Published in final edited form as:

Pain. 2020 August ; 161(8): 1872–1883. doi:10.1097/j.pain.0000000000001876.

Placebo hypoalgesia: racial differences

Chika Okusogu^{1,*}, Yang Wang^{1,2,*}, Titilola Akintola^{1,2}, Nathaniel R. Haycock¹, Nandini Raghuraman¹, Joel D. Greenspan^{2,3}, Jane Phillips³, Susan G. Dorsey^{1,2}, Claudia M. Campbell⁴, Luana Colloca^{1,2,5}

¹Department of Pain and Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, USA

²Center to Advance Chronic Pain Research, University of Maryland, Baltimore, USA

³Department of Neural and Pain Sciences and Brotman Facial Pain Clinic, School of Dentistry, Baltimore, USA

⁴Department of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine, Baltimore, MD

⁵Departments of Anesthesiology and Psychiatry, School of Medicine, University of Maryland, Baltimore, University of Maryland, Baltimore, USA

Abstract

No large-cohort studies that examine potential racial effects on placebo hypoalgesic effects exist. To fill this void, we studied placebo effects in healthy and chronic pain participants self-identified as either African American/black (AA/black) or white. We enrolled 372 study participants, 186 with a diagnosis of temporomandibular disorder (TMD) and 186 race-, sex-, and age-matched healthy participants to participate in a placebo experiment. Using a well-established paradigm of classical conditioning with verbal suggestions, each individual pain sensitivity was measured to calibrate the temperatures for high- and low-pain stimuli in the conditioning protocol. These 2 temperatures were then paired with a red and green screen, respectively, and participants were told that the analgesic intervention would activate during the green screens to reduce pain. Participants then rated the painfulness of each stimulus on a visual analog scale ranging from 0 to 100. Racial influences were tested on conditioning strength, reinforced expectations, and placebo hypoalgesia. We found that white participants reported greater conditioning effects, reinforced relief expectations, and placebo effects when compared with their AA/black counterparts. Racial effects on placebo were observed in TMD, although negligible, short-lasting, and mediated by conditioning strength. Secondary analyses on the effect of experimenter-participant race and sex concordance indicated that same experimenter-participant race induced greater placebo hypoalgesia in TMDs while different sex induced greater placebo hypoalgesia in healthy

Correspondence to: Luana Colloca, MD, PhD, MS 655 W. Lombard Street Suite 729, Baltimore, MD, 21201; Phone: +1 410-706-8244; Fax: +1 410-706-5427; colloca@umaryland.edu.

*Equal contribution

Author contribution. Luana Colloca designed the study. Titilola Akintola and Nathaniel R. Haycock collected the data. Yang Wang analyzed the data in collaboration with Luana Colloca. All authors contributed to the interpretation of the results and drafted manuscript. All authors commented on and approved the final draft.

Competing interests. CO, YW, TA, NRH, NR, JDG, JP, SGD, CMC have no conflicts of interest to report.

participants. This is the first and largest study to analyze racial effects on placebo hypoalgesia and has implications for both clinical research and treatment outcomes.

Keywords

Placebo; Chronic pain; Race; Temporomandibular disorder; Conditioning; Expectation

Introduction

Chronic pain affected an estimated 50 million American adults in 2016 [19], with an estimated cost of over \$600 billion in medical expenses and lost productivity [30]. A positive correlation exists between the severity of chronic pain and the number of comorbidities present, the frequency of health care utilization, and the degree of disability, which suggests that the presence of chronic pain can often lead to poorer health status [65]. However, because pain is a uniquely subjective experience, it is especially difficult to tailor effective treatments to individual patients of chronic pain disorders. This is especially salient within the complex chronic orofacial pain disorder Temporomandibular Disorder (TMD), which affects about 5–12% of the U.S. population [22; 48; 69].

Among racial groups, studies have clearly demonstrated differences in the experience of clinical and experimental pain [12; 18; 25; 52; 53; 58] that are attributable to various genetic [39; 45], cognitive-emotional [14], and sociocultural factors [32]. Ethnic differences in pain have been demonstrated in Native Americans, who have been shown to exhibit dampened pain responses and heightened painful tolerance when compared to Non-Hispanic Whites (NHW) [73]. On the other hand, African-American/Blacks (AA), Asians, and Hispanics have been found to show lower painful tolerance and higher pain ratings than NHW, but not universally so [12; 52; 53; 61; 78].

The association between chronic pain and impaired endogenous pain modulation (EPM) has been well-documented in previous literature [24; 66; 71; 85; 89]. Accordingly, chronic pain may also impair placebo hypoalgesia. Therefore, it is imperative that the current study evaluates individuals with chronic pain and pain-free controls to better understand the role of chronic pain in placebo hypoalgesia.

Studies with the goal of characterizing racial differences in pain often rely on measured outcomes such as pain sensitivity, pain relief, and conditioned pain modulation (CPM), which refers to the counterintuitive phenomenon in which the perceived pain of a noxious test stimulus is reduced through another noxious stimulus [94]. When compared to Whites, AA/Blacks and other minority groups experience greater sensitivity to pain, as well as less efficient descending pain inhibition evaluated through CPM [1; 13; 63; 78; 79; 83]. These differences in pain may be in part driven by the EPM systems. Placebo hypoalgesia has been seen as a form of EPM because it depends on the activation of descending neural pathways that inhibit nociceptive signaling [7; 8]. Placebo hypoalgesia arises from top-down EPM, including conditioning and verbally-induced expectations of pain relief [14; 17; 54; 70], and can be carefully investigated in the lab and used as a powerful “tool” to explore the contribution of endogenous descending modulatory systems on the experience of pain. There

has not been a large matched-participants experimental study examining racial effects on placebo hypoalgesia. Here, we examine the effect of race and chronic pain (i.e. TMD) on placebo hypoalgesia, pain sensitivity, reinforced expectations, and conditioning strength. Secondary analysis was conducted on the effect of experimenter-participant race and sex concordance on placebo hypoalgesia.

Methods and Materials

Participants

We enrolled a total of 390 TMD and healthy controls (HC) participants for this study. 9 dyads (9 TMD and 9 HC) were excluded because of reported mixed race, leaving a sample of 186 HC with 186 TMD. HC were matched for sex, age, and race with participants who suffered from TMD (Table 1). A diverse set of recruitment methods were strategically implemented, including the distribution of flyers and brochures at the university campus and greater Baltimore area, “word of mouth,” social media postings, online advertisements, health and wellness fairs, written correspondence to dental clinicians, and letters to past patients of the Brotman Facial Pain Clinic University of Maryland Baltimore. Prospective participants were pre-screened over the phone by trained research personnel to determine eligibility and were then invited for a more in depth in-person screening. All eligible participants gave written consent to participate in this study after a thorough explanation of the experimental procedures, compensation, rights, risks, and benefits of their participation. Because deceptive information was used during the experimental procedure, HC participants were debriefed at the end of their experimental round using a study exit form that detailed the nature and the involvement of deception. Debriefed participants were offered the opportunity to withdraw their data from the study. No participants withdrew from the study and each participant was compensated \$100 (via check or gift cards) upon completion of the entire study (\$25 was given whether or not they passed the in-person screening portion.) The study was approved by the University of Maryland Baltimore Institutional Review Board (IRB Protocol # HP-00068315) and conducted in accordance with the World Policies of the Declaration of Helsinki.

Eligibility Criteria

All participants were between the ages of 18 – 65 years (mean age = 33.97, SD = 12.20) and were pre-screened over the phone based on DC/TMD screening instrument [31] to determine their potential eligibility as either a HC or TMD participant. Final screenings took place in person to ensure eligibility. All participants were able to speak and understand English (spoken and written). All potential participants were excluded if they had presence of degenerative neuromuscular diseases; cervical pain (i.e. stenosis or radiculopathy); a diagnosis of cardiovascular, neurological, kidney, or liver disease; pulmonary abnormalities; cancer within the past three years; color-blindness; or uncorrected impaired hearing. In addition to these criteria, individuals that were currently pregnant or breast-feeding were excluded from participating. A lifetime history of alcohol or drug dependence or a history of alcohol or drug abuse in the past year excluded individuals from participating. In addition, individuals with any severe psychiatric condition requiring medication or hospitalization in the last three years were excluded. All participants were excluded for the occurrence of

facial trauma in the prior 6 weeks prior or a history of severe facial trauma in the last 2–3 months.

Healthy participants.—186 participants were deemed eligible and enrolled as HC participants (54 men, 132 women). In addition to the aforementioned criteria, HC participants were also disqualified if they had mania, schizophrenia, or other severe psychological disorders (i.e., anxiety disorder, depression, obsessive compulsive disorder, or attention deficit hyperactivity disorder). Final determination of eligibility was made in person at the University of Maryland School of Nursing by a clinician on the research team.

TMD participants.—186 participants were deemed eligible and enrolled as TMD participants (54 men, 132 women). TMD participants were screened in person by a dental clinician at the Brotman Facial Pain Clinic at the University of Maryland School of Dentistry to confirm a self-reported history of jaw, head, or facial pain for at least the prior three months and to determine the phenotypic classification and eligibility of their orofacial pain condition.

TMD-associated pain includes myalgia located in any of the muscles of mastication and/or arthralgia in one or both temporomandibular joints. Participants who met the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [84; 95] were included in the study, as listed below: 1. History positive for pain in the immediate 30 days prior to exam 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. Exam 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. Of the 186 TMD participants, 173 (93%) had myalgia; 16 (9%) had myofascial pain with referral; 134 (72%) had right arthralgia; 131 (70%) had left arthralgia; and 94 (51%) had TMD headache.

Given that chronic pain participants often had concurrent emotional distress such as anxiety and depression, in contrast to healthy participants, only a personal history of mania, schizophrenia, or other severe psychoses would disqualify a TMD participant.

Experimental Procedures

The experiment took place at the University of Maryland School of Nursing clinical research space for a session that lasted approximately 4 hours. The participants were given an overview of the study procedures and provided written informed consent. Vital signs (i.e. heart rate, height, and weight, Table 1) were collected for monitoring purposes prior to testing. Demographic information on marital status, race, ethnicity, education, and income was also collected (Table 1).

Race and other assessments—Race was determined by self-report via a questionnaire based on the NIH Collaboratory Race/Data Standard (<https://www.ncbi.nlm.nih.gov/books/NBK219764/>). This tool captures both race and ethnicity (Hispanic vs. Non-Hispanic participants). We included 60 AA/Black, and 126 White TMD participants matched with

186 HC participants for race, sex, and age. We found no significant differences for ethnicity (see Results) and therefore we did not discuss these findings.

For TMD, clinical pain was also assessed with Axis II evaluation via the Graded Chronic Pain Scale (GCPS) [23], Jaw Function Limitation Scale [67], and the Oral Behaviors Checklist for parafunctional behaviors [68]. In particular, the GCPS was used for intensity of clinical pain and pain interference.

Pain Sensitivity Assessment and Calibration—Individual pain sensitivity measurements (warmth, heat-pain threshold, and heat-pain tolerance) were assessed to explore pain sensitivity and also tailor temperature levels used for the conditioning and testing phases (see below) to each individual participant. This assessment was performed using the methods of limits [29]. The PATHWAY - Pain and Sensory Evaluation System (Medoc Advanced Medical Systems, Rimat, Yishai, Israel) equipment was used with a 3×3cm thermode. Thermal stimuli were delivered at the same location on the arm each time to avoid the potential confound of regional variation in sensitivity.

Stimulations starting from 32 ° C to 52 ° C were delivered to the participant's dominant forearm with the thermode secured firmly in place with an elastic self-adherent wrap. At the start of pain sensitivity assessment, the participant was given a control (stop) button and instructed to report when they first detected warm (but not painful) thermal heat sensation by pressing the button to stop the heat. Next, they were asked to press the stop button when they felt minimal heat-pain threshold. Similarly, participants were instructed to indicate their medium level of pain as well as the maximum tolerable level of heat stimulation. Warmth, heat-pain threshold, medium level of pain and maximum tolerable pain levels were assessed four times each. Additionally, participants were asked to report their experience using a Visual Analogue Scale with 0=no pain at all and 100=maximal tolerable pain. The VAS was used for the pain sensitivity part to facilitate interaction with the experimenter and prompt interruption of the stimulations whenever appropriate. The average temperature of these four levels were then used to determine each participants' heat intensities to be used during the subsequent conditioning and testing phases.

Temperatures were set at 2 degrees °C lower than the participant's maximum tolerance for the red screens and 6 degrees °C lower than the maximum tolerance for the green screen (conditioning phase). During the testing phase, the temperatures for red- and green-paired stimulation were set at the same level corresponding to 1 degrees °C lower than the temperature used for the red screens. Intensity levels were confirmed with subjective VAS ratings to identify painful stimulations corresponding approximately to 20 (green) and 80 (red) on the VAS.

Conditioning Phase—We used an established and validated paradigm of conditioning and verbal suggestion for the placebo manipulation [16] (Fig. 1) in which two conditioning phases were conducted before the testing phase. During the two conditioning phases, each participant was informed that they would be undergoing a test of their endogenous pain modulation system. A sham electrode probe (the placebo intervention) was attached to their arm above the thermode, and the participant was informed that it would deliver a sub-

threshold (imperceptible) electrical stimulation to relieve the heat pain from the thermode. The participant was also told that they would have been showed a green screen when the electrode was activated and a red screen when it was off. Participants were informed that the temperature was set the same for both red and green screens so that any difference in pain intensity was caused by the intervention (the placebo electrode). Based on the calibration phase, the temperatures were initially set at 2 degrees °C lower than the participant's maximum tolerance for the red screens and 6 degrees °C lower than the maximum tolerance for the green screen (conditioning phase). Intensity levels were confirmed with subjective VAS ratings to identify painful stimulations corresponding approximately to 20 (green) and 80 (red) on the scale.

Assessments of expectations—Participants rated their baseline expectations of pain relief before the beginning of the conditioning phase and their reinforced expectations of pain relief immediately after the conditioning phase. A VAS was used to assess baseline and reinforced expectations using a script (ePrime, Inc.) and a hand-shape device (Celeritas, Inc) that allows the movement of a square cursor on a 0–100 line to address the question: “How much do you think this procedure will reduce your pain?”

Testing Phase—The testing phase consisted of one block of alternating red and green screens (6 each according to the random sequence). Unbeknownst to the participant, both red- and green-paired intensities of stimulations were surreptitiously set at the same level of heat thermal stimulations corresponding to 1 degrees °C lower than the temperature used for the red screens for each participant. Any difference in red- versus green-paired ratings was operationally defined as ‘placebo hypoalgesia’. Importantly, procedures were standardized for all participants. Participants were randomized to one of four generated screen color sequences to control for potential sequence effects.

Statistical Analyses

The primary outcome of the study was the magnitude of placebo hypoalgesia, computed as the difference scores between red- and green- trial ratings of heat pain during the testing phase. We also studied conditioning strengths, computed as the differences between red- and green- ratings of pain during the conditioning phase, as well as baseline and reinforced expectations of pain relief. Effects of race on pain sensitivity were also analyzed.

Race and group differences in demographic, socio-economic, and clinical factors—First, we used independent t-test and χ^2 analyses to examine how race (AA/Black vs. White) influenced the demographic and socioeconomic status within TMD participants and the age (range of five years), sex, and race matched HC participants. The demographic and socioeconomic variables that showed significant differences between races were treated as potential covariates in the main analyses. Next, univariate ANCOVA with group (TMD vs. HC) and race (AA/Black vs. White) set as between-subjects factors was used to test the race and group differences in heat-pain threshold and maximum pain tolerance. We controlled for demographic and socioeconomic variables (age, sex, and educational level). Post-hoc analyses were conducted and Bonferroni corrections were applied for multiple comparisons. We also conducted a separate univariate ANCOVA within the TMD

participants to explore the effect of race on clinical pain intensity and pain interference assessed by Graded Chronic Pain Scale (GCPS, [23]). In this separate analysis, we controlled for age, sex, educational level, and BMI.

Race and group differences in conditioning strengths—To determine the race and group differences in conditioning strengths, LMM analysis was conducted in red-green differences of pain intensity ratings during the conditioning phase. Race (AA/Black vs. White) and group (TMD vs. HC) were treated as fixed factors. Age, sex, educational level, and heat stimulus temperature used in the conditioning phase were set as covariates. The LMM was chosen because it provided an advantage in dealing with the unbalanced data structure (252 Whites and 120 AA/Black participants).

Race and group differences in expectations—We conducted a Linear Mixed Models (LMM) analysis of participants' expectation ratings, treating group (TMD vs. HC), race (AA/Black vs. White), and time (baseline vs. reinforced expectations) as fixed factors. Age, sex, and educational level were treated as covariates.

Race and group differences in placebo hypoalgesia—To compare race and group differences in placebo hypoalgesia (red-green differences of pain ratings during the testing phase), a LMM analysis was ran with race, group and trials set as fixed factors. Age, sex, educational level, and heat stimulus temperature used in testing phase were set as covariates. Regardless of the significance, all the interactions remained in the model [21].

To examine how race affected placebo hypoalgesia across trials during the testing phase, we included a race by group interaction factor for each trial. Planned pair-wise comparisons were conducted between AA/Blacks and Whites within each group and at each trial [21; 43; 44]). Bonferroni corrections for multiple comparisons were applied.

A mediation model [40; 41] was used to explore the potential driving force of the race differences in placebo hypoalgesic effects. We assumed a linear relationship among race, conditioning strength, reinforced expectations and placebo hypoalgesia. We also assumed independence, and homoscedasticity of the residuals in dependent variable estimation. Therefore, in this mediation model, race was treated as the independent variable (X), while red-green difference of pain intensity ratings (trial 1) during the testing phase was set as the dependent variable (Y). Conditioning strength (the mean red-green difference of pain intensity ratings during the conditioning phase) and reinforced expectations were considered as the two mediators (M1, and M2). The indirect effects were tested with a bias-corrected bootstrapping method based on resampling of 5,000 times. If the 95% bootstrapped confidence interval (BCI) did not contain zero, the indirect effects were considered to be significant. A mediating effect was considered to be significant when the indirect effects and the total effects were significant.

Experimenter race's and sex's influences on expectations and placebo hypoalgesia—Finally, we conducted separate LMM analyses within TMD and HC groups. Race (White vs. AA/Black), participant-experimenter race (same vs. different), and participant-experimenter sex (same vs. different) as fixed factors to examine any potential

influence of matching or mismatching the experimenter's and participant's race and sex on expectations (baseline and post-conditioning phases) and placebo hypoalgesia. Age, sex, and educational level were controlled. Stimulus heat temperature used in testing phase were additionally controlled when exploring placebo hypoalgesia. Pair-wise comparisons were conducted with Bonferroni corrections for multiple comparisons. We conducted this part of analyses to the sub-cohort of AA/Black and White experimenters (n=371) only.

All analyses were performed using Statistical Package for Social Sciences (SPSS), vers. 26 and SAS vers. 94 software. An alpha level of 0.05 ($p < 0.05$) was considered statistically significant.

Results

Demographic factors for the TMD vs. HC cohorts

The TMD and HC cohorts were fully matched by age, sex, and race. The proportion of Non-Hispanic participants for TMD (94%) was not different from HC (91%, $\chi^2=1.39$, $p=0.238$). Ethnicity did not influence the placebo effects in the current study ($F_{1,2204.45}=2.63$, $p=0.105$) and thus was not discussed here. In terms of social economic status, TMD and HC did not differ in educational level ($\chi^2=0.98$, $p=0.323$), annual income ($\chi^2=0.04$, $p=0.833$) or marriage status ($\chi^2=1.79$, $p=0.181$).

As part of the clinical examination, vital signs were collected and we observed expected differences between TMD and HC. TMD showed significantly higher systolic ($t_{369}=3.75$, $p<0.001$) and diastolic blood pressure ($t_{369}=5.37$, $p<0.001$) than HC. TMD also had larger BMI (mean=27.58, sem=0.46) compared to HC (mean=25.94, sem=0.43)

We examined race (AA/Blacks vs. Whites) differences between the demographic and social economic status within TMD and HC cohorts, separately. Within both TMD and HC, AA/Blacks and Whites did not show any difference in ethnicity (TMD: $\chi^2=0.13$, $p=0.715$; HC: $\chi^2=3.60$, $p=0.058$).

Within TMD, AA/Blacks were older than Whites ($t_{184}=2.03$, $p=0.044$) but no age differences were observed between AA/Blacks and Whites within HC participants ($t_{184}=1.41$, $p=0.161$). Because older age was associated with smaller placebo analgesic effects ($r=-0.16$, $p=0.029$), we included age as a covariate in the main analyses. Moreover, the proportion of White women (79%) was significantly higher than that AA/Black women (55%) for both TMD and HC ($\chi^2=10.96$, $p=0.001$, Table 1). Given that women showed greater placebo hypoalgesia across groups after controlling for temperature used in testing phase ($F_{1,2208.08}=6.11$, $p=0.014$), we also treated sex as a covariate in the main analyses.

Regarding social economic status, for TMD participants, White participants reported both significantly higher level of education ($\chi^2=22.10$, $p<0.001$) and higher annual income than AA/Black participants ($\chi^2=13.83$, $p<0.001$) but showed no differences in marital status ($\chi^2=3.12$, $p=0.078$). For HC participants, on the other hand, White participants had higher educational attainment than AA/Black participants ($\chi^2=17.32$, $p<0.001$) but no differences were observed between groups in annual income ($\chi^2=1.88$, $p=0.172$) or marital status

($\chi^2=0.16$, $p=0.690$) (see Table 1). Given that participants with higher educational level ($F_{1,2207.02}=5.60$, $p=0.018$) displayed greater placebo hypoalgesia, we treated educational level as covariate in the main analyses. Annual income did not influence placebo hypoalgesia ($F_{1,2193.66}=0.72$, $p=0.399$), and thus was not controlled for in further analyses. In terms of vital signs, within TMD, AA/Blacks showed higher level of systolic blood pressure than Whites ($p=0.023$). AA/Black participants had greater BMI than Whites in both TMD ($t_{184}=4.42$, $p<0.001$) and HC ($t_{184}=3.25$, $p=0.001$, Table 1).

Race and group differences in heat-pain threshold and tolerance

Controlling for age, sex, and educational level, the ANCOVA with group (TMD vs. HC) and race (Whites vs. AA/Blacks) revealed a significant main effect of group on heat-pain threshold ($F_{1,365}=6.01$, $p=0.015$). Overall, HC participants had significantly higher level of heat-pain threshold (mean=37.95 ° C, sem=0.28) than TMD participants (mean=36.99 ° C, sem=0.28). Neither the main effect of race ($F_{1,365}=0.01$, $p=0.929$) nor its interaction with group was significant ($F_{1,365}=0.64$, $p=0.424$), suggesting that race did not influence heat-pain threshold within either TMD or HC.

In terms of heat-pain tolerance, the main effect of race (White vs. AA/Black) was significant ($F_{1,361}=15.98$, $p<0.001$) with White participants displaying higher heat-pain tolerance (mean=49.16 ° C, sem=0.13) than AA/Black participants (mean=48.18 ° C, sem=0.20) after controlling for age, sex and educational levels (Fig. 2a). When comparing TMD and HC, we found a marginally significant difference for heat-pain tolerance between groups ($F_{1,361}=13.07$, $p=0.071$) with a non significance race by group interaction ($F_{1,361}=1.80$, $p=0.180$).

Additionally, we examined the influences of race on the severity of TMD pain, including clinical pain intensity ratings and pain interference levels as assessed by the GCPS tool. Race did not show a significant influences on clinical pain intensity ($F_{1,179}=1.51$, $p=0.222$) after controlling for age, sex, educational level and BMI. However, there was a significant main effect of race on GCPS interference subscale ($F_{1,179}=4.30$, $p=0.04$) indicating that AA/Black TMD participants experienced higher pain interference (mean=33.05, sem=3.39) than White TMD participants (mean=22.81, sem=2.23, Fig. 2b). This effect was independent of participants' age, sex, level of education and BMI.

Race and group differences in conditioning phases

Controlling for the individual painful stimulation intensities used for the conditioning, age, sex and educational levels, the LMM indicated a significant main effect of race ($F_{1,4376.12}=96.78$, $p<0.001$) and group ($F_{1,4376.12}=83.53$, $p<0.001$) on the red-green differences in pain intensity ratings during the conditioning phase. Specifically, White had greater conditioning strength (mean=63.36, sem=0.37) than AA/Black participants (mean=56.51, sem=0.56, $p<0.001$). Moreover, HC participants displayed stronger conditioning effects (mean=62.83, sem=0.45) than TMD participants (mean=57.04, sem=0.45, $p<0.001$). There was a significant group and race interaction on conditioning strength ($F_{1,4376.12}=25.25$, $p<0.001$). The differences between White and AA/Black participants within TMD (mean=10.02, sem=0.94) were larger than the differences within

HC (mean=3.68, sem=0.94), independently of the individual painful stimulation intensities used for the conditioning. The intensities of heat stimuli used during the conditioning phase are shown in Table 2.

Race and group differences in pain relief expectations *before* and *after* conditioning

After controlling for age, sex, and educational levels, the LMM revealed a significant main effect of before vs. after conditioning pain relief expectations ($F_{1,731.90}=226.15$, $p<0.001$), indicating that expectations *after* conditioning phase (mean=72.92, sem=1.41) were significantly greater than *before* the conditioning phase took place (mean=43.85, sem=1.35). We found a significant main effect of race ($F_{1,732.54}=4.21$, $p=0.041$) with Whites reporting overall across groups a greater pain relief expectations (mean=60.59, sem=1.14) than AA/Blacks (mean=56.18, sem=1.71). Main effects of group ($F_{1,731.64}=0.64$, $p=0.425$) and race by group ($F_{1,731.59}=0.05$, $p=0.817$) as well as race by group by time interactions ($F_{1,731.59}=0.15$, $p=0.696$) were not significant. Additionally, we observed a significant race by time interaction ($F_{1,731.79}=8.33$, $p=0.004$). Whites displayed greater reinforced expectations than AA/Blacks ($p=0.001$), while *before* the conditioning phase, there were no racial difference in pain relief expectations ($p=0.679$, Fig. 3).

Race differences in placebo hypoalgesia

Heat intensity values used to test for placebo effects are shown in Table 2.

Controlling for age, sex, educational level, and heat temperature used during the testing phase, there was an overall significant main effect of race on placebo hypoalgesia ($F_{1,2195.95}=12.05$, $p=0.001$). Independently of the TMD vs HC cohorts, White participants reported greater placebo hypoalgesia (VAS mean reduction=19.15, sem=0.55) compared to AA/Black participants (VAS mean reduction =15.81, sem=0.79, $p=0.001$).

The main effect of group (TMD vs. HC) on placebo hypoalgesia was not significant ($F_{1,2195.95}=0.13$, $p=0.723$). The main effect of trials was significant ($F_{5,635.25}=11.18$, $p<0.001$). The race by trial interaction was not significant ($F_{5,636.106}=0.449$, $p=0.814$). However, planned pair-wise comparisons indicated that trial 1 reached significance for racial difference in placebo effect ($p=0.013$, Fig. 4A). This effect extinguished rapidly with no racial differences in placebo hypoalgesia for trial 2 ($p=0.086$), trial 3 ($p=0.232$), trial 4 ($p=0.449$), trial 5 ($p=0.190$), or trial 6 ($p=0.348$).

Afterwards, we explored the race by group ($F_{1,2195.95}=1.87$, $p=0.172$) and the race by group by single trial interactions (trial 1: $p=0.357$; trial 2: $p=0.467$; trial 3: $p=0.612$; trial 4: $p=0.400$; trial 5: $p=0.507$; trial 6: 0.730)

Although these interactions were not significant, we explored the race effects within each cohort at each trial based on recommendation for clinical data analyses [21]. The AA/Black TMD cohort displayed significantly smaller placebo hypoalgesic effects than the White TMD cohort for the *first* set of red- and green- VAS scores only ($p=0.023$, Fig. 4B). For the remaining trials, there was no significant difference between AA/Black and White participants (all $p>0.230$). In the HC cohort, we did not observe any significant effects of race on magnitude of placebo hypoalgesia at each trial (all $p>0.416$, Fig. 4C).

Given AA/Blacks participants displayed smaller conditioning strength, SMALLER reinforced expectations post-conditioning phase and placebo hypoalgesia during trial 1, we conducted the mediation analysis to determine whether conditioning strength and reinforced expectations mediated these small and negligible racial differences in placebo hypoalgesia. Conditioning strength mediated the race difference on the short-lasting placebo hypoalgesia (M1, indirect effect $a_1b_1=1.85$, 95%BCI=0.922 to 3.037). Reinforced expectations (M2, indirect effect $a_2b_2=0.01$, 95%BCI=-0.321 to 0.361) did not mediate the effect of race on placebo hypoalgesia (for details, see Fig. 5). Strength of conditioning was significantly linked to racial differences in placebo hypoalgesic effect of trial 1 (direct path $b_1=0.33$, $p<0.006$), whilst reinforced expectations were not significantly linked to placebo hypoalgesia (direct path $b_2=0.01$, $p=0.969$).

Participant-experimenter race and sex effects for expectations and placebo hypoalgesia

A separate set of analyses evaluated the participant-experimenter race and sex effects jointly on baseline and reinforced expectations (before and after conditioning phase) as well as placebo effects. To test how participant-experimenter race and sex jointly influenced expectations, participant race (AA/Black vs. White), participant-experimenter race (same vs. different), participant-experimenter sex (same vs. different), and time (baseline vs. post-conditioning phases) were treated as fixed factors.

In the cohort of TMD participants, neither the main effect of participant-experimenter race ($p<0.761$) nor participant-experimenter sex ($p<0.781$) was significant. We found a significant interaction between participants' and participant-experimenter' race in overall pain relief expectations ($F_{1,353.00}=15.07$, $p<0.001$). Moreover, participant-experimenter' sex and race interacted with participants' race only on reinforcement expectations ($F_{1,353.00}=4.19$, $p=0.041$). AA/Black participants who were tested by the same race experimenter but different experimenter sex showed greater reinforced expectations (mean=86.38, sem=6.65) than those who were tested by the same race and same sex experimenter (mean=67.63, sem=5.18, $p=0.031$). On the contrary, White participants who were tested by the same race and same sex experimenters displayed greater reinforced expectations (mean=81.87, sem=3.42) than same race and different sex experimenter (mean=65.54, sem=4.20, $p=0.003$).

In the cohort of HC, neither the main effect of participant-experimenter race ($p<0.282$) nor participant-experimenter sex ($p<0.384$) was significant. HC participants showed significant interaction between race and participant-experimenter race (same vs. different) on overall expectations ($F_{1,336.78}=5.71$, $p=0.017$) with no interaction with participant-experimenter sex ($F_{1,335.61}=2.32$, $p=0.129$). In HC AA/Blacks, the same participant-experimenter race showed greater baseline and reinforced expectations about pain relief (mean=65.28, sem=4.37) compared to the different participant-experimenter race (mean=51.98, sem=2.89, $p=0.010$). In contrast, in HC Whites, whether the participants were tested by experimenters of the same or different race did not influence overall expectations ($p=0.323$).

Similar to the analysis for expectations, we conducted separate LMM within TMD and HC groups with participant-race (White vs. AA/Black) and participant-experimenter race (same vs. different), and participant-experimenter sex (same vs. different) as fixed factors on the

red-green differences of pain intensity ratings during the testing phase. Age, sex, educational level, and the heat temperature were used in the testing phase served as covariates.

For TMD participants, we found a main effect of participant-experimenter race with a significant interaction with participant-experimenter sex as elaborated below. The main effect of participant-experimenter race ($F_{1,1071.66}=10.72$, $p=0.001$) on placebo hypoalgesia indicated the same participant-experimenter race group displaying greater placebo hypoalgesia (mean=19.79, sem=0.97) than different participant-experimenter race (mean=14.74, sem=1.24, $p=0.001$, Fig. 6). The interaction between participant-experimenter race and participant-experimenter sex was significant ($F_{1,1072.77}=13.60$, $p<0.001$). TMD participants tested by the same race and the same sex of the experimenter displayed greater placebo hypoalgesia as compared to different sex and same race ($p=0.001$). In contrast, when TMD participants were tested by different experimenter race, experimenter sex did not influence placebo hypoalgesic effects ($p=0.126$).

For HC cohorts, we observed only a significant main effect of participant-experimenter sex ($F_{1,1046.16}=5.15$, $p=0.023$, Fig. 6), with different sex experimenter inducing greater placebo hypoalgesia (mean=21.40, sem=1.73) as compared to concordant sex (mean=16.62, sem=0.96).

Discussion

Despite the body of evidence suggesting notable differences in pain experiences between racial groups [12; 52; 53; 61; 78], previous research has not adequately taken into account the crucial interplay of race in modulating expectations and conditioning driven placebo effects. This research fills a critical gap in the larger body of pain and placebo research in understanding the role of race in placebo formation. Using a well-established paradigm of conditioning and verbal suggestion within a large cohort of chronic orofacial pain patients and healthy participants, we observed robust placebo effects and shed light on the relationship between race and placebo hypoalgesia. We found that White participants reported stronger expectations of pain relief, greater conditioning strength effects, and greater although short-lasting extinguishable placebo hypoalgesia when compared to their AA/Black counterparts and limited to the TMD participants. This finding was mediated by strength of conditioning but not reinforced expectations, suggesting that prior experience was of principle importance. Interestingly, concordance between experimenter-participant race resulted in greater placebo hypoalgesia in TMDs while different between experimenter-participant sex resulted greater placebo hypoalgesia in healthy participants.

The results of this study are consistent with the previous literature regarding racial influences on heat-pain threshold, heat-pain tolerance, and chronic pain experiences. AA/Black and White participants did not significantly differ in heat-pain *threshold*. However, White participants displayed higher heat-pain tolerance than AA/Black participants. Both phenomena have been reported previously [12; 52; 53; 61; 78]. Consistent with the literature [2; 34; 47; 92], AA/Black participants within the TMD groups reported greater pain interference than the Whites with their activities of daily living. This could potentially be attributed to poorer psychosocial support for AA/Black chronic pain sufferers when compared

to Whites, as well as underlying physiological differences in pain. Race group differences in TMD symptoms may also be a byproduct of the under treatment of pain for AA/Blacks. Racial identity in the US unfortunately serves as a social determinant of health in the lives of AA/Blacks [26; 80]. AA/Blacks are more likely to experience longer wait times at emergency departments [46; 74], encounter a shortage of opioid medications in local pharmacies [35], and be administered less analgesics in various healthcare settings, such as emergency departments and labor & delivery units [33; 49; 50; 57; 62; 81; 86]. Joynt and colleagues' work is especially striking as the results of their study suggest that discrimination in healthcare, either implicit or explicit, spans socioeconomic status (SES) as AA/Blacks and Hispanics were less likely to receive opioid medications *independently* of SES [50]. Systemically, AA/Blacks are more likely to live in poor neighborhoods with features hostile towards health and wellbeing [56; 60; 80].

The personal experience of pain is unique to each person and marked by a dynamic interaction that goes beyond drug pharmacodynamics and pharmacokinetics, or treatment efficacy. The drug or therapy itself is only one factor in the greater framework of pain relief. The phenomenon of placebo hypoalgesia forces clinicians and researchers to appreciate the rich *context* in which therapies are administered [6; 9; 20; 72; 82]. While the majority of research on placebo hypoalgesia relies on pain-free, healthy participants, a growing subset of the population is affected by chronic pain [19]. Moreover, with chronic pain comes a multitude of co-morbidities, such as anxiety and depression, lack of quality sleep, and constant fatigue [27].

We found no difference in placebo hypoalgesia between TMD and HC indicating that the dearth of findings found in healthy participants [15] might translate to pain patients. However, there are potential barriers that are preventing AA/Blacks chronic pain patients from experiencing the same benefits.

The presence of chronic pain impairs the inhibitory mechanisms of EPM and this relationship is well-documented [24; 66; 71; 85]. In previous studies, AA/Blacks reported greater pain interference than their White counterparts [65]. This mirrors our findings within the TMD group, with AA/Blacks self-reporting greater pain interference and exhibiting reduced placebo hypoalgesia when compared to their White counterparts. Future research with neurobiological approaches can further explore other potential race-based mechanistic differences (i.e. epigenetic differences [3], DNA hypermethylation [5; 90]).

Race may affect group trustworthiness and decisions [87; 88], perception of in- and out-group dynamics [55] and the neural representation of Black and White faces [11]. Because of this literature and the fact that placebo hypoalgesia often depends on the quality of patient-clinician interactions [6; 9; 76], we conducted further analysis on the effects of experimenter race on expectations and placebo hypoalgesia.

Interestingly, within the TMD cohort, AA/Black participants with an experimenter of the same race reported greater expectation. This pattern was echoed in placebo hypoalgesia, because TMD participants with same-race experimenters displayed greater placebo

hypoalgesia than those with different race experimenters. The results mimics what we see clinically, where same race providers are more closely aligned with clinical pain [42].

Various reasons could explain these differences. Implicit biases held by health care providers are often characterized by more positive views towards Whites and negative views against AA/Black participants [37]. As such, a prolonged history of mistrust in healthcare by AAs/Blacks, coupled with the potential for bias from healthcare professionals, could result in poor quality interactions with providers of a different race [64; 75]. As the majority of healthcare providers identify as White [93], interactions with providers of a different race is more likely than not to occur for AAs/Blacks.

To summarize, we found robust placebo effects in both cohorts. In terms of race and placebo hypoalgesia, we found that racial effects were short lasting and extinguishable over time and observable in the TMD cohort only. Initially, the aforementioned modifiers of placebo hypoalgesia will produce statistically significant differences between White and AA/Blacks. However, given the shortness of racial effects over successive trials, it is unclear if those differences will be clinically significant. This is especially important when considering potential real-world therapies, as they are often repeated over a period of time, providing partial reinforcement [4].

The current study does have some limitations that can lead to improvements for future research. First, while data were collected on individuals that self-identified as more than one racial/ethnic identity, only data gathered from participants that self-identified as only one racial identity was included in the results. The decision to exclude multi-racial participants from the data analysis was to remove potential confounding influences associated with multi-racial identities. Another limitation includes the difficulties of using set definitions of race to classify participants. While the participants self-reported their racial identities, there is a growing push that race is crude proxy for describing groups of people in clinical settings [10; 38; 51]. Qualifiers for racial groups has changed throughout recorded human history[91]. Furthermore, this paper only includes and compares two broad racial groups: AAs/Blacks and Whites. Given the clear diversity in today global community, these results may not be generalizable to the larger U.S. and worldwide population. Finally, we did not use a tool, such as the implicit association test created by Greenwald and colleagues [1; 36], to capture racial biases of the experimenters nor the participants. Implicit biases do exist bi-directionally in healthcare interactions between patients and providers and has the potential to reduce therapeutic benefits of healthcare [28; 37; 59; 77], including the risk of minimizing placebo effects in daily clinical settings.

Acknowledging the limitations of this study, there are several strengths that bolster the reliability of the results obtained. Foremost, to the best of our knowledge, this is the first study exploring racial influences on placebo effects, conditioning strength and reinforced expectations enrolling the largest number of participants to obtain high-quality data. Next, this study matched chronic pain patients and healthy controls based on race, sex, and age while controlling for individual pain sensitivity. This reduced the influence of individual variation and increased the confidence in the findings observed. Finally, having used a well-

validated paradigm for eliciting placebo effects further boosts the data quality, and allows us to draw the conclusions presented in this study.

Conclusion

Race influences on placebo hypoalgesia were short-lasting, extinguishable rapidly and observable in TMD participants only. Yet, the experimenter-participant race concordance affected both reinforced expectations and placebo effects. Given that false beliefs about pain perception between AA/Blacks and Whites might drive biased medical judgments, healthcare professionals may want to consider the interactions between in- and out-groups carefully, as the quality of these interactions could interfere with reinforced expectations and placebo effects and thereby ultimately limit responses to pain therapies.

Acknowledgments.

We thank all participants for taking their precious time to participate in research project. We thank Maxie Blasini, Nicole Corsi, Cindy Renn, Kathy Ryan, Lieven Schenk, and Sharon Thomas who assisted with this project in different ways. We also thank the biostatistician Shuo Chen for his help with data analyses.

This research is supported by NIDCR (R01 DE025946, PI: Colloca) and by University of Maryland Strategic Partnership MPowering the State Scholars Program (CO). The funding agencies have no roles in the study. LC reported having received support for Invited Lectures outside the submitted work.

References

- [1]. Ahn H, Weaver M, Lyon DE, Kim J, Choi E, Staud R, Fillingim RB. Differences in Clinical Pain and Experimental Pain Sensitivity Between Asian Americans and Whites With Knee Osteoarthritis. *The Clinical journal of pain* 2017;33(2):174–180. [PubMed: 28060784]
- [2]. Allen KD, Helmick CG, Schwartz TA, DeVellis RF, Renner JB, Jordan JM. Racial differences in self-reported pain and function among individuals with radiographic hip and knee osteoarthritis: the Johnston County Osteoarthritis Project. *Osteoarthritis and cartilage* 2009;17(9):1132–1136. [PubMed: 19327733]
- [3]. Aroke EN, Joseph PV, Roy A, Overstreet DS, Tollefsbol TO, Vance DE, Goodin BR. Could epigenetics help explain racial disparities in chronic pain? *J Pain Res* 2019;12:701–710. [PubMed: 30863142]
- [4]. Au Yeung ST, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. *Pain* 2014;155(6):1110–1117. [PubMed: 24602997]
- [5]. Barcelona de Mendoza V, Huang Y, Crusto CA, Sun YV, Taylor JY. Perceived Racial Discrimination and DNA Methylation Among African American Women in the InterGEN Study. *Biol Res Nurs* 2018;20(2):145–152. [PubMed: 29258399]
- [6]. Placebo Benedetti F. and the new physiology of the doctor-patient relationship. *Physiol Rev* 2013;93(3):1207–1246. [PubMed: 23899563]
- [7]. Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* 2014;84(3):623–637. [PubMed: 25442940]
- [8]. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. *J Neurosci* 2005;25(45):10390–10402. [PubMed: 16280578]
- [9]. Blasini M, Peiris N, Wright T, Colloca L. The Role of Patient-Practitioner Relationships in Placebo and Nocebo Phenomena. *Int Rev Neurobiol* 2018;139:211–231. [PubMed: 30146048]
- [10]. Bonham VL, Callier SL, Royal CD. Will Precision Medicine Move Us beyond Race? *The New England journal of medicine* 2016;374(21):2003–2005. [PubMed: 27223144]
- [11]. Brosch T, Bar-David E, Phelps EA. Implicit race bias decreases the similarity of neural representations of black and white faces. *Psychol Sci* 2013;24(2):160–166. [PubMed: 23300228]

- [12]. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain management* 2012;2(3):219–230. [PubMed: 23687518]
- [13]. Campbell CM, France CR, Robinson ME, Logan HL, Geffken GR, Fillingim RB. Ethnic differences in diffuse noxious inhibitory controls. *The journal of pain : official journal of the American Pain Society* 2008;9(8):759–766.
- [14]. Colloca L. Placebo, nocebo, and learning mechanisms. *Handb Exp Pharmacol* 2014;225:17–35. [PubMed: 25304524]
- [15]. Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol* 2019;59:191–211. [PubMed: 30216744]
- [16]. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain* 2006;124(1–2):126–133. [PubMed: 16701952]
- [17]. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philosophical transactions of the Royal Society of London Series B, Biological sciences* 2011;366(1572):1859–1869. [PubMed: 21576143]
- [18]. Cruz-Almeida Y, Sibille KT, Goodin BR, Petrov ME, Bartley EJ, Riley JL 3rd, King CD, Glover TL, Sotolongo A, Herbert MS, Schmidt JK, Fessler BJ, Staud R, Redden D, Bradley LA, Fillingim RB. Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis & rheumatology (Hoboken, NJ)* 2014;66(7):1800–1810.
- [19]. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR Morbidity and mortality weekly report* 2018;67(36):1001–1006. [PubMed: 30212442]
- [20]. Daniali H, Flaten MA. A Qualitative Systematic Review of Effects of Provider Characteristics and Nonverbal Behavior on Pain, and Placebo and Nocebo Effects. *Frontiers in psychiatry* 2019;10:242. [PubMed: 31037059]
- [21]. Davis S. Mixed models for repeated measures using categorical time effects (MMRM). *Clinical Trials with Missing Data: A Guide for Practitioners* 2014:130–184. John Wiley & Sons, New Delhi, India
- [22]. Diatchenko L, Fillingim RB, Smith SB, Maixner W. The phenotypic and genetic signatures of common musculoskeletal pain conditions. *Nature reviews Rheumatology* 2013;9(6):340–350. [PubMed: 23545734]
- [23]. Dixon D, Pollard B, Johnston M. What does the chronic pain grade questionnaire measure? *Pain* 2007;130(3):249–253. [PubMed: 17257751]
- [24]. Edwards RR, Mensing G, Cahalan C, Greenbaum S, Narang S, Belfer I, Schreiber KL, Campbell C, Wasan AD, Jamison RN. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. *J Pain Symptom Manage* 2013;46(1):30–42. [PubMed: 23102562]
- [25]. Edwards RR, Moric M, Husfeldt B, Buvaendran A, Ivankovich O. Ethnic similarities and differences in the chronic pain experience: a comparison of african american, Hispanic, and white patients. *Pain medicine (Malden, Mass)* 2005;6(1):88–98.
- [26]. Feagin J, Bennefield Z. Systemic racism and U.S. health care. *Soc Sci Med* 2014;103:7–14. [PubMed: 24507906]
- [27]. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep medicine reviews* 2013;17(3):173–183. [PubMed: 22748562]
- [28]. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. *BMC medical ethics* 2017;18(1):19. [PubMed: 28249596]
- [29]. Fruhstorfer H, Lindblom U, Schmidt W. Method for quantitative estimation of thermal thresholds in patients. *Journal of Neurology, Neurosurgery & Psychiatry* 1976;39(11):1071–1075.
- [30]. Gaskin DJ, Richard P. The economic costs of pain in the United States. *The journal of pain : official journal of the American Pain Society* 2012;13(8):715–724.
- [31]. Gonzalez YM, Schiffman E, Gordon SM, Seago B, Truelove EL, Slade G, Ohrbach R. Development of a brief and effective temporomandibular disorder pain screening questionnaire: reliability and validity. *J Am Dent Assoc* 2011;142(10):1183–1191. [PubMed: 21965492]

- [32]. Goodin BR, Kronfli T, King CD, Glover TL, Sibille K, Fillingim RB. Testing the relation between dispositional optimism and conditioned pain modulation: does ethnicity matter? *Journal of behavioral medicine* 2013;36(2):165–174. [PubMed: 22367226]
- [33]. Goyal MK, Kuppermann N, Cleary SD, Teach SJ, Chamberlain JM. Racial Disparities in Pain Management of Children With Appendicitis in Emergency Departments. *JAMA Pediatr* 2015;169(11):996–1002. [PubMed: 26366984]
- [34]. Green CR, Anderson KO, Baker TA, Campbell LC, Decker S, Fillingim RB, Kalauokalani DA, Lasch KE, Myers C, Tait RC, Todd KH, Vallerand AH. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain medicine (Malden, Mass)* 2003;4(3):277–294.
- [35]. Green CR, Ndao-Brumblay SK, West B, Washington T. Differences in prescription opioid analgesic availability: comparing minority and white pharmacies across Michigan. *J Pain* 2005;6(10):689–699. [PubMed: 16202962]
- [36]. Greenwald AG, McGhee DE, Schwartz JL. Measuring individual differences in implicit cognition: the implicit association test. *Journal of personality and social psychology* 1998;74(6):1464–1480. [PubMed: 9654756]
- [37]. Hall WJ, Chapman MV, Lee KM, Merino YM, Thomas TW, Payne BK, Eng E, Day SH, Coyne-Beasley T. Implicit Racial/Ethnic Bias Among Health Care Professionals and Its Influence on Health Care Outcomes: A Systematic Review. *American journal of public health* 2015;105(12):e60–76.
- [38]. Harawa NT, Ford CL. The foundation of modern racial categories and implications for research on black/white disparities in health. *Ethnicity & disease* 2009;19(2):209–217. [PubMed: 19537235]
- [39]. Hastie BA, Riley JL 3rd, Kaplan L, Herrera DG, Campbell CM, Virtusio K, Mogil JS, Wallace MR, Fillingim RB. Ethnicity interacts with the OPRM1 gene in experimental pain sensitivity. *Pain* 2012;153(8):1610–1619. [PubMed: 22717102]
- [40]. Hayes AF. An Index and Test of Linear Moderated Mediation. *Multivariate Behav Res* 2015;50(1):1–22. [PubMed: 26609740]
- [41]. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. *Br J Math Stat Psychol* 2014;67(3):451–470. [PubMed: 24188158]
- [42]. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proceedings of the National Academy of Sciences* 2016;113(16):4296–4301.
- [43]. Howell DC. *Statistical methods for psychology*: Cengage Learning, 2009 Cengage Learning, Wadsworth, Belmont, CA, United States.
- [44]. Hsu J *Multiple comparisons: theory and methods*: Chapman and Hall/CRC, Florida, United States, 1996.
- [45]. Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology* 2014;121(4):825–834. [PubMed: 25102313]
- [46]. James CA, Bourgeois FT, Shannon MW. Association of race/ethnicity with emergency department wait times. *Pediatrics* 2005;115(3):e310–315. [PubMed: 15741357]
- [47]. Janevic MR, McLaughlin SJ, Heapy AA, Thacker C, Piette JD. Racial and Socioeconomic Disparities in Disabling Chronic Pain: Findings From the Health and Retirement Study. *The journal of pain : official journal of the American Pain Society* 2017;18(12):1459–1467.
- [48]. Johansson A, Unell L, Carlsson GE, Soderfeldt B, Halling A. Gender difference in symptoms related to temporomandibular disorders in a population of 50-year-old subjects. *J Orofac Pain* 2003;17(1):29–35. [PubMed: 12756928]
- [49]. Johnson JD, Asiodu IV, McKenzie CP, Tucker C, Tully KP, Bryant K, Verbiest S, Stuebe AM. Racial and Ethnic Inequities in Postpartum Pain Evaluation and Management. *Obstet Gynecol* 2019;134(6):1155–1162. [PubMed: 31764724]
- [50]. Joynt M, Train MK, Robbins BW, Halterman JS, Caiola E, Fortuna RJ. The impact of neighborhood socioeconomic status and race on the prescribing of opioids in emergency departments throughout the United States. *J Gen Intern Med* 2013;28(12):1604–1610. [PubMed: 23797920]

- [51]. Kaplan JB, Bennett T. Use of race and ethnicity in biomedical publication. *Jama* 2003;289(20):2709–2716. [PubMed: 12771118]
- [52]. Kim HJ, Greenspan JD, Ohrbach R, Fillingim RB, Maixner W, Renn CL, Johantgen M, Zhu S, Dorsey SG. Racial/ethnic differences in experimental pain sensitivity and associated factors - Cardiovascular responsiveness and psychological status. *PLoS One* 2019;14(4):e0215534.
- [53]. Kim HJ, Yang GS, Greenspan JD, Downton KD, Griffith KA, Renn CL, Johantgen M, Dorsey SG. Racial and ethnic differences in experimental pain sensitivity: systematic review and meta-analysis. *Pain* 2017;158(2):194–211. [PubMed: 27682208]
- [54]. Kirsch I, Kong J, Sadler P, Spaeth R, Cook A, Kaptchuk T, Gollub R. Expectancy and Conditioning in Placebo Analgesia: Separate or Connected Processes? *Psychol Conscious (Wash D C)* 2014;1(1):51–59. [PubMed: 25093194]
- [55]. Kubota JT, Banaji MR, Phelps EA. The neuroscience of race. *Nat Neurosci* 2012;15(7):940–948. [PubMed: 22735516]
- [56]. Landrine H, Corral I. Separate and unequal: residential segregation and black health disparities. *Ethn Dis* 2009;19(2):179–184. [PubMed: 19537230]
- [57]. Lee P, Le Saux M, Siegel R, Goyal M, Chen C, Ma Y, Meltzer AC. Racial and ethnic disparities in the management of acute pain in US emergency departments: Meta-analysis and systematic review. *Am J Emerg Med* 2019;37(9):1770–1777. [PubMed: 31186154]
- [58]. Lu Q, Zeltzer L, Tsao J. Multiethnic differences in responses to laboratory pain stimuli among children. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2013;32(8):905–914.
- [59]. Maina IW, Belton TD, Ginzberg S, Singh A, Johnson TJ. A decade of studying implicit racial/ethnic bias in healthcare providers using the implicit association test. *Social science & medicine (1982)* 2018;199:219–229. [PubMed: 28532892]
- [60]. Maly A, Vallerand AH. Neighborhood, Socioeconomic, and Racial Influence on Chronic Pain. *Pain Manag Nurs* 2018;19(1):14–22. [PubMed: 29422123]
- [61]. Miller VE, Poole C, Golightly Y, Barrett D, Chen DG, Ohrbach R, Greenspan JD, Fillingim RB, Slade GD. Characteristics Associated With High-Impact Pain in People With Temporomandibular Disorder: A Cross-Sectional Study. *The journal of pain : official journal of the American Pain Society* 2019;20(3):288–300.
- [62]. Mills AM, Shofer FS, Boulis AK, Holena DN, Abbuhl SB. Racial disparity in analgesic treatment for ED patients with abdominal or back pain. *Am J Emerg Med* 2011;29(7):752–756. [PubMed: 20825892]
- [63]. Morris MC, Walker L, Bruehl S, Hellman N, Sherman AL, Rao U. Race Effects on Conditioned Pain Modulation in Youth. *The journal of pain : official journal of the American Pain Society* 2015;16(9):873–880.
- [64]. Murray B, McCrone S. An integrative review of promoting trust in the patient–primary care provider relationship. *Journal of Advanced Nursing* 2015;71(1):3–23. [PubMed: 25113235]
- [65]. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain* 2015;16(8):769–780. [PubMed: 26028573]
- [66]. Nasri-Heir C, Khan J, Benoliel R, Feng C, Yarnitsky D, Kuo F, Hirschberg C, Hartwell G, Huang CY, Heir G, Korzeniewska O, Diehl SR, Eliav E. Altered pain modulation in patients with persistent postendodontic pain. *Pain* 2015;156(10):2032–2041. [PubMed: 26098442]
- [67]. Ohrbach R, Larsson P, List T. The jaw functional limitation scale: development, reliability, and validity of 8-item and 20-item versions. *Journal of orofacial pain* 2008;22(3):219–230. [PubMed: 18780535]
- [68]. Ohrbach R, Markiewicz MR, McCall WD Jr. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *Eur J Oral Sci* 2008;116(5):438–444. [PubMed: 18821986]
- [69]. Ohrbach R, Slade GD, Bair E, Rathnayaka N, Diatchenko L, Greenspan JD, Maixner W, Fillingim RB. Premorbid and concurrent predictors of TMD onset and persistence. *Eur J Pain* 2019.
- [70]. Okusogu C, Colloca L. Placebo hypoalgesia: above and beyond expectancy and conditioning. *Curr Opin Behav Sci* 2019;26:75–81. [PubMed: 31538101]

- [71]. Owens MA, Bulls HW, Trost Z, Terry SC, Gossett EW, Wesson-Sides KM, Goodin BR. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Med* 2016;17(8):1452–1464. [PubMed: 26814298]
- [72]. Palese A, Cadorin L, Testa M, Geri T, Colloca L, Rossetini G. Contextual factors triggering placebo and nocebo effects in nursing practice: Findings from a national cross-sectional study. *J Clin Nurs* 2019;28(9–10):1966–1978. [PubMed: 30706543]
- [73]. Palit S, Kerr KL, Kuhn BL, Terry EL, DelVentura JL, Bartley EJ, Shadlow JO, Rhudy JL. Exploring pain processing differences in Native Americans. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2013;32(11):1127–1136.
- [74]. Park CY, Lee MA, Epstein AJ. Variation in emergency department wait times for children by race/ethnicity and payment source. *Health Serv Res* 2009;44(6):2022–2039. [PubMed: 19732167]
- [75]. Parks FR, Kennedy JH. The impact of race, physical attractiveness, and gender on education majors' and teachers' perceptions of student competence. *Journal of Black Studies* 2007;37(6):936–943.
- [76]. Peiris N, Blasini M, Wright T, Colloca L. The Placebo Phenomenon: A Narrow Focus on Psychological Models. *Perspect Biol Med* 2018;61(3):388–400. [PubMed: 30293977]
- [77]. Popper-Giveon A. Preferring patient-physician concordance: the ambiguity of implicit ethnic bias. *Ethnicity & health* 5 20, 2019:1–17.
- [78]. Rahim-Williams B, Riley JL 3rd, Williams AK, Fillingim RB. A quantitative review of ethnic group differences in experimental pain response: do biology, psychology, and culture matter? *Pain medicine (Malden, Mass)* 2012;13(4):522–540.
- [79]. Rahim-Williams FB, Riley JL 3rd, Herrera D, Campbell CM, Hastie BA, Fillingim RB. Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. *Pain* 2007;129(1–2):177–184. [PubMed: 17296267]
- [80]. Richardson LD, Norris M. Access to health and health care: how race and ethnicity matter. *Mt Sinai J Med* 2010;77(2):166–177. [PubMed: 20309927]
- [81]. Rosenbloom JM, Burns SM, Kim E, August DA, Ortiz VE, Houle TT. Race/Ethnicity and Sex and Opioid Administration in the Emergency Room. *Anesth Analg* 2019;128(5):1005–1012. [PubMed: 29863607]
- [82]. Rossetini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord* 2018;19(1):27. [PubMed: 29357856]
- [83]. Rowell LN, Mechlin B, Ji E, Addamo M, Girdler SS. Asians differ from non-Hispanic Whites in experimental pain sensitivity. *European journal of pain (London, England)* 2011;15(7):764–771.
- [84]. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF, International Rdc/Tmd Consortium Network IafDR, Orofacial Pain Special Interest Group IAftSoP. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. *Journal of oral & facial pain and headache* 2014;28(1):6–27. [PubMed: 24482784]
- [85]. Shahidi B, Maluf KS. Adaptations in Evoked Pain Sensitivity and Conditioned Pain Modulation after Development of Chronic Neck Pain. *Biomed Res Int* 2017;2017:8985398.
- [86]. Singhal A, Tien YY, Hsia RY. Racial-Ethnic Disparities in Opioid Prescriptions at Emergency Department Visits for Conditions Commonly Associated with Prescription Drug Abuse. *PLoS One* 2016;11(8):e0159224.
- [87]. Stanley DA, Sokol-Hessner P, Banaji MR, Phelps EA. Implicit race attitudes predict trustworthiness judgments and economic trust decisions. *Proc Natl Acad Sci U S A* 2011;108(19):7710–7715. [PubMed: 21518877]

- [88]. Stanley DA, Sokol-Hessner P, Fareri DS, Perino MT, Delgado MR, Banaji MR, Phelps EA. Race and reputation: perceived racial group trustworthiness influences the neural correlates of trust decisions. *Philos Trans R Soc Lond B Biol Sci* 2012;367(1589):744–753. [PubMed: 22271789]
- [89]. Staud R Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother* 2012;12(5):577–585. [PubMed: 22550986]
- [90]. Sukenaga N, Ikeda-Miyagawa Y, Tanada D, Tunetoh T, Nakano S, Inui T, Satoh K, Okutani H, Noguchi K, Hirose M. Correlation Between DNA Methylation of TRPA1 and Chronic Pain States in Human Whole Blood Cells. *Pain Med* 2016;17(10):1906–1910. [PubMed: 26849948]
- [91]. Tehranian J Performing whiteness: Naturalization litigation and the construction of racial identity in America. *The Yale Law Journal* 2000;109(4):817–848.
- [92]. Vina ER, Ran D, Ashbeck EL, Kwok CK. Natural history of pain and disability among African-Americans and Whites with or at risk for knee osteoarthritis: A longitudinal study. *Osteoarthritis and cartilage* 2018;26(4):471–479. [PubMed: 29408279]
- [93]. Xierali IM, Nivet MA. The Racial and Ethnic Composition and Distribution of Primary Care Physicians. *Journal of health care for the poor and underserved* 2018;29(1):556–570. [PubMed: 29503317]
- [94]. Yarnitsky D Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol* 2010;23(5):611–615. [PubMed: 20543676]
- [95]. Zakrzewska JM. Differential diagnosis of facial pain and guidelines for management. *Br J Anaesth* 2013;111(1):95–104. [PubMed: 23794651]

Fig. 1.

Experimental paradigm. An ATS thermode was applied to the dominant arm of the participant to induce pain experience. A sham electrode was applied proximal to the ATS thermode. Participants were told that when the sham electrode was activated, it would reduce pain experiences. The conditioning phase included 2 blocks with 6 red and 6 green trials in each block. A red screen was paired with a high level of heat pain stimulation while a green screen was paired with a low level of heat pain stimulation. After each heat pain stimulus, participants were shown a VAS scale from 0 (no pain at all) to 100 (maximum tolerable pain) to rate their pain intensity experience. The interstimulus interval (ISI) was set randomly between 10 and 13 seconds. During testing phase, both the red screen and green screen were paired with moderate-level pain stimulation. Participants rated their pain intensity using a VAS scale from 0 (no pain at all) to 100 (maximum tolerable pain). For both conditioning and testing phases, red and green trials were displayed using one of the 4

preprogrammed sequences that were randomly assigned. Expectations were also assessed before and after the conditioning phase. VAS, Visual Analogue Scale.

a

b

Fig. 2. Race differences in heat-pain tolerance. (a) Overall, Whites displayed greater heat-pain tolerance compared to AA/Blacks. (b) Within the TMD cohort only, AA/Blacks reported greater TMD chronic pain interference than Whites. Data are presented as median $\pm$ quartile (a) and (b) *** $p < 0.001$; * $p < 0.05$.

Fig. 3.

Race differences in pain relief expectations and placebo hypoalgesia. For both TMD and HC cohorts, White and AA/Black participants did not differ in expectations *before* the conditioning phase, but expectations *after* the conditioning phase were greater for White than AA/Black participants. Overall, reinforced expectations of pain relief after the conditioning phase were significantly greater than baseline expectations. The data are presented separately for TMD and HC. Data are presented as mean $\pm$ sem *** $p < 0.001$.

Fig. 4.

Race differences in placebo hypoalgesia. Overall, White participants displayed a greater magnitude of placebo hypoalgesia limited to trial one compared to AA/Blacks. The race differences in placebo hypoalgesia was only significant for the first trial of the testing phase (about one minute). When exploring trial-by-trial placebo effects, TMD but not HC participants showed a difference in placebo hypoalgesia with AA/Blacks displaying smaller effects than Whites did.

The data are presented overall with mean $\pm$ sem * $p < 0.050$. Time is expressed in minutes with a variation of up to 8 seconds due to the jittering.

Fig. 5.

Mediation models testing the mediating role of conditioning strength (M1) and reinforced expectations (M2) in race-placebo hypoalgesia association for trial one. Conditioning strength but not reinforced expectations drove the racial difference in the magnitude of placebo hypoalgesia. Solid lines represented that the pathway was significant, while dashed lines represented non-significant pathways.

Fig. 6.

Participant-experimenter race's and sex's impact on placebo hypoalgesia. For TMD participants, same participant-experimenter race group displayed greater placebo hypoalgesia compared to different participant-experimenter race group; while experimenter sex did not influence the magnitude of placebo hypoalgesia within TMD participants. For HC cohort, on the contrary, experimenter RACE did not show any influences on placebo hypoalgesia. The different participant-experimenter SEX group displayed greater placebo hypoalgesia compared to the same participant-experimenter SEX group. The data are presented separately for TMD and HC, with mean $\pm$ sem, *** $p < 0.001$, * $p < 0.050$. Time is expressed in minutes with a variation of up to 8 seconds due to the jittering.

Table 1.

Sociodemographic characteristics and vitals

	TMD (N=186)			Healthy participants (N=186)		
	AA/Blacks ^a (N=60)	Whites (N=126)		AA/Blacks (N=60)	Whites (N=126)	
Age (year, mean ± sem)	37.25 (1.55)	33.53 (1.03)	t₁₈₄=2.03, p=0.044	35.08 (1.61)	32.31 (1.12)	t ₁₈₄ =1.41, p=0.161
Sex ^b	33	99	χ²=10.96, p=0.001	33	99	χ²=10.96, p=0.001
Ethnicity ^c	57	118	χ ² =0.13, p=0.715	58	111	χ ² =3.60, p=0.058
Educational level ^d	24	95	χ²=22.10, p<0.001	29	99	χ²=17.32, p<0.001
Annual income ^e	13	63	χ²=13.83, p<0.001	21	57	χ ² =1.88, p=0.172
Marital status ^f	8	31	χ ² =3.12, p=0.078	15	35	χ ² =0.16, p=0.690
Blood pressure (mmHg, mean ± sem)						
Systolic	128.85 (2.04)	124.02 (1.09)	t₁₈₄=2.29, p=0.023	122.59 (12.35)	119.06 (1.31)	t ₁₈₄ =1.60, p=0.111
Diastolic	81.08 (1.44)	79.23 (0.79)	t ₁₈₄ =1.23, p=0.222	75.05 (1.40)	73.91 (0.89)	t ₁₈₄ =0.70, p=0.483
Heart rate (beats/min, mean ± sem)	71.10 (1.44)	71.56 (0.95)	t ₁₈₄ =-0.27, p=0.789	70.59 (1.66)	71.26 (1.01)	t ₁₈₄ =-0.36, p=0.718
BMI (mean ± sem)	30.40 (0.85)	26.24 (0.51)	t₁₈₄=4.42, p<0.001	27.89 (0.80)	24.97 (0.50)	t₁₈₄=3.25, p=0.001

^aAA = African-American^bSex: The number of women was reported for each subgroup^cEthnicity: The number of Non-Hispanic was reported for each subgroup^dEducational level: college graduation or higher vs. some college or lower. The number of college graduation or higher was reported for each subgroup^eAnnual income: more than \$60,000 vs. less than \$60,000. The number of \$60,000 or higher was reported for each subgroup^fMarital Status: The number of participants who are married/living with a partner was reported for each subgroup.

Heat stimulation intensities (expressed as Celsius degrees) used for the conditioning and testing phase

Table 2.

	TMD (mean ± sem)		HC (mean ± sem)		F-tests		
	AA/Blacks (N=60)	Whites (N=126)	AA/Blacks (N=60)	Whites (N=126)	Group	Race	Group X Race
Conditioning phase							
Red-paired stimuli	46.37 (0.27)	47.18 (0.18)	47.35 (0.27)	47.75 (0.19)	HC > TMD; p<0.001	Whites > AA/Blacks; p=0.008	p=0.375
Green-paired stimuli	40.65 (0.28)	41.37 (0.19)	41.80 (0.28)	41.85 (0.19)	HC > TMD; p<0.001	p=0.103	p=0.155
Testing phase							
Red- and Green-paired stimuli	45.57 (0.45)	46.69 (0.31)	46.10 (0.45)	46.19 (0.31)	p=0.965	p=0.120	p=0.188