgesia in acute and chronic pain states.

C. The placebo effect in endogenous pain modulation

Placebo and nocebo effects are widely observed in clinical trials of pain treatments (Collcoa and Miller, 2011, Vachon-Presseau et al., 2018). Although placebo effects have been well-studied in experimental and clinical pain, they can influence any treatment and condition (Ong et al., 2019). When a no-treatment arm is included in clinical trials, placebo effects can be separated from confounding variables such as regression to the mean and spontaneous remission (Colloca, 2019). While once considered a clinical nuisance or a nonspecific effect affecting only subjective symptoms and not biological processes, the placebo phenomenon is now backed by systematic research that suggests that placebo effects engage neurobiological and physiological mechanisms to modulate clinical outcomes resulting from the expectancies of the patient, proxy, and provider (Colloca 2019, Ong et al., 2019).

Neurobiological mechanisms of the placebo effect

At the neural level, placebo effects result in neuropeptide release and modulation of brain regions involved in pain signaling and expectancy formation. Functional magnetic resonance imaging (fMRI) studies show that placebo analgesia is associated with decreased activation of pain-responsive regions such as the thalamus and insula (Lu et al.,

2010), while expectancies underlying hypoalgesic placebo effects elicit increased activation of the descending pain modulatory pathways (Atlas et al., 2014).

Placebo effects leverage the descending neural pathways to inhibit nociceptive signaling, beginning at the prefrontal cortex (PFC), which underlies executive functions and representational knowledge (Ong 2019), with a descending modulation of the nucleus accumbens to ventral striatal pathway (NAc–VS), a reward circuit involved in the mediation of motivational and emotional processes (David et al., 2005), the PAG, the primary control center for descending pain modulation whose activation attenuates incoming pain signals in the spinal cord (Ong et al., 2019), and RVM, which sends descending inputs to the spinal trigeminal nucleus in the brainstem or spinal cord for pain modulation (Wager and Atlas, 2015). Along with the descending pain pathway, placebo effects leverage the endogenous endocannabinoid, oxytocin, vasopressin, and dopamine systems, as well as the opioidergic pathway to induce analgesia through the release of endogenous opioids (Levine et al., 1978, Amanzio et al., 1999, Eippert et al., 2009, Scott et al., 2008, Wager et al., 2007, Zubieta and Stohler, 2009). Positron emission tomography (PET) studies using [^{11}C]carfentanil, a mu-opioid selective radiotracer, show that placebo effects are associated with activation of endogenous opioid neurotransmission in pain-responsive regions (Wager et al., 2007, Scott et al., 2008, Zubieta and Stohler, 2009). Introducing an opioid antagonist such as naloxone reverses placebo effects (Levine et al., 1978, Benedetti et al., 1996, Amanzio et al., 1999, Eippert et al., 2009), and when compared to opioid medications, placebo elicits similar reductions in pain compared to morphine, further linking placebo effects and the endogenous opioid system in regards to pain relief (Ong et al., 2019).

Psychological mechanisms of the placebo effect

Throughout the ages, it has been evident that an individual's relationship to pain is affected by their beliefs and context (Rey, 1993). Similarly, placebo-induced hypoalgesia results from positive patient and provider expectancies – their beliefs – regarding measurable treatment outcomes (Colloca, 2019). Verbal suggestions that a treatment will provide a benefit, classical conditioning (i.e., experiencing pain reduction firsthand), observation of pain relief in another individual receiving a treatment, and the patient-clinician relationship (Kaptchuk et al., 2008) contribute to the generation of expectancies that can result in psychoneurobiological changes (Raghuraman et al., 2024). Thus, the neural and psychological mechanisms underlying placebo effects are mediated by positive expectancies. When positive expectancies are consciously accessed and able to be measured, they are called expectations (Colloca, 2020). Just as expectancies can elicit a benefit, they may also generate nocebo effects; negative effects which may elicit pain or other adverse symptoms following, for example, a verbal suggestion of worsening symptoms (Kam-Hansen et al., 2014). Classical conditioning induces placebo effects via repetitive exposure to interventions or treatments that induce analgesia, both active and inert (Colloca et al., 2013). Placebo effects can also occur via observation, even in the absence of conditioning and prior experience, because information used to build expectations of pain relief can be acquired through observation of a therapeutic benefit in others (Colloca et al., 2013). Placebo analgesic effects following the observation of a benefit in another person are similar in magnitude to those induced by directly experiencing an analgesic benefit (Fusaro et al., 2016, Goubert et al., 2011, Raghuraman

et al., 2019) making placebo effects a powerful determinant of health outcomes (Colloca, 2019).

Interindividual differences in placebo responses

While 'placebo effects' refer to the beneficial effects produced by placebos, 'placebo responses' refer to the interindividual variability in response to placebos in clinical settings (Neogi and Colloca, 2023). In both clinical and experimental settings, placebo responses vary greatly among individuals, ranging from no response to over 50% analgesia (Stein et. al, 2012) to complete pain relief (Colloca et al., 2013). As a result, much research is dedicated to identifying biopsychosocial markers that influence interindividual differences in placebo responses. Psychological traits such as anxiety, optimism, coping, and empathy have been associated with placebo responses with conflicting results (Colloca et al., 2013). In general, optimism, suggestibility, empathy, and neuroticism appear to be positively associated with response to placebo, while anxiety, pessimism, and catastrophizing, which refers to a negative cognitive–affective response to anticipated or actual pain (Quartana et al., 2009), appear to be associated with a higher likelihood of nocebo responses (Corsi and Colloca, 2017, Frisaldi et al., 2018, Kern et al., 2020).

Brain imaging approaches such as magnetic resonance imaging (MRI) and PET imaging have uncovered some of the neurobiological correlates and potential predictors of placebo responses. fMRI studies have revealed that the medial thalamus, dorsal anterior cingulate cortex, PAG, and secondary somatosensory cortex-dorsal posterior insula show decreased activation following placebo treatment, while the ventromedial PFC (vmPFC),

dorsolateral PFC (dlPFC), lateral orbitofrontal cortex, NAc-VS pathway, PAG and RVM show increased activation (Wager and Atlas, 2015). Further, Vachon-Presseau et al. found that subcortical limbic volume asymmetry, sensorimotor cortical thickness, and functional coupling of the PFC, ACC, and PAG regions were predictive of interindividual placebo response (Vachon-Presseau et al., 2018). PET imaging has revealed that the mechanism of placebo analgesia involves endogenous opioid release in response to noxious stimuli (Wager, 2007). Electroencephalography (EEG) has also provided insights into the neural correlates of placebo analgesia, for example, Raghuraman et al. found that smaller event-related potential amplitudes elicited by anticipatory cues were correlated with greater placebo analgesia, and that resting state peak alpha frequency (PAF) positively predicted placebo effects (Raghuraman et al., 2019).

Genetic differences have also been linked to placebo responses in a few studies. In patients with IBS, COMT Met/Met homozygotes of the COMT rs4680 polymorphism, associated with cognition and emotion, showed the largest placebo analgesic response under a supportive patient-provider interaction, while Val/Val homozygotes were less responsive to this condition and showed smaller placebo effects (Hall et al., 2012). In multiple studies, the FAAH rs324420 polymorphism has been selectively associated with placebo effects (Peciña et al., 2014, Colloca et al., 2014). Recently, we showed that upregulation of six differentially expressed genes (DEGs) was positively associated with placebo responses in individuals with chronic pain (Colloca et. al, 2024). The DEGs included CCDC85B, FBXL15, HAGHL, PI3, SELENOM, and TNFRSF4, some of which encode proteins important for CNS function, and others which play a role in cellular metabolic processes and survival (Colloca et al., 2024).

Additionally, sex has been shown to influence the magnitude of placebo effects in the context of pain in healthy individuals (Vambheim and Flaten, 2017) and individuals with chronic pain (Vambheim and Flaten, 2017, Olson et al., 2021). Previously, some studies reported that men show greater placebo effects compared to women (Aletky and Carlin, 1975, Abrams and Kushner, 2004, Aslaksen and Flaten, 2008, Bjorkedal and Flaten, 2011), while others show the opposite (Colloca et al., 2006, Haltia et al., 2008, Klosterhalfen et al., 2009, Krummenacher et al., 2014, Olson et al., 2021) or lack a sufficient number of women participants for sex-related comparisons (Hadamitzky et al., 2018). Consequently, there is no reliable consensus on the influence of sex on placebo effects, and there remains a need for further research prioritizing collection and analyses on data regarding sex differences in placebo effects (Shafir et. al, 2022) and pain (Mogil, 2012, Bartley and Fillingim, 2013).

D. Sexual dimorphism in pain and placebo effects

Sex differences in pain

In 2016, the National Institutes of Health (NIH) implemented the Sex as a Biological Variable (SABV) policy, requiring the consideration of SABV in NIH-funded research (Arnegard, 2020). Previously, biomedical research focused on male animals and cells (National Institutes of Health), limiting the applicability of this research for clinical interventions due to the exclusion of women. Consequently, the SABV policy was introduced to promote understanding of the influence of sex on health processes and outcomes (National Institutes of Health). Currently, women account for nearly half of all participants in NIH-supported clinical research to account for the sex disparities that exist

in the metabolism and reactivity to drugs, the incidence of conditions and diseases, and the experience, manifestation, and intensity of pain (National Institutes of Health). Experimental pain studies which report sex differences largely confirm sex-specific differences in pain experience, suggesting that women are more sensitive and less tolerant to pain compared to men (Mogil, 2012, Bartley and Fillingim, 2013). Further, women have increased risk for clinical pain and distinct responsivity to pain interventions, though these effects are inconsistent and depend on treatment type and pain and provider characteristics (Bartley and Fillingim, 2013). However, it is clear that women are disproportionately affected by chronic pain, as a number of common chronic pain syndromes can only occur in women and of the syndromes that are found in both sexes, more than 80% of cases in which treatment is sought are in women (Mogil, 2012). Epidemiological studies have reported that women have higher rates of chronic migraine than men, with greater severity of migraine-related symptoms (Kuba, 2005, Allais et al., 2020, Rossi et al., 2022). The prevalence and severity of symptoms for Temporomandibular joint disorder (TMD), musculoskeletal pain, osteoarthritis, rheumatoid arthritis, and fibromyalgia are also greater among women (Kuba 2005, Mogil, 2012, Bueno et al., 2018). Sex differences in chronic pain suggest potential contributions of sex hormones to the pathophysiology of chronic pain conditions. However, research on sex hormone effects on pain is still very limited (Bartley and Fillingim, 2013), highlighting the need for further research on the biological mechanisms underlying sex differences in pain.

Biological mechanisms

Sex differences in pain imply that sex steroid hormones such as estradiol, progesterone, and testosterone modulate pain sensitivity. Though all sex hormones are produced in each sex, the absolute levels in women and men represent one of the profound physiological differences between the sexes (Vincent and Tracey, 2008). In general, the absolute levels of estradiol and progesterone levels are higher in women while the levels of testosterone are higher in men. In women, fluctuating levels of ovarian hormones correspond to the different phases of the menstrual cycle. During the follicular phase of the menstrual cycle, estrogen levels increase and peak prior to ovulation, then decrease during the luteal phase. After ovulation, progesterone levels increase and peak during the luteal phase. By the end of the luteal phase, estrogen and progesterone levels decrease (Sherman and LeResche, 2006). The changes in hormone levels in women appear to coincide with increases or decreases in pain sensitivity. For example, both during pregnancy and after cesarean delivery, women with higher progesterone levels reported lower pain levels compared to women with lower levels of progesterone (Vincent et al., 2018, Kashanian et al., 2018). In a study on sex differences in chronic pain, patients with fibromyalgia with higher progesterone levels compared to those with lower levels reported lower pain severity (Schertzinger 2017). In contrast, estrogen levels are thought to modify gene expression and G-coupled proteins along the CNS and PNS, and increase during nociception (Athnaiel et al., 2023). Currently it is thought that in cisgender women, the cyclical fluctuation of sex hormone levels, rather than the increase or decrease of estrogen or progesterone across different menstrual phases, leads to differences in pain sensitivity (Vincent and Tracey, 2008, Veldhuijzen et al., 2013, Athnaiel et al., 2023, Zhang et al., 2023). For example, Pogatzki-Zahn et al. observed that women exhibited

increased sensitivity to experimental pain during the luteal phase of the menstrual cycle compared to the follicular phase (Pogatzki-Zahn et al., 2019). However, over the years, female hormonal cyclicity has complicated research on hormones and pain (Mogil, 2012), and there remains a need for further research that may elucidate the mechanisms linking the two.

Of the sex hormones, testosterone is thought to have protective effects against pain (Craft, 2007). In animals, orchiectomy surgeries in male mice produced longer durations of induced pain, while increased testosterone in female mice led to similar durations of induced pain compared to male mice without surgery (Lesnak et al., 2020). In human studies, Basaria et al. found that men with opioid-induced androgen deficiency assigned to a testosterone arm experienced higher pain tolerance compared to those assigned to the placebo arm (Basaria et al., 2015). In another study of patients diagnosed with fibromyalgia, higher testosterone levels were associated with increases in pain threshold and decreases in pain perception (White and Robinson, 2015).

Sex differences in pain sensitivity may also be related to the endogenous opioidergic system and genetics (Bartley and Fillingim, 2013). In one study using PET, women in high oestradiol states, compared to women in low oestradiol states, showed decreased pain sensitivity and increased mu-opioid receptor binding (Smith et al., 2006). In studies on genetic influences on sex-related pain differences, women with two variant alleles of the melanocortin-1 receptor (MC1R) gene experienced greater analgesia to an opioid (Mogil et al., 2003), while sensitivity to pressure pain in men was associated with the A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) (Fillingim et al., 2005).

Although these studies provide insight into the biological mechanisms underlying sex differences in pain, some suffer from methodological limitations and small effect sizes (Bartley and Fillingim, 2013). Therefore, further studies addressing these shortcomings are needed to corroborate these findings.

Psychosocial mechanisms

While sex is a biological determinant of pain outcomes, gender is a fluid, social construct that can interact with sex to shape the experience of pain. For instance, experimental research demonstrates that pain coping strategies such as pain catastrophizing (Quartana et al., 2009) and self-efficacy, which refers to the conviction that an individual can successfully achieve a goal (Bandura 1977), differ between men and women (Bartley and Fillingim, 2013). Specifically, some studies show that women engage in pain catastrophizing more often than men (Bartley and Fillingim, 2013, Le et al., 2024) and Edwards et al. found that catastrophizing mediated sex differences in daily pain (Edwards et al., 2004), however, this effect may be influenced by factors other than sex hormones, such as personality disposition (Bartley and Fillingim, 2013). Self-efficacy has been shown to be greater among men and boys compared to women and girls (Chan, 2022, Robinson et al., 2022) and lower self-efficacy has been associated with higher pain reports and symptoms (Jackson et. al, 2002). Sociocultural beliefs regarding femininity and masculinity within society have also been shown to influence gender expectancies on pain (Bartley and Fillingim, 2013). Wise et al. found that men are less willing to report pain compared to women, while Fowler et al. found that men reported increased pain when primed with a female gender role cue (Wise et al., 2002, Fowler et al., 2011). Early

exposure to adverse events such as pain and abuse may also contribute to sex differences in pain. In women, history of childhood abuse was associated with decreased pain sensitivity (Bartley and Fillingim, 2013). Less consistent are findings on the impact of family history on pain; some studies show that women with a family history of pain report greater pain symptoms and severity compared to men (Edwards et al., 1985a, Fillingim, 2000), while others show that this difference disappears after accounting for menstrual pain (Koutantji et al., 1998).

Sex differences in placebo and nocebo effects

Sex differences in pain are not limited to painful experiences or the manifestation of chronic pain states. In clinical trials of pain treatments, sex differences are observed in both placebo and nocebo effects (Shafir et al., 2022). One systematic review reported that in healthy participants and participants with IBS, placebo effects were observed more often in men compared to women (Vambheim and Flaten, 2017). The method used to induce placebo influenced sexually dimorphic placebo effects as well; verbal suggestions induced greater placebo effects in men, and conditioning induced greater nocebo effects in women (Vambheim and Flaten, 2017). However, other studies found no sex differences in placebo effects in randomized control trials (RCTs) (Vambheim and Flaten, 2017) or healthy participant studies (Enck and Klosterhalfen, 2019). Therefore, although sex has been shown to have a profound influence on both placebo effects (Olson et al., 2021) and pain (Bartley and Fillingim, 2013), research on sex differences in either are conflicting and inconclusive (Shafir et al., 2022), and the mechanisms underlying sexual dimorphism in these phenomena remain elusive. Our group conducted a large

study on placebo effects in individuals with TMD and found that women with TMD experienced lower pain tolerance, greater pain severity, larger conditioning and placebo effects, and greater reinforced expectations compared to men (Olson et al., 2021). However, this study only assessed the effects of ovarian hormones on conditioning, expectations, and placebo effects using about a quarter of the sample size that is analyzed in this work. Though the study was powered to observe sex differences in placebo hypoalgesia, it is unclear whether this extended to the effects of sex hormones, which was only examined in premenopausal women in an explorative approach. The natural next step is to determine the effects ovarian hormones on placebo effects in the full sample, and importantly, to examine the effects of testosterone, which may be more consistently anti-nociceptive and protective in nature (Bartley and Fillingim, 2013), on placebo hypoalgesia in TMD patients. In theory, if testosterone elicits anti-nociceptive effects, then there would be a smaller difference in pain ratings between placebo and control conditions, thereby generating smaller placebo effects. Ultimately, further research on sexual dimorphism in pain and placebo effects is critical for developing individually tailored options for pain treatment and management.

E. Translational approaches for acute and chronic pain management

Shortcomings in effective treatments for acute and chronic pain are due, in part, to diagnostic uncertainty (Von Roenn et al., 1993), limited knowledge about the best ways to treat pain (Sarzi-Puttini 2012, Raeder, 2022) and individual and subjective experiences of pain that depend on biopsychosocial factors, including social, neural, and sex factors (Bartley and Fillingim, 2013, van Hecke et al., 2013). Individual experiences of pain lead

to different duration and effects of treatment among individuals. Inadequate treatment may elicit detrimental side effects, such as substance dependence and abuse (Martel et al., 2015, Stoicea et. al, 2015, Volkow and Blanco, 2021, Dydyk and Conermann, 2024) urging the development of effective, non-pharmacological options for pain management. Placebo treatments are particularly promising due to evidence showing that placebos reduce pain-related responses in the brain as a form of top-down descending pain modulation (Wager and Atlas, 2015).

Pharmacological, neuroimaging, behavioral, and physiological approaches have been used to help elucidate the mechanisms underlying placebo effects in human research settings (Colloca, 2019). These realms of research have supported the development of translational approaches, such as learning and contextual methods (Colloca, 2019) to examine the influence of biopsychosocial factors on the experience of pain and the generation of placebo effects that induce analgesia.

However, although many studies have attempted to explain placebo effects using these approaches, no single method alone seems to explain the variety of placebo effects observed in clinical trials and clinical practice (Colloca, 2019). An integrative model using instructional, experiential, and social learning methods may be critical for addressing this issue (Colloca and Miller, 2011). Two of the most common methods used to induce placebo effects are classical conditioning and observational, or social, learning (Raghuraman et al., 2024). In both methods, quantitative sensory testing (QST) can be used to assess pain sensitivity for each participant by delivering stimuli followed by detection or rating of the stimulus intensity by the participant (Mücke et al., 2021) with, for example, a visual analogue scale (VAS) (Raghuraman et al., 2019, Olson et al., 2021,

Wang et al., 2022). To test for placebo effects, different cues are surreptitiously paired with individually tailored, identical pain levels in the testing phase following conditioning (Olson et al., 2021, Wang et al., 2022, Colloca et al., 2024) or observation (Raghuraman et al., 2019, Schenk and Colloca, 2020), and the difference in ratings between the cues are operationalized as placebo effects (Olson et al., 2021, Wang et al., 2022, Colloca et al., 2024). Due to the individually tailored nature of placebo paradigms, various phenomena can be studied, including sex differences, treatment expectancy, and neurobiological mechanisms.

Classical conditioning model and expectations

In the classical conditioning approach used to study placebo effects, the placebo is the conditioned stimulus and placebo effects are conditioned responses (Babel, 2019). In the classical conditioning paradigm developed by Voudouris, Peck, and Coleman, surreptitious pairing of an inactive cream with decreasing nociceptive stimulation strengthened the placebo effect following verbal suggestion of an analgesic benefit of the cream (Voudouris et al., 1989). This study pioneered research on placebo effects induced by classical conditioning, and later came the discovery that placebo analgesia can be induced by classical conditioning alone and without verbal suggestions, e.g., if an inert treatment is surreptitiously paired with decreasing nociceptive stimulation (Colloca, 2013). Many works and studies note that the effects of classical conditioning on placebo effects are specifically mediated by expectancies (Kirsch, 1985) which are acquired by decoding neural information from psychosocial contexts such as conditioned stimuli (Colloca and Miller, 2011). Therefore, including expectation measurements can assess

the role of expectations on placebo effects within the classical conditioning context (Babel, 2019).

Social learning model and empathy

Observational or social learning is among the most commonly studied manipulations to investigate placebo analgesia in laboratory contexts (Raghuraman, 2024). In the social learning model, the participant observes another individual in pain before receiving pain themselves and reporting their pain ratings. In one study, children observed their mothers' exaggerated reactions to cold water and subsequently showed lower pain thresholds (Goodman and McGrath, 2003). Colloca and Benedetti demonstrated that observation of a treatment, that was actually a sham, induced placebo analgesia (Colloca and Benedetti, 2009). These findings were corroborated by further studies showing that changes in behaviors and outcomes related to observation of others elicits placebo analgesic effects comparable in magnitude to those induced by direct experiences (Colloca and Miller, 2011, Swider and Babel, 2013, Hunter et al., 2014, Egorova et al., 2015).

Social learning-induced placebo effects can be harnessed through observation of a therapeutic benefit in others via vicarious feelings of empathy (Colloca and Benedetti, 2009, Schenk et al., 2017). MRI studies show that empathy of pain induced by observation of others in pain engages pain-responsive brain regions (Martucci et al., 2014). Behaviorally, Hartmann et al. found that placebo responders had more prosocial tendencies, fewer psychopathic traits, and greater pain-related empathetic concerns compared to placebo non-responders (Hartmann et al., 2023), and a review on empathy

and placebo effects concluded that the higher the trait empathy, referring to a stable capacity for empathic responses (Wallmark et al., 2018), the higher the subsequent placebo effects (Meeuwis et al., 2023). Less is known about influence of state empathy on placebo effects. State empathy refers to an individual's perception of another person's state that generates the individual's associated automatic and behavioral responses (Shen 2010). To date, no studies have intentionally manipulated state empathy in the context of social learning, warranting studies that test the modifiability of state empathy following observation.

Brain imaging approaches

Magnetic resonance imaging

Magnetic resonance imaging (MRI) combines strong magnetic fields with radiofrequency pulses to display high spatial resolution T1 and T2 structural images (Martucci et al., 2014), while functional magnetic resonance imaging (fMRI) is used to detect dynamic patterns of activity in the brain (Buxton, 2013) via the blood oxygen level dependent (BOLD) signal (Wager and Atlas, 2015). MRI and fMRI have elucidated how neural correlates of acute and chronic pain affect pain perception and neural activity (Martucci et al., 2014). In fMRI studies on pain, several key regions have emerged as regions associated with pain perception, including the insula, somatosensory and motor cortices, ACC, thalamus, basal ganglia, and parietal cortex, PFC, hippocampus, amygdala, PAG, and cerebellum (Ahmad and Aziz, 2014, Martucci et al., 2014, Yang and Chang, 2019). These regions are primarily involved in sensory and affective components of pain processing and perception, motor function, and higher order brain processing and

integration (Martucci et al., 2014). In an early study, Coghill et al. classified participants as low, moderate, and high pain sensitive people and acquired fMRIs. The individuals with the highest pain sensitivity had increased activity in the primary somatosensory cortex, ACC, and PFC (Coghill et al., 2003), while activity in the thalamus remained the same between the groups. These findings demonstrated that the thalamus is important in general for pain processing, but subjectivity of pain experience and sensitivity relies on higher order cortical areas.

fMRI experiments show that during placebo analgesia, placebo effects and expectations for reduced pain elicit reliable increases in activation of the PFC (Wager and Atlas, 2015) and that placebo effects are positively correlated with connectivity in the dlPFC (Stein et al., 2012). In some chronic pain conditions, the probability of placebo response in patients can be predicted due to the neuronal interactions between the PFC and pain processing regions, such as the PAG (Vachon-Presseau et al., 2018). Further, during placebo analgesia, little extinction occurs, and effects persist after the discontinuation of reinforcement. This has been shown to be related to the suppression of prediction error processing in the ventral striatum, a region integral to movement and reward processing, by the PFC (Schenk et al., 2017).

While there is extensive literature surrounding activation of the brain by placebos (Wager and Atlas, 2015), less is known about the structural brain correlates of pain and placebo effects. MRI studies on pain demonstrate that chronic pain is distinct from acute pain and may occur following CNS changes that occur during chronic pain (Ong et al., 2019). Cortical changes can be measured using voxel-based morphometry (VBM) to assess gray matter volume (GMV) changes, and cortical thickness (CTh) analysis (Martucci et al.,

2014). From these studies, increases and decreases in GMV and CTh have been observed across various chronic pain conditions, including fibromyalgia, migraine, chronic low back pain (cLBP) and TMD (Martucci et al., 2014). However, the extent to which these findings translate to placebo hypoalgesia is still in question, particularly due to the lack of studies examining the phenomenon or inconsistencies among the studies that do exist (Schweinhardt et al., 2009, Vachon-Presseau et al., 2018, Hartmann et al., 2023), warranting studies investigating the neuroanatomical determinants of placebo response.

Electroencephalography and peak-alpha frequency

In addition to MRI, several studies have employed electroencephalography (EEG) to measure electrical activity of the brain for pain biomarker development (Furman et al., 2018, Furman et al., 2020, Raghuraman et al., 2019). The neural oscillations captured by EEG are labeled according to their frequency, with delta, theta, alpha, and beta waves representing the smallest to largest waveforms. EEGs in healthy adults typically capture low-amplitude, mixed frequency background or desynchronized rhythms (Britton et al., 2016). When the patient is relaxed with closed eyes, the background is characterized by the alpha rhythm, which decreases in amplitude and presence once the eyes open (Adrian & Matthews, 1934, Britton et al., 2016). In a normal state, the alpha rhythm is symmetrical on either side of the posterior head regions (Britton et al., 2016). Thus, slower alpha on one side indicates abnormal cerebral functioning on the slower side (Britton et al., 2016, Moretti et al., 2004; Garcés et al., 2013). The wave frequency containing the alpha band's maximum power is referred to as the peak alpha frequency (PAF) (Angelakis et al. 2004). PAF varies between individuals, but most healthy

individuals show PAFs between 8-12 Hz. Higher or faster PAF indicates greater brain wave amplitude at higher frequencies of the alpha spectrum (Raghuraman et al., 2024) and has been shown to be associated with reduced experimental pain intensity (Furman et al. 2018) and sensitivity (Furman et al. 2020). In individuals with chronic pain, slower PAF is associated with disease presence (Sarnthein et al., 2006). These findings suggest that PAF may represent a promising biomarker of pain outcomes in acute and chronic pain populations.

I. Specific Aims

This set of studies aimed to build a biopsychosocial model to study placebo effects, focusing on the social, sex, and neural factors that influenced experimental placebo hypoalgesia in pain-free adults and adults diagnosed with temporomandibular disorders (TMD), referring to chronic orofacial pain. Three central hypotheses were tested to study the contributions of empathy, sex, and brain morphology on the generation of placebo effects using social learning and classical conditioning approaches:

1. Observing a human demonstrator in pain will result in increased state empathy. This enhanced state empathy will mediate socially induced hypoalgesia which in turn will be predicted by individual PAF. 2. Women will show greater conditioning strength, treatment expectations and placebo hypoalgesia compared to men, and higher levels of testosterone will be associated with lower chronic pain severity and placebo hypoalgesia. 3. Finally, whole brain morphometry will correlate with the individual magnitude of placebo effects. The specific aims were as follows:

Aim 1: Determine the effect of state empathy on socially induced hypoalgesia.

a. Determine the effect of state empathy for a human demonstrator compared to an avatar on placebo hypoalgesia using immersive VR.

b. Determine whether PAF predicts socially induced placebo effects using EEG.

Prediction: Observing a human demonstrator, compared to an avatar, in VR, compared to non-VR, will result in greater state empathy. This enhanced state empathy will mediate socially induced hypoalgesia, which in turn will be predicted by individual PAF.

Aim 2: Determine the role of sex and gonadal hormones on pain experience, treatment expectancies, and placebo effects.

a. Determine the role of sex-specific expectations on placebo effects in pain free-individuals and individuals diagnosed with TMD using classical conditioning.

b. Determine the effects of gonadal hormone levels on pain severity, conditioning strength, expectations, and placebo effects in pain-free individuals and individuals diagnosed with TMD.

Prediction: Women in both groups will have greater conditioning strength and treatment expectations compared to their male counterparts, which will be associated with greater placebo effects. Further, higher testosterone levels will be associated with lower chronic pain severity and placebo hypoalgesia.

Aim 3: Determine the association between neural traits and placebo hypoalgesia.

a. Identify the placebo responders and placebo non-responders among participants with TMD using classical conditioning.

b. Identify the structural brain correlates of individual placebo responses in participants with TMD using voxel-based morphometry.

Prediction: Placebo responders will exhibit significantly greater placebo effects compared to placebo non-responders. Further, whole-brain cortical thickness will correlate with placebo effects in individuals with TMD.

Chapter II: Effects of state empathy on socially induced hypoalgesia using immersive virtual reality

A. Abstract

Observing another person experiencing pain reduction from a treatment influences one's placebo responses to the same treatment. We determined the effects of state empathy on socially induced hypoalgesia using VR with a human versus avatar demonstrator to intentionally manipulate empathic responses in observers. We used baseline PAF to predict socially induced placebo effects. Participants observed a human or an avatar demonstrator experiencing pain changes with placebo versus control conditions in VR and non-VR settings. We measured their state empathy ratings for the demonstrator's pain intensity and pain unpleasantness sensations. Subsequently, participants underwent the same treatments seen during observation but with identical thermal intensities to test for placebo effects. Baseline PAF was measured as a predictor of placebo effects. Independent of VR and non-VR settings, observation increased state empathy for pain intensity and unpleasantness. However, observation of the human demonstrator induced greater empathy compared to the avatar. Observation subsequently induced significant placebo effects for pain intensity and pain unpleasantness in VR and non-VR, with larger placebo effects in non-VR. Demonstrator-type elicited different effects on placebo hypoalgesia depending on the VR setting. Within VR, placebo hypoalgesia was greater with the avatar compared to the human demonstrator, while the opposite trend was seen within non-VR. Cognitive state empathy mediated the relationship between demonstrator-type and placebo effects. Finally, faster PAF in somatosensory and frontal

regions predicted greater placebo effects. These findings may hold clinical relevance with the perspective of customizing VR and social learning interventions tailored to patients' needs.

B. Introduction

Mental processing of social information often induces both vicarious learning and feelings of empathy. (Olsson et al., 2005, Olsson et al., 2007, Olsson et al., 2007) Empathy has been found to influence the perception of emotional pain and mentalizing processes (Singer et al., 2004, Kanske et al., 2015, Shamay, 2011, Winter et al., 2017) and vicarious learning has been specifically investigated in the context of placebo effects (Colloca and Benedetti, 2009, Goubert et al., 2011, Raghuraman et al., 2019, Schenk et al., 2017). Namely, we and others have previously demonstrated that hypoalgesic placebo effects can occur without formal conditioning and direct prior experience, because crucial information necessary to build empathy and social learning can be acquired through observation of a therapeutic benefit in others (Colloca and Benedetti, 2009, Schenk et al., 2017). Placebo analgesic effects following the observation of a benefit in another person are similar in magnitude to those induced by directly experiencing an analgesic benefit (Goubert et al., 2011, Raghuraman et al., 2019) and a recent meta-analysis on socially induced (also referred to as observationally induced) placebo effects and empathy (mostly traits) indicated that the higher the empathy, the higher the subsequent placebo effects (Meeuwis et al., 2023). However, no studies have intentionally manipulated state empathy, a process in which an individual's perception of another person's state generates the individual's associated automatic and behavioral responses (Shen, 2010) in the context of social learning.

To address the gap, we manipulated state empathy by using VR with a human demonstrator and an avatar. VR refers to computer-generated, three-dimensional interactive environments (Wann et al., 1996) and can diminish pain experiences in the

context of laboratory and clinical settings (Morris et al., 2009, Hoffman et al., 2011, Indovina et al., 2018,). Moreover, studies have shown that VR experiences can increase empathy towards stigmatized groups or conditions (Seinfeld et al., 2022). In this study, we used VR to investigate the modifiability of individuals' empathetic state and subsequent responses to placebo manipulation via social learning. A limited number of prior experimental studies have noted the potential to evoke varying degrees of empathy by utilizing demonstrators with different characteristics (de Borst and de Gelder, 2015). In general, human demonstrators with visible facial expressions seem to induce higher empathy and brain responses than avatars showing less or no facial expression (de Borst and de Gelder, 2015).

Together with VR, we adopted a high-resolution electroencephalography (EEG) approach as a non-invasive means to study the neural processes related to state empathy and pain changes. The PAF measured with EEG has been found to be associated with pain sensitivity to heat (Furman et al., 2020) and baseline PAF before exposure to capsaicin predicted pain intensity ratings during capsaicin-heat pain (Furman et al., 2018). In a previous study, we found that observation of a video demonstrator receiving analgesic and control creams induced placebo effects that were positively associated with baseline PAF in placebo responders (Raghuraman et al., 2019)

This study expands upon current literature by determining the impact of state empathy on socially induced placebo effects (Colloca and Benedetti, 2009, Hunter et al., 2014, Meeuwis et al., 2023, Raghuraman et al., 2019, Swider et al., 2013, Vögtle et al., 2013) using VR to manipulate state empathy. We hypothesized that observing the human demonstrator in VR would result in increased state empathy (Shen et al., 2010) This

enhanced state empathy would mediate socially induced hypoalgesia which in turn could be predicted by individual PAF.

C. Methods

Participants

Data from 47 participants (mean age 29.2; 18-61 age range, 31 females) for this two-day study at the University of Maryland, Baltimore were included in the present analysis. The University of Maryland, Baltimore Institutional Review Board (IRB) approved the study (Prot. HP-#00085382), and all participants gave verbal and written informed consent including an authorized deception approach (Raghuraman et al., 2019). All procedures were conducted in accordance with the Declaration of Helsinki and with the relevant guidelines and regulations. Participants were debriefed at the end of the experiment using a study exit form that stated the complete nature of the study and the use of deception (Raghuraman et al., 2019). Participants were given the option to withdraw their data from the study after debriefing, however none did. Participants were compensated $180 for completing all procedures of the study.

Eligibility criteria

Participants were screened over the phone and in person to confirm their eligibility as a healthy volunteer. The following criteria excluded a potential participant from the study: impaired hearing; color blindness; any allergies or sensitivities to creams and/or food colorings; any history of chronic pain; current ongoing pain; neurological, cardiovascular, pulmonary, kidney and liver diseases; psychiatric disorders; and/or use of pain and other medications, and pregnancy or breastfeeding. We used a toxicology test for detection of amphetamines, methamphetamines, cocaine, opioids, and THC before starting the

experimental procedures on day one and again on day two if more than 24 hours had passed. Participants with positive tests were deemed ineligible for the study.

Heat pain stimulation

A CHEPS thermode (PATHWAY System, Medoc, Ramat Yishai, Israel) was used to deliver painful thermal heat stimuli. Participants underwent a quantitative sensory pain test to assess pain sensitivity using the limits paradigm (Fruhstorfer et al., 1976) During the pain calibration, participants rated their pain intensity for a series of 12 heat painful stimulations (pulses) which lasted less than a second each (for a destination temperature of 46°C, the total pulse time was around 890ms, with a maximal temperature duration of approximatively 20ms). Participants reported their pain intensity using a visual analogue scale (VAS; see Measurements) ranging from 0 = no pain to 100 = maximum tolerable pain. This allowed a moderate level of pain (i.e., VAS ratings of 50–60) tailored to each participant's pain sensitivity to be used for the experience phase of the experiment. The average pain sensitivity was 35.4°C, (sem = 1.2°C, ranging from 34.4°C to 49.4°C). The mean temperature used for the experience phase was 47.1°C (sem = 0.3°C, ranging from 43°C to 50 °C). The temperature ramped up from 32°C (baseline) with an increasing rate of 70°C/s, maintained plateau for less than a second (pulse), and ramped down to baseline with a decreasing rate of 40°C/s. The duration of the increase (ramp-up time) and decrease (ramp-down time) in temperature varied for each participant to induce a painful stimulation rating of 5 out of 10 on the VAS. For a temperature of 46°C the mean ramp-up time was 291ms and the mean ramp-down time was 612ms, similar to Roberts et al. (Roberts et al., 2008).

EEG recording

EEG data were collected using a high-resolution 64-channel Brain Vision actiCAP system (Brain Products GmbH, Munich, Germany). Electrodes were labeled in accordance with an extended international 10–20 system. All electrodes were referenced online to the FCz site. Brain activity was continuously recorded within a 0.01–100 Hz bandpass filter and with a digital sampling rate of 1000 Hz. The 64-channel electrode cap (Brain Vision actiCAP system, Brain Products GmbH, Munich, Germany) was set up and placed on the participant's head using a high-viscosity gel and electrode impedances were maintained below 5 kΩ.

Virtual reality and 2D content

A high-resolution HTC Vive Eye Pro virtual reality headset (HTC. Inc, San Francisco, California) was set up and operated on the SteamVR platform (Windows, Linux). The headset was placed on the participant's head on top of the 64-channel electrode cap (see: EEG recording), using a pad to limit contact with the electrodes and, therefore, limit EEG artifacts. This allowed for simultaneous acquisition of EEG data and behavioral responses.

The content for the immersive VR and non-VR (control) conditions was developed by engineers at the University of Maryland, College Park's College of Computer, Mathematical, and Natural Sciences. The University of Maryland School of Nursing (UMSON) and University of Maryland College Park (UMD) teams planned, designed, and filmed the content for the VR and non-VR conditions. The UMD team also developed a synchronized network socket module to receive signals from the E-Prime

stimulus presentation software (Psychology Software Tools, Sharpsburg, PA, USA). The module ensures visual content shown in the VR and non-VR conditions follows test patterns dictated by E-Prime and matches the recorded EEG signal timestamps.

3D 360-degree videos of a human demonstrator receiving painful and non-painful stimulation in concomitance with two treatments were filmed using an Insta 360 Pro 2 camera. The human demonstrator was filmed in plain clothes (see Fig. 1) and showed painful and neutral facial expressions during the stimulations for the control and treatment conditions, respectively. The content was copyedited to clearly show the context for social learning during the control and treatment conditions. The content was meant to manipulate empathic states during observation and prior to the experiential phase of the experiment. Once the content for the observation phase was deemed completed and approved by both research teams, non-VR content was extracted and generated using the same 360-degree footage. The non-VR content was a reprojected 2D version of the 3D 360-degree video focused on the human demonstrator. Finally, the demonstrator was modeled using Autodesk Maya to create a non-human avatar version. The avatar was rigged to have the same shape and natural posture as the human demonstrator. Then it was rendered in Unity software to match the position and depth of the 360-degree video. The human demonstrator appeared to be sitting in the same position when viewed in both the VR and 2D version. For the creation of the CG avatar, the same clothes, treatments, and contexts were modeled to mirror that of the human demonstrator. The facial expression on the avatar was intentionally kept neutral during both the control and treatment conditions to assess empathy changes in the observer between the human and avatar demonstrations.

The VR conditions consisted of observing the human or avatar demonstrator through the HTC Vive Eye Pro virtual reality headset, separated by short periods of simple visual cues such as a blue or green cross, followed by user responses on the VAS. We created 8 different scenarios for the human demonstrator, each scenario having 5 variations. In addition, we created 8 different complimentary scenarios for the avatar demonstrator. The non-VR conditions served as a control for the effect of immersion [51] and consisted of observing the human or avatar demonstrator on a computer screen as opposed to in VR. The human or avatar demonstrator 2D content was extracted from the footage captured in the 3D 360-degree video, having the same number of scenarios and variations. All other visual cues and VAS were identical 2D versions of their 3D counterpart. This maintained consistency between the two conditions. Behavioral responses were acquired through interaction with the HTC wireless motion tracked controller during VR sessions. The VR application was developed using the Unity game engine (Unity Technologies, San Francisco, California). The UMD team developed 3D VAS rendered directly in the VR headset to facilitate behavioral responses without interrupting the immersive VR session. A 2D VAS input visual was also derived from the 3D implementation for use in the non-VR conditions.

Experimental procedures

The experiment took place at the UMSON Clinical Suites, Baltimore, during two sessions on two separate days no more than ten days apart.

During the first session, participants completed a drug test and were given an overview of the study. They were informed that we were investigating how brain activity relates to the experience of pain. Prior to starting the experimental procedures, vitals (blood pressure, heart rate, height, and weight) were collected to assist with study monitoring (see Table 1).

Participants were then instructed about the first session experimental tasks, which consisted of the quantitative sensory pain test (see: Heat pain stimulation). During the second session, participants were informed that the session consisted of four conditions (VR-Human, VR-Avatar, Non-VR-Human, Non-VR-Avatar; counterbalanced) with each condition divided into two phases – the observation phase followed by the experiential phase.

Before the observation phase, a resting state EEG was acquired for 10 minutes total - with 5 mins each of closed and open eyes. Then, the observation phase started with each participant following the paradigm described below and depicted in Fig. 1.

For the observation phase, participants were told they would watch a human demonstrator, or the same demonstrator converted into an avatar, receiving painful heat stimulation on his non-dominant forearm where two creams were applied. As opposed to establishing a treatment expectancy context, participants were simply told that blue and green creams with different ingredients were applied to the demonstrator's forearm before receiving pain on the site of each cream. They were not told whether one of the creams had analgesic properties. This allowed the participants to learn about the effectiveness of the creams solely by observing the analgesic experience of the demonstrator in the visual cues. Following the observation phase, the same creams were

applied to the participants' non-dominant forearm along with heat pain for the experiential phase. Both creams were actually CeraVe Daily Moisturizing Lotion (L'OREAL, Active Cosmetics Division, New York, United States of America), a hypoallergenic, commercially available cream that is free of dyes, fragrances, masking fragrances, lanolin, parabens, and formaldehyde. This cream was colored in either blue or green using FDA-approved food dyes. The color associated with the observed "treatment" (a placebo) was counterbalanced among participants to avoid linking the supposed efficacious cream to the color prior to the observation phase. The location of the application of the cream (upper versus lower ventral forearm) was also counterbalanced across participants. Since experimenter sex and race may influence pain-related outcomes (Olson et al., 2021), one experimenter collected all behavioral data, keeping constant the experimenter sex and race.

Study design and measurements

We used a within-subjects design with each participant going through four conditions, each with placebo and control manipulations in the VR or non-VR (i.e., simply observing the demonstrator on a computer screen as opposed to in VR) settings and observing either a human demonstrator or an avatar of this demonstrator.

The observation phase of each condition consisted of two blocks (treatment and control cues) of 10 trials for each cue, for a total of 20 trials. The blocks were counterbalanced across participants (see Fig. 1). During each trial, participants first saw a colored cue (blue or green, 2s) indicating the color of the cream on which the demonstrator would receive a heat stimulus. Then, they observed a video of the demonstrator (2.5s). Here, the

human demonstrator showed a painful facial expression during the control block and a neutral facial expression during the treatment block. The avatar lacked realistic human facial expressions and therefore always showed a neutral expression.

After a delay, the pain intensity and pain unpleasantness ratings of the demonstrator were measured (see: Measurements) with VAS (5s). For the treatment condition, the demonstrator rated his pain on the VAS between 10–30 and 70–90 for the control condition. This was followed by an inter-trial interval (4–7s). At the end of each observation block, participants were asked to assess state (affective and cognitive) empathy answering the four questions described below (see: Measurements) and depicted in Fig. 1.

The experiential phase of each condition contained two blocks (treatment and control cues) of 20 trials for each cue, for a total of 40 trials (Fig. 1). During each trial, an anticipatory cue (blue or green, 2s) indicated the upcoming heat stimuli, followed by the stimulation itself (2s, with an additional 0.5s due to the time required for the thermode to ramp up to temperature). After a delay (2s), participants rated their pain intensity and pain unpleasantness on a VAS from 0 = no pain to 100 = maximum tolerable pain (infinite time allotted until response). The temperature used for the heat pain stimuli were kept constant for both the treatment and control conditions and was derived from a previously-performed pain calibration corresponding to a moderate pain level (i.e., VAS ratings of 50–60). The trials ended with an inter-trial interval (4–7s). The pain intensity and pain unpleasantness rating (VAS) data were acquired using E-Prime v3 (Psychology Software Tools, Sharpsburg, PA, USA).

Measurements

Intensity and unpleasantness pain levels were measured using a VAS anchored from 0 = no pain to 100 = maximum tolerable pain. Participants were trained to separate the physical sensation from the emotional uncomfortable experience associated with the heat stimulations by reporting VAS ratings for pain intensity and pain unpleasantness, respectively. VAS were electronically displayed inside the headset for the VR conditions and on a 2D monitor for non-VR conditions.

Affective and cognitive state empathy. The core dimensions of state empathy involve both affect and cognition (Bagozzi and Moore, 1994, Preston and Waal, 2002, Campbell and Babrow, 2004, Decety and Jackson, 2006, Decety and Lamm, 2006, Shen, 2010). Affective state empathy refers to the understanding and sharing of others' emotions (Decety and Jackson, 2006, Zillmann, 2006), while cognitive state empathy refers to recognizing, comprehending, and adopting another person's point of view (perspective-taking) (Shen 2010). Both state empathy dimensions were measured using Berti et al.'s approach (Shen 2010). Questions 1 and 2 assessed affective state empathy: 1) How intense was your experience of pain while watching the demonstrator receive the stimulation? (sensory, self-referred) 2) How unpleasant was your experience of pain while watching the demonstrator receive the stimulation? (emotional, self-referred) and questions 3 and 4 assessed cognitive state empathy: 3) How intense do you think was the sensation the demonstrator experienced while receiving the stimulation? (sensory, other-referred) and 4) How unpleasant do you think was the sensation the demonstrator experienced while receiving the stimulation? (emotional, other-referred) on a VAS anchored from 0 to 100 (infinite until response; see Fig. 1) (Betti et al., 2009).

Trait empathy, anxiety, and depression were assessed at baseline. A privacy-compliant link was sent via Research Electronic Data Capture (REDCap) for completion of the measurements (Harris et al., 2009, Harris et al., 2019). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The Interpersonal Reactivity Index (IRI) evaluated the responses of one individual to the seen experience of another individual (Davis, 1980). It contains 4 subscales: a) empathic concern (EC, which assesses the tendency to experience feelings of sympathy and compassion for others in need), b) personal distress (PD, which assesses the extent to which an individual feels distress as a result of witnessing another's emotional distress), c) perspective-taking (PT, which assesses the dispositional tendency of an individual to adopt the perspective of another), and d) fantasy scale (FS, which assesses an individual's propensity to become imaginatively involved with fictional characters and situations).

The Basic Empathy Scale (BES) evaluated an individual's trait empathy with 2 subscales: a) cognitive empathy and b) emotional empathy (Carré et al., 2013). The BES is based specifically on the definition of empathy put forth by Cohen and Strayer (Cohen and Strayer, 1996) and allows for a focus on both affect congruence (affective empathy) and the understanding of another's emotions (cognitive empathy).

Finally, we controlled for individual anxiety and depression using the State-Trait Anxiety Inventory (STAI) which measured state and trait anxiety (Spielberger et al., 1970), Beck

Anxiety Inventory (BAI) which measured anxiety symptom severity (Beck et al., 1988) and the Beck's Depression Inventory (BDI) which measured depression symptom severity (Beck et al., 1961).

Statistical analysis

Sociodemographic and clinical characteristics.

Descriptive analyses were conducted to characterize the study population. Data are presented in Table 1 and expressed as count numbers or means and percentages or standard error means.

Power calculation

Based on our previous studies (Schenk et al., 2020) a total number of 47 was required to achieve 0.8 statistical power to detect an effect size of Cohen's f = 0.35 at an alpha level of 0.001 on behavioral pain changes. Based on previous PAF results (Raghuraman et al., 2019) the power analysis indicated that a minimum number of 37 was required to have 0.8 statistical power to observe an effect size of Cohen's f^2=0.590 at an alpha level of 0.05 applying Bonferroni correction for seven EEG electrodes. Thus a total number of 47 participants were included for this study, accounting for 20% of data that are deemed unanalyzable.

Behavioral data analysis

Similar to previous studies (Hunter et al., 2014, Raghuraman et al., 2019), we analyzed behavioral results primarily consisting of pain intensity and pain unpleasantness ratings recorded during the testing phase to determine if significant socially induced placebo hypoalgesia (delta scores of the pain intensity and pain unpleasantness ratings for

treatment trials subtracted from the pain intensity and pain unpleasantness ratings for control trials) had been developed following observation.

Participants underwent four randomized, counterbalanced conditions with VR or non-VR conditions as within-subjects variables (VR_Human vs. VR_Avatar vs. Non-VR_Human vs. Non-VR_Avatar) on pain intensity and pain unpleasantness VAS ratings. Socially induced placebo hypoalgesia was quantified by subtracting the trial-by-trial VAS ratings obtained during the placebo treatment condition from the VAS ratings obtained during the control condition (VAScontrol - VASplacebo). The normality of these score differences was assessed using three methods: visually analyzing the distribution, conducting the Shapiro-Wilk test, and examining the skewness and kurtosis values. Upon analyzing the distribution, we observed that the data predominantly adhered to the expected Gaussian distribution, with a notable clustering of 0 values. The Shapiro-Wilk test suggested that the data did not follow a normal distribution ($p<0.001$). The skewness values indicated that the data followed a normal distribution (intensity: skewness=0.6, sem=0.02; unpleasantness: skewness=0.5, sem=0.02), however, the kurtosis values were slightly elevated, but lower than 3 (intensity: kurtosis=2.3, sem=0.04; unpleasantness: kurtosis=2.6, sem=0.04). The results suggest that a non-normal distribution could be accounted for by the prevalence of the value "0" which appears to be more common than other values. It is therefore not possible to successfully transform the distribution to reach normality. To mitigate the possibility of encountering false positives, we used Bonferroni corrected p-values for the following analysis to increase the likelihood of accurate results.

We used a Linear Mixed Model (LMM) to evaluate the modulating effects of VR versus non-VR and the demonstrator's nature (human vs. avatar) on participants' state empathy regarding pain intensity and pain unpleasantness during the observation phase.

Moreover, we used a LMM to analyze the differences between the experiential pain intensity and pain unpleasantness ratings in the treatment and control conditions. The color of the treatment cue (blue vs. green), order of blocks (treatment first vs. control first), and cream site (treatment cream on top vs. control cream on top) were randomized and set as covariates.

Finally, we also analyzed the mediation effect of state empathy on socially induced hypoalgesia using Rockwood's Multilevel Mediation Model MLmed Beta 2 (Hayes and Rockwood, 2020, Hu et al., 2020). All significances were set at $p = 0.05$ and the analyses were conducted using IBM® SPSS Statistics software version 29.0.

Resting state peak alpha frequency (eyes closed)

The EEG recordings acquired before the experimental task with five minutes of closed eyes were preprocessed using the EEGLAB toolbox (Delorme and Makeig, 2004). The first step involved band-pass filtering the EEG with a cut-off of 0.5 Hz to remove the drift of baseline. The Surface Laplacian (SL) was used to transform the scalp-recorded EEG into estimates of radial current flow. The direction of the radial currents was denoted with a positive and negative sign. The positive values represent the flow of current from the brain to the scalp (sources) while negative values represent the flow from the scalp to the brain (sinks) (Srinivasan et al., 2006). After rebuilding the FCz electrode, independent component analysis (ICA) was done to correct for vertical and

horizontal eye movements as well as muscle artifacts. Time frequency representations were generated using the FieldTrip toolbox (Oostenveld et al., 2011) in Matlab. Five minutes from the EEG recording was used and eyes closed was segmented into five seconds epochs. Power spectral density in the 2–40 Hz range was derived for each epoch in 0.2 Hz bins (Srinivasan et al., 2006). The center of gravity (CoG) method was used to derive the PAF where CoG is calculated using the following formula: $= \sum^{n}_{i} f_i * ai / \sum^{n}_{i} ai;$ f_i is i-th frequency bin including and above 7.2 Hz, n is the number of frequency bins between 7.2 and 12 Hz, and a_i is the spectral amplitude for f_i. The averaged PAF across epochs was then identified as the peak frequency (Furman et al., 2018). To explore the associations between PAF during resting state and socially induced placebo hypoalgesia, we performed linear regressions between PAF at electrodes Fp1, Fp2, C3, Cz, C4 (Raghuraman et al., 2019), T7 and T8 (Nir et al., 2010, Raghuraman et al., 2019) and socially induced placebo hypoalgesia.

D. Results

The study population consisted of a cohort of 47 healthy participants with an average age of 29.2 years and prevalence of women (n = 31). Clinically speaking, all participants scored within the ranges considered normal for anxiety and depression (see Table 1).

	N/mean (normal range)	%/SEM
Sex		
Women	31.0	66.0
Men	16.0	34.0
Race		
White	27.0	57.4
Non-White	20.0	42.6
Age (in years)	29.2	0.5
Blood Pressure (mmHg)		
Diastolic	113.5	2.4
Systolic	76.7	1.7
Heart Rate (bpm)	73.4	1.6
Height (inches)	65.5	0.5
Weight (lb)	154.2	5.9
BMI (kg/m)	24.9	0.7
Psychological surveys		
IRI	67.5	1.7
BES (cognitive; affective)	18.6; 26.2	0.7; 0.9
Mood surveys STAI	37.0 (20-37)	1.4
BAI	4.9 (0-7)	1.3
BDI	8.7 (0-9)	1.5

Table 1. Participants' characteristics. Abbreviations: Interpersonal Reactivity Index (IRI), Basic Empathy Scale (BES), State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Beck Depression Inventory (BDI)

Observation phase and state empathy manipulation

During the observation phase, our goal was to manipulate the levels of affective and cognitive state empathy by showing a human versus avatar demonstrator experiencing pain in the no-treatment and pain relief condition whereby the demonstrator reported the treatment as hypoalgesic (see Fig. 2).

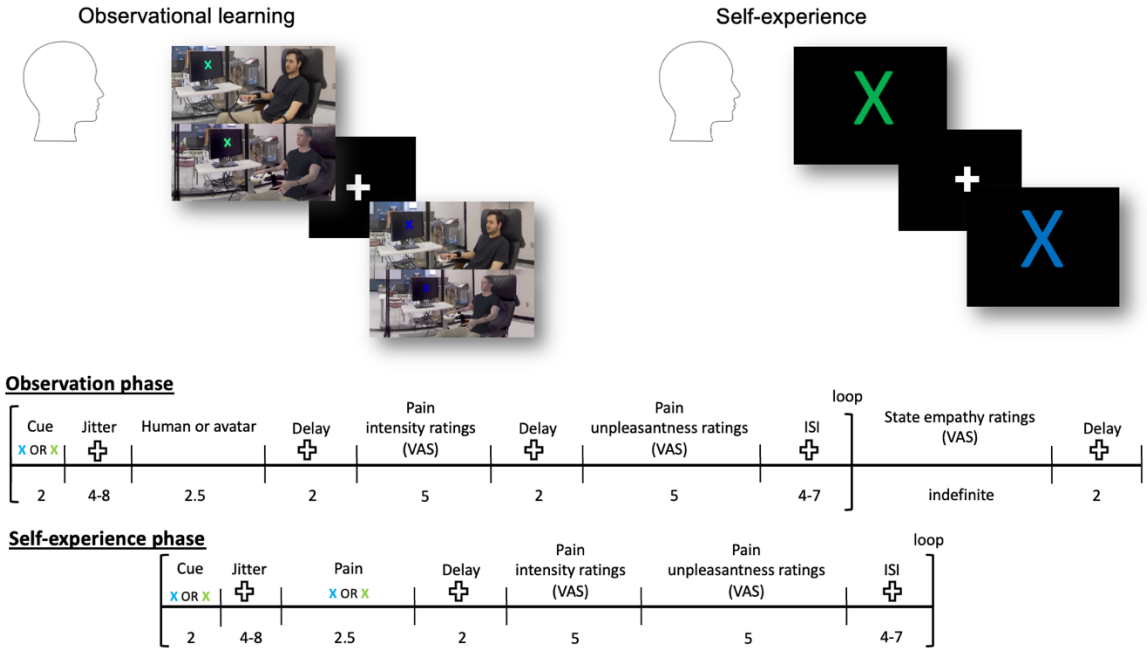


Figure 2. Experimental procedure for state empathy manipulation (observation phase) and socially induced placebo hypoalgesia (the self-experiential phase). For the observation phase, participants observed a blue or green cue followed by a human or avatar demonstrator experiencing pain and reporting their pain intensity and pain unpleasantness ratings (visual analogue scale (VAS) from 0 (no pain) to 100 (maximum tolerable pain)) on a loop for 10 trials per cue for a total of 20 trials for the observation phase. At the end of the observation phase, participants reported their affective and cognitive state empathy ratings (VAS) for self (shown) and for the demonstrator, respectively. For the self-experiential phase, participants saw a blue or green cue before receiving a thermal painful stimulation on the forearm on a loop for 20 trials per cue for a total of 40 trials for the self-experience phase. After each trial, participants reported their pain intensity and pain unpleasantness ratings (VAS). ISI = inter-trial interval.

The LMM revealed significant main effects of treatment (control vs. treatment) condition on state empathy ratings ($F_{(1,186)}$=20.2, p<0.001; $F_{(1,186)}$=31.2, p<0.001; $F_{(1,174)}$=616.1; p<0.001; $F_{(1,170)}$=617.8; p<0.001) as well as a main effect of demonstrator-type (human vs. avatar: intensity: ($F_{(1,174)}$=30.9; p<0.001), unpleasantness: ($F_{(1,170)}$=37.7; p<0.001). Moreover, there was a significant treatment by demonstrator-type interaction for cognitive empathy (intensity: $F_{(1,174)}$=12.1; p<0.001, unpleasantness: $F_{(1,170)}$=13.1; p<0.001) but not affective empathy (intensity: p=0.769, unpleasantness: p=0.084). Specifically, both affective and cognitive state empathy scores were higher during the control condition than the treatment condition (affective empathy for pain intensity: $F_{(1,186)}$=20.2, p<0.001; affective empathy for pain unpleasantness: $F_{(1,186)}$=31.2, p<0.001; cognitive empathy for pain intensity; $F_{(1,174)}$=616.1; p<0.001; cognitive empathy for pain unpleasantness; $F_{(1,170)}$=617.8; p<0.001; see Fig. 2). Planned post-hoc Bonferroni-corrected comparisons revealed higher state empathy ratings when observers witnessed the demonstrators receiving painful stimuli with no treatment (control); (affective and cognitive empathy ratings for pain intensity and pain unpleasantness: p<0.001; p<0.001; p<0.001; p<0.001), suggesting that participants engaged in cognitive empathy to assess the demonstrator's perceived pain intensity and pain unpleasantness. Additionally, affective empathy was evidenced by participants experiencing some pain intensity and pain unpleasantness themselves through mere observation of the conditions.

We observed higher cognitive state empathy towards the human demonstrator as compared to the avatar version of the same demonstrator, for pain intensity ($F_{(1,174)}$=30.9; p<0.001) and pain unpleasantness ($F_{(1,170)}$=37.7; p<0.001), (see Fig. 3). Post-hoc analyses applying Bonferroni correction confirmed that cognitive empathy ratings were greater

following observation of the human demonstrator as compared to the avatar (pain intensity, $p<0.001$; pain unpleasantness, $p<0.001$). The results suggest that participants demonstrated greater empathy when observing a human receiving painful stimuli compared to an avatar. This was reflected in higher ratings of pain intensity and pain unpleasantness for the human demonstrator. However, the type of demonstrator (human vs. avatar) did not significantly impact participants' own perceived pain or unpleasantness in terms of affective empathy. In terms of VR settings, we found no significant main direct effect of VR settings (VR vs. non-VR) on either affective or cognitive state empathy for both pain intensity and pain unpleasantness (affective: $p=0.627$; $p=0.084$; cognitive: $p=0.728$; $p=0.588$). There was a significant interaction between demonstrator-type and treatment for cognitive empathy only, for pain intensity (other-referred sensory empathy) ($F_{(1,174)}=12.1$; sem=0.32, $p<0.001$) and pain unpleasantness (other-referred emotional empathy) ($F_{(1,170)}=13.1$; sem=0.31, $p<0.001$; see Fig. 2). Post-hoc analyses applying Bonferroni correction indicated that the pain ratings associated with the human demonstrator were significantly higher compared to the avatar during the control (intensity: mean difference=19.7; sem=0.61; $p<0.001$, unpleasantness: mean difference=21.9; sem=0.60; $p<0.001$) and placebo conditions (intensity: mean difference=4.5; sem=0.17; $p<0.001$, unpleasantness: mean difference=4.3; sem=0.18; $p<0.001$).

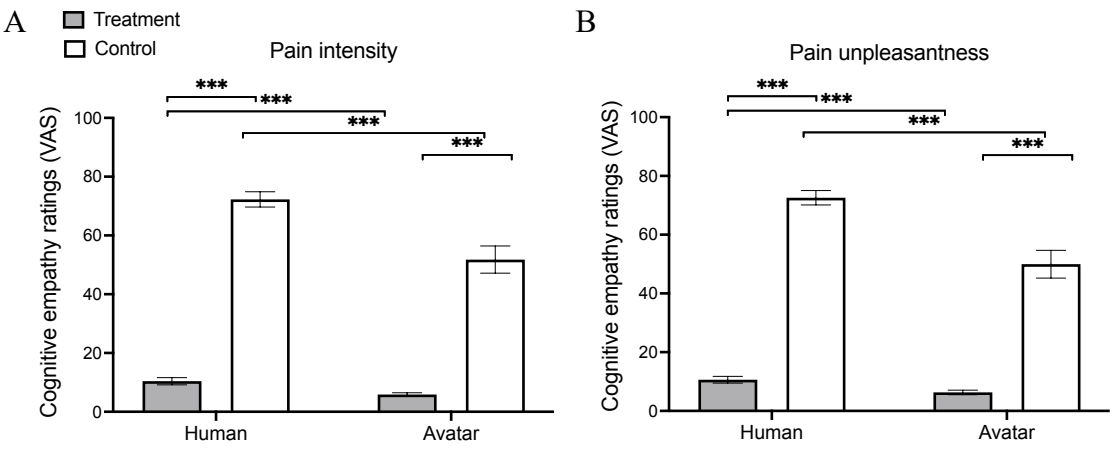


Figure 3. Main effects of control and treatment conditions and cognitive (other-referred) empathy ratings (reported on a visual analogue scale (VAS) from 0 (no pain) to 100 (maximum tolerable pain)) for the human and avatar demonstrators. Participants' cognitive state empathy (i.e., empathy for the experience of the demonstrator) was assessed using empathy questions 3 and 4 assessed for (A) pain intensity (question 3) and (B) pain unpleasantness (question 4). Data are mean ± SEM. ***p<0.001

Across all state empathy assessments, sex had a fixed effect on all treatment conditions during observation, with women scoring higher than men for both affective and cognitive state empathy ratings (control, pain intensity: $F_{(1,105)}$=13.9; p<0.001; treatment, pain intensity: p<0.001; $F_{(1,145)}$=13.2; p<0.001; control, pain unpleasantness: $F_{(1,139)}$=6.9; p=0.010; treatment, pain unpleasantness: $F_{(1,138)}$=14.4; p<0.001). We observed an effect of race on cognitive pain intensity only ($F_{(1,139)}$=5.6; p=0.020), with higher empathy ratings for non-Caucasian participants compared to Caucasian participants. The order of the presentation of the demonstrators (human first vs. avatar first) as well as VR settings (VR first vs. non-VR first) had no significant effect on all empathy ratings (p>0.05). Since we observed a general influence of sex on empathy, we also examined the correlations between the baseline psychological assessments and the participant's biological sex. We found greater empathy scores for women compared to men regarding the total IRI questionnaire (r=-0.4, p<0.001) and subscales (empathic concern: r=-0.2,

$p<0.001$, personal distress: $r=-0.3$, $p<0.001$, perspective-taking: $r=-0.2$, $p<0.001$, and fantasy scale: $r= -0.1$, $p<0.001$), as well as the BES questionnaire ($r=0.4$, $p<0.001$) and subscales (affective: $r=0.5$, $p<0.001$, cognitive: $r=0.2$, $p<0.001$). Due to the exploratory nature of the analyses between psychological assessments and sex, no multiple comparison corrections were applied for the correlations.

Socially induced placebo hypoalgesia

After seeing the demonstrator receive painful stimulation with or without an analgesic treatment, participants underwent trial-by-trial painful stimulations surreptitiously set at the same intensity. We asked them to rate the self-experienced pain intensity and pain unpleasantness levels after each trial.

For pain intensity, an omnibus analysis indicated a significant main effect of treatment (placebo vs. control: $F_{(1,6248)}=80.2$; $p<0.001$) and VR setting (VR vs. non-VR: $F_{(1,6538)}=7.5$; $p=0.006$), but not the demonstrator-type (human vs. avatar: $p=0.546$). However, there was a significant 2-way interaction between VR setting and demonstrator-type ($F_{(1,6538)}=34.4$; $p=0.006$) and a significant 3-way interaction among treatment-condition, VR setting, and demonstrator-type ($F_{(1,6538)}=11.3$; $p<0.001$). Post-hoc analyses applying Bonferroni correction confirmed that the pain ratings were higher during the control condition compared to the placebo for pain intensity (mean difference=4.4; sem=:0.07; $p<0.001$). This indicated that socially induced placebo effects for pain intensity were successfully generated with this new VR-based procedure (see Fig. 4).

We therefore conducted second-level analyses and found no significant direct main effect of the nature of the demonstrator on socially induced placebo effects for pain intensity ($p=0.546$). In terms of VR settings, we found a significant effect of VR setting (VR vs. non-VR) for pain intensity ($F_{(1,6730)}=7.5$; $p=0.006$). Post-hoc analyses applying Bonferroni correction indicated that socially induced placebo effects were greater within the non-VR compared to the VR setting for pain intensity (mean difference=-1.5; sem=0.08; $p<0.001$) suggesting that learning may occur at a greater level in the non-VR setting compared to VR. Moreover, there was an interaction between the VR settings (VR vs. non-VR) and the demonstrator's type (human vs. avatar); (intensity: $F_{(1,6729)}=34.4$; $p<0.001$). In the VR setting, placebo hypoalgesia was greater for the avatar condition compared to the human (intensity: mean difference=2.8; sem=0.09; $p<0.001$). In the non-VR setting, placebo hypoalgesia was greater for the human condition compared to the avatar (intensity: mean difference=3.6; sem=0.09; $p<0.001$).

For placebo effects related to pain intensity scores, we found fixed effects for biological sex ($F_{(1,6630)}=19.8$; $p<0.001$) with greater placebo hypoalgesia for men compared to women. Race also influenced placebo effects ($F_{(1,6651)}=124.2$, $p<0.001$) with greater placebo hypoalgesia for non-Caucasian participants compared to Caucasian participants. Moreover, the level of pain used during the experiment ($F_{(1,6643)}=121.0$, $p<0.001$), as well as the VR setting sequence ($F_{(1,6639)}=35.7$, $p<0.001$), affected placebo effects, with greater placebo hypoalgesia for participants that received higher temperatures for the painful stimulation and that started the experiments with the VR setting compared to participants who started the experiments with non-VR. The demonstrator-type sequence (i.e., human

or avatar presented first) and the color of the placebo cream had no effect on socially induced hypoalgesia ($p>0.05$).

We conducted similar analyses for pain unpleasantness ratings. The omnibus analyses indicated a significant main effect of treatment (placebo vs. control: $F_{(1,6099)}=76.9$; $p<0.001$) and VR setting ($F_{(1,6283)}=15.9$; $p<0.001$), but not the demonstrator-type ($p=0.172$). However, there was a significant 2-way interaction between VR setting and demonstrator-type ($F_{(1,6283)}=26.4$; $p<0.001$) and a significant 3-way interaction among treatment-condition, VR setting, and demonstrator-type ($F_{(1,6283)}=8.9$; $p=0.003$). Post-hoc analyses applying Bonferroni correction confirmed that the pain ratings were higher during the control condition compared to the placebo for pain unpleasantness (mean difference=4.2; sem=0.07; $p<0.001$). This indicated that socially induced placebo effects for pain unpleasantness were successfully generated with this VR-based procedure (see Fig. 4).

We therefore conducted second-level analyses and found no significant direct main effect of the nature of the demonstrator on socially induced placebo effects on pain unpleasantness ($p=0.172$). Like pain intensity, we found a significant effect of VR setting for pain unpleasantness ($F_{(1,6330)}=15.9$; $p<0.001$) and socially induced placebo effects were greater within the non-VR compared to the VR setting (unpleasantness: mean difference=-2.1; sem=0.08; $p<0.001$, Bonferroni corrected). There was an interaction between the VR settings and the demonstrator's type for pain unpleasantness ($F_{(1,6328)}=26.4$; $p<0.001$) where placebo hypoalgesia in the VR setting was greater for the avatar condition compared to the human (unpleasantness: mean difference=2.0;

sem=0.08; $p<0.001$) and the opposite trend was observed in the non-VR setting (unpleasantness: mean difference=3.6; sem=0.09; $p<0.001$).

For pain unpleasantness, we found fixed effects for biological sex ($F_{(1,5804)}=6.8$; $p=0.009$), race ($F_{(1, 5844)}=98.7$, $p<0.001$), the level of pain used during the experiment ($F_{(1, 5831)}=200.2$, $p<0.001$), the VR setting sequence ($F_{(1, 5824)}=62.4$, $p<0.001$), the demonstrator-type sequence ($F_{(1, 5817)}=4.9$, $p=0.026$), as well as the color of the placebo cream ($F_{(1, 5824)}=67.3$, $p<0.001$). We found greater placebo hypoalgesia for men compared to women, for non-Caucasian participants compared to Caucasian and for participants that received higher temperatures for the painful stimulation, as well as those that started the experiments with VR or with the human demonstrator, and for participants having the green cream for the placebo treatment compared to participants having the blue cream as placebo treatment.

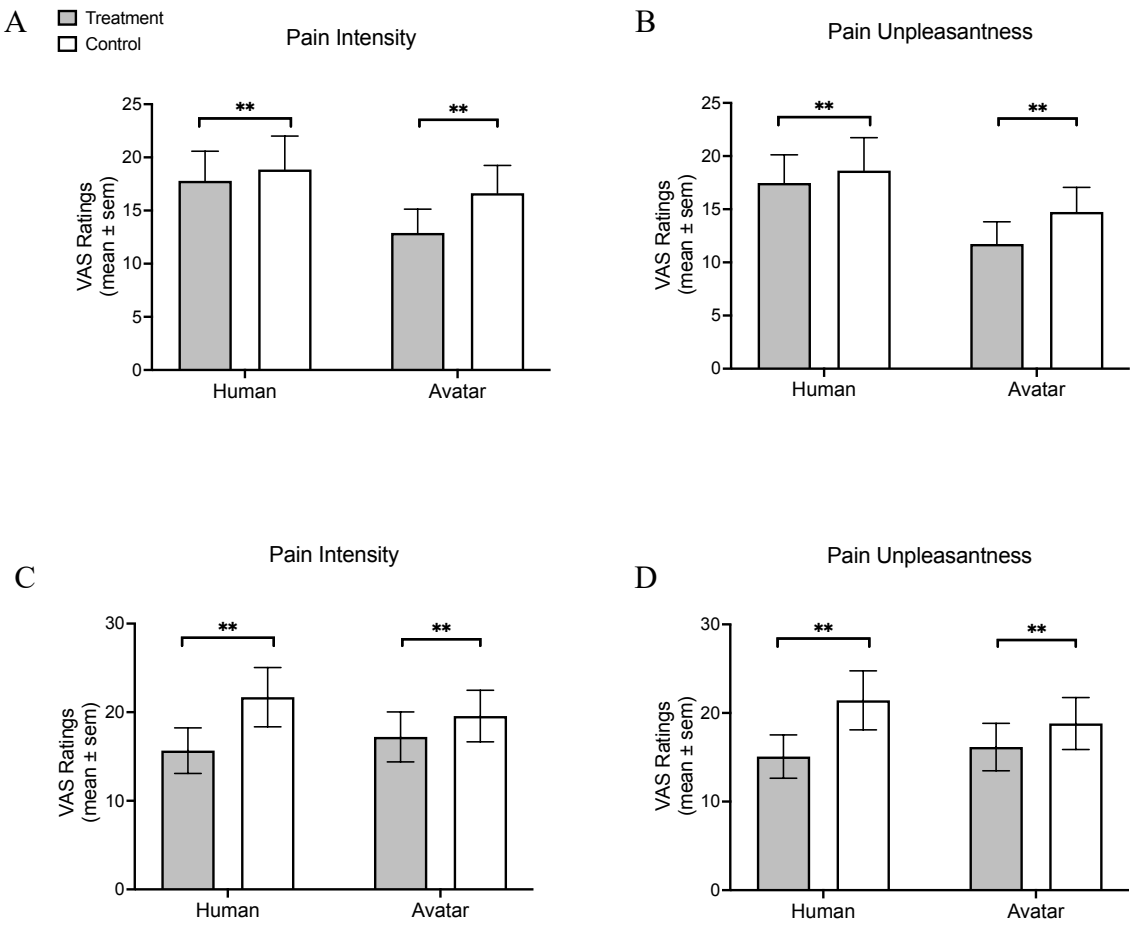


Figure 4. Socially induced placebo hypoalgesia. There was a significant pain reduction in treatment trials compared to control trials for (A) pain intensity and (B) pain unpleasantness ratings (reported on a visual analogue scale (VAS) from 0 (no pain) to 100 (maximum tolerable pain)) in VR settings. There was a significant pain reduction in treatment trials compared to control trials for (C) pain intensity and (D) pain unpleasantness ratings (VAS) in non-VR settings. Data are mean ± SEM. **$p < 0.01$. No extinction was found across conditions.

Time-course of placebo effects for pain intensity and pain unpleasantness

We calculated the trial-by-trial delta differences for the placebo and control ratings to test for potential extinction over time. We found no significant direct or interaction effect of trials (all p-values >0.05) for pain intensity ratings, which suggests that placebo hypoalgesia did not significantly differ over time. Similarly, there was no extinction for pain unpleasantness ratings.

Mediation of state empathy on placebo effects

After examining the impact of observation on state empathy levels and the factors influencing it, we evaluated whether state empathy mediated subsequent placebo effects (see Fig. 5A-B). A multilevel mediation analysis revealed that cognitive state empathy regarding unpleasantness mediated the relationship between demonstrator-type and placebo effects for pain unpleasantness ratings during the experiential phase (β:3.9[-9.11; -0.17]) in the non-VR setting only. Our results indicate that participants with higher cognitive empathy ratings regarding unpleasantness of the demonstrator during the observation phase also had greater reductions in pain unpleasantness during the experiential phase in the non-VR human demonstrator phases, as compared to the avatar phases.

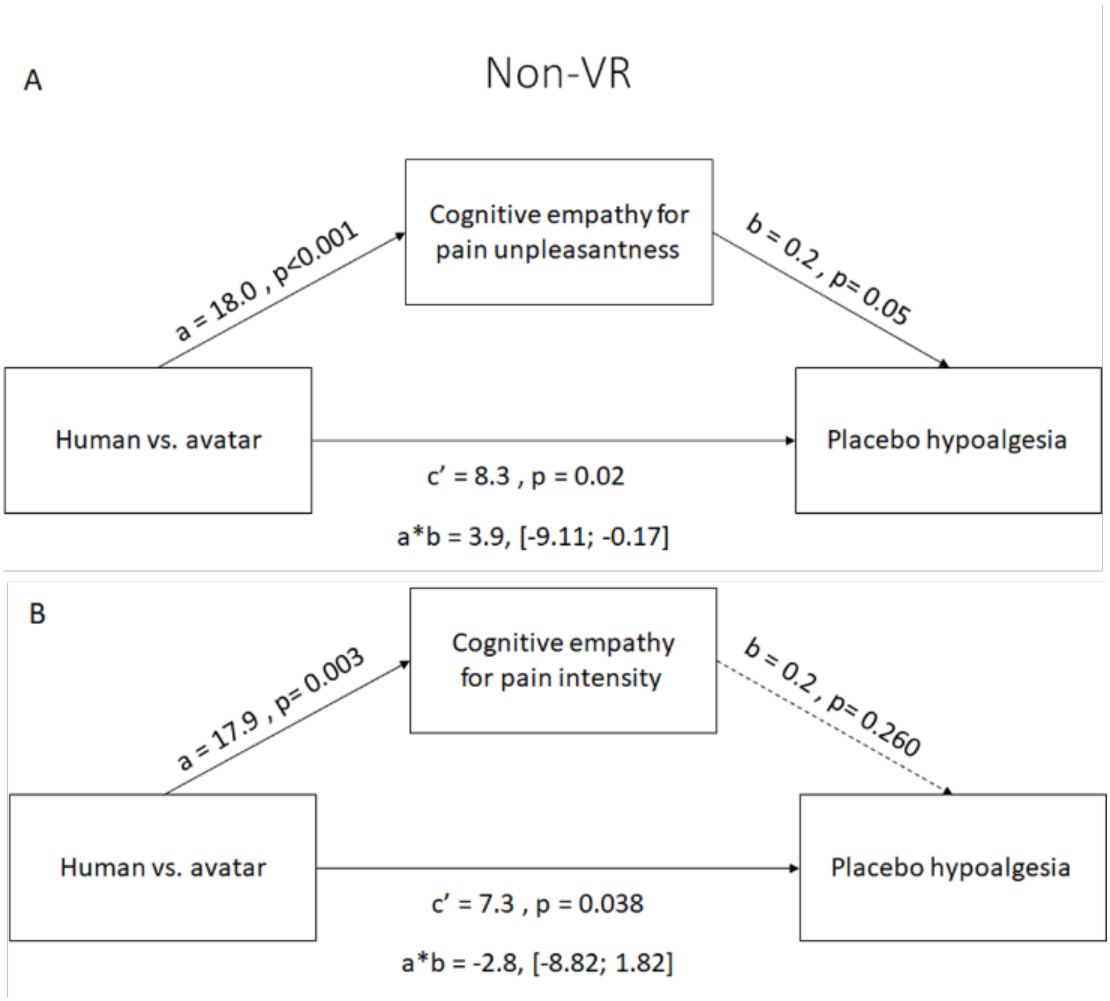


Figure 5. Mediation model of cognitive state empathy pain unpleasantness and pain intensity ratings on socially induced placebo hypoalgesia in non-VR. (A). Higher pain unpleasantness ratings (reported on a visual analogue scale (VAS) from 0 (no pain) to 100 (maximum tolerable pain)) for the demonstrator during the observation phase drove greater placebo effects for pain unpleasantness in the human demonstrator phases as compared to the avatar phases in non-VR settings. (B). There was no mediation effect of cognitive state empathy pain intensity ratings on placebo hypoalgesia for pain intensity.

Effects of psychological and mood surveys on state empathy and socially induced hypoalgesia

We used multiple linear regressions to examine the effects of baseline IRI trait empathy on the variables used for our main analysis (affective and cognitive empathy for pain intensity and pain unpleasantness), as well as socially induced placebo hypoalgesia on pain intensity and pain unpleasantness, to replicate previous findings on empathy and placebo effects (Bieniek and Babel, 2022, Meeuwis et al., 2023). The model variables were introduced in the models using a stepwise method. All significance levels were Bonferroni corrected according to the number of dependent variables (p-values multiplied by six).

Affective empathy ratings for pain intensity were predicted by IRI scores of empathic concern, perspective-taking, fantasy scale, as well as cognitive and total BES scores. Affective empathy ratings for pain unpleasantness were predicted by IRI scores of perspective-taking, fantasy scale, and total IRI, as well as affective and cognitive BES scores (see: Table 2 for statistical values).

Cognitive empathy ratings for pain intensity were predicted by IRI scores of empathic concern, fantasy scale, and total IRI, as well as affective and total BES scores. Cognitive empathy ratings for pain unpleasantness were predicted by IRI scores of empathic concern as well as cognitive BES scores. Socially induced placebo hypoalgesia for pain intensity was predicted by the perspective-taking IRI, fantasy scale IRI, cognitive BES, total BES, STAI, and BAI (Table 2). Socially induced placebo hypoalgesia for pain unpleasantness was predicted by the perspective-taking IRI, total IRI, affective BES, cognitive BES, STAI, and BAI (Table 2).

	Affective empathy		Cognitive empathy		Placebo hypoalgesia	
	Intensity	**Unpleasant**	**Intensity**	**Unpleasant**	**Intensity**	**Unpleasant**
IRI tot	p=0.081	**β=-0.4*** **	**β=-0.1*** **	p=0.411	p=0.0.094	**β=0.1** **
EC	**β=-0.1*** **	p=0.346	**β=0.1*** **	**β=0.1*** **	p=0.342	p=0.291
PD	p=0.453	p=0.308	p=0.222	p=0.752	p=0.535	p=0.451
PT	**β=0.2*** **	**β=0.3*** **	p=0.253	p=0.549	**β=-0.1*** **	**β=-0.1*** **
FS	**β=0.2*** **	**β=0.3*** **	**β=0.1*** **	p=0.796	**β=0.04** **	p=0.225
BES tot	**β=-0.1*** **	excluded	**β=0.2*** **	p=0.753	**β=-0.2*** **	excluded
Aff	excluded	**β=-0.1*** **	**β=-0.1*** **	p=0.337	excluded	**β=-0.1*** **
Cog	**β=0.3*** **	**β=0.3*** **	excluded	**β=0.1*** **	**β=0.3*** **	**β=0.1*** **
STAI	**β=-0.1*** **	p=0.776	**β=-0.2*** **	**β=-0.2*** **	**β=-0.2*** **	**β=-0.1*** **
BAI	p=0.690	p=0.919	p=0.644	p=0.648	**β=0.2*** **	**β=0.2*** **
BDI	p=0.667	p=0.808	p=0.102	p=0.138	p=0.569	p=0.544

Table 2. Effects of psychological and mood surveys on state empathy and observationally induced hypoalgesia. Abbreviations: Interpersonal Reactivity Index (IRI), empathic concern (EC), personal distress (PD), perspective taking (PT), and fantasy scale (FS), Basic Empathy Scale (BES), Affective BES (Aff), Cognitive BES (Cog), State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI). *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. excluded = the variable was completely excluded from the analysis with the listwise method.

Electroencephalogram peak alpha frequency

Aligning with our previous study on the neural changes related to socially induced hypoalgesia, we examined linear regressions of Fp1, Fp2, C3, Cz, C4, T7 and T8 (Nir et al., 2010, Raghuraman et al., 2019) with socially induced placebo effects for pain intensity and pain unpleasantness. Since we used 7 predictors (7 EEG sensors), the significant results were Bonferroni corrected (p-values multiplied by 7). While we found no significant relationship between PAF frequencies and pain threshold or pain tolerance, we found a significant relationship between PAF frequencies in T7 (β=-0.030; p=0.017) and T8 (β=-0.067; $p<0.001$) and individual pain ratings of control trials during the experiential phase. We examined the direct effect of the predictive influence of PAF on empathy and pain using linear regressions to control for sex, ethnicity/race, the color of the placebo cream, as well as the order of conditions (VR vs. non-VR and human vs. avatar). PAF did not predict pain empathy ratings ($p>0.05$) during the observation phase. We then examined the effect of PAF predictive influence on socially induced placebo hypoalgesia for pain intensity and pain unpleasantness using linear regressions to control for sex, ethnicity/race, the color of the placebo cream, as well as the order of conditions (VR vs. non-VR and human vs. avatar). PAF predicted socially induced placebo hypoalgesia for the VR setting only (for the non-VR, all p-values > 0.05, Bonferroni corrected, Table 3).

	Human				Avatar			
	Intensity		Unpleasantness		Intensity		Unpleasantness	
T7	-	p=1.701	-	p=0.532	**β=0.1**	**p=0.007**	**β=0.2**	**p<0.001**
T8	**β=0.1**	**p=0.010**	**β=0.1**	**p<0.001**	-	p=0.539	**β=0.1**	**p=0.001**
Cz	-	p=0.952	-	p=0.070	**β=0.2**	**p<0.001**	**β=0.2**	**p<0.001**
C3	**β=0.1**	**p=0.044**	**β=0.1**	**p=0.003**	-	p=0.168	**β=0.1**	**p=0.001**
C4	-	p=4.557	-	p=1.176	**β=0.1**	**p=0.027**	**β=0.2**	**p<0.001**
Fp1	-	p=3.969	-	p=5.929	**β=0.2**	**p<0.001**	**β=0.2**	**p<0.001**
Fp2	-	p=0.413	-	p=0.056	**β=0.3**	**p<0.001**	**β=0.3**	**p<0.001**

Table 3. Regression results for electroencephalogram peak alpha frequency within VR. Bonferroni corrected (multiplied by 7).

In general, a faster PAF in the sensorimotor area predicted larger socially induced placebo hypoalgesia for pain intensity and pain unpleasantness for both the human and the avatar demonstrators. Greater socially induced placebo hypoalgesia induced by the *human* demonstrator was predicted by faster PAF at electrodes T8 and C3. Greater socially induced placebo hypoalgesia induced by the *avatar* demonstrator was predicted by faster PAF at electrodes T7, T8, C3, C4, Cz, Fp1, and Fp2 (Fig. 6). These results suggest that within the VR setting, the participants with faster PAF frequency in the frontal and somatosensorial areas at resting state also experienced greater socially induced placebo hypoalgesia.

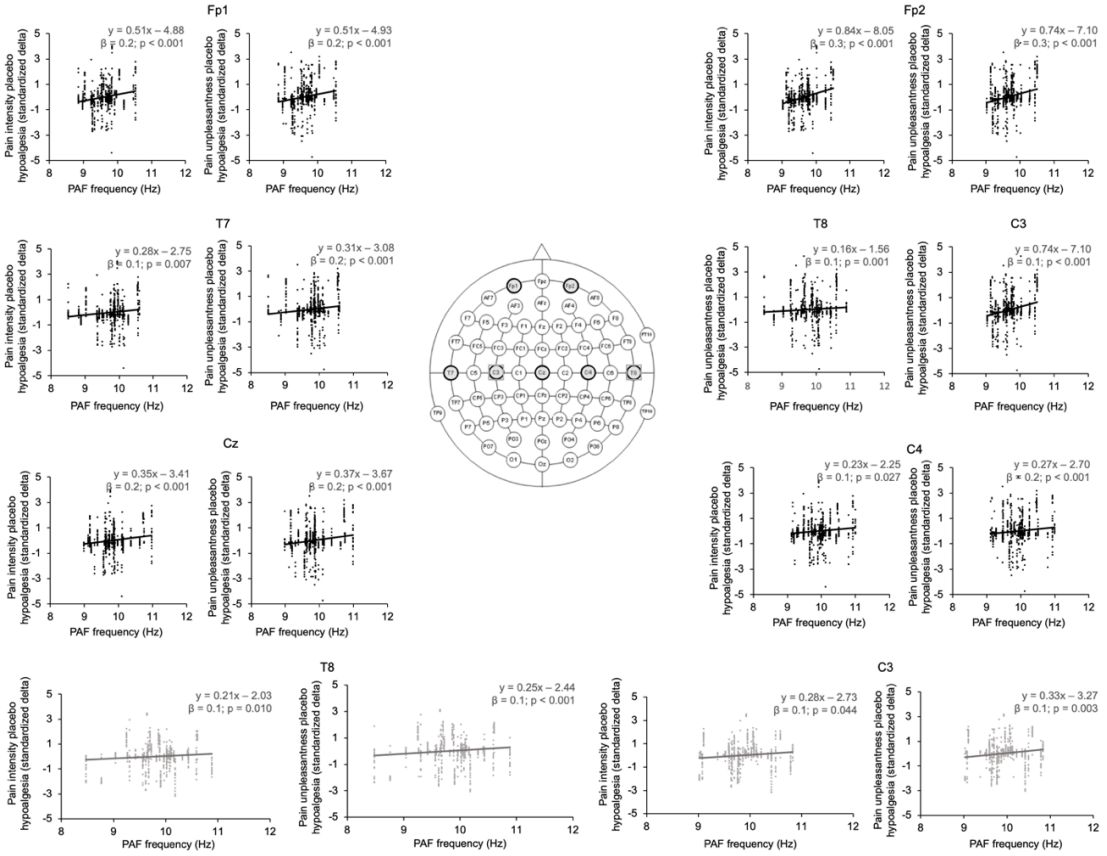


Figure 6. Linear regressions for PAF frequencies (Hz) within VR with a human and avatar demonstrator. Fp1, Fp2, T7, T8, Cz, C3 and C4 PAF frequencies and participants' placebo effects (difference between control versus treatment conditions) are plotted for pain intensity and pain unpleasantness for the avatar (symbols in black) and human (symbols in grey) demonstrator phases in immersive VR.

E. Discussion

We studied the role of empathy in socially induced placebo effects. We adopted existing methods of social learning to manipulate empathic state within and outside VR with a human demonstrator and an avatar version of the same demonstrator. We also studied neural markers of observation-induced placebo effects. First, we demonstrated that state empathy was higher with a human than an avatar demonstrator. Second, we demonstrated socially induced placebo effects in both VR and non-VR settings, with a larger magnitude in non-VR. Third, we found greater placebo hypoalgesia with the human compared to the avatar demonstrator within the non-VR setting, but the opposite within the VR setting. Cognitive empathy towards pain unpleasantness mediated observation-induced placebo effects within the non-VR setting only. Fourth, baseline trait empathy was predictive of both empathetic states following observation of a demonstrator experiencing pain and analgesia, and subsequent socially induced placebo effects. Finally, faster PAF in frontal and somatosensorial areas was associated with higher socially induced hypoalgesia within the VR condition only.

In line with previous findings that empathy and social (observational) learning can elicit placebo effects (Colloca and Benedetti, 2009, Goubert et al., 2011, Fusaro et al., 2016, Schenk et al., 2017, Raghuraman et al., 2019, Wu and Han, 2021), we found that our experimental procedures successfully captured the participants' affective and cognitive empathetic responses, as evidenced by their ability to modify empathy ratings after observing a supposedly pain-relieving treatment. Specifically, participants reported higher ratings during the control versus placebo condition for all ratings regardless of the demonstrator's type, supporting our hypothesis that participants' empathy pain ratings

would be lower when observing a demonstrator receiving pain stimulations paired with an analgesic treatment.

Previous studies showed a positive relationship between analgesic responses and IRI-measured empathic concern when observers watched a live demonstrator (Hunter et al., 2014, Kanske et al., 2014). Here, we manipulated state empathy and found that participants exhibited higher cognitive empathy after exposure to a human demonstrator than an avatar. This agrees with studies showing that empathy is weaker for robots than for humans (Suzuki et al., 2015). A recent study demonstrated that even when both demonstrators are avatars, cognitive empathy is higher with a human avatar compared to a robot avatar (Hapuarachchi et al., 2023). Together with our results, this suggests that there is a unique element, possibly the presence of human facial expressions or the plausibility of a demonstrator (i.e., its perceived likeness to a real human (Hapuarachchi et al., 2023), to person-to-person interaction, which cannot be replicated via the use of robots or human avatars (Leibovici, 2009, Hoffman et al., 2011, Perry et al., 2014, Wiederhold et al., 2014, Won, 2017).

The VR settings (VR vs. non-VR) had no effect on affective and cognitive empathy ratings for pain intensity or pain unpleasantness. Previous literature suggested that VR is a medium to increase empathy (Schutte and Stilinovic, 2017, Ingram et al., 2019, Cohen et al., 2021, Martingano et al., 2021). However, some of these studies include engagement, connection and bonding with a demonstrator or a situation (Schutte and Stilinovic, 2017, Ingram et al., 2019, Cohen et al., 2021), which refers to associative empathy and is distinct from affective and cognitive empathy (Shen, 2010). A meta-analysis reported that VR did not improve cognitive empathy but improved “emotional”

empathy (Schutte and Stilinovic, 2017, Ingram et al., 2019, Cohen et al., 2021) also referring to associative empathy (Martingano et al., 2021). Additional studies assessing empathy in the context of pain are needed to elucidate the effect of VR on various types of empathy.

In line with previous findings on socially induced placebo analgesia (Colloca and Benedetti, 2009, Goubert et al., 2011, Fusaro et al., 2016, Schenk et al., 2017, Raghuraman et al., 2019, Wu and Han, 2021) we found that the observation procedures reduced participants' pain experiences and induced hypoalgesia. The nature of the demonstrator (human vs. avatar) had no direct effect on socially induced placebo hypoalgesia for both pain intensity and pain unpleasantness within the VR condition. Through an interaction effect, placebo hypoalgesia was greater with the avatar than the human demonstrator in the VR setting. In contrast, the human demonstrator elicited greater socially induced placebo hypoalgesia than the avatar within the non-VR setting. Moreover, non-VR elicited greater socially induced hypoalgesia than VR. These findings resonate with a recent meta-analysis showing that passive VR, (i.e., the participant is immersed in VR but does not have the ability to interact with the environment (Xiang et al., 2021)), elicits higher pain ratings and reduced divided attention than more immersive or active VR settings (Hoffman, 2021)

Extended to our results, this suggests that immersive VR is more distractive than non-VR (Leibovici et al., 2009, Hoffman et al., 2011, Wiederhold et al., 2014). Distraction due to VR might interfere with the establishment of socially induced placebo effects since the virtual environment's components may capture participants' attention more than the demonstrator (Hoffman et al., 2011, Leibovici et al., 2009, Wiederhold et al., 2014,

Hoffman, 2021). Specifically, observation of the more active video VR setting with the expressive human demonstrator, contrasted with the more passive VR setting with the neutral avatar, may explain larger subsequent placebo effects following observation of the avatar in VR due to decreased distraction, and, potentially, greater induced social learning. This trend was opposite in the non-VR conditions, where, as we expected, observing the human demonstrator elicited larger placebo effects outside of immersive conditions. In our study, we did not measure attention during VR, thus we cannot ascertain whether distraction played a role. However, our results regarding analgesic treatment inducing cognitive empathy in both humans and avatars supports distraction as a potential confounding factor during social learning through VR-based observation. Distraction during VR may explain greater perceived pain relief observed in the non-VR setting rather than state empathy or ability to acquire socially induced placebo hypoalgesia. Further research is necessary to provide a comprehensive understanding of how distraction affects placebo effects in VR settings (Leibovici et al., 2009, Hoffman et al., 2011, Perry et al., 2014, Wiederhold et al., 2014, Won et al., 2017). Finally, the mediation effect of cognitive empathy (pain unpleasantness ratings for the demonstrator) on demonstrator-type and placebo effects within the non-VR condition highlights a significant influence of learning in several contexts, namely the placebo effect and the development of empathy (Colloca and Benedetti, 2006, Bräscher et al., 2019, Lumish et al., 2022).

Neuronal correlates of socially induced placebo responses

In this cohort, we replicated previous results indicating that PAF is linked to individual pain ratings in the control trials (Raghuraman et al., 2019) We also examined the relationship between PAF frequencies and pain threshold and tolerance and found no significant results, as opposed to the significant relationship between pain ratings during the control trials and a slower PAF (negative association). Moreover, faster resting state PAF in the frontal and somatosensorial areas was associated with stronger socially induced placebo effects within the VR setting. These results align with our previous study where PAF was positively correlated with hypoalgesia in placebo responders (Raghuraman et al., 2019). However, several groups have observed other neural measures associated with placebo hypoalgesia. Zhang et al. reported lower P2 amplitude and higher N2 ERP amplitude differences in the prefrontal area when experiencing placebo analgesia (Zhang et al., 2009). Li et al. found that alpha oscillations in frontal-central areas were positively correlated to placebo analgesia (Li et al., 2016). Similar to our study, previous studies reported different brain activities associated with demonstrators with different features. Joyal et al. reported reduced alpha power in the sensorimotor area when observing an avatar expressing pain (Joyal et al., 2018). In summary, our findings highlight the importance of expanding the literature with research which evaluates the potential predictive behavioral and neural markers of placebo hypoalgesia.

Chapter III: Effects of gonadal hormones on sexually dimorphic placebo effects

A. Abstract

Sexual dimorphism in pain outcomes is often not considered in clinical settings because the mechanisms underlying this disparity remain unclear. A possible explanation lies in the different concentrations of sex hormones both between and within women and men. The protective effects of testosterone have been previously demonstrated, yet the extent to which these effects translate to placebo analgesic outcomes remain unclear. This study aimed to investigate the effects of testosterone on pain, treatment expectations, and placebo hypoalgesia in a large cohort of chronic pain and healthy participants.

401 chronic pain patients diagnosed with Temporomandibular disorders (TMD) and 400 pain-free participants were included in the current analysis for a total of 801 participants, 634 of whom provided a biological sample for determining hormone levels. Each participant completed a classical conditioning paradigm in which, during the conditioning phase, two distinct levels of individually tailored high and low painful stimuli were used to reinforce participants' expectations of hypoalgesia. During the testing phase, both levels was surreptitiously set to a moderate pain level to test for placebo effects. Expectations regarding treatment effectiveness were assessed at baseline, post-conditioning, and post-treatment. We used mediation analysis to determine how hormones influence sex differences in placebo effects.

Women and men showed similar conditioning strength, while women showed greater expectations and larger placebo effects than men. Testosterone levels were negatively correlated with chronic pain severity in women with TMD, and higher testosterone levels

were associated with lower placebo effects. In all participants, estradiol levels mediated reinforced expectations following conditioning. In participants with TMD, reinforced expectations mediated placebo effects.

The findings of this study suggest that, independent of chronic pain condition, women experience larger expectations and placebo effects compared to men, and that hormones drive these sexually dimorphic effects, highlighting the importance of sex as a biological variable to be considered in drug development trials and pain management when placebo components are involved.

B. Introduction

Chronic pain is the most prevalent and economically burdensome human health problem worldwide (Mogil 2020). Many large epidemiological studies of chronic pain syndromes show that women are overrepresented among chronic pain patients and show higher sensitivity and greater reporting of pain for chronic conditions featuring pain as a symptom (Bartley and Fillingim, 2013, Mogil, 2020, Templeton, 2020, Osborne and Davis, 2022). Temporomandibular disorders (TMD), characterized by pain in and around the temporomandibular joint (TMJ), are such conditions that disproportionately affect women, with the highest TMD prevalence being among women of reproductive age (LeResche et al., 1997, Schmid-Schwap et al., 2013, Bueno et al., 2018, Häggman-Henrikson et al., 2020) and eighty percent of patients treated for TMD being women (LeResche et al., 1997, Warren and Fried, 2001, Bagis, 2012).

Sexual dimorphism in TMD may influence the effectiveness of therapeutic interventions aimed at managing TMD pain, such as placebo interventions aimed at inducing hypoalgesia. We and others have previously demonstrated that women with TMD were more sensitive to clinical and experimental pain (Olson et al., 2021, Knuutila et al., 2022) and experienced greater placebo hypoalgesia compared to men (Olson et al., 2021). The effects of sex on TMD pain and placebo hypoalgesia in women suggests a possible role of the female hormonal axis. However, an exploratory analysis in premenopausal women with TMD revealed that these effects occurred independently of estradiol and progesterone levels (Olson et al., 2021) while testosterone levels were not assessed. Here, we expanded the scope of the previous study by assessing the effects of estradiol,

progesterone, and testosterone on conditioning strength, expectations, and placebo hypoalgesia, in women and men patients with TMD and healthy controls.

Although understanding the effects of estradiol and progesterone on pain sensitivity is complex due to their pro- and anti-nociceptive properties, testosterone appears to be more consistently anti-nociceptive and protective in nature (Bartley and Fillingim, 2013). For example, chronic pain is associated with decreased concentrations of androgen in men (Lee and Lee, 2016). In women, testosterone's effects are varied, for instance, decreasing and increasing androgen concentrations are associated with chronic diseases associated with life-impacting pain (Crestani et al., 2020, Dinsdale and Crespi, 2021). These conflicting findings warrant studies that rigorously test the effects of sex hormones on pain and modulators of pain like placebo.

To address the gap, we studied the effects of conditioning strength, expectations, and sex hormones on sexually dimorphic placebo effects. Both pain outcomes (Atlas and Wager, 2012) and placebo effects (Colloca, 2020) are elicited by patients' prior therapeutic experiences (Colloca and Benedetti, 2006, Colloca et al., 2020) and expectations (Wager et al., 2004; Atlas and Wager, 2012) regarding treatment. Previous research shows that women and men's expectations regarding gender roles may contribute to sex differences in experimental pain (Wise et al., 2002) and pain-sensitivity (Robinson et al., 2001). In our previous study, we showed that conditioning strength was higher in women with TMD compared to their male counterparts, and reinforced expectations, i.e., expectations regarding treatment efficacy after conditioning, drove greater placebo hypoalgesia in women compared to men (Olson et al., 2021). Although estradiol and progesterone levels

did not influence the results of this study, it is unknown whether testosterone affected sex-related expectations or placebo analgesia in these participants.

This study expands upon the previous study and current literature by investigating the effects of testosterone on sexual dimorphism in treatment expectations and placebo hypoalgesia, using classical conditioning to induce placebo effects. We hypothesized that women would show greater conditioning strength, expectations regarding pain relief following an intervention, and greater placebo effects compared to men, similar to the previous study using a subset of this cohort (Olson et al., 2021). Additionally, we hypothesized that, similar to a previous study in this cohort (Colloca et al., 2020), participants with chronic pain would report higher expectations for pain relief compared to healthy participants, while placebo effects would be similar in magnitude between the two groups. Further, we hypothesized that higher testosterone levels would be associated with lower chronic pain severity in participants with TMD, and lower placebo effects in all participants. Finally, since we expanded the previous study (Olson et al., 2021) to include all participants, we reassessed the effects of ovarian hormones and menstrual phase on conditioning strength, treatment expectations, and placebo hypoalgesia.

C. Methods

Participants

This study was approved by the University of Maryland Institutional Review Board (HP-00068315) and was conducted in accordance with the Declaration of Helsinki (1964). We recruited adult participants aged 18-65 years in the Baltimore, Maryland community using flyers, social media campaigns, health fairs, and throughout the University of Maryland, Baltimore campus from August 2016 - January 2020. Participants were pre-screened over the phone to determine whether they were a potential participant with TMD or a healthy control for a larger parent study on placebo effects, the findings of which have been reported (Colloca et al., 2020, Okusogu et al., 2020, Olson et al., 2021). Participants gave verbal and written informed consent prior to an in-person screening for study participation. All participants were compensated $100 for completing the study procedures.

Demographic, socioeconomic, and clinical factors for participants with TMD are presented in Table 4.

Eligibility criteria

Participants with TMD: 401 participants with TMD were enrolled in the study. Following phone screening, potential participants with TMD underwent a clinical diagnostic appointment at the University of Maryland, School of Dentistry, Brotman Facial Pain Clinic to verify TMD diagnosis and study eligibility in individuals with self-reported history of jaw, head, or facial pain for a period of time equal to or exceeding the past 3 months. To be included in the study, potential participants with TMD had to meet the

Axis I Diagnostic Criteria for TMDs (DC/TMD): (1) History of pain in the immediate 30 days before examination for both of the following: (a) pain in the jaw, temple, in the ear, or in front of the ear; and (b) pain modified with jaw movement, function, or parafunction; and (2) positive for myalgia and/or arthralgia: (a) confirmation and duplication of pain location(s) in the temporalis, masseter, or other masticatory muscle(s); and/or (b) confirmation and duplication of pain in one or more of the temporomandibular joints.

The following criteria excluded potential participants with TMD: the presence of degenerative neuromuscular disease; cervical pain (e.g., stenosis or radiculopathy); a diagnosis of cardiovascular, neurological, kidney, or liver disease; pulmonary abnormalities; cancer within the past 3 years; color blindness; or uncorrected impaired hearing, pregnancy or breastfeeding. Additionally, any individuals who had facial trauma in the last 6 weeks or a history of severe facial trauma in the past 2 to 3 months were excluded from participating in the study.

Healthy participants: 400 healthy participants were enrolled in the study. The following criteria excluded potential healthy participants during phone screening: suffered from any chronic pain condition, presence of pain disorders, presence of degenerative neuromuscular, cardiovascular, neurological, kidney or liver disease, pulmonary abnormalities, diffuse cancer within the past three years, any uncorrected impaired hearing, color-blindness, pregnancy, or breast-feeding. Participants who passed phone screening also underwent an in-person interview by trained personnel to ensure their eligibility.

For potential TMD and healthy control participants, a licensed psychiatrist screened cases of psychiatric problems based on Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V). Participants who had severe psychiatric conditions such as mania, dementia, bipolar disorder, schizophrenia, major depression, obsessive-compulsive disorder, or lifetime dependence on alcohol or drugs were excluded from the study.

Of the 801 participants enrolled in the study, 634 participants (309 TMD; 325 HC; 439 women; mean age 35.4 (sem=0.5)) opted to provide biological samples (blood) for gonadal hormone analysis.

Personality assessment

Prior to undergoing the experimental paradigm, participants completed demographic and medical history questionnaires in addition to questionnaires assessing personality characteristics. All questionnaires have been validated for use in clinical populations. In particular, the NEO Five-Factor Inventory (NEO-FFI), which assesses neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness, was used to examine the role of personality traits in sexual dimorphism in placebo hypoalgesia, similar to our previous study (Olson, 2021).

Clinical measurements

Graded Chronic Pain Scale (GCPS): Participants with TMD completed the GCPS as part of the Axis I Diagnostic Criteria for TMDs (DC/TMD). The GCPS is a short, reliable, and valid 3-item instrument that measures chronic pain severity and interference (Von Korff et al., 1992). The two GCPS subscales are: (1) Characteristic Pain Intensity (CPI),

which reliably measures pain intensity, with ≥ 50/100 considered "high intensity," and (2) the pain-disability rating, which is based on number of days that pain interferes with usual daily activity. High pain and high interference, or moderate to severe disability (Grades 3 or 4), should be interpreted as disability due to pain (Schiffman et al., 2014).

Oral Behavior Checklist (OBC): Participants with TMD completed the OBC, which is a 21-item instrument that measures the frequency of oral parafunctional behaviors (Schiffman et al., 2014).

Study procedures

Throughout the experimental procedures, none of the experimenters were informed about the intention to determine sex differences in placebo hypoalgesia. For the procedures, participants underwent the following protocols during the 3- to 4-hour experimental paradigm: (1) a pain sensitivity assessment and (2) conditioning and testing phases of the placebo procedure.

Heat pain stimulation

Thermal heat stimuli were applied through the Medoc Pathway system (Medoc Advances Medical System, Ramat Yishai, Israel), with heat stimulations beginning at 32 degrees Celsius and rising at a rate of 1.0C/s either until the participant signaled to stop the stimulation according to instruction or the temperature reached its maximum of 52C. The heat increase was set at 0.3C/s to establish warmth and heat pain threshold. A probe (30 X 30 mm ATS thermode) on the ventral side of a participant's dominant forearm was

used to deliver the heat stimuli. To assess individual pain sensitivity, we used the methods of limits along with applying an ascending series of contact thermal heat stimuli to tailor the level of high and low painful stimuli to each participant. This enabled the identification of heat-warmth detection, heat-pain threshold, and heat-pain tolerance limits specific to each participant. “Warmth detection” was defined as the minimum degrees Celsius temperature that the participant was able to detect warmth sensation. “Painful threshold” was defined as the degrees Celsius temperature that was perceived as minimally painful by each participant. Lastly, “painful tolerance limit” was defined as the degrees Celsius temperature at which each participant could no longer tolerate the heat-pain stimuli.

Participants were instructed to press the Pathway remote button for each stimulus associated with each modality, with each modality being tested 4 times. To calibrate the pain modulation assessment, the average temperature for each sensitivity level was calculated. Additionally, participants were asked to verbally verify their reports with a visual analogue scale (VAS) from 0 (no pain) to 100 (maximally tolerable pain) each time the Pathway remote button was pressed.

The VAS scores were then used to establish the intensities of heat-pain stimuli that would be used in the conditioning phase. The pain sensitivity assessment yielded the average temperatures for minimum, moderate, and maximum levels of painful stimulations, which were then applied to the conditioning and testing phases.

The average temperatures used in conditioning phase was 41.2°C (sem=0.1) for the green cue and 46.9°C (sem=0.1) for the red cue, and the average temperature used for the testing phase was 46.1°C, (sem=0.1) (Table 1).

Experimental procedures

After the pain sensitivity assessment, participants received instructions about the experimental procedures. Participants were informed that they would receive painful stimulation from a thermode attached to the arm when an electrode placed above the thermode was on (signaled by a green screen) and when the electrode was off (signaled by a red screen). Participants were told that when on, the electrode would release a "subthreshold electrical stimulus" which may reduce their pain. The experiment consisted of 36 trials (24 conditioning trials followed by 12 testing trials) during which a 10-second visual cue (green or red; counterbalanced) was paired with a 10-second heat painful stimulus. After each trial, participants were asked to report their pain rating (VAS 0 (no pain) to 100 (maximally tolerable pain)). During the conditioning phase, green screen trials were paired with a temperature set 6C lower than the maximum tolerance. During red screen trials, the temperature was raised to pain tolerance, established as 2C lower than the maximum tolerance. To confirm the experimental settings, participants were to rate their pain after each trial. Self-reported scores verified the pain as 20 (green) and 80 (red) out of a 100 on the VAS. The last 12 trials were the testing phase, in which the temperature remained the same regardless of screen color to test for placebo effects. The temperature for these testing phase trials were surreptitiously set at 1C lower than the temperature for the red screen trials in the conditioning phase. During the conditioning phase, a difference in red-minus green trial VAS ratings was operationally defined as "conditioning strength". During the testing phase, the delta between red-minus green VAS ratings was operationally defined as "placebo hypoalgesia".

Expectations

To determine baseline expectation of intervention, participants were asked to "Please rate your expectation about how well the electrode intervention will work" prior to the conditioning phase. Following the conditioning phase, participants were asked to "Please rate how well you think the electrode intervention worked" to assess reinforced expectations. Lastly, participants were asked to "Please rate how well you think the electrode intervention worked this time" following the testing phase to assess intervention efficacy.

Hormonal and menstrual data acquisition

Data regarding menstrual cycle, such as the regularity of menses, the date of last menstrual period, the length of menses, the length of bleeding, and birth control method were collected as part of female participants' medical histories, enabling us to investigate the effects of gonadal hormone levels on conditioning, treatment expectations, and placebo effects. To confirm menstrual phase of pre-menopausal women (total N=244; TMD=101, HC=143), we measured levels of estradiol and progesterone. Specifically, to calculate the phase of the menstrual cycle at the time of testing, we considered the days since last menstruation, with mid-follicular phase defined as 4-8 days since last menstrual bleed and luteal phase defined as 18-22 days since last menstrual bleed. Through utilization of quantitative competitive ELISAs, testosterone, estradiol and progesterone were measured for all participants who provided biological specimens (blood) (n=634; 439 women) at the Institute for Clinical and Translational Research Core Laboratory at Johns Hopkins University, in order to confirm menstrual phase results. ELISAs were

used following the manufacturer's protocol (ALPCO, Salem, NH). The biochemical definition in line with the classifications proposed by Allen et al. was used to define menstrual phases (Allen et al., 2016).

Statistical analysis

Power calculation

Power analysis was used to determine the minimum number of participants required to assess sex differences. Due to the higher prevalence of TMD in women, the statistical power was calculated based on an unequal sample size at a ratio of 3:1 between women and men. We found that a sample size (N) of 801 (544 women and 257 men) for the sex differences analysis and a sample size (N) of 634 (439 women and 195 men) for the hormonal data analysis would be sufficient to have a statistical power of 0.8, when assuming a moderate effect size of sex differences on placebo hypoalgesia. This statistical power allowed us to observe a moderate sex difference effect size, with Cohen's d 0.5, at the alpha level of 0.05.

Sex differences in conditioning strength, expectations, and placebo hypoalgesia

Given the unequal sample size of each cell, Nonparametric Mann-Whitney U tests and Kruskal-Wallis H tests were used to assess the differences in demographic and socioeconomic variables between sexes. Due to the sex differences observed for chronic pain severity, educational level, and heat-pain stimulations, those variables were treated as covariates for the analyses. A Linear Mixed Model (LMM) was used to conduct an omnibus analysis to determine that both sexes had significant pain reduction experiences

during the conditioning phase and showed significant placebo analgesic effects during the testing phase. The VAS pain ratings for each of the trials were treated as the dependent variable for the omnibus analysis. Given this, the color of the trials (red vs green) and sex (women vs men) were set as fixed factors. Factoring in the unequal data structure, LMM was superior to repeated-measures analysis of variance to compensate for any missing data. Following this, the calculation for conditioning strength was formatted as the difference between red- and green- associated pain ratings during the conditioning phase. Placebo hypoalgesia was calculated as the difference between red- and green- associated pain ratings during the testing phase. During the conditioning phase, a total of 12 differences (deltas) were obtained from each participant. During the testing phase, 6 differences (deltas) were obtained from each participant. LMM was utilized to investigate the sex differences in conditioning strength and placebo hypoalgesia. For conditioning strength, the 12 repeated delta measures for each individual were treated as repeated variables. For placebo hypoalgesia, the 6 repeated delta measures for each individual were treated as repeated variables. The levels of heat-pain stimulation during the conditioning phase and the testing phase were treated as the covariates in the LMM models, as well as chronic pain severity, education, and race. Post hoc analyses applying Bonferroni corrections were conducted where significant interactions were observed.

Hormonal data analysis

Estradiol, progesterone and testosterone data were collected for both men and women participants who provided a biological sample (n= 634, 439 women; see *Hormonal and menstrual data acquisition*). For all women who self-reported as premenopausal (n=243)

progesterone levels were used to confirm menstrual phase. Women in the follicular phase were defined as having progesterone levels <2ng/mL and women in the luteal phase were defined as having progesterone levels >2ng/mL. To determine the menstrual phase difference in expectations, conditioning strength and placebo hypoalgesia, an LMM was used with menstrual phase (luteal vs follicular) set as a fixed factor.

Estradiol, progesterone, and testosterone levels were used to examine the associations between gonadal hormones and expectations, conditioning strength, and placebo hypoalgesia using LMM.

Mediation approach

In two separate analyses, the mediation approach was used to determine the causal influence of hormones on expectations, and expectations on placebo hypoalgesia. The independent variable (X) was defined as sex (women vs men). The dependent variable (Y) was defined as placebo hypoalgesia, which was computed as the average of red-minus-green delta scores of pain ratings during the testing phase. Estradiol levels were modeled as the mediator in the first analysis, and reinforced expectations were modeled as the mediator in the second analysis. The covariates in the mediation analyses were chronic pain severity, education, age, and level of heat-pain stimulation used during the testing phase. To test for indirect effects, we used a bias-corrected bootstrapping method with 5000 times resampling. If the 95% bootstrapped confidence interval (BCI) did not contain a zero, then the indirect effect would be considered significant. Mediation analyses were conducted using the PROCESS macro for IBM® SPSS Statistics software version 29.0 (Hayes, 2022).

For all analyses, all significances were set at $p = 0.05$ and the analyses were conducted using the IBM® SPSS Statistics software version 29.0.

D. Results

Participants. The study population consisted of a cohort of 801 participants with an average age of 35.4 years and prevalence of women (n = 544) (see Table 4).

	N/mean	%/SEM
Sex		
Women	544	67.5
Men	257	31.9
Race		
White	393	48.8
Non-White	408	50.7
Group		
TMD	401	49.8
Pain- free	400	49.6
Education		
Did not complete high school	0	0
Completed high school	67	8.3
Some college	194	24.1
College graduate	320	39.7
Professional or post-graduate level	220	27.3
Age (in years)	35.4	0.5
Blood Pressure (mmHg)		
Diastolic	77.0	0.4
Systolic	125.4	1.7
Heart Rate (bpm)	71.9	1.2
Height (inches)	66.3	0.1
Weight (lb)	168.5	1.6
BMI (kg/m)	26.9	0.2
Clinical surveys		
GCPS interference (women; men)	50.05; 39.28	1.37; 2.77
OBC (women; men)	29; 24	0.76; 1.57
Temperature used Conditioning phase		
Green cue	41.2°C	0.1
Red cue	46.9°C	0.1
Testing phase	46.1°C	0.1

Table 4. Participant's characteristics. Abbreviations: Graded Chronic Pain Scale (GCPS) Oral Behavior Checklist (OBC).

A well-established classical conditioning paradigm (Olson et al., 2021, Wang et al., 2022) was used to induce placebo effects (see Fig. 7). Gonadal hormone levels were determined from blood samples using competitive ELISA.

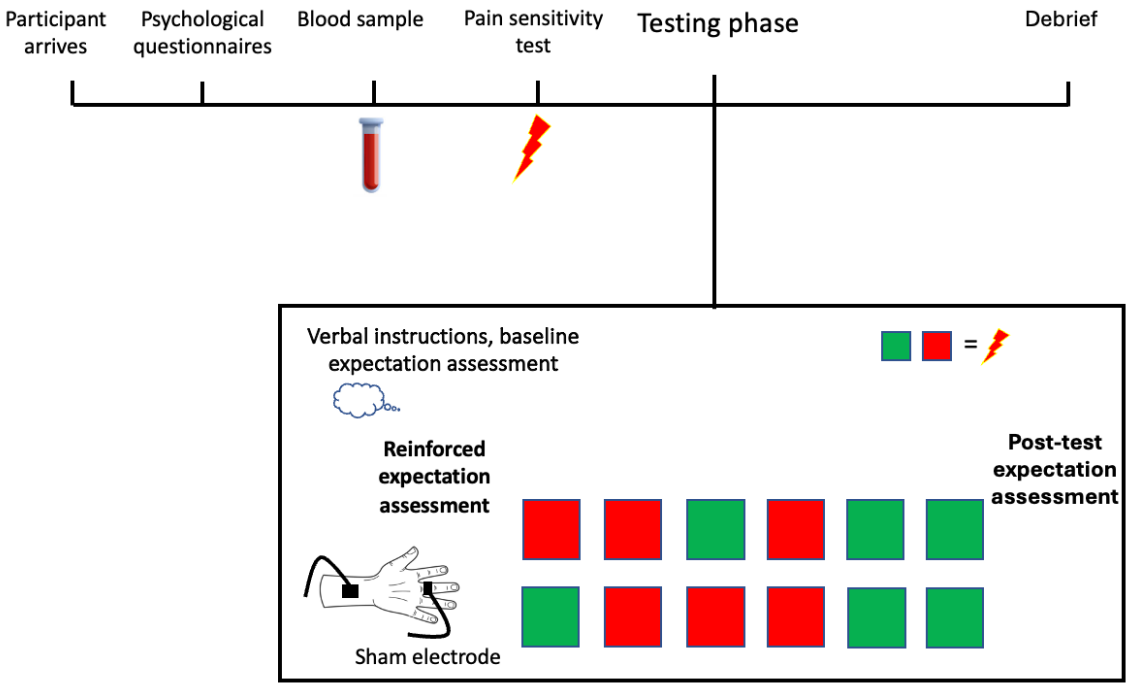


Figure 7. Experimental procedure for classical conditioning-induced placebo hypoalgesia. Participants were told that an electrode (a sham) placed on the middle finger may provide analgesia from a thermal stimulation delivered by a thermode on the forearm. They were then instructed that they would see two screens, colored red or green (counterbalanced as shown), indicating that the sham was off or on, respectively. During the conditioning phase, two distinct levels of painful stimulations (high and low pain paired with observation of the red and green screen, respectively) were delivered on the forearm to reinforce expectations and provide a hypoalgesia experience. During the testing phase, both pain levels were surreptitiously set at a moderate pain level to test for placebo effects. Pain was assessed using the visual analogue scale (VAS) from 0 (no pain) to 100 (maximum pain tolerance). Expectations were assessed at three points during the experiment; once prior to the conditioning phase (baseline expectations) once after the conditioning phase (reinforced expectations) and once after the testing phase (post-test expectations). Participants also completed a psychological assessment and provided a blood sample for gonadal hormone analysis.

Sex differences in clinical temporomandibular disorder pain severity and interference

To replicate previous findings (Olson et al., 2021), we tested sex differences in clinical TMD pain and experimental heat pain threshold and tolerance limits and confirmed that women were more sensitive to clinical (GCPS interference score, U=11 423.5, p=0.003; OBC score, U=10 928.0, p<0.001) and experimental (pain sensitivity: U=61 255.5, p=0.005; pain tolerance: U=53 943.0, p<0.001) pain. Further, correlation analysis revealed that higher testosterone levels in women with TMD were correlated with lower chronic pain severity (R=-0.14, p=0.03).

Sex differences during the conditioning phase

We observed that participants demonstrated significantly lower pain ratings for green trials compared to red trials during the conditioning phase, as revealed by the significant main effect of the color of the trials (red vs green, $F_{1,6464.5}$ = 34 409.2, p<0.001). Within each sex, the pain ratings for green trials were significantly lower than that for red trials during the conditioning phase for both women ($F_{1,4666.2}$ = 29 759.4, p<0.001) and men ($F_{1,3616.5}$ = 17 889.6, p<0.001), suggesting successful learning in both sexes. Among TMD patients, LMM revealed an effect of sex (F=4.430, p=0.035), but this result was not significant with post-hoc Bonferroni correction (p=0.975). In healthy controls, there was no difference in conditioning between women and men (p=0.249).

Sex differences in expectations

Expectations regarding the efficacy of the sham device were assessed at baseline prior to conditioning and again prior to testing (reinforced expectation) (“On a scale from 0 to

100%, how likely do you believe this treatment intervention will work?" and "On a scale from 0 to 100%, how well do you believe this treatment worked?", respectively). There was a difference in baseline expectation observed between women and men ($F_{1,4187}$=11.85, p<0.001) at the beginning of the experimental session prior to conditioning. In general, women reported higher expectations than men (mean=2.7, p<0.001). There was also a significant difference between TMD patients and healthy controls ($F_{1,4187}$=12.6, p<0.001), where TMD patients had higher expectations than healthy controls (mean=3.1, p<0.001). There was also significant interaction effect between sex and groups ($F_{1,4187}$=6.6, p=0.010), where the Bonferroni corrections showed greater expectations for women within the healthy control group (mean=4.7, p<0.001). We further found significant interaction effects of women's menstrual phase on baseline expectations ($F_{3,4183}$=18.6, p<0.001). For TMD patients, women, regardless of phase, had similar expectations compared to men (p=0.561). Among healthy control participants, women reported higher expectations at baseline than men (mean=4.7, p<0.001), but upon splitting women by menstrual phase, these effects were only significant for women in the luteal phase (mean=2.7, p=0.050) and postmenopausal women (mean=7.2, p<0.001), and not women in the follicular phase (p=0.096) compared to men.

After the conditioning phase and prior to testing, women had greater reinforced expectations than men ($F_{1,4187}$=16.2, p<0.001). There was in interaction effect with group ($F_{1,4187}$=11.9, p<0.001), where this difference was significant for TMD patients only (mean=2.7, p=0.050), and not for healthy controls (mean=0.2, p<0.001). More specifically, this difference was observed among women with TMD in the follicular

phase (mean=0.2, p<0.001) and post-menopausal women (mean=0.2, p<0.001), but not women in the luteal phase (p=0.242).

After the testing phase, women with TMD reported greater perceived treatment effectiveness than men with TMD ($F_{1,4187}$=5.6, p=0.018). This was true for women in the luteal phase (mean=0.1, p=0.002), but not for women in the follicular phase (p=0.075) or postmenopausal women (p=0.308). In general, TMD patients had higher post-test expectations than healthy controls ($F_{1,4187}$=8.7, p=0.003), but there was no interaction effect between sex and group (p=0.179) (see Fig. 8).

Figure 8. Effects of sex and menstrual phase on treatment expectations. While baseline expectations did not differ between women and men with TMD (A), women in the healthy control (HC) (B) group in the luteal and postmenopausal phases showed greater baseline expectations compared to men. While women with TMD in the follicular and postmenopausal phases showed greater reinforced expectations compared to men with TMD, reinforced expectations did not differ between women and men in the healthy control group. Finally, while women with TMD in the follicular phase of the menstrual cycle showed greater post-test expectations compared to men with TMD, post-test expectations did not differ between women and men in the healthy control group. Abbreviations: BE = baseline expectations, RE = reinforced expectations, PTE = post-test expectations. *p<.01 **p<.001

A

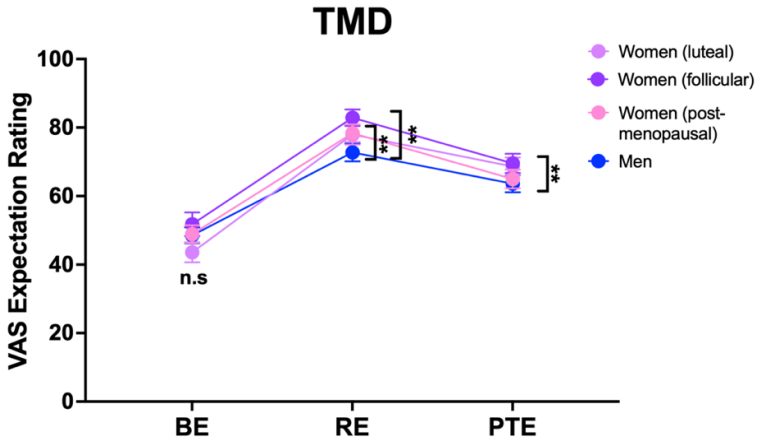
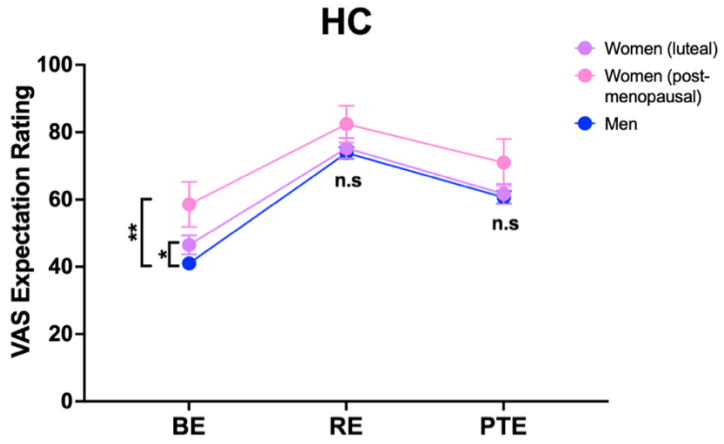


Figure 8 (continued).

B



Sex differences in placebo hypoalgesia

Both sexes showed evidence of placebo effects during the testing phase. For all participants, we found an effect of sex ($F_{1,4158.8}$=18.2, p<0.001), where women exhibited larger placebo hypoalgesia than men (mean=2.9, p<0.001). This result was true for women in the luteal phase (mean=3.5, p<0.001), but not women in the follicular phase (p=0.077) or postmenopausal women (p=1.000). There was no significant difference in placebo effects between TMD patients and healthy controls. Importantly, controlling for chronic pain severity, educational level, and heat-pain stimulations used in the testing phase, there was a significant sex (women vs. men) by color of the trials (red vs. green) interaction. Specifically, for green trials, we found a significant effect of sex ($F_{1,5733.5}$=32.5, p<0.001) and group ($F_{1,5733.5}$=6.4, p=0.011). Women reported significantly lower pain intensity ratings than their male counterparts in both groups (mean=17.6, p<0.001) and TMD patients showed higher pain intensity than healthy controls (mean=0.8, p=0.011). Similar differences were found in pain ratings for red trials (sex:

$F_{1,6178.7}$: 7.0, p=0.008; $F_{1,6178.7}$: 21.5, p<0.001). Women reported significantly lower pain levels than men (mean=12.8, p=0.016); (see Fig. 9), but the group differences were not confirmed when Bonferroni corrected (p=0.087).

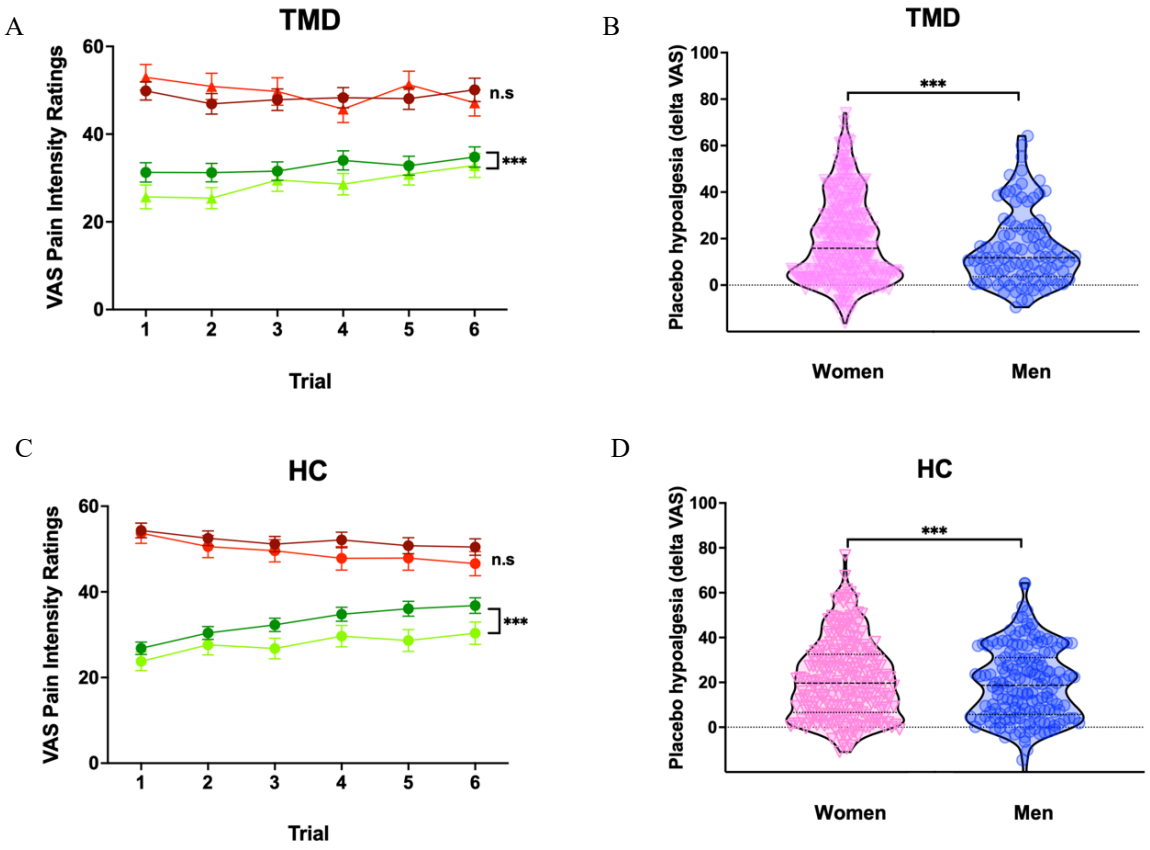


Figure 9. Effects of sex on placebo hypoalgesia. (A) Time course of conditioning-induced placebo effects in individuals with TMD. There was a significant difference in pain ratings for green trials between women (triangle) and men (circle) with TMD that did not extinguish over time. (B) Delta scores of conditioning-induced placebo effects in individuals with TMD. Women with TMD exhibited significantly larger placebo effects compared to men with TMD. (C) Time course of conditioning-induced placebo effects in healthy controls. There was a significant difference in pain ratings for green trials between women (triangle) and men (circle) in the healthy control group that did not extinguish over time. (D) Delta scores of conditioning-induced placebo effects in healthy controls. Women in the healthy control group exhibited significantly larger placebo effects compared to men. ***p<.0001

Role of gonadal hormones in conditioning, expectations, and placebo hypoalgesia

We measured the levels of estradiol, progesterone, and testosterone in all participants. We examined these levels as potential determinants of sex differences in conditioning strength, expectations, and placebo effects to elucidate whether larger expectations and placebo effects observed in women compared to men were to some extent attributable to differences in hormone levels using LMM.

In all participants, we observed that estradiol was significantly associated with conditioning strength, but not progesterone and testosterone (estradiol: $F_{1,1430}$=9.1, p=0.003; progesterone: p=0.123; testosterone: p=0.233). We observed similar results for reinforced expectations (estradiol: $F_{1,1424}$=4.8, p=0.029; progesterone: p=0.552; testosterone: p=0.817). However, the opposite was found for placebo effects, where estradiol was not significantly associated to placebo hypoalgesia, while progesterone and testosterone were (estradiol: p=0.119; progesterone: $F_{1,1416}$=4.3, p=0.039; testosterone: $F_{1,1416}$=17.3, p<0.001).

In women, estradiol was significantly associated with conditioning strength, but not progesterone and testosterone (estradiol: $F_{1,1430}$=10.2, p=0.001; progesterone: p=0.074; testosterone: p=0.226). A linear regression analysis revealed that higher levels of estradiol were associated with greater conditioning strength (β=0.081, p=0.001). We found no effect of group, indicating that women with TMD and healthy control women exhibited similar levels of conditioning strength. We observed similar results for reinforced expectations (estradiol: $F_{1,1424}$=4.4, p=0.035; progesterone: p=0.299; testosterone: p=0.980). Higher levels of estradiol were associated with greater reinforced expectations (β=0.107, p<0.001). We found no effect of group, indicating that women with TMD and healthy control women exhibited similar levels of reinforced expectations.

The opposite was found for placebo effects, where estradiol was not significantly associated with placebo analgesia, but progesterone and testosterone were (estradiol: $p=0.123$; progesterone: $F_{1,1416}=4.2$, $p=0.042$; testosterone: $F_{1,1416}=17.5$, $p<0.001$). Progesterone levels were not significant when using a regression analysis ($p=0.981$), while higher testosterone levels were associated with lower placebo effects ($\beta=-0.059$, $p=0.027$). Further, we found a direct effect of group ($F_{1,1416}=3.9$, $p=0.048$), but the pairwise comparison using Bonferroni correction was not significant ($p=0.656$).

In men, gonadal testosterone levels were the only hormone significantly associated with conditioning strength (estradiol: $p=0.132$; progesterone: $p=0.082$; testosterone: $F1,1141=7.7$, $p=0.006$). A linear regression revealed that lower testosterone levels were associated with greater conditioning strength ($\beta=-0.060$, $p=0.039$). Reinforced expectations were significantly associated with both estradiol and testosterone levels (estradiol: $F1,1135=3.4$, $p<0.001$; progesterone: $p=0.052$; testosterone: $F1,1135=4.9$, $p=0.026$). The regression analysis confirmed that greater estradiol levels were associated with greater reinforced expectations ($\beta=0.128$, $p<0.001$), but the effect of testosterone levels was not significant ($p=0.743$). Placebo effects were not associated with hormone levels in men (estradiol: $p=0.356$; progesterone: $p=0.163$; testosterone: $p=0.876$) We found no effect of group, indicating that men with TMD and healthy controls exhibited similar levels of placebo effects.

Hormone	**Estradiol**		**Testosterone**	
TMD	**Women**	**Men**	**Women**	**Men**
Chronic pain severity	ns	ns	ns	**R=-0.14, p=0.03**
Conditioning strength	**β=0.081, p=0.001**	ns	ns	**β=-0.060, p=0.039**
BE	ns	ns	ns	ns
RFE	**β=0.107, p<0.001**	**β=0.128, p<0.001**	ns	ns
PTE	ns	ns	ns	ns
Placebo hypoalgesia	ns	ns	**β=-0.059, p=0.027**	ns
HC	**Women**	**Men**	**Women**	**Men**
Conditioning strength	**β=0.081, p=0.001**	ns	ns	**β=-0.060, p=0.039**
BE	ns	ns	ns	ns
RFE	**β=0.107, p<0.001**	**β=0.128, p<0.001**	ns	ns
PTE	ns	ns	ns	ns
Placebo hypoalgesia	ns	ns	**β=-0.059, p=0.027**	ns

Table 5. Effects of gonadal hormones on pain severity, conditioning strength, baseline (BE), reinforced (RE) and post-test (PT) expectations, and placebo hypoalgesia. ns= non-significant.

Mediation approach

Using the mediation approach, we were able to statistically define the causal effects of hormones and reinforced expectations, i.e., expectations regarding treatment

effectiveness that were assessed following conditioning and prior to testing, in determining the sex differences in placebo hypoalgesia. Estradiol emerged as a significant mediator in determining sexually dimorphic reinforced expectations in all participants, regardless of group (estradiol: a*b=.5056, 95%BCI=.1766 to .8540) while reinforced expectations emerged as a partially significant mediator in determining sexually dimorphic placebo effects in TMD participants (reinforced expectations: a*b=1.0525, 95%BCI=.2465 to 2.2853; see Fig.10).

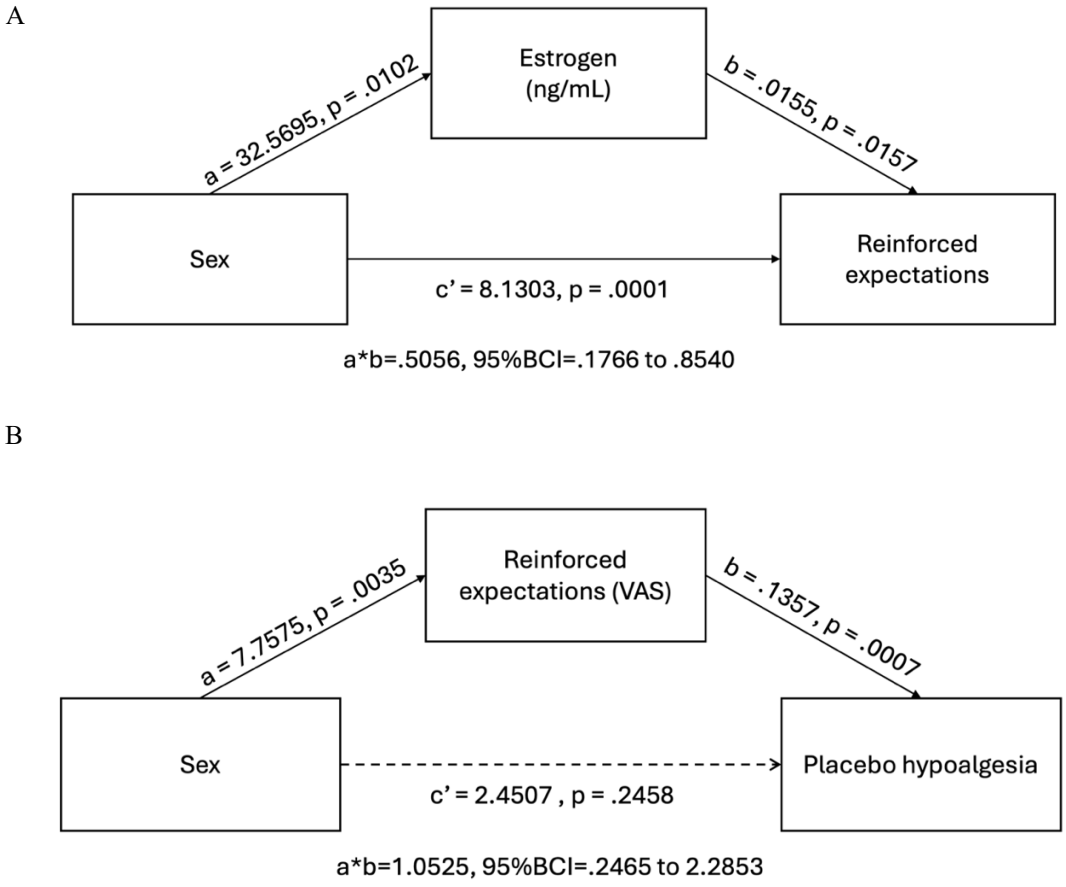


Figure 10. Mediation effects of estradiol on treatment expectations and treatment expectations on placebo hypoalgesia (above). (A) Higher estradiol levels fully drove greater sexually dimorphic reinforced expectations in all participants, regardless of group. (B) Higher reinforced expectations partially mediated greater sexually dimorphic placebo effects in individuals with TMD.

Sex differences in personality traits

In the current study, women did not differ from men in terms of agreeableness (p=0.090), neuroticism (p=0.685), extraversion (p=0.901), openness (p=0.509) or conscientiousness (p=0.166). The 5 NEO personality traits were not linked to the magnitude of placebo hypoalgesia in the current study (neuroticism: p=0.140; extraversion: p=0.066; openness: p=0.158; agreeableness: p=0.860; conscientiousness: p=0.227), indicating that personality characteristics did not explain the sex differences in placebo hypoalgesia.

E. Discussion

This study investigated the role of sex and sex hormones in conditioning strength, expectations for treatment effectiveness, and placebo hypoalgesia in healthy adults and adults diagnosed with TMD. In an exploratory analysis, we replicated previous results indicating sexual dimorphism in TMD pain sensitivity, whereby women showed lower pain threshold and tolerance than men, and higher TMD pain severity. Further, we replicated previous results indicating that participants reported higher treatment expectations compared to healthy controls, while placebo effects were of similar magnitude between the two groups. For the experimental procedure, we adopted existing methods of classical conditioning to examine sex differences in placebo effects and expectations assessed before and after exposure to positive treatment outcomes. Further, we assessed the role of sex hormones in sex differences related to expectations and placebo effects. Specifically, we used mediation analysis to determine how gonadal hormone levels and expectations impacted sex differences in placebo effects. We demonstrated that, independent of chronic pain severity, age, race, educational level, and individual heat pain tolerance, women showed larger expectations and placebo effects compared to men, replicating earlier findings (Olson et al., 2021). Estradiol levels mediated sexually dimorphic reinforced expectations following the conditioning phase, and in turn, reinforced expectations mediated sexually dimorphic placebo effects.

Sex differences in conditioning

Participants successfully demonstrated learning of the classical conditioning paradigm, as evidenced by the significant main effect of trial color on conditioning strength. However,

there were no significant sex differences in conditioning for TMD patients or healthy controls. While there was an effect of sex on conditioning strength among participants with TMD, this effect was not significant after correcting for multiple comparisons. Numerous early studies report that women and men perform differently on some types of learning tasks (Spence and Spence, 1966, Collins and Kimura 1997, Astur et al., 1998, Stark et al., 2006), and that there are sex differences in learning and memory (de Frias et al., 2006, Sambeth et al., 2007, Hausmann et al., 2009). These differences are hypothesized to be attributed to sex differences in stress (Stark et al., 2006) brain development (Kimura, 2002), and memories, which are reinforced with experience (Olson et al., 2021). However, many of these findings suffer from small effect sizes or merely result from the experimental design (Dalla and Shors, 2009). As a result, sex differences in human learning and cognition, if they exist, are difficult to observe and interpret (Dalla and Shors, 2009).

Sex differences in expectations

We found that both women with TMD and women in the healthy control group indicated greater expectations regarding treatment effectiveness compared to men, and that expectations assessed after conditioning mediated placebo effects, replicating previous findings; the first of their kind (Olson et al., 2021). Although several studies have highlighted the importance of patients' expectations for health outcomes (Sherman et al., 2010, Laferton et al., 2017), it appears to be less known whether treatment expectations differ among men and women. However, sexually dimorphic pain responses appear to be driven by expectations (Bartley and Fillingim, 2013) and pain experiences may reinforce

treatment expectations (Olson et al., 2021). Previous literature suggests that beliefs regarding femininity and masculinity play an important role in pain responses among sexes (Bartley and Fillingim, 2013). In general, pain expression appears to be more socially acceptable among women, which may lead to biased pain reporting (Bartley and Fillingim, 2013). Robinson et al. found that women and men believed that men are less likely to report pain compared to women (Robinson et al., 2001). Further, sexually dimorphic expectations regarding gender roles may contribute to sex differences in experimental pain (Wise et al., 2002). For example, priming with a female gender role led men to report increased cold pressor pain (Fowler et al., 2011). Moreover, cultural differences can influence pain-related beliefs and views on pain sensitivity; as an example, in one study, Israeli women and men reported more "macho" attitudes regarding pain sensitivity and willingness to report pain compared to American women and men (Defrin et al., 2009, Bartley and Fillingim, 2013). Extended to our results, this suggests a critical role of sociocultural beliefs in generating sex-related expectations for pain, which subsequently influences pain reports among women and men. Expectation-induced pain reporting may then, in turn, reinforce expectations of pain relief in a sex-specific manner.

Sex differences in placebo effects

We demonstrated that in both TMD and healthy control groups, women exhibited greater placebo effects compared to men, replicating previous findings in the TMD group (Olson et al., 2021) and aligning with studies reporting greater placebo effects in women versus men (Yildiz et al., 2011, Ondo et al., 2013). However, other studies show that men

exhibit greater placebo effects than women (Vambheim and Flaten, 2017), and some lack a sufficient number of women participants to draw sex-related conclusions on interindividual differences in placebo effects (Olson et al., 2021). Two large systematic reviews concluded that there were no differences in placebo responses between sexes in randomized clinical trials (RCTs) (Weimer et al., 2015, Enck and Klosterhalfen, 2019). A recent call-to-action argued that these inconsistent findings may be due to small datasets, low-quality data, and aggregation of diseases with different sex-dependent prevalences and symptoms within reviews and metanalyses (Shafir et al., 2022). Therefore, the field is not positioned to draw conclusions on sex differences in placebo analgesic affects (Shafir et al., 2022). This study aimed to address these challenges by examining sex differences in placebo hypoalgesia in a large study of individuals with TMD, the prevalence of which has a 3:1 women to men ratio, and healthy controls. We used gonadal hormone levels to investigate the mechanisms underlying sexually dimorphic pain experience, treatment expectations, and placebo effects.

Role of gonadal hormones

We found that in women with TMD, testosterone levels were negatively correlated with chronic pain severity, suggesting a potentially anti-nociceptive role of testosterone in TMD pain. The anti-nociceptive effects of testosterone have been reported in previous studies (Craft, 2007, Basaria et al., 2015, White and Robinson, 2015, Lee and Lee, 2016). For example, Lee and Lee investigated 8,336 adult males and found that males with levels of testosterone less than 3.5 ng/mL had significantly higher rates of chronic pelvic pain than males with levels of testosterone more than 3.5ng/mL (Lee and Lee, 2016). In females, a shorter anogenital length, representing lower levels of androgens during fetal

development, is correlated with a higher prevalence of endometriosis (Crestani et al., 2020) and increased pain (Evans et al., 2021). In contrast, a longer anogenital length in females, representing higher levels of androgens during fetal development, has been associated with an increased prevalence of Polycystic Ovarian Syndrome (PCOS) (Dinsdale et al., 2021). Though conflicting findings make it difficult to guess whether testosterone will have protective effects against experimental pain in women with TMD, it can be reasonably hypothesized that if testosterone produces anti-nociceptive effects, then pain severity and placebo analgesia will be influenced by testosterone levels. Specifically, the anti-nociceptive effects of testosterone may elicit a smaller difference in pain ratings between the placebo and control conditions, thereby generating smaller placebo effects observed in men with TMD (Olson et al., 2021). We further found that estradiol levels mediated sex differences in reinforced expectations, which in turn mediated sexually dimorphic placebo effects. Estrogen, which facilitates higher cognitive functions in the PFC and hippocampus (Hara et al., 2015) may be especially involved in the formation of expectancies, which mediate placebo effects (Babel, 2019) by leveraging regions involved in pain modulation, such as the PFC (Wager et al., 2004). As demonstrated by Basaria and colleagues and Lesnak and colleagues (Basaria et al., 2015, Lesnak 2020), manipulating hormone levels would enable us to draw conclusions regarding the mechanisms underlying the effects of hormones on clinical pain and, in this study, placebo effects.

In summary, the inclusion of sex as a biological variable (SABV) in pain research is critical for the development of medical interventions and treatments tailored to patients' needs. It is clear that sex differences exist in the prevalence and progression of chronic

pain, treatment efficacy, and clinical outcomes such as placebo effects (Shafir, 2022). However, sex effects in the clinical and experimental settings remain understudied due to lack of inclusion of females in animal studies (Arnegard et al., 2020, Shafir 2022) and sex rarely being included as a variable in analyses in human translational and clinical studies (Shafir 2022). Even when sex is included as a biological variable in analyses of pain and placebo studies, the mechanisms underlying any observed effects, e.g., the role of the hormonal axis (Vincent and Tracey, 2008) are difficult to explain. This study is the first of its kind, to our knowledge, to demonstrate that varied concentrations of sex hormones contribute to differences in pain experience, including pain sensitivity, expectations regarding pain relief, and placebo effects in individuals with TMD. The findings of this study may be used to advance current knowledge on sex differences as they relate to individual pain experiences and outcomes.

Chapter IV: Brain morphologic correlates of placebo hypoalgesia in chronic pain

A. Abstract

Temporomandibular disorders (TMD) are chronic orofacial pain conditions that affect the jaw, jaw joint (temporomandibular joint) and surrounding facial muscles. TMD affects approximately 5-12% of the U.S. population and adversely impact patients' quality of life. Recent experimental research shows a promising role of placebo treatment in inducing hypoalgesia in this population. However, predictors of varying levels of placebo responses among TMD individuals, such as differences in brain structure, remain elusive. Here, we assessed the placebo effect magnitude of participants with TMD using a well-established classical conditioning paradigm. Voxel-based morphometry (VBM) analysis of T1-weighted images was then used to detect changes in local grey matter volume (GMV) that were associated with individual placebo effect magnitude.

72 participants with TMD completed the classical conditioning with verbal suggestions paradigm to study placebo phenotypes. We tested for placebo effects by using two distinct levels of individually tailored painful stimulations (high pain and low pain) to reinforce expectations and provide a hypoalgesic experience (conditioning phase). Afterwards, in a single-blind manner, both levels of pain were set at a moderate pain level to test for placebo effects (testing phase) while participants underwent an MRI scan. Pain was assessed as the primary outcome using visual analogue scale.

Behaviorally, responders exhibited significantly greater placebo effects than non-responders. Single-group VBM correlation analysis revealed a significantly positive correlation between placebo response and GMV in the TMD phase 2 cohort ($p < .05$,

TFCE-corrected), suggesting a role for brain structure in the generation of placebo effects.

B. Introduction

Pain is a subjective experience that is perceived by the brain via integration of bottom-up nociception input and top-down descending pain modulation (Martucci et al., 2014). Experimental research shows that long-lasting pain can alter the brain's structure and function, resulting in distinct gray matter distribution in the cortex in chronic pain patients when compared to healthy population (Maeda et al., 2015, Magon et al., 2018). However, the changes in brain structure contributing to endogenous pain modulatory mechanisms such as placebo effects remain elusive.

Neuroimaging research on chronic pain has primarily focused on identifying brain regions that show altered structure and activity in chronic pain states (Ong et al., 2019). VBM studies suggest that pain sensitivity is significantly correlated to the morphology of the PFC (Ong et al., 2019) and the ACC, parahippocampal gyrus (PHG) and left temporal pole (Kotikalapudi et al., 2023).

For placebo effects, many structural differences between placebo responders and non-responders are found in various regions of the brain's prefrontal cortex. However, different studies identify different regions, and there is no consensus on a specific brain structure consistently differing between responders and non-responders (Neogi & Colloca, 2023). This variation may stem from different neural mechanisms involved in various conditions and study designs. Hartmann and colleagues combined data from four studies with a total of 237 healthy participants and found that responders had less gray matter volume and cortical surface area in the supramarginal gyrus and the inferior and middle temporal gyrus compared to non-responders (Hartmann et al., 2023), although this conflicted with an early study that found a positive correlation between placebo effects

and gray matter density in the VS, insula, and PFC (Schweinhardt et al., 2009). Both studies conflict with a recent analysis of multiple sclerosis treatments using graph theory that found no significant difference in brain volume or regional cortical thickness between responders and non-responders but noted more uniform cortical thickness covariance patterns and stronger small-world attributes in non-responders (Cherkasova et al., 2022). Similarly, in a study of participants with cLBP, there were no differences in GMV between responders and non-responders, rather, asymmetry of subcortical limbic volume in the NAc, right hippocampus, and amygdala, and cortical thickness of the right superior frontal gyrus, predicted placebo responses (Vachon-Presseau et al., 2018). Given these diverse findings, further research is needed to identify the neural correlates of placebo effects, particularly for specific treatment conditions.

In this study, we used placebo effects as a proxy for endogenous descending pain modulation to determine individual placebo effects. VBM analysis was used to examine the association between placebo effects and GMV in a cohort of chronic pain patients diagnosed with TMD. We used a whole-brain analysis rather than ROI analysis to capture all potential effects between GMV and placebo effects in an unbiased manner (Giuliani et al., 2005).

C. Methods

Participants

Participants with TMD from Phase 1 of the TMD parent study (Wang et al., 2022) were recontacted to potentially participate in Phase 2 of study. 87 participants with TMD from Phase 1 were enrolled in Phase 2. Data from 15 participants were excluded for brain imaging preprocessing issues or excessive head motion (average field displacement ≥ 0.500 mm), for a final N of 72 participants with TMD included in the present analysis. The current study is a secondary data analysis study that was an independent project (SGD & LC/JW, R21 DE032532) associated with a larger study on placebo effects in participants with TMD (LC, R01-DE025946-01). The characteristics of the 72 participants with TMD included in the analyses are presented in Table 6. All participants were compensated $100 for completing the study procedures.

	N/mean	%/SEM
Sex		
Women	57	79.2%
Men	15	20.8%
Race		
Asian	7	9.7%
Black/A.A	19	26.4%
White	42	58.3%
Mixed race	4	5.6%
Age (in years)	43.2	1.7

Table 6. Participants' characteristics.

Inclusion and exclusion criteria

Potential participants with TMD underwent a clinical diagnostic appointment at the University of Maryland, School of Dentistry, Brotman Facial Pain Clinic to reconfirm TMD diagnosis from Phase 1 and study eligibility. To be included in the study, potential participants with TMD had to meet the Axis I Diagnostic Criteria for TMDs (DC/TMD): (1) History positive for pain in the immediate 30 days before examination for both of the following: (a) Pain in the jaw, temple, in the ear, or in front of the ear; and (b) pain modified with jaw movement, function, or parafunction; and (2) examination positive for myalgia and/or arthralgia: (a) confirmation and duplication of pain location(s) in the temporalis, masseter, or other masticatory muscle(s); and/or (b) confirmation and duplication of pain in one or more temporomandibular joints.

The following criteria excluded potential participants with TMD: the presence of degenerative neuromuscular disease; cervical pain (e.g., stenosis or radiculopathy); a diagnosis of cardiovascular, neurological, kidney, or liver disease; pulmonary abnormalities; cancer within the past 3 years; color blindness; or uncorrected impaired hearing, pregnancy or breastfeeding. Additionally, any individual who had facial trauma in the last 6 weeks or a history of severe facial trauma in the past 2 to 3 months were excluded from participating in the study.

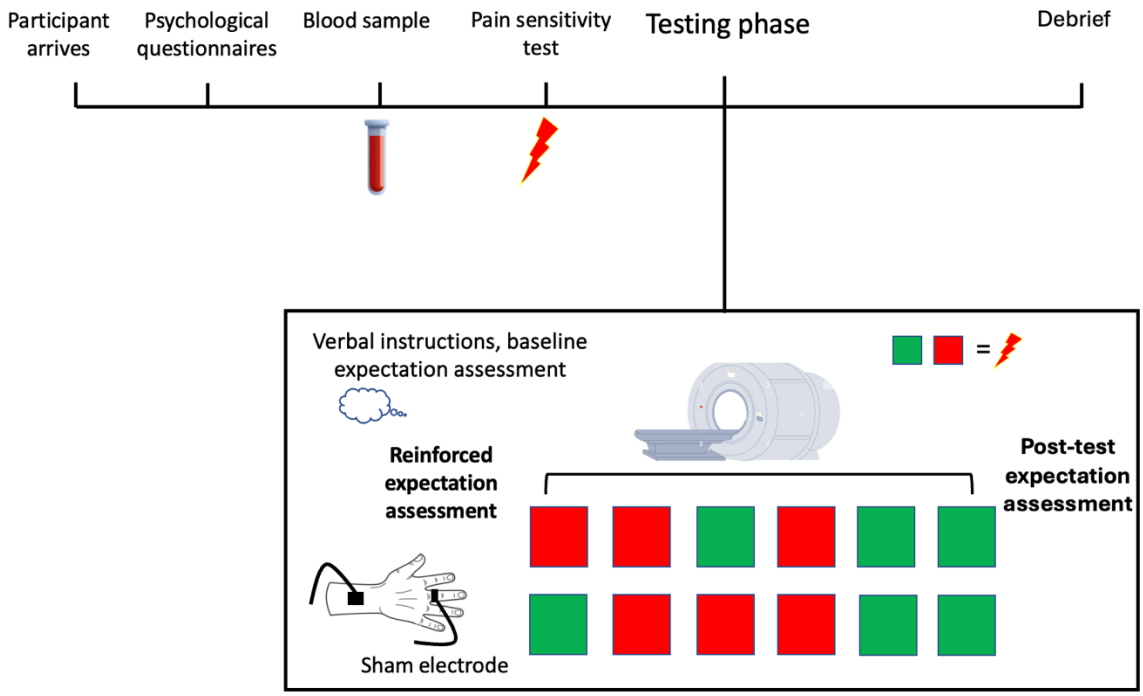
MRI contraindications included non-removable metal objects or implants in the body, claustrophobia, history of working in metal fields, surgical clips or shrapnel in or near the brain or blood vessels, wires or devices concentrating radiofrequency fields, and head trauma with loss of consciousness in the last year/functional impairment due to and persisting after head trauma.

For potential participants with TMD, a licensed psychiatrist screened cases of psychiatric problems based on Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V) (Regier et al., 2013) Participants who had severe psychiatric conditions such as mania, dementia, bipolar disorder, schizophrenia, major depression, Obsessive-compulsive disorder, or lifetime dependence on alcohol or drugs were excluded from the study.

Study procedure

Study design: Participants underwent the following protocols during the 3- to 4-hour experimental paradigm: (1) a pain sensitivity assessment, and (2) conditioning and testing phases of the placebo procedure. The testing phase of the procedure was completed while participants underwent MRI (see Fig. 11).

Figure 11: Experimental procedure for classical conditioning induced placebo hypoalgesia in MRI. Participants were told that an electrode (a sham) placed on the middle finger may provide analgesia from a thermal stimulation delivered by a thermode on the forearm. They were then instructed that they would see two screens colored red or green (counterbalanced as shown), indicating that the sham was off or on, respectively. During the conditioning phase, two distinct levels of painful stimulations (high and low pain paired with observation of the red and green screen, respectively) were delivered on the forearm to reinforce expectations and provide a hypoalgesia experience. During the testing phase, both pain levels were surreptitiously set at a moderate pain level to test for placebo effects. During the testing phase, participants underwent MRI during which an anatomical acquisition scan and a resting state scan were acquired. Pain was assessed using the visual analogue scale (VAS) from 0 (no pain) to 100 (maximum pain tolerance). Expectations were assessed at three points during the experiment; once prior to the conditioning phase (baseline expectations) once after the conditioning phase (reinforced expectations) and once after the testing phase (post-test expectations). Participants also completed a psychological assessment and provided a blood sample for gonadal hormone analysis.



Heat pain stimulation

Thermal heat stimuli were applied through the Medoc Pathway system (Medoc Advances Medical System, Ramat Yishai, Israel), with heat stimulations beginning at 32 degrees Celsius and rising at a rate of 1.0C/s either until the participant signaled to stop the stimulation according to instruction or the temperature reached its maximum of 52C. The heat increase was set at 0.3C/s in order to establish warmth and heat pain threshold. A probe (30 X 30 mm ATS thermode) on the ventral side of a participant's dominant forearm was used to deliver the heat stimuli. To assess individual pain sensitivity we used the methods of limits along with applying an ascending series of contact heat thermal stimuli to tailor the level of high and low painful stimuli to each participant. This allowed for the identification of heat-warmth detection, heat-pain threshold, and heat-pain tolerance limits specific to each participant. “Warmth detection” was defined at the minimum degrees Celsius temperature that the participant was able to detect warmth.

"Painful threshold" was defined as the degrees Celsius temperature that was perceived as minimally painful by each participant. Lastly, "Painful Tolerance limit" was defined as degrees Celsius temperature at which each participant could no longer tolerate the heat-pain stimuli.

Participants were instructed to press the Pathway remote button for each stimulus concerning each modality, with each modality being tested 4 times. To calibrate the pain modulation assessment, the average temperature for each sensitivity level was calculated. Additionally, participants were asked to verbally verify their reports with a VAS from 0 to 100 each time the Pathway remote button was pressed.

The VAS scores were then used to establish the intensities of heat-pain stimuli that would be used in the conditioning phase. The pain sensitivity assessment yielded the average temperatures for minimum, moderate, and maximum levels of painful stimulations, which were then applied to the conditioning phase and testing phase.

Magnetic resonance imaging data

Brain imaging data from 87 participants with TMD (final N=72, see *Participants*) were collected at the University of Maryland School of Medicine (CT-TRIM) with a 3 Tesla system (Magnetom TIM Trio, Siemens, Erlangen, Germany) equipped with a 32-channel head coil. High resolution anatomical T1-weighted scans data acquisition was acquired using an MPRAGE sequence with a voxel size of 1x1x1mm3. T1-weighted data were analyzed for differences in local grey matter volume using FSL-VBM (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). Briefly, structural images

were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The normalized images were then averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Then, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxelwise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

Experimental procedures

Participants received instruction about the experimental procedure following the completion of the pain sensitivity assessment. Just above the thermode on the participant's arm, a sham electrode was placed, and participants were told that when active, the electrode would release a "subthreshold electrical stimulus" which may effectively reduce their pain. For the experimental procedure, participants were told that they would undergo 36 trials during which they would receive painful stimulation when the electrode was on (signaled by a green screen) and when the electrode was off (signaled by a red screen). Each visual cue was present for 10 seconds and at the same time as the thermode delivered painful stimuli for 10 seconds. After each trial, participants were asked to report their pain (VAS 0 to 100). The conditioning phase comprised of the first 24 trials, and for any green screen trials in this phase the temperature settings were lowered 6C lower than maximum tolerance. During red screen

trials, the temperature was raised to pain tolerance, established as 2C lower than the maximum tolerance. To confirm the experimental settings, participants were asked to rate their pain after each trial, and self-reported scores verified the pain as 20 (green) and 80 (red) out of a 100 on VAS. The last 12 trials were the testing phase, in which the temperature was consistent regardless of screen color as the screen alternated between red and green. The temperature for these 12 trials was set at 1C lower than the temperature for the red screen trials in the conditioning phase. Participants were not informed of any temperature changes during the experiment. During the conditioning phase, differences in red-minus green-associated pain reports were operationally determined as a "conditioning strength". During the testing phase, the delta between red-minus green-associated pain reports was operationalized as "placebo hypoalgesia".

Statistical analysis

Behavioral analysis

The methods reported here are similar to those reported in a previous study on placebo effects in TMD patients (Colloca et al., 2024). For behavioral data analysis, we used repeated measures ANCOVA analysis to determine the occurrence and magnitude of placebo effects, using the average of the six pain ratings scores of the placebo trials and the control trials from the testing phase. The experimental condition (placebo vs. control) was treated as a within-subjects factor. Sex and age were set as covariates to be consistent with the brain imaging analyses. In an exploratory analysis, we classified participants into high placebo responder (HPR) and low placebo responder (LPR) groups based on an average reported pain score cutoff of 30 out of 100 points (low response (<30) vs. high

response (> = 30)). Absolute difference changes were used to avoid misleading and biased reductions in pain: percentile changes from baseline may fail when there is an imbalance of baseline and outcome data that is non-normally distributed.

Calculation of placebo effect size

To calculate placebo effect sizes, Cohen's d was calculated using the formula |M1 − M2|/SD pooled * sqrt (2*(1 − r)) (Colloca et al., 2024) where M1 and M2 were the average of pain ratings for red and green conditions, respectively, SD pooled was the pooled standard deviation calculated as sqrt(S1 + S2 − r*S1*S2), and r was the correlation coefficient between pain ratings from red and green trials. S1 and S2 were standardized deviations for red and green trials, respectively. The level of significance P was set at 0.05 for the level of statistical significance. The Statistical Package for Social Sciences (SPSS) software v29 was used to analyze behavioral placebo effects.

Brain imaging analysis

A GLM design was used to create a cross subject statistical model with a design contrast and matrix (Winkler et al., 2014). The single-group average with additional covariate GLM was used to create the statistical model. 72 participants with TMD were entered in the GLM as one group. Demeaned placebo effect magnitude values, high or low placebo responder status, and placebo responder and non-responder status were entered as EVs (variables) in the design matrix. For each contrast, an "effective" regressor was formed using the design matrix and the contrast, as well as new "effective confound regressors" which were removed from the data prior to running permutation testing. Sigma=3mm

smoothing was chosen for threshold-free cluster-based analysis. Then, voxelwise general linear model (GLM) was applied using randomize, i.e., permutation-based non-parametric testing, correcting for multiple comparisons across space. Since voxels were not selected *a priori*, voxel-wise corrected p-values were generated to correct for multiple comparisons across voxels. Finally, the generated (1-p) corrected p-value images were viewed in FSLeyes. The threshold for the images was set at a minimum of 0.95 and a maximum of 1 to keep only the significant clusters in the statistical map. Voxel significance was assessed by cluster size.

D. Results

Individual placebo effects

We identified placebo responsiveness using permutation tests, similar to previous methods (Wang et al., 2022, Colloca et al., 2024), on the repeated measures of pain intensity ratings during the testing phase involving 6 red and 6 green trials. First, we calculated the observed difference (Tobs) as the average difference between pain ratings of the red and green trials. We then resampled 1000 times from the pooled pain ratings of the red and green trials to create a new distribution of possible difference scores under the null hypothesis, which assumes that pain ratings for red and green trials come from the same distribution.

The p-value was determined based on the observed difference (Tobs) and the resampled distribution. If Tobs fell within the central 95% of the resampled distribution, the null hypothesis was not rejected, indicating a non-significant permutation test. However, if the absolute value of Tobs was greater than or equal to the 95th percentile of the resampled difference scores, the null hypothesis was rejected, indicating a significant permutation test. This suggested that pain ratings from red trials were different from those of green trials. The significance level was set at p=0.05. An individual was classified as a placebo responder if the observed difference was positive (pain ratings of red > pain ratings of green) and the permutation test was significant.

In this cohort of participants with TMD, placebo responders exhibited significantly greater pain ratings from red trials than green trials compared to placebo non-responders (main effect of the condition (red vs. green pain-intensity ratings) $F_{1,69} = 60.41$, $p < .001$), controlling for age, sex, and race Exploratively, participants with TMD were identified as

high placebo responders and low placebo responders. 4 out of 72 participants were classified as high placebo responders, and 68 out of 72 participants were classified as low placebo responders. High placebo responders exhibited significantly greater placebo effects compared to low placebo responders ($F_{1,69} = 63.75$, $p < .001$) controlling for age, sex and race (see Fig. 12).

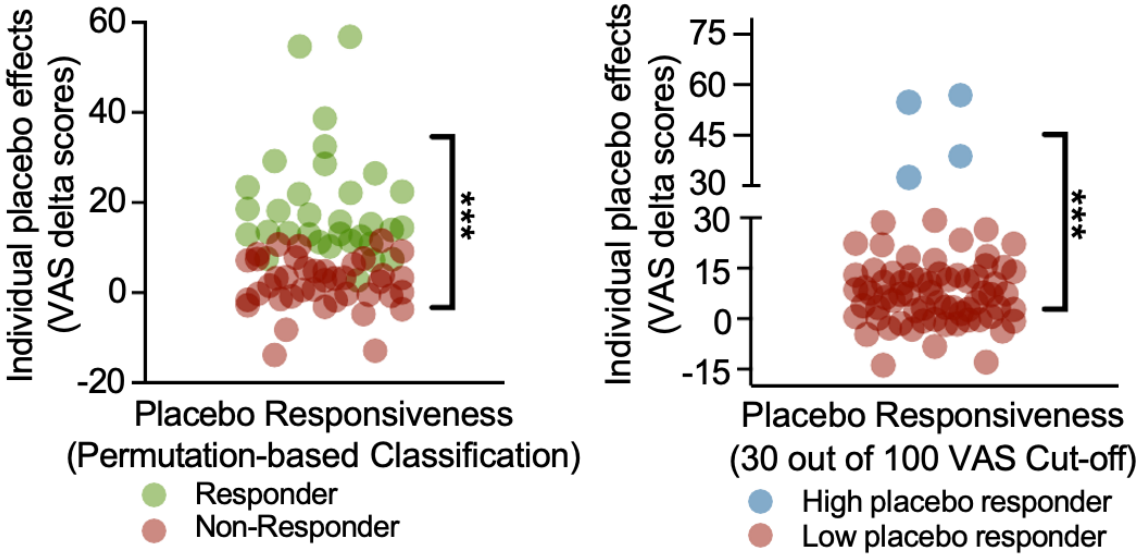


Figure 12. Distribution of placebo effects in the TMD phase 2 cohort. Data on 72* participants with TMD identified 32 individuals as responders, and the remaining 40 as non- responders in Phase 2. 4 out of 72 individuals were identified as HPRs, and the remaining 68 as LPRs in Phase 2. Behaviorally, responders exhibited significantly greater pain ratings from red trials than green trials than non-responders ($F_{1,69}$=60.41, $p<0.001$), and HPRs exhibited significantly greater placebo effects than LPRs ($F_{1,69}$=63.75, $p< 0.001$) controlling for age, sex and race.
*87 participants with TMD completed Phase 2 of the study. 15 participants were excluded from the present analysis due to brain imaging preprocessing issues or excessive head motion (average field displacement ≥ 0.500 mm). Final N=72.

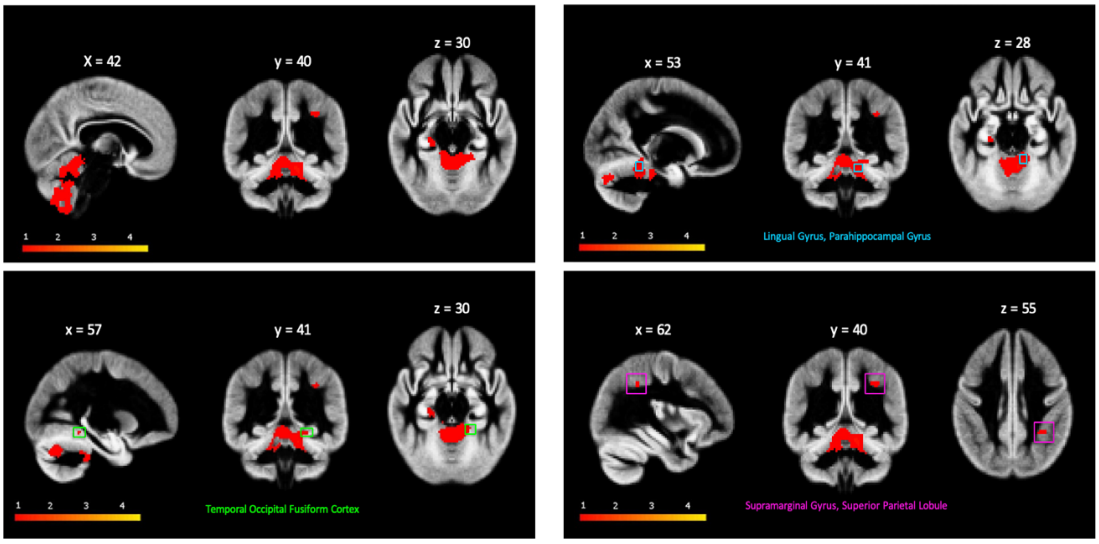
Whole-brain VBM analysis

T1-weighted images were analyzed for differences in local grey matter volume and single-group correlation between GMV and placebo responsiveness using FSL-VBM, an

optimized VBM protocol carried out with FSL tools (Good et al., 2001, Smith et al., 2004, Douaud et al., 2007). The between-group whole-brain VBM analysis, where placebo phenotype was treated as a binary variable (placebo responder or non-responder and high placebo responder or low placebo responder, respectively) was not informative. Specifically, whole-brain VBM analysis of participants with TMD did not show a significant difference in the GMV of placebo responders compared to placebo non-responders ($p > 0.05$), nor was there as significant difference in GMV between high placebo responders and low placebo responders ($p > 0.05$).

Single-group whole-brain VBM analysis with behavioral measurement (placebo response), where placebo response was treated as a continuous variable, revealed a significant positive correlation between placebo response and GMV of the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, superior parietal lobule, and cerebellum in participants with TMD (max. cluster $p < 0.05$; TFCE FWE-corrected) (see Fig. 13).

Figure 13. Statistical map of single-group VBM correlation analysis with behavioral measurement (placebo response). The statistical map represents a significant positive correlation between placebo responsiveness and GM volume in participants with TMD (max. $p<0.05$, TFCE FWE-corrected) overlaid on the study-specific grey matter template (created by FSL-VBM protocol) on the sagittal (x), coronal (y) and axial (z) plane. Areas of significance include Lingual Gyrus (blue), Parahippocampal Gyrus (blue), Temporal Occipital Fusiform Cortex (green), Supramarginal Gyrus (pink), Superior Parietal Lobule (pink).



The anatomical structures, i.e., the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, and superior parietal lobule and associated voxel sizes and maximum intensity (MAX; (1-p) are presented in Table 7.

Cluster	Voxels	MAX	Anatomical Structures
1	**70**	**0.952**	**Supramarginal Gyrus, Superior Parietal Lobule**
2	**28**	**0.95**	**Parahippocampal Gyrus, Lingual Gyrus**
3	**11**	**0.95**	**Temporal Occipital Fusiform Cortex**

Table 7. Size and labelled anatomical structures of the single-group VBM analysis significant clusters ($p < 0.05$, TFCE FWE-corrected). The voxel coordinates (in mm) in Harvard-Oxford Cortical Structural Atlas for the location of the maximum intensity (MAX; (1-p) TFCE FWE-corrected p- value) are presented.

E. Discussion

This study aimed to assess the generation of placebo effects in chronic pain participants diagnosed with TMD. Further, we aimed to detect changes in local GMV that were associated with placebo response in TMD patients using VBM analysis of T1-weighted images. We used a model of placebo effects, which consisted of pain reduction in response to a placebo manipulation (Olson et al., 2021, Wang et al., 2022, Colloca et al., 2024), in an experimental setting to identify structural brain phenotypes associated with response to placebo. We identified six subcortical regions in which GMV increased with increasing placebo effect magnitude: the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, superior parietal lobule, and cerebellum. Similar to a previous study (Vachon-Presseau et al., 2018), we found that comparing subcortical volumes between groups, i.e., placebo responders and placebo non-responders, was not informative, nor was comparing volumes between high placebo responders and low placebo responders. Rather, using the continuous variable approach (Vachon-Presseau et al., 2018) whereby placebo response was treated as a continuous variable instead of a binary variable, we observed that increased GMV in the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, superior parietal lobule, and cerebellum positively correlated with placebo effects in participants with TMD. The results indicated that capturing the spectrum of placebo magnitude among individuals may be more informative than group classification. Since placebo effects vary widely among individuals, the continuous variable approach allowed us to capture the range of low to high placebo responses between participants and the associated cortical changes.

The lingual gyrus makes up part of the medial occipital lobe and is necessary for basic and higher-level visual processing (Palejwala et al., 2021) and modulating visual stimuli. Zhang et al. found that GMV of the lingual gyrus mediated the relationship between inhibition function and divergent thinking (DT) (Zhang et al., 2016). DT involves creative thinking linked to increases in PFC activity that is observed in cognitive tasks involving top-down control, or inhibition function (Zhang et al., 2016). Extended to our findings, the lingual gyrus may drive placebo-leveraging of the PFC for top-down inhibition of nociceptive input.

The parahippocampal gyrus (PHG) lies along the ventromedial edge of the temporal lobe near the hippocampus and is involved in emotional processing, memory coding and retrieval, and contextual processing (Aminoff et al., 2013, Luck et al., 2010). PHG morphology has been found to contribute to pain experience; one VBM study reported that PHG structure was positively associated with individual pain sensitivity (Ruscheweyh et al., 2018). In the context of placebo, the PHG may be linked to placebo effects through memory formation. Placebo effects can be mediated by past experiences and learned associations (Benedetti et al., 2011, Colloca, 2018). Specifically, memories of prior therapeutic experiences can generate treatment expectations that induce placebo effects (Colloca et al., 2020). Emotional processing by the PHG may trigger placebo effects by reducing anxiety related to pain perception.

The supramarginal gyrus is involved in language processing (Deschamps et al., 2014) and is linked to empathy (Silani et al., 2013, Wada et al., 2021), while the temporal occipital fusiform cortex is involved in object and face recognition (Palejwala et al., 2020). Language processing is particularly critical for the generation of placebo effects through

verbal suggestions (Carlino et al., 2014). Further, placebo hypoalgesia can be induced by observation and empathy (Colloca and Benedetti, 2009, Schenk et al., 2017, Raghuraman et al., 2019, Schenk and Colloca, 2020). Specifically, cognitive empathy is associated with face processing (Moret-Tatay et al., 2023). In a study on placebo, Hartmann et al. observed distinct changes in GMV and cortical surface area of the supramarginal gyrus and temporal cortex in placebo responders compared to placebo non-responders (Hartmann et al., 2023). Further, the superior parietal lobule plays a role in spatial orientation and attention. Placebo effects elicit benefits by altering pain perception (Klinger et al., 2018) and the superior parietal lobule's involvement in attentional processes may influence these changes to induce analgesia.

The cerebellum is traditionally associated with motor control (Manto et al., 2012, Welniarz et al., 2021). However, early placebo research highlights cerebellar involvement in pain modulation and emotional processing. An early fMRI study on placebo revealed that the cerebellum and cerebellar vermis are activated along with the “classic pain matrix” when a painful stimulus, like a shock, is applied (Wager et al., 2004).

When interpreting VBM results, it is important to consider what changes in grey matter mean on a biological level. Brain development during childhood and adolescence is characterized by proliferation of synapses and dendritic growth, leading to increases in gray matter density increases in some regions (Gennatas et al., 2017). As the brain matures, synaptic pruning leads to decreases in GMV to optimize neural network functioning (Sakai, 2020, Faust et al., 2021). However, with increasing age, age-related reductions in GMV in the prefrontal cortical areas are associated with cognitive aging and decline (Terribili et al., 2011).

Thus, GMV increases or decreases are not only age but region-specific. Mechanistic approaches such as PET imaging (de la Fuente-Fernandez et al., 2001, Zubieta et al., 2005) and deep brain stimulation (Pollo et al., 2002, Benedetti et al., 2004) have elucidated the mechanisms underlying cortical changes associated with placebo effects, such as increased endogenous opioid neurotransmission in the PFC.

The findings of this study indicated that increased GMV in these six regions is positively associated with placebo effects in participants with chronic pain, suggesting potential roles of these regions in mediating placebo responses within this cohort. Future directions involve delineating the molecular mechanisms by which these regions contribute to the generation of individual placebo responses. Ultimately, elucidating the mechanisms underlying morphological changes associated with placebo effects may advance the development of therapeutic approaches that leverage placebo effects to improve pain and clinical outcomes.

Chapter V: Summary of Findings and Future Directions

A. Hypothesis and Approach

While acute pain signals normal nociceptive function, chronic pain is a debilitating disease that serves no useful purpose once a diagnosis is made (Markenson, 1996, Katz et al., 2015, Stucky and Mikesell, 2021). Individuals with chronic pain suffer from persistent and pathological pain that may interfere with daily functioning (Treede et al., 2019, Dydyk and Conermann, 2024). Current treatments for chronic pain are limited (Castroman et al., 2022) or mildly efficacious (Reinecke et al., 2015), and of the treatments that are available, some may produce adverse side effects (Martel et al., 2015, Stoicea et. al, 2015, O'Brien and Roman, 2021, Nalamachu, 2013, Volkow and Blanco, 2021, Dydyk and Conermann, 2024). Additionally, treatment outcomes are largely influenced by modifiable and non-modifiable risk factors such as substance use, age, and sex (Hecke et al., 2013) which vary between individuals. Therefore, effective therapy for chronic pain should rely on multidisciplinary approaches, including non-invasive and nonpharmacologic treatment (Qaseem et al., 2017). Because they engage neurobiological and physiological mechanisms to induce analgesia, placebo effects observed in experimental and clinical settings present a promising opportunity to develop nonpharmacological therapies for pain (Neogi and Colloca, 2023).

The placebo effect results from a patient's positive expectations regarding their health (Colloca, 2019, Barsky et al., 2002) and is a powerful modulator of health outcomes across many diseases and encounters (Benedetti, 2008). In the context of pain, placebo effects have been shown to induce analgesia through the release of endogenous opioids

(Wager et al., 2007, Scott et al., 2008, Zubieta and Stohler, 2009) and activation of brain regions represented in the descending pain modulatory pathways (Atlas et al., 2014, Colloca et al., 2019, Ong et al., 2019). However, not everyone will respond to a placebo manipulation, and of those that do, there is a wide range of the magnitude of placebo response between individuals. Experimental research shows that the interindividual variability of placebo responses is influenced by various biopsychosocial factors, such as genetics (Colloca et al., 2024), sex (Olson et. al, 2021), and brain structure and function (Vachon-Presseau et al., 2018). Culture (Brody and Colloca, 2013, Garcia et al., 2019) environment (Neogi and Colloca, 2023), and personality traits and disposition (Wang et al., 2022) have also emerged as determinants of expectations and placebo response. In order to maximize the effectiveness of placebo analgesia for pain management, it is critical to understand the mechanisms underlying the influence of biopsychosocial factors on individual placebo responses.

Here, I investigated whether trait and state empathy, sex differences, and neural changes, namely individual PAF and brain morphometry, influenced the generation of individual placebo effects. To test these hypotheses, I used social learning and classical conditioning placebo paradigms to induce placebo hypoalgesia in healthy adults and adults living with chronic orofacial pain. In the social learning paradigm described in Chapter 2, healthy adults observed a demonstrator receiving heat pain on control and treatment (placebo) creams and reporting pain ratings on a VAS scale. After, the participants reported their state empathy ratings for the demonstrator before performing the same experiment that they observed. The difference in pain ratings between the control and placebo conditions during the testing phase was operationalized as state empathy-induced placebo effects. In

the classical conditioning paradigm described in Chapters 3 and 4, individually tailored high and low temperature thermal stimuli paired with two colored cues were used during conditioning to manipulate expectations of treatment effectiveness. Then, in the testing phase, both cues were surreptitiously paired with identical temperature thermal stimuli to test for placebo effects. This paradigm allowed us to examine sexual dimorphism in placebo hypoalgesia in individuals with chronic pain and healthy controls, and the morphological correlates of placebo effects in individuals with chronic pain.

Together with the social learning and classical conditioning paradigms, virtual reality, electroencephalography, and MRI were used to capture the behavioral and neural changes underlying placebo effects. If empathy, sex and neural traits influence interindividual differences in placebo effects, then individual measurements of each factor should correlate with or predict individual placebo effect magnitude.

B. Main Findings

Socially induced state empathy and placebo hypoalgesia

In Chapter 2, we investigated the effects of trait empathy and socially induced state empathy on placebo hypoalgesia. Baseline trait empathy was predictive of both empathetic states following observation of a demonstrator experiencing pain and analgesia, and subsequent socially induced placebo effects. Specifically, the empathic concern, personal distress, perspective-taking, and fantasy scale dimensions of the Interpersonal Reactivity Index and the affective and cognitive dimensions of the Basic Empathy Scale were predictive of socially induced affective and cognitive state empathy ratings and placebo hypoalgesia. These findings are in line with previous work on empathy and placebo effects, which generally conclude that the higher the trait empathy, the higher the subsequent placebo effects (Meeuwis et al., 2023). Further, in this study, cognitive state empathy for pain unpleasantness fully mediated the effect of observation of a demonstrator on socially induced placebo effects. Similar to these findings, Hartmann et al. found that empathic discomfort fully mediated the impact of placebo pain relief on prosocial decisions. In our study, this may suggest that empathic discomfort, modeled as pain unpleasantness, drives prosocial decision-making, reflected by higher empathy ratings for a demonstrator in pain.

We investigated the effects of demonstrator type (human versus avatar) on state empathy ratings. State empathy was higher following observation of a human demonstrator in pain compared to an avatar version of the demonstrator. Empathy goes hand in hand with mentalizing, or the ability to cognitively understand the mental states of others (Allen, 2003, Frith and Frith, 2006, Kampe et al., 2003). Several studies show that when

participants observe a real human and an avatar, or even a humanlike avatar compared to a robot avatar, observer empathy is higher for the human or plausible human avatar compared to the robot (de Borst and de Gelder, 2015, Kegel et al., 2020).

Socially induced placebo effects following observation of the demonstrator were observed in both VR and non-VR settings, with a larger magnitude of placebo effects observed in non-VR. Further, cognitive empathy towards pain unpleasantness mediated observation-induced placebo effects within the non-VR setting only. One explanation for the effects of non-VR may lie in the importance of learning for generating placebo effects (Colloca et al., 2008). In this study, Colloca and colleagues studied the role of learning in nocebo and placebo effects using a verbal suggestion alone procedure, and a conditioning procedure. While nocebo effects were similar between the two paradigms in response to tactile and painful stimuli, placebo effects were significantly larger during the conditioning procedure compared to the verbal suggestions alone paradigm. The findings suggested a crucial role of learning in inducing placebo effects. Extended to our results, the distractive effects of VR that make it effective for pain management (Morris et al., 2009, Hoffman et al., 2011, Indovina et al., 2018) may have implications for whether VR is the best medium for inducing placebo effects.

Finally, we assessed the predictive nature of peak alpha frequency measurements acquired from electroencephalogram recordings on placebo effects. Individual responses to socially induced placebo hypoalgesia in VR were predicted by baseline peak alpha frequency. We replicated findings from a previous study (Raghuraman et al., 2019) where faster PAF in the frontal and somatosensorial areas were correlated with larger placebo effects. Further, increased task-based activity in the frontal region is observed

during observation of a demonstrator perceiving pain relief during the treatment (placebo) condition versus decreased activity when the demonstrator expresses pain during the control condition (Schenk et al., 2020). Together, these findings and ours suggest an important role of frontal and somatosensory activity in building empathy and subsequent placebo effects.

Sex, gonadal hormones and placebo hypoalgesia

In Chapter 3, we replicated previous findings on sex differences in clinical TMD pain severity and interference. As assessed by the Oral Behavior Checklist, Graded Chronic Pain Scale, and quantitative sensory testing, women with TMD reported greater sensitivity to clinical and experimental pain. To test for placebo effects in individuals with TMD and healthy controls, we adopted a well-established classical conditioning paradigm (Olson et al., 2021, Wang et al., 2022) as an experimental model. During the conditioning phase of the experiment, all participants reported significantly lower pain ratings for green (treatment) trials compared to red (control) trials. However, conditioning strength, that is, the pain ratings between green and red trials during the conditioning phase, were not significantly different between sexes.

Expectations regarding effectiveness of the treatment for reducing pain was assessed at three points during the experiment, once at baseline prior to the conditioning phase, referred to as baseline expectations, once after the conditioning phase and prior to the testing phase, referred to as reinforced expectations, and once after the testing phase, referred to as post-test expectations or perceived effectiveness (Olson et al., 2021). Overall, TMD patients had higher expectations compared to healthy controls, replicating

previous findings (Colloca et al., 2020). The differences in expectations between participants with TMD and healthy controls may be explained by prior exposure to treatment in the TMD group with, for example, transcutaneous electrical nerve stimulation (TENS) (Olson et al., 2021). Prior therapeutic experiences can greatly influence expectations for treatment effectiveness (Colloca, 2019). However, prior exposure to TENS was not assessed in this study. Future studies should include measurements that assess elements that may modulate treatment expectations (Olson et al., 2021).

Further, women in both groups reported higher expectations compared to men. As mentioned in Chapter 3, sexually dimorphic pain responses appear to be driven by expectations (Bartley and Fillingim, 2013) and pain experiences may reinforce treatment expectations (Olson et al., 2021). In the context of this study, direct hypoalgesic experiences may reinforce greater expectations for pain relief in women compared to men (Olson et al., 2021). Future studies assessing sociocultural beliefs regarding pain prior to assessing treatment expectations and perceived pain relief may elucidate the mechanisms underlying expectations in women versus men.

We assessed the effects of gonadal hormones on the observed sex differences in expectations and placebo effects. We hypothesized that higher testosterone levels in women would be associated with lower chronic pain severity and lower placebo effects. Correlation analysis revealed that testosterone levels in women with chronic pain were negatively related to chronic pain severity, assessed with the Graded Chronic Pain Scale. Further, LMM revealed that higher testosterone levels, and not estradiol or progesterone levels, were associated with lower placebo effects in women in the TMD and healthy

control groups, and not in men. As mentioned in Chapter 3, testosterone is thought to be anti-nociceptive and protective in nature (Craft 2007, Basaria et al., 2015, White and Robinson, 2015) while estradiol and progesterone exhibit anti and pro-nociceptive effects (Bartley and Fillingim, 2013), possibly depending on the phase of the menstrual cycle (Vincent and Tracey, 2008, Veldhuijzen et al., 2013, Pogatzski-Zahn et al., 2019, Athnaiel et al., 2023, Zhang et al., 2023). Extended to our findings, if testosterone in women produces anti-nociceptive effects when heat painful stimuli is delivered, then smaller differences between placebo and control conditions may yield smaller placebo effects.

At the group level, sex differences in expectations were dependent on expectation type and menstrual cycle phase. While individuals with TMD demonstrated similar levels of baseline expectations, women in the luteal and postmenopausal phases in the healthy control group reported greater baseline expectations compared to men. After the conditioning phase of the experiment, women with TMD in the follicular and postmenopausal phases reported significantly greater reinforced expectations compared to men with TMD. Finally, after the testing phase, women with TMD in the luteal phase of the menstrual cycle reported greater perceived treatment effectiveness compared to their male counterparts. Further, both sexes exhibited placebo effects, with larger placebo effects being observed among women in the luteal phase of the menstrual cycle compared to men in both the TMD and healthy control groups, independent from chronic pain severity, race, educational level, as well as the heat-pain stimulation used in the testing phase.

The luteal phase of the menstrual cycle is marked by an increase and peak of progesterone levels in women (Sherman and LeResche, 2006). During pregnancy and after birth, women with higher progesterone levels have reported lower pain levels compared to women with lower levels of progesterone (Vincent et al., 2018, Kashanian et al., 2018). In patients with fibromyalgia, higher progesterone levels were associated with lower pain severity reports (Schertzinger, 2018). In contrast, Pogatzski-Zahn and colleagues observed increased sensitivity to experimental pain in healthy volunteers during the luteal phase of the menstrual cycle compared to the follicular phase (Pogatzski-Zahn et al., 2019). In our study, while progesterone levels were associated with placebo effects in a preliminary analysis, these effects disappeared after regression analysis. Current research on sex hormones suggests that in regard to pain, the cyclical fluctuation of sex hormone levels, rather than the increase or decrease of estrogen or progesterone across different menstrual phases, leads to differences in pain sensitivity (Vincent and Tracey, 2008, Veldhuijzen et al., 2013, Athnaiel et al., 2023, Zhang et al., 2023). In this cohort, placebo analgesia may be more closely related to the fluctuation of hormones during the luteal phase rather than progesterone levels.

During the follicular phase of the menstrual cycle, estradiol levels increase and peak prior to ovulation. In this study, higher estradiol levels in men and women in both groups were associated with higher reinforced expectations. The mediation approach confirmed statistically causal effects of estradiol on reinforced expectations, and further, we confirmed statistically causal effects of reinforced expectations on sexually dimorphic placebo effects in the TMD group, whereby higher reinforced expectations drove greater placebo effects in women with TMD in the follicular and postmenopausal phases

compared to men with TMD. The results suggests that estrogen drove expectation-related cognition following conditioning. While pain is likely influenced by the cyclical fluctuation of hormones, cognitive function in the PFC and hippocampus is facilitated by estrogen (Hara et al., 2015), and some studies suggest improved performance on tasks that probe PFC function when estradiol levels are high (Poromaa and Gingnell, review, 2014).

Neural correlates of placebo hypoalgesia

In chapter 4, we examined the association between brain morphology and response to placebo in participants with chronic pain. Placebo responders and placebo non-responders were classified using permutation tests on 12 repeated measures trials (6 red trials and 6 green trials) that measured pain intensity ratings during the testing phase (Wang et al., 2022). Placebo responders exhibited significantly greater pain ratings from red trials than green trials compared to placebo non-responders controlling for age, sex and race, indicating a clear and robust effect of conditioning on placebo analgesia that varied between individuals and groups. We also aimed to stratify participants by high placebo responders or low placebo responders based on the average reported pain score cutoff of 30 out of 100 points (Wang et al., 2022). Participants with less than 30 points were classified as low placebo responders, while participants with 30 points or higher were classified as high placebo responders. Absolute difference changes were used to avoid misleading and biased pain reductions, since percentile changes from baseline may fail when there are baseline imbalance and non-normally distributed outcome data

(Colloca et al., 2024). Controlling for age, sex and race, high placebo responders exhibited significantly greater placebo effects compared to low placebo responders.

We used whole-brain VBM analysis (Douaud et al., 2007, Good et al., 2001, Smith et al., 2004, Andersson and Smith, 2007) to detect changes in GMV that were associated with placebo effects. We chose whole-brain analysis over ROI analysis due to the exploratory power of whole-brain analysis that allows for an unbiased analysis of the brain, rather than potentially missing findings in areas outside of predefined regions (Giuliani et al., 2005). We identified six cortical regions in which GMV significantly increased with placebo response: the lingual gyrus, parahippocampal gyrus, temporal occipital fusiform cortex, supramarginal gyrus, superior parietal lobule, and cerebellum. Across several studies, these regions have been linked to cognitive functioning, pain processing, empathy, and placebo effects (Wager et al. 2004, Zhang et al., 2016, Ruscheweyh et al., 2018, Palejwala et al., 2021). For example, although the cerebellum is historically associated with motor control and coordination, several studies now suggest that this region plays a role in cognitive functions that are associated with placebo effects, for example, pain perception and modulation via connectivity with the PFC in humans and in animals (Krienen and Buckner, 2009, Watson et al., 2014). Morphological changes within the supramarginal gyrus and temporal cortex were specifically observed in placebo studies (Hartmann et al., 2023). Still, very little studies report findings of these six regions within the context of placebo effects; the regions discussed in the Introduction, such as the PFC and PAG, are much more extensively covered, highlighting the need for further studies exploring placebo-related changes of these regions with ROI analysis.

C. Limitations

Socially induced state empathy and placebo hypoalgesia

Our study showed that the demonstrator nature (human vs. avatar) and its mode of delivery (VR vs. non-VR) can affect socially induced hypoalgesia via cognitive empathy. Our mediation analysis suggested an important role of empathy on socially induced placebo hypoalgesia. Further, individuals' responses to socially induced placebo hypoalgesia in VR were predicted by baseline peak alpha frequency. To improve our understanding of the applicability of these findings, it is essential to scrutinize certain parameters and outcomes within the scope of this study.

Although previous research showed the distractive effects of VR, we did not measure attention during VR with, for example, eye-tracking (Clay and Koenig, 2019, Adhanom et al., 2023). Future studies should measure attention alongside behavioral responses during VR to determine the potentially distractive effects of VR on placebo effects.

Second, our rationale for the use of a human versus avatar demonstrator lied in the expectation that empathy would be higher for a human, based on previous studies (de Borst and de Gelder, 2015, Suzuki et al., 2015, Hapuarachchi et al., 2023). However, since the avatar was expressionless, we are unable to exclude the effects of facial pain expression on differences in placebo effects. Future studies may replicate the pain expression in a human in an avatar to address this confound, or assess empathy for two avatars, one which is humanlike and the other a robot (Hapuarachchi et al., 2023).

Regarding the results for placebo effects, illustrated in Figure 4 in Chapter 2, most participants reported no self-experienced pain and unpleasantness during the observation

phase, reflected by a rating of zero on the 100-point VAS scale. Consequently, affective empathy ratings in both VR and non-VR conditions exhibited minimal variability. Lastly, our findings were obtained within a controlled experimental setting involving healthy individuals, not in a clinical context. Extrapolating these results directly to a clinical population with chronic pain may yield different outcomes.

Sex and placebo hypoalgesia

In Chapter 3, one of the main findings involved the role of gonadal hormones on placebo hypoalgesia. An important question for sex differences in pain is whether estrogens predispose people to pain, or if androgens are protective (Evans et al., 2021). Although the findings of this study support a role of sex hormones in sexually dimorphic expectations and placebo effects, it is difficult to suggest a mechanistic role without, for example, hormone treatment (Basaria et al., 2015).

It is also important to note that biological sex is assigned at birth based on external genitalia, but also includes chromosomal, hormonal, and reproductive patterns and falls on a spectrum consisting of female, male, and intersex assignments (Shafir, 2022). *Gender* is a social construct referring to the societal roles and expectations attributed to men and women (Phillips 2005, CIHR Institute of Gender and Health, 2018, Osborne and Davis, 2022). Yet, while related, the concepts have been historically conflated to not fully consider the gendered spectrum of "maleness" and "femaleness". Experimental research shows that gender identity may play a more significant role in pain sensation than genetic sex (Strath 2020). While 'sex' in this study refers to cisgender women and men, studies

considering the gendered spectrum are critical for providing a comprehensive understanding of sex differences in pain and the generation of placebo effects.

Morphological correlates of placebo hypoalgesia

In Chapter 4, we used whole-brain VBM analysis to identify several cortical regions, namely the lingual gyrus, PHG, temporal occipital fusiform cortex, supramarginal gyrus, and superior parietal lobule, in which GMV increased with placebo response. VBM studies for pain have reported that pain sensitivity is correlated to the morphology of the cingulate cortex, precuneus, primary somatosensory cortex, putamen, insula, and PHG (Kotikalapudi et al., 2023). Placebo effects are correlated to morphology of the supramarginal gyrus, inferior and middle temporal gyrus, dlPFC, insula, and NAc, among others (Schweinhardt et al., 2009, Vachon-Presseau et al., 2018, Cherkasova et al., 2022, Hartmann et al., 2023). However, although these studies have shed light on the neurobiological mechanisms of placebo effects, several disadvantages of VBM reduce the replicability and reproducibility of the results. For instance, surface-based morphometry techniques, such as CTh analysis (Fischl, 2012), can provide a better account for gyrification compared to VBM (Fischl et al., 2001, Kotikalapudi et al., 2023). CTh measurements may be more reliable than GMV measurements due to their independence from brain surface area and head size, unlike GMV (Kotikalapudi et al., 2023). Although VBM is mostly automated, it is rarely practiced consistently across studies (Henley et al., 2010) and correction procedures are not sufficiently standardized, which may introduce artifacts (Kotikalapudi et al., 2023). While this study used whole-brain analysis for its exploratory power, other studies have used ROI-based analysis

(Vachon-Presseau et al., 2018), which has the advantage of being hypothesis driven, more sensitive to changes that may be overlooked by whole-brain pipelines, easier interpretability, and reduced problems with multiples comparisons. In contrast, whole-brain VBM involves many statistical tests which increases the risk of false positives (Gaonkar et al., 2011). For these reasons, some argue that VBM is not a replacement for ROI-based analyses (Guiliani et al., 2005). Kotikalapudi and colleagues mention that one way to address this issue is with multivariate predictive models that integrate small effects across the brain into predictions with large effect sizes (Kotikalapudi et al., 2023). The next step for this study is to examine the relationship between CTh measurements and placebo response (Vachon-Presseau et al., 2018, Fischl, 2012). Further, fMRI analysis may provide insight into the functional correlates of placebo hypoalgesia (Wager et al., 2004) in individuals with TMD. Importantly, since the aim of this study was to identify the neural correlates of placebo response in chronic pain, healthy controls were not enrolled in the study. However, without a control group, it can be argued that the observed effects are specific to the chronic pain condition (Schweinhardt and Bushnell, 2010), particularly since the identified regions play a role in pain perception. One way to address this is to combine structural imaging analysis with functional analysis (Vachon-Presseau et al., 2018), the latter of which can determine the activity of the identified regions during placebo manipulation.

Another key part of this chapter was to identify placebo responders and placebo non-responders. Extensive literature on studies identifying placebo responders indicates that the reliability of such studies is uncertain. Individuals may not consistently respond to placebos and may react differently to various placebo manipulations (Wang et al., 2022).

In summary, while this work has numerous strengths, it also has some limitations. Since all of the studies presented in this work were cross-sectional studies, we did not address the causal effects of empathy, sex, and neural traits on placebo outcomes. Due to the use of cross-sectional study designs, the findings offer only a snapshot of the biopsychosocial factors that influence placebo effects using social learning and classical conditioning paradigms. Although personality and biological traits were measured simultaneously with placebo manipulation, literature suggests that even stable personality and biological traits can change over time (Wang et al., 2022). Thus, caution is necessary when generalizing these findings to other placebo paradigms, such as verbal suggestion alone, open-label placebos, and contextual factors (Wang et al., 2022). Longitudinal studies will be critical for determining stable biopsychosocial determinants of placebo effects over time and across different placebo procedures.

D. Future Directions

Since times of ancient civilization, the placebo effect has been considered a false pretense of healing rather than a legitimate treatment (Colloca, 2019). Due to this, intentional clinical applications of placebo are uncommon, and many physicians instead prescribe impure placebos used solely for their placebo benefits (Aujla et al., 2020). This research aimed to challenge the notion that the placebo effect is just a nuisance in clinical settings; instead, placebo effects are powerful modulators of clinical outcomes that, in the context of pain, carry vast implications for treatment as a form of endogenous pain modulation (Colloca, 2019). Current pharmacological treatments available to doctors are often expensive, especially in the United States, and may be accompanied by adverse side effects and addiction risks (Martel et al., 2015, Stoicea et. al, 2015, O'Brien and Roman, 2021, Nalamachu, 2013, Volkow and Blanco, 2021, Dydyk and Conermann, 2024). Some of the most pressing issues in pain medicine today are the opioid crisis and high medical costs, which disproportionately affect high-risk patient populations and underserved communities in the United States (Barber and Gibson, 2009, Gaskin and Richard, 2012). Placebo-based treatments and practices may provide a new option for patient care that is cost-effective, low-risk, versatile, and effective. The existing and growing body of evidence supporting placebo-based treatments and practices underscores some of the most affordable and easily implementable solutions to these problems.

In the context of treatment, social learning provides a way to study how observation of an individual's emotional and physical response to an intervention influences the way we learn about the potential benefit of that intervention (Raghuraman et al., 2019, Schenk et al., 2020) and our associated responses (Shen, 2010). As mentioned in Chapter 2, socially

induced analgesia can be elicited without conditioning or prior therapeutic experiences because empathy and social learning can be built through observation of therapeutic benefits in others (Colloca and Benedetti, 2009, Schenk et al., 2017). While this illustrates the behavioral aspect of observational, or social learning, a comprehensive understanding of the mechanisms underlying observationally, or socially induced placebo effects is necessary for developing translational, clinically relevant approaches for pain therapies that harness social learning. Several studies have examined the neuropsychological mechanisms of social learning in human placebo effects. For instance, Raghuraman et al. found that faster PAF was associated with greater observationally induced placebo effects in healthy participants (Raghuraman et al., 2019). Schenk and colleagues observed that functional connectivity between the dorsolateral PFC and temporal parietal junction mediated observationally induced placebo effects (Schenk et al., 2020). Further, Zhao et al. observed reduced activation in the posterior insula when participants observed pictures of others in pain (Zhao et al., 2020). In our recent review, we recommended three future directions to advance knowledge on the mechanisms underlying social learning in human placebo effects: 1. Future studies should examine the molecular bases of socially induced placebo effects in humans. For example, PET may be used to study the role of the endogenous opioid system in social learning. 2. Future studies should elucidate the social determinants that influence socially induced placebo effects, such as implicit racial bias. 3. Future studies should investigate how adverse childhood experiences affect empathy and mentalizing processes and, in turn, socially induced placebo effects (Raghuraman et al., 2024). Elucidating the mechanisms underlying socially induced placebo effects may facilitate its use in the clinic in

combination with digital therapeutics, such as augmented and virtual reality, for pain management (Raghuraman et al., 2024).

Expanding the placebo study population

Research on pain shows that sex differences in pain may be able to be explained, in part, by organizational or activational effects of sex hormones (Craft et al., 2012, Mogil 2012). The onset of puberty in humans is marked by estrogen- and progesterone-induced increases in the GABAergic inhibitory tone of the PFC (Sisk, 2017) a region that is integral to not only executive functioning, but also acute and chronic pain processing through changes in neurotransmitters, gene expression, glial cells, and neuroinflammation (Ong et al., 2019). This triggers a critical window of brain maturation (Sisk, 2017) that may imprint cognitive control over pain processing related to placebo responses. If this is the case, it is plausible that the emergence of pubertal hormones may yield organization of the brain with an effect on placebo hypoalgesia (Olson et al., 2021). Despite the prevalence of TMD in young people, particularly girls (List et al., 1999), and placebo effects being higher in children compared to adults (Rheims et al., 2008, Benninga and Mayer, 2009, Bridge et al., 2009, Saps et al., 2009, Weimer et al., 2013), children have been largely excluded from placebo effect studies (Weimer et al., 2013). Pubertal hormonal effects on the brain, particularly in girls, may provide insight on the mechanisms underlying greater placebo hypoalgesia in women with TMD. Therefore, it is worth expanding the study population to youth with TMD (Olson et al., 2021), though this must accompany guidelines for ethical and safe use of placebos in pediatric research and trials (Flynn, 2003, Weimer et al., 2013, Faria et al., 2017, Momper et al., 2021).

Predicting pain and placebo effects

While research has aimed to understand clinical factors that influence interindividual pain experience and placebo responses, the field has yet to provide a comprehensive solution to understand pain (Raja et al., 2020) and placebo effects (Smith et al., 2022). Currently, the field is moving towards machine learning (ML) to predict pain sensitivity and the magnitude of placebo responses (Vachon-Presseau et al., 2018, Kotikalapudi et al., 2023). Vachon-Presseau and colleagues used Least Absolute Shrinkage and Selection Operator (LASSO) regression to predict placebo effect magnitude using questionnaire and resting state fMRI data (Vachon-Presseau et al., 2018). Kotikalapudi et al. used cross validation to train multicenter cortical thickness data that was fit to LASSO to predict individual pain sensitivity (Kotikalapudi et al., 2023). A recent review highlighted the potential use of artificial intelligence (AI) and ML in understanding or addressing placebo effects in drug development with the advantage of being able to analyze large volumes of data (Smith et al., 2022). Predictive AI algorithms present a promising opportunity for determining whether an individual will experience placebo effects at baseline, and, further, enabling exclusion of high placebo responders to improve the interpretation of results from clinical trials. Since most data can be inputted into a ML model, a direct application of ML for this work would be to input individual social, sex, and neural data into the model to predict placebo responders prior to an experiment. Further, the effects of biopsychosocial factors on placebo hypoalgesia, for example, the effects of empathy on socially induced placebo hypoalgesia, may be predicted by other biopsychosocial factors such as gender. Thus, multiple factors may be considered when interpreting the results of placebo studies. For example, in Chapter 2, women exhibited

greater empathy compared to men, consistent with previous findings indicating that gender influences empathetic state (Toussaint and Webb, 2005, Christov-Moore et al., 2014, McDonald and Kanske, 2023). As mentioned previously, sex hormones exert both organizational and activational effects on the brain (Craft et al., 2012, Mogil 2012). AI/ML could be used to determine the predictive influence of gender on empathy, and hormones on placebo-related brain changes, or any combination of factors. In the clinic, AI/ML may have the potential to identify relationships between clinical trial design factors and placebo responses in patients based on biopsychosocial factors such as patient psychological traits (Smith et al., 2022).

E. Ethical considerations

Perhaps one of the most controversial topics in placebo research is the ethical implications of placebo treatment (Miller, 2000, Miller and Brody, 2002, Lau et al., 2003, Millum and Grady, 2013, Kaufman, 2015, Annoni, 2018, Colloca and Howick, 2018, Mollica et al., 2023). A key aspect driving this controversy is the use of deception in placebo treatments and interventions (Colloca and Howick, 2018, Stoessl, 2020). This is especially the case in regards to including children in clinical trials and placebo research (Weimer et al., 2013, Momper et al., 2020). This creates a distinctive dilemma – while placebos may have a strong treatment potential in practice, psychologists and health practitioners have an obligation to convey truthful information to patients to preserve their autonomy. Additionally, despite plentiful research on the strong modulatory effects of placebos on treatment outcomes, some argue that placebos are less effective than active treatments, violating the ethical requirement of beneficence for healthcare

providers (Temple and Ellenberg, 2000, Stang et al., 2005). There are also ethical considerations regarding AI/ML as prediction tools for placebo responses. First, excluding high placebo responders would reduce the population size of a clinical trial of drug development, possibly leading to safety concerns (Smith et al., 2022). Second, if the goal of the trial is to reduce placebo effects, which are beneficial (Finniss et al., 2010, Neogi and Colloca, 2023), predicting them may lead to study redesign that may limit the benefit to participants (Smith et al., 2022).

Although the use of deception is typically an integral part of placebo paradigms, open-label placebo (OLP) is shown to be effective in inducing placebo effects of similar (Colloca, 2019) or greater (Schaefer et al., 2023) magnitude compared to those induced by traditional placebo paradigms, even when the patient is aware of the placebo (Colloca and Howick, 2018). OLP efficacy has been examined in a plethora of conditions, including IBS, cLBP, depression, rhinitis, cancer-related fatigue, and menopausal hot flashes (Neogi and Colloca, 2023) in which OLP induced reduction of condition-related symptoms (von Wernsdorff et al., 2021). However, since many OLP studies lack comparison with the best treatment available, future studies are needed to test the comparative efficacy of both options (Colloca and Howick, 2018). One way to incorporate active treatment into OLP is through dose-extending placebo treatment, in which a cue is paired with a pharmacological treatment such that the cue induces therapeutic effects with or without the active treatment. Dose-extending placebo procedures can therefore decrease the total dose of active treatments such as preoperative opioids, which are linked to adverse postoperative outcomes (Quinlan et al., 2021, Ravi et al., 2021).

However, dose-extending placebo treatments still rely on the use of pharmacological treatments combined with conditioning to elicit therapeutic benefits. Additionally, using drugs or procedures primarily based on their placebo effects carries its own ethical risks if there are adverse side effects (e.g., nocebo effects) or if the treatment is costly (Neogi and Colloca, 2023). As mentioned in the Introduction and covered more extensively in Chapter 2, placebo effects can occur without formal conditioning or prior therapeutic experiences (Colloca and Benedetti, 2009, Schenk et al., 2017). Some ways to leverage placebo effects without conditioning or giving physical placebos are to discuss treatments in a positive manner to improve treatment outcomes (Suarez-Almazor et al., 2010) and to support positive patient expectations of improvement (Neogi and Colloca 2023).

Conclusion

Barriers to effective treatment for both acute and chronic pain can negatively impact patient-provider relationships and deter patients from seeking treatment. The most effective way to manage pain is by employing a comprehensive, biopsychosocial strategy (Cohen et al., 2021, Knopp-Sihota et al., 2022, Sturgeon et al., 2024) that demonstrates an appreciation and careful consideration of the biological, psychological, and social factors that contribute to pain experience and treatment outcomes. In addition to reducing pain, biopsychosocial strategies can help patients and their loved ones manage pain. The current findings provided evidence that placebo effects can be induced in multiple contexts and are influenced by multiple biopsychosocial factors. A promising future direction involves determining the predictive nature of these factors, with, for example, machine learning methods.

In conclusion, developing a comprehensive understanding of the biopsychosocial factors influencing the generation of placebo effects can provide crucial insights for acute and chronic pain treatment. The findings of this work may contribute to gaining knowledge in the development of low-cost, feasible, and easy-to-implement non-pharmacological tools for acute and chronic pain management by harnessing placebo effects.

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