Neural and Sociocultural Mediators of Ethnic Differences in Pain

Elizabeth A. Reynolds Losin[1,2], Chong-Wan Woo[1,3], Natalia Alina Medina[2], Jessica Andrews-Hanna[1,4], Hedwig Eisenbarth[1,5], Tor D. Wager[1]

Institute of Cognitive Science, University of Colorado Boulder[1]; Department of Psychology, University of Miami[2], Center for Neuroscience Imaging Research, Institute for Basic Science[3]; Department of Psychology, University of Arizona[5] , University of Southampton[4]

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Corresponding author:

Elizabeth A. Reynolds Losin

Department of Psychology

University of Miami

5665 Ponce de Leon Boulevard

Coral Gables Florida, 33146-0751

Phone: (305) 284-8672

Email: e.losin@miami.edu

Abstract

Understanding ethnic differences in pain is important for addressing disparities in pain care. A common belief is that African-Americans are hyposensitive to pain compared to whites, but African-Americans show increased pain sensitivity in clinical and laboratory settings. The neurobiological mechanisms underlying these differences are unknown. We studied an ethnicity/gender-balanced sample of African-Americans, Hispanics, and non-Hispanic whites using fMRI during thermal pain. Higher pain in African-Americans was mediated by perceived discrimination and paralleled by increases in fronto-striatal circuits associated with pain rating, discrimination, experimenter trust, and extra-nociceptive aspects of pain in other studies. In contrast, expression of the Neurologic Pain Signature, a neuromarker sensitive and specific to nociceptive pain, discriminated levels of painful heat in all groups but was unaffected by ethnicity. Findings identify a brain basis for higher pain in African-Americans related to interpersonal context and extra-nociceptive central pain mechanisms, and suggest that nociceptive pain processing is similar across ethnicities.

Keywords: culture, race, pain, health disparities, fMRI, biomarker

A common belief since the time of American slavery is that African-Americans feel less pain than whites [1]. This belief has been related to under treatment of pain in African-Americans[2], which contributes to widespread and persistent racial and ethnic health disparities[3]. Paradoxically, African-Americans, and in some cases Hispanics, actually report more pain than non-Hispanic whites in both clinical[4] and laboratory[5,6] settings. In order to reduce pain assessment and treatment disparities, we need to better understand the mechanisms contributing to higher pain sensitivity amongst African-Americans.

Ethnic differences in pain sensitivity may be related to multiple factors[7-9]. Higher pain reported by African-Americans may be due in part to variation in the basic sensory and affective processes specific to pain. Findings of less effective descending pain modulation [4,10,11] and lower prevalence of antinociceptive single nucleotide polymorphisms in African-Americans compared to non-Hispanic whites[12] suggest potential differences in nociceptive sensitivity. Higher pain reported by African-Americans may also be due in part to sociocultural variation in life experiences that affect how people value, explain, and respond to (e.g. avoid or cope with) pain[7] (i.e. the extra-nociceptive aspects of pain). African-Americans experience higher incidences of discrimination[13,14] and stressful and traumatic life events[15] compared to non-Hispanic whites, and engage in increased hypervigilance[16], pain catastrophizing[16], and religious pain coping[17]. In particular, increased hypervigilance[16] and discrimination[18-21] are associated with higher reported pain amongst African-Americans.

The relative contributions of these nociceptive and extra-nociceptive factors to ethnic differences in pain sensitivity are still unclear. Brain measures can help resolve this confusion by providing measures of the multiple central nociceptive and extra-nociceptive systems that

contribute to pain processing [22]. Here we use fMRI during experimental thermal pain induction (Fig. 1) in conjunction with a battery of sociocultural measures to test whether potential nociceptive and extra-nociceptive mechanisms differ across ethnic groups and relate to ethnic group differences in pain. We employ a sample of 28 African-American (AA), 30 Hispanic Americans (HA), and 30 non-Hispanic White Americans (WA; see Table 1 for sample characteristics).

To examine sociocultural contributors to pain processing we tested whether a range of sociocultural factors previously found to influence pain mediated group differences in pain rating. We also searched across the brain for regions that responded differently to painful heat across ethnic groups and exhibited relationships with sociocultural factors and pain rating. If ethnic differences in pain are due in part to enhanced pain valuation and avoidance motivation elicited in response to a more adverse sociocultural context, we would expect to find heightened activity and relationships with pain ratings and sociocultural context measures in brain systems related to the extra-nociceptive aspects of pain such as the pathway connecting the ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAc), which has been shown to be involved in emotion regulation[23,24], pain valuation [25,26], and pain chronification[27], and can exhibit changes in response to chronic stress[28].

To examine nociceptive sensitivity, we looked at activity in brain regions previously linked to nociception (e.g. SII and dorsal posterior insula (dpINS)[22,29]) in whole brain analyses and tested responses in a multivariate fMRI activity pattern that closely tracks the intensity and affect of evoked nociceptive pain[30], termed the “Neuorologic Pain Signature” (NPS). The NPS does not explain all aspects of pain but is sensitive and specific to pain in the 90-100% range

across multiple fMRI studies (for a review see[31]), providing an objective measure that responds strongly to pain evoked by noxious input in particular, but not to several types of psychological 'pain' and negative emotion[32-34]. If African-Americans are more sensitive to pain than non-Hispanic whites due in part to enhanced nociceptive input (e.g., receptor genetics or reduced descending inhibition), then we would expect brain systems related to nociception and pain affect to exhibit heightened activity and to relate to higher pain rating in African-Americans, including the NPS.

We found that higher pain in African-Americans was paralleled by a steeper dose-response relationship between noxious stimulus intensity and activity in brain regions related to emotion regulation and valuation including the vmPFC and NAc, which correlated with pain rating, perceived discrimination, and reduced trust in the experimenter. In contrast, the NPS strongly tracked increases in noxious stimulus intensity and comparably across all ethnic groups, suggesting that nociceptive pain processing is similar across ethnic groups. Thus, the findings identify a brain basis for higher pain in African-Americans related to sociocultural context and extra-nociceptive central pain mechanisms, suggesting that interventions geared towards reducing discrimination and increasing clinician trust may be promising ways to mitigate ethnic disparities in pain.

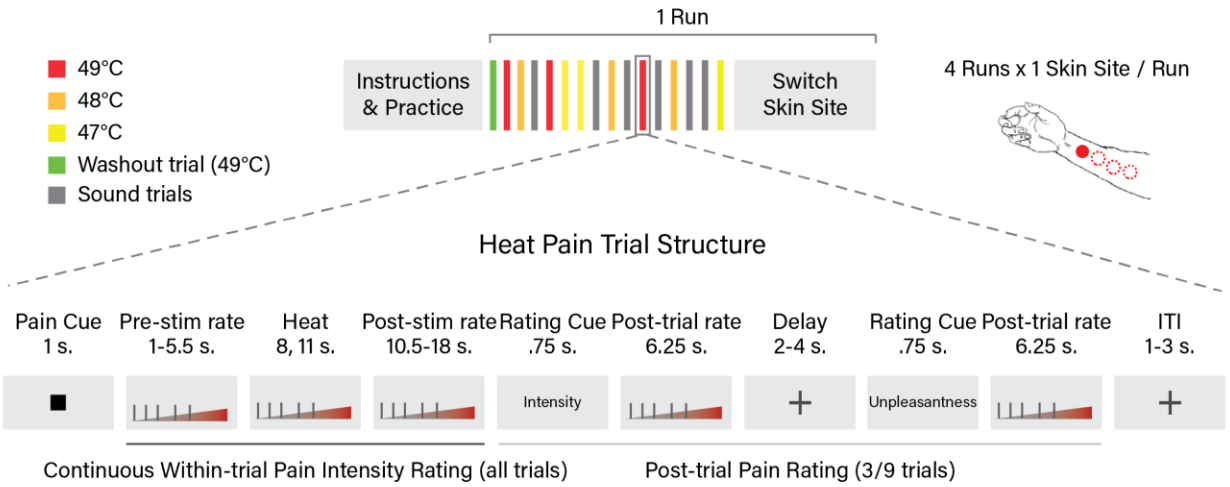

Figure 1. fMRI thermal stimulation task design. Each participant experienced 4 runs of noxious thermal stimulation on four sites on their inner forearm (1 skin site per run) at three different temperatures (yellow-red bars, 3 of each per run). Heat trials were interspersed with trials of emotionally or physically aversive sounds (gray bars, 3 of each per run), which were not used in the present analysis. Each run started with a single unanalyzed trial at the highest temperature (green bar): a "washout trial" to allow for habituation of the specific skin site to thermal stimulation. All trials included continuous pain intensity rating before, during, and after thermal stimulation. The area under the curve of the continuous within-trial pain intensity rating was used as the pain rating metric in the pain rating mediation analyses and all fMRI analyses (see Online Methods for rating details). One third of the heat trials in each run (one at each temperature) also included post-trial average pain unpleasantness and pain intensity ratings (order counterbalanced).

Table 1

Sample Characteristics

	White American	African-American	Hispanic American		
Measure	*N or M(SD)*	*N or M(SD)*	*N or M(SD)*	χ^2/F	*p*
Analyzed Sample	30	28	30		
Gender (m,f[a])	15	14	15	0	1
Age	27.98 (3.97)	30.34 (7.74)	28.25 (4.64)	1.5	.23
Recruitment (IBG[b])	16	11	15	1.24	.54
fMRI Sequence (MB[c])	8	6	11	1.72	.42

Note: χ^2 values are from Pearson's Chi-squared tests comparing actual subject counts in each group for each measure to counts for perfectly balanced groups. *F* values are from linear models in R (command lm) for the ethnicity effect (coded as a three level factor) on each measure.

[a]m = male, f = female

[b]IBG = University of Colorado Boulder Institute for Behavioral Genetics, other recruitment source was Denver metro area Craigslist

[c]MB = Multiband (8 simultaneous slice acquisition, TR = .46 sec.), other fMRI sequence was standard (single slice acquisition, TR = 1.3 sec.)

Results

African-American Participants Report Pain as More Intense and Unpleasant Than Non-Hispanic White and Hispanic Participants

Participants continuously rated moment-to-moment pain intensity during thermal stimulation at three intensity levels (L = 47, M = 48, H = 49 ^{o}C) (see Online Methods for details about within-trial pain intensity rating). All stimulus intensities were above the median temperature associated with reported pain in prior studies[30] and the activation of specific nociceptors[35] (>45 ^{o}C). On average, participants rated their maximum pain intensity for each temperature between 17 (Moderate) and 53 (Very Strong) on the 0-100 generalized labeled magnitude scale (L: *M* =32.10, *SD* = 20.22; M: *M* = 41.94 , *SD* = 20.36; H: *M* =50.34 , *SD* = 21.20).

As expected, the area under the curve of within-trial pain intensity rating (hereafter referred to as pain rating) increased with increasing temperature, showing a dose-response relationship ($\hat{\beta}$ = 6.67, t_{84} = 17.04, $p < 0.0001$; Fig. 2a), and this effect was seen in each ethnic group when analyzed separately (all $p < .0001$; Fig. 2a). Consistent with prior studies of experimental and clinical pain report[4-6], we found that the AA participants rated their pain as more intense than HA and WA participants ($\hat{\beta}$ = 9.73, t_{84} = 2.79, p = 0.01; Fig. 2a left graph), and exhibited a steeper dose-response relationship between noxious stimulus intensity and pain rating ($\hat{\beta}$ = 2.10, t_{84} = 2.47, p = .02; Fig. 2a right graph). Comparing HA versus WA participants yielded no difference in pain rating or the dose-response relationship between temperature and pain (all $p > .7$; Fig. 2a). Similar results were found for post-trial pain intensity and unpleasantness ratings (Fig. 2b; see Supplementary Table 1 for statistics, see Online Methods for post-trial rating details).

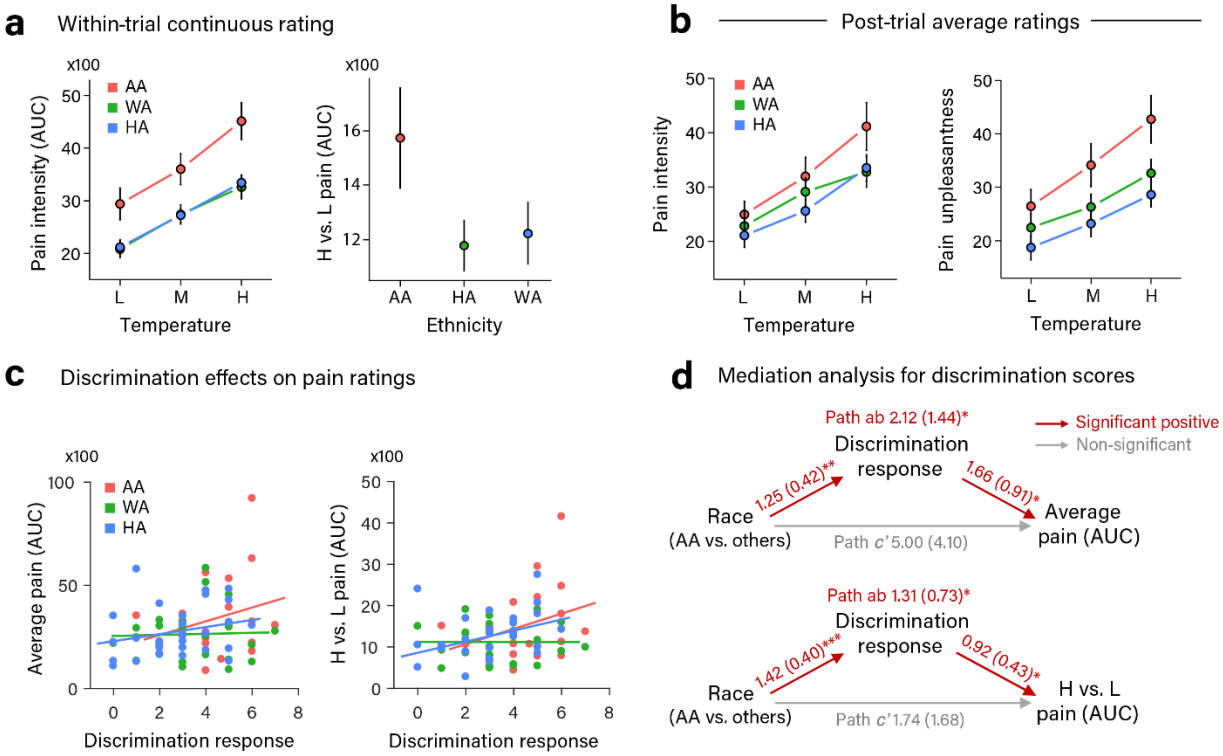

Figure 2. Differences in pain rating across ethnic groups and mediation by discrimination. (a) Graphs of mean area under the curve of within-trial pain intensity rating (present on all trials) at each temperature of heat stimulation (left graph) and the difference between high and low heat stimulation (right graph) in each ethnic group. (b) Graphs of mean post-trial pain intensity (left graph) and pain unpleasantness (right graph) rating (present on 1/3 of trials) at each temperature of heat stimulation in each ethnic group. (a-b) Error bars represent within-subject SEM. (c) Relationship between participants' frequency of responding to discrimination (e.g. by filing a complaint) and the area under the curve of their within-trial pain intensity rating. Average pain rating across three stimulation temperatures is depicted in the left panel, and average pain rating for high temperatures minus average pain rating for low temperatures is depicted on the right panel. (d) Path diagrams and statistics for mediation analyses of participant race effects [AA vs (HA +WA)] on pain rating by participants' frequency of responding to discrimination. Path coefficients are listed for each path with standard errors in parentheses. Values for area under the curve of continuous within-trial pain intensity rating depicted on Y axes have been divided by 100. * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

African-American Participants Report Higher Discrimination and Lower Trust in Experimenter

Compared to WA and HA participants, AA participants reported having experienced more incidences of daily and major discrimination ($\hat{\beta} = 8.74$, $t_{80} = 5.58$, $p < .0001$), having more frequently responded to discrimination (e.g., by filing a complaint; referred to hereafter as *discrimination response*) ($\hat{\beta} = 1.45$, $t_{78} = 3.60$, $p = .01$), and feeling less trust in the experimenter (the same white male in his mid-30s for all participants) ($\hat{\beta} = -3.89$, $t_{83} = -3.49$, $p = .01$). AA

participants did not differ from WA and HA participants in other hypothesized contributors to ethnic differences in pain report, including socioeconomic status, stressful life events, and hypervigilance. Thus, discrimination history and trust in the experimenter were the most likely sociocultural candidate mediators to explain the higher pain rating by the AA group (see Table S2 for group means and statistics for all measures).

History of Discrimination Mediates Higher Pain Intensity Rating by African-American Participants

Among the three candidate mediators, only participants' history of responding to discrimination ('Discrimination response' in Fig. 2c-d) mediated the relationship between their ethnicity and their pain ratings (see Fig. 2d for statistics). Frequency of responding to discrimination was higher in AA participants than in WA and HA participants, which in turn predicted higher pain rating and a steeper dose-rating relationship controlling for participant ethnicity. Together, these findings suggest that a history of responding to discrimination may predispose individuals to react more strongly to physically painful stimuli.

Fronto-striatal Regions are More Responsive to Increases in Painful Heat in African-American Participants

Next, we used a whole brain voxel-wise GLM analysis to test whether the higher levels of pain intensity reported by AA participants were accompanied by brain systems that responded differently to painful heat or exhibited a different dose-response relationship with stimulus intensity in AA versus HA and WA participants. A set of brain regions associated with the extra-nociceptive rather than nociceptive aspects of pain exhibited a steeper dose-activity

relationship in AA participants compared to HA and WA participants. These regions included fronto-striatal regions previously associated with pain valuation[25,26], modulation[23,24], and chronification[27]: the ventromedial prefrontal cortex (vmPFC), medial prefrontal cortex (mPFC), and bilateral nucleus accumbens (NAc), as well as bilateral portions of the middle frontal gyrus (mFG) (Fig. 3a; Supplementary Table 3; all voxel-wise results reported are significant at an FDR corrected threshold of $q < .05$ ($p < .000047$)). Data from each of these regions is shown in Fig. 3b. Tests of average activity across stimulus intensity levels did not reveal any regions that responded differentially in AA compared to HA and WA participants at FDR $q < .05$.

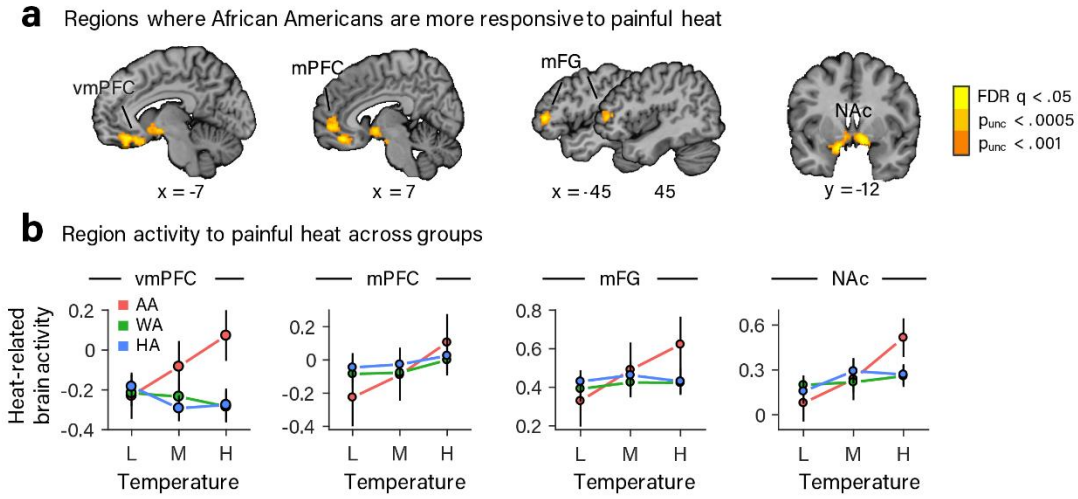

Figure 3. Results of whole-brain voxelwise GLM analysis showing brain regions exhibiting a steeper dose-activity relationship in AA participants and their relationships with pain rating. (a) vmPFC, mPFC, bilateral mFG and bilateral NAc were significantly more responsive to increases in painful heat (H-L) in AA compared to HA and WA participants (FDR corrected $q < .05$ ($p < .000047$)). For the purposes of display, we included voxels meeting two additional, more liberal, uncorrected voxel-wise thresholds: $p < .0005$ and $p < .001$ that were in contact with voxels meeting the more stringent FDR corrected threshold. (b) Data from the four regions (defined at

$p < .001$, uncorrected and combining across hemispheres for bilaterally activated NAc and mFG). Average parameter estimates from each cluster for each temperature and heat condition compared to rest were extracted from the first-level GLM analysis and averaged across heat conditions to yield one value per temperature per participant. The mean parameter estimate for each temperature across participants is plotted with error bars representing the within-subject SEM.

During painful heat, higher activity in fronto-striatal regions is related to higher pain rating, more discrimination, and less trust

Follow-up analyses of the relationship between activity within each cluster from the GLM and pain rating revealed that without controlling for the effects of stimulus intensity, activity within the mPFC ($\hat{\beta} = .004$, $t_{26} = 1.81$, $p = .08$), mFG ($\hat{\beta} = .006$, $t_{26} = 3.45$, $p < .01$), and NAc ($\hat{\beta} = .003$, $t_{26} = 1.85$, $p = .08$) clusters was correlated with trial-by-trial pain ratings in AA participants, whereas only the NAc cluster was correlated with pain ratings in the other groups (HA: $\hat{\beta} = .005$, $t_{28} = 2.20$, $p = .04$; WA: $\hat{\beta} = .004$, $t_{28} = 2.29$, $p = .03$). When controlling for the effects of stimulus intensity, only mFG activity was marginally related to pain rating and only in the AA group ($\hat{\beta} = .004$, $t_{26} = 1.92$, $p = .07$). These findings suggest that in addition to these regions (vmPFC, mPFC, NAc and mFG) only encoding painful stimulus intensity in AA participants, the mPFC and mFG may also exhibit a unique relationship with pain rating in AA partiticipants.

We also conducted follow-up exploratory analyses of the relationship between each of the candidate sociocultural mediators described above and activity and the dose-activity

relationship within each cluster from the GLM, correcting tests across ethnic groups for multiple comparisons (Bonferroni, $p < .05$). We found that activity within the NAc cluster increased with increasing discrimination frequency ($\hat{\beta} = .03$, $t_{75} = 3.49$, $p = .02$), and this relationship was stronger for the AA group ($\hat{\beta} = .04$, $t_{75} = 2.19$, $p = .03$; Fig. 4). Tests of each group separately showed a positive correlation in the AA group ($\hat{\beta} = .05$, $t_{21} = 2.72$, $p = .01$) and a marginally positive correlation in the HA group ($\hat{\beta} = .02$, $t_{25} = 1.72$, $p = .1$)(Fig. 4). This finding suggests that the NAc may become sensitized to painful stimuli in those with a history of negative social treatment.

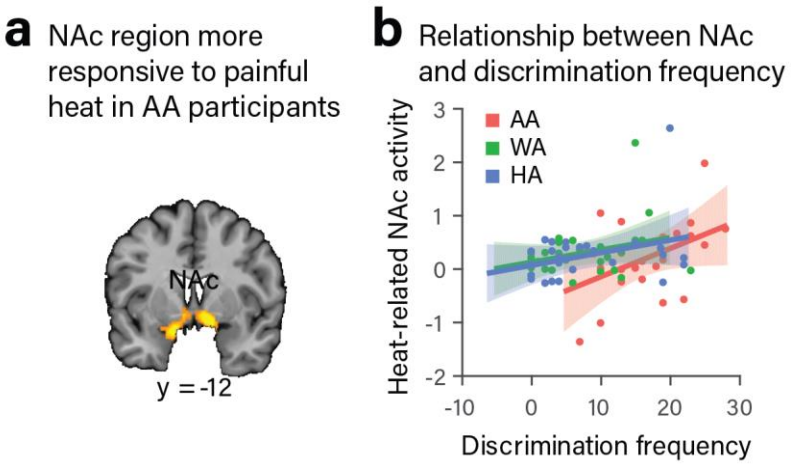

Figure 4. Relationship between activity within the NAc region exhibiting a steeper dose-activity relationship in AA participants and discrimination frequency. (a) NAc region exhibiting a steeper dose-activity relationship in AA participants from the GLM analysis. (b) A graph of parameter estimates from the NAc regions depicted in (a) during painful heat versus discrimination frequency with regression lines and standard error bands for each ethnic group.

There was also a trust by group interaction within the NAc and mPFC clusters, such that activity within the NAc ($\hat{\beta}$ = -.08, t_{78} = -4.00, p < .01) and mPFC ($\hat{\beta}$ = -.1, t_{78} = -3.33, p = .03) was strongest for those with least trust in the experimenter, particularly for the AA compared to the WA and HA groups. This finding suggests that trust may have buffered against activation of these regions in AA participants who trusted the experimenter more. NAc activity was strongest in AA participants with the least trust ($\hat{\beta}$ = -.04, t_{24} = -1.95, p = .06), whereas it was strongest in HA ($\hat{\beta}$ = .04, t_{26} = 2.73, p = .01) and WA ($\hat{\beta}$ = .03, t_{24} = 2.13, p = .04) participants with the most trust. mPFC activity was also strongest in AA participants with the least trust in the experimenter ($\hat{\beta}$ = -.06, t_{24} = -2.00, p = .06). We did not find any significant relationships between the dose-activity relationship within any of the clusters from the GLM and any of the candidate mediators when correcting for multiple comparisons.

Neurologic Pain Signature Responses are Equivalent Across Ethnic Groups

Next we conducted a more sensitive test (compared to the whole-brain GLM) for ethnic group differences in nociception sensitive brain systems using the NPS[30] (Fig. 5a). Replicating our previous findings[31], the NPS responded more strongly with increasing painful stimulus intensity ($\hat{\beta}$ = 4.03, t_{84} = 8.16, p < .0001) (Fig. 5b). The linear dose-response effect of stimulus intensity on NPS response was seen in each ethnic group when analyzed separately (all p < .01). Furthermore, there were no differences among ethnic groups in the magnitude of the NPS response or the stimulus intensity-NPS response relationship (All p > .3, see Fig. 5 legend for statistics). These findings suggest that the brain system represented by the NPS, which receives nociceptive input from the spinothalamic and spinoreticular pathways and is particularly

strongly associated with evoked pain, is unlikely to underlie the higher pain reported by AA participants. The combination of positive findings for temperature effects and negative ethnicity effects suggests that nociceptive pain systems operate similarly across ethnicities, and demonstrates that our fMRI measures are roughly equally sensitive and our hemodynamic model fits equally well across ethnic groups.

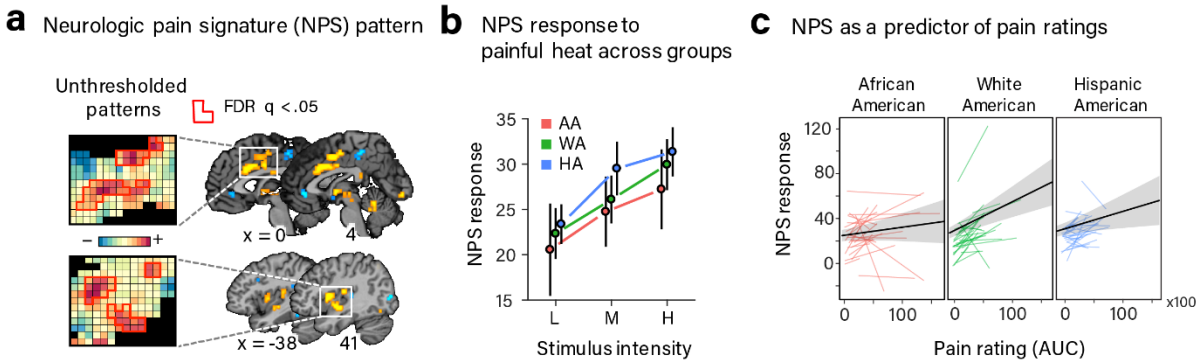

Figure 5. Neurologic pain signiture (NPS) responses to painful heat and relationship with pain rating across ethnic groups. (a) the NPS pattern, an *a priori* multivariate pattern of fMRI signal that is sensitive and specific to nociceptive physical pain [30]. (b) Mean NPS respopnse each temperature of heat stimulation in each ethnic group. Error bars represent within-subject SEM. NPS response values indicate the strength of the signature response pattern expression and are calculated by taking a dot-product of the NPS pattern weights and activation maps for each single heat trial. Neither the average NPS response nor the NPS response to temperature differed between ethnic groups ([AA – (HA+ WA)]: average response: $\hat{\beta}$ = -2.90, t_{83}= -.92, p= .36, temperature response: $\hat{\beta}$ = -.06, t_{84} = -.05, p= .96; [HA-WA]: average response: $\hat{\beta}$ = 1.25, t_{83} = .70, p = .48; temperature response: $\hat{\beta}$ = .05, t_{84} = .09, p = .93). (c) The NPS-pain rating relationship within

each ethnic group from the linear mixed effects model with accompanying point-wise 95% confidence interval band overlaid on individual regression lines for this relationship in each subject.

Neurologic Pain Signature Response Has Weaker Relationships with Pain Ratings in African-American Participants

Next, we tested the relationship between single-trial NPS responses and pain rating, and compared the strength of this relationship between ethnic groups. Given our findings of similar painful heat responses of the NPS across ethnic groups and differential painful heat responses of extra-nociceptive regions in AA compared to HA and WA participants, we expected a weaker relationship between the NPS and pain rating in AA compared to HA and WA participants (due to the additional contributions of extra-nociceptive regions to pain ratings in AA participants). Consistent with this prediction, we found that the relationship between the NPS and pain rating was weaker in the AA participants than HA and WA participants ($\hat{\beta}$ = -.13, t_{84}= -2.04, p = .04; Fig 5c), although the NPS did exhibit a strong positive relationship with pain ratings across ethnic groups when not controlling for the effects of stimulus intensity on NPS response ($\hat{\beta}$ = .16, t_{84} = 5.08, p < .0001; Fig. 3c). When ethnic groups were tested separately, there was a significant relationship between the NPS and pain rating in the WA ($\hat{\beta}$ = .27, t_{28} = 4.34, p < .001) and HA groups ($\hat{\beta}$ = .15, t_{28} = 3.56, p < .01), but not in the AA group ($\hat{\beta}$ = .06, t_{26}= 1.11, p = .28).

When controlling for the effects of stimulus intensity on NPS response, the overall relationship between the NPS and pain rating was marginal ($\hat{\beta}$ = .06, t_{84} = 1.69, p < .1); though it

was significant in several other studies[30,36]. There was a trend towards a weaker relationship between the NPS and pain rating in the AA group compared to the HA and WA groups ($\hat{\beta}$ = -.10, t_{84}= -1.58, p = .12) and the HA compared to the WA group ($\hat{\beta}$ = -.07, t_{84} = -1.69, p = .09). When groups were tested separately, only the WA group exhibited a significant relationship between the NPS and pain rating when controlling for the effects of stimulus intensity (WA: $\hat{\beta}$ = .20, t_{28}= 2.73, p = .01; HA, AA: p > .6), suggesting that extra-nociceptive brain systems may have contributed to pain ratings to a greater degree in AA and HA than WA participants. Additionally, we did not find relationships between any of the candidate sociocultural mediators and NPS pattern expression or the dose-NPS pattern expression relationship when correcting for multiple comparisons (Bonferroni, p < .05), suggesting that the NPS is not related to sociocultural factors that mediate ethnic differences in pain rating.

Discussion

African-Americans consistently exhibit increased pain sensitivity compared to non-Hispanic whites in clinical and laboratory settings [4-6]. Yet, neurobiological mechanisms underlying these differences are unknown, likely contributing to the persistence of ethnic disparities in pain and pain treatment. We replicated findings of higher pain report amongst African-Americans compared to Hispanic and non-Hispanic whites [4-6], and found that frequency of responding to discrimination mediated pain reporting differences. For the first time, we demonstrated that higher pain report amongst AA participants was accompanied by differences in brain activation during pain. Fronto-striatal regions including those previously associated with pain valuation [25,26], regulation [23,24] and chronification [27] (vmPFC, mPFC, and NAc),

exhibited a steeper dose-response relationship between painful stimulus intensity and brain activity among AA compared to HA and WA participants. Activity within some of these regions was also related to pain rating and to discrimination frequency and experimenter trust. In contrast, the NPS, a multivariate signature associated with the nociceptive aspects of pain, did track painful stimulus intensity as in previous studies[30], but did not differ between ethnic groups, and was not related to discrimination or trust.

Our finding that fronto-striatal regions are more responsive to increases in painful heat in AA participants compared to WA and HA participants suggests that higher pain reports by African-Americans in response to clinical and experimental pain are unlikely to solely arise at the level of pain report, but instead may be related to heightened responsivity with the vmPFC and NAc. The vmPFC and NAc have not typically been found to track experimentally induced pain intensity [37,38] (as seen here in WA and HA participants) but do track intensity of pain once it has become chronic [37,39,40]. The vmPFC-NAc pathway has also been found to undergo plasticity as a result of chronic stress[28], and activity within this pathway predicts the transition to chronic pain[27], a disorder also associated with previous stress, trauma and early life adversity[41]. Thus, the vmPFC-NAc pathway in AA participants may have become responsive to pain due to the chronic stress associated with discrimination, a hypothesis further supported by our findings of higher levels of discrimination in the AA group and a positive relationship between activity in the NAc during pain and frequency of experiencing discrimination.

Furthermore, in healthy participants, the vmPFC-NAc pathway has been found to track stimulus-independent aspects of pain, increasing in activation when pain is uncontrollable [42]. Thus, heightened vmPFC and NAc responses to increases in painful heat in AA participants

could also result from heightened expectations of harm from the painful stimulus and decreased feelings of control that may be related to previous negative experiences with medical care, previously found to be more common in African-American compared to non-Hispanic White American populations [43]. Although we did not measure participants' previous experiences with medical care directly, the hypothesis that negative feelings regarding the medical context may be related to heightened NAc-vmPFC responsivity to pain in our AA participants is supported by our finding of a negative relationship between average NAc and mPFC activity and experimenter trust in AA participants. Together, these findings support the hypothesis that increased exposure to stressful life experiences such as discrimination, and accompanying changes in brain systems related to pain valuation, modulation and chronification, may contribute to heightened pain report in African-Americans compared to non-Hispanic white Americans.

Previous studies have suggested that physiological variation in peripheral and central mechanisms of nociception and pain affect may also contribute to higher pain report amongst African-Americans compared to non-Hispanic White Americans[4,10-12,44,45]. However, our finding of equivalent expression of the NPS pattern on average and in response to increases in stimulus intensity across African, Hispanic and white Americans challenges that view, and suggests that nociceptive contributions to pain may be similar across these different ethnic groups. Furthermore, our finding of a weaker relationship between NPS pattern expression and pain rating in AA participants than in WA and HA participants suggests that there may be brain features related to pain in African Americans, particularly in fronto-striatal systems, that the NPS does not capture and that these systems may contribute more to pain ratings in African

363 Americans and account for higher pain ratings in African Americans compared to non-Hispanic
364 whites. Future studies should focus on models of activity in fronto-striatal systems that
365 contribute to pain independent of the NPS, and which may account for variability in pain
366 sensitivity across ethnic groups.

367 Our findings of neural differences related to sociocultural factors are in line with a
368 growing literature in cultural neuroscience. This literature has demonstrated differences brain
369 function underlying cultural variation in a variety of social and cognitive domains including
370 emotion processing, perception of the self and others, sensory perception, and attention (for
371 reviews see [46,47]). Our findings extend these cultural neuroscience findings by demonstrating
372 that sociocultural variability can also be seen in brain systems connected to health outcomes[48].
373 Our findings also provide important evidence against the counterfactual and damaging view
374 held by both clinicians and lay people that African Americans are *less sensitive* to pain that
375 whites[1]. In addition to providing another replication of *higher* pain sensitivity among African
376 Americans compared to whites, our findings also reveal a potential neurobiological mechanism
377 underlying these differences.

378 Findings in the present study should be interpreted in light of several limitations. First,
379 there was greater head movement in the AA participants than in the WA and HA participants.
380 However, we believe it is extremely unlikely that head movement explains the observed group
381 differences in brain activity or brain-pain correlations for the for three reasons: 1) we took
382 extensive measures to minimize the influence of head movement on our results both using
383 standard movement corrections (e.g., image realignment) as well as more stringent movement
384 controls (e.g. removal of image intensity outliers and trials suggested to have high

multicollinearity with movement regressors); 2) When we repeated all analyses additionally controlling for average head motion during each trial, results were qualitatively unchanged (Supplementary Tables 4-7); 3) The pattern of ethnic group differences in head movement was not consistent with the pattern of ethnic group differences in neural responses to pain. Specifically, we found evidence of a weaker relationship between NPS and pain ratings in both the AA and HA groups compared to the WA group when controlling for painful stimulus intensity, whereas we only found a group difference in head motion between the AA and WA groups.

Second, ethnic group differences in the effects of the experimental context including racial/ethnic concordance with the experimenter and familiarity with research participation and the MR environment may have contributed to our findings. However, although we did find ethnic differences in feelings of trust and racial/ethnic similarity towards the experimenter, neither of these measures were related to ethnic group differences in pain rating or neural responses. Future studies will be needed to better characterize the contributions that ethnic group differences in the effects of the experimental/clinical context make to ethnic differences in pain and its neural correlates.

Third, relationships between sociocultural variables hypothesized to contribute to higher pain ratings in AA participants (discrimination and experimenter trust) were not consistent across pain rating and fMRI results. Frequency of responding to discrimination mediated higher average and temperature related aspects of pain rating. In contrast, discrimination response did not exhibit a significant relationship with activity in regions more responsive to increases in painful heat in AA participants or any other regions in whole-brain

analyses. Instead, average activity within the NAc and mPFC clusters from the GLM was positively related to frequency of experiencing discrimination (more strongly so in AA participants), and negatively related to experimenter trust (only in AA participants). Although these results suggest that sociocultural factors related to negative interpersonal experiences may contribute to heightened pain responses, larger studies may be required to definitively identify the strongest sociocultural predictors of pain sensitivity and their brain correlates.

Finally, we did not find heightened pain report by HA participants compared to WA participants as has been found in some previous studies [49,50] and results from HA and WA participants were similar in most of our fMRI analyses. Hispanic American individuals vary widely in culture and background, and pain sensitivity in Hispanic Americans may vary substantially with the particular groups studied. Further exploration of sociocultural and neural factors contributing to pain report, particularly among Hispanic Americans, is needed in future studies.

Together, our findings support the hypothesis that higher levels of reported pain amongst African-Americans compared to non-Hispanic White Americans may arise in part from differences in extra-nociceptive brain systems implicated in pain modulation, valuation, and chronification, which may result from the long-term effects of negative social treatment. Ethnic minorities, particularly African-Americans, bare a disproportionate burden of pain and its negative health and financial consequences [4-6,51]. Our findings suggest that the higher levels of pain reported by African-Americans in experimental and clinical settings likely reflect differences in the internal valuation of pain and its consequences for behavior, and that

428 interventions aimed at decreasing racial discrimination and increasing clinician trust amongst
429 African-Americans may help to alleviate these pain disparities.

Online Methods

Participants

Participants were 97 individuals (47 male, age 19-54 years old; *M* = 28.98, *SD* = 5.56), 33 African-American (AA) subjects (15 male), 32 Non-Hispanic White American (WA) subjects (16 male), and 32 Hispanic White American (HA) subjects (16 males), based on self-reported ethnicity. Participants were recruited from the greater Denver area through Craigslist or one of three different subject pools from the University of Colorado Boulder Institute for Behavioral Genetics (IBG) in order to capitalize on existing genetic data on these participants in future analyses. Participants reported no current or recent (past 6 months) neurological or psychiatric diagnosis and reported no current use of psychoactive or pain medications. Participants also reported no pain-related medical conditions, no reason to believe they would be especially sensitive or insensitive to contact heat, and did not report currently experiencing an unusual amount of pain.

Nine participants were excluded from the present analyses for the following reasons: thermal stimulator error (4), claustrophobia (1), didn't fit in head coil (1), metallic thread in hair extensions (1), found pain intolerable (1), didn't meet demographic criteria (1). These exclusions resulted in a final sample of 88 participants (28 AA, 30 WA, 30 HA), age 19-54 (*M* = 28.82, *SD* = 5.67) (see Table 1 for additional demographic details on final sample). The final sample of 88 participants was utilized in all analyses except those involving the self-report measures, in which case the sample was limited to participants with data for the self-report measure in question. See Table S2 for number of participants with responses for each self-report measure. Ethnicity groups were matched on age, gender, recruitment source (craigslist

vs IBG), and fMRI sequence type (See Table 1 for statistics). The study was approved by the University of Colorado Boulder Institutional Review Board and we complied with all relevant ethnical regulations when carrying out the study. Written informed consent was obtained from all participants.

Self-report Measures

In order to test potential psychological and sociocultural contributors to ethnic group differences in pain report related to our hypothesized mechanisms, all participants completed the following questionnaires online prior to their lab visit via Qualtrics: Barratt Simplified Measure of Social Status (BSMSS) [52,53], Life Events Checklist (LEC) [54], The Williams Major and Everyday Discrimination questions (WQ) [55], Brief History of Pain Questionnaire (BHPQ; an in-house measure with questions adapted from the McGill Pain Qiuestionnaire [56] and painDETECT [57]), Trait Positive and Negative Affect Schedule (PANAS) [58] State and Trait Anxiety Inventory form X (STAI) stats subscale [59], Penn State Worry Questionnaire (PSWQ) [60], Pain Beliefs Questionnaire (PBQ) [61], Fear of Pain Questionnaire-III (FOP) [62], Kohn Reactivity Scale (KRS) [63], Pain Catastrophizing Scale (PCS-EN) [64], Perceived Similarities Measure (PSM)[65], Wake Forest Physician Trust Scale (WFPTS) [66]. Note that questionnaires that were modified (WFPTS and PCS: modified to refer to the experimenter rather than a physician) or for which not all subscales were administered (STAI) may have different psychometric properties than those previously published. Questionnaires for which significant group differences were found in the present analyses are described in detail below. In the same session, participants also completed additional questionnaires that pertained to other analyses not reported in the current paper. Additional questionnaires were intermixed with the questionnaires described below.

The *Williams Major and Everyday Discrimination questions (WQ)* [55] asked whether participants had experienced nine different types of major discrimination, e.g. being unfairly denied a bank loan (sum = major discrimination subscale score), and ten different types of daily unfair treatment, e.g., being treated with less courtesy than other people (sum = daily unfair treatment subscale score). We combined the major discrimination and daily unfair treatment subscales to create a total frequency of discrimination score, which we use in the present analyses. We did so by multiplying the major discrimination subscale score by 3 and adding it to the daily unfair treatment subscale score yielding a score ranging from 0 (no experience with discrimination) to 37 (highest experience with discrimination). Participants were also asked whether they had ever engaged in each of seven different responses to discrimination, e.g. filing a complaint. We calculated a discrimination response subscale score by summing responses to yield a total score ranging from 0 (no history of responding to discrimination) to 7 (most extensive history of responding to discrimination).

The *Wake Forest Physician Trust Scale (WFPTS)* [66] consists of 10 statements about patients' trust in their physician, e.g., "Your doctor is extremely thorough and careful" and "All in all, you have complete trust in your doctor". We adopted these statements to apply to the experimenter, the same white male in his mid-30s for all participants for the full length of the ~4 hour experimental session. Immediately after the scanning session, participants rated agreement with each statement on a scale from 1 (strongly agree) to 5 (strongly disagree). We reversed and summed responses to each measure resulting in a total score ranging 10 (least trust in experimenter) to 50 (most trust in experimenter).

When missing data was present within these self-report measures, the missing response was replaced with the mean of that participant's responses on the given subscale if 50% or more of responses were present, otherwise the missing response was replaced with an NA and treated as missing data (case-wise deletion). The average percentage of missing data (participants) per survey measure was 2.75%, (SD = 3.42%, Range = 0-8.00%).

fMRI Task

The thermal stimulation task analyzed in the present manuscript was collected as part of a larger study that included several other pain tasks. The present task was always administered second in the scanning order following a high-resolution structural scan and 7-minute resting state scan. During the thermal stimulation task, participants experienced painful thermal stimulation and provided ratings of the experience.

Thermal stimulation. Thermal stimulation was delivered to four evenly spaced locations (one per run) on the volar surface of the left forearm using a 16 mm x 16 mm contact Peltier thermode (Medoc, Inc). Thermal stimulation was delivered at three temperatures (47, 48, 49 ^{o}C), all above the median temperature associated with reported pain in prior studies[30] and the activation of specific nociceptors[35] (>45 ^{o}C). All heat stimuli consisted of a sustained period of time (plateau) at the target temperature flanked by 1.7 second ramp periods to get to/from the target temperature to the 32^{o}C baseline. Heat stimuli were delivered with three different temporal profiles: *Short* - 8 sec., 4.6 sec plateau; *Long* - 11 sec., 7.3 sec. plateau; and *Offset* - 11 sec., 7.3 sec. plateau with a 1 sec., 1 ^{o}C temperature spike. For analyses in the present manuscript we either collapsed across or statistically controlled for differences in temperature profiles as they were not of interest here. Each heat trial was preceded by a cue, and all parts of

the trial were separated by variable delays to allow for effective deconvolution of the BOLD signal associated with each trial element. See Fig. 1 for more details of the trial and task structure. Participants underwent a total of 36 heat trials, consisting of one trial at each temperature with each temporal profile in each of four runs. Trial order was randomized for each participant according to the following constraints: 1) trials within each temperature profile were evenly split between and randomly distributed within the first and second half (*Short* and *Long* trials) or between thirds (*Offset* trials) of each run, 2) temperatures were then randomly distributed across trials within each temperature profile. At the start of each run, a single 49 ^{o}C long duration (11 sec.) stimulus was delivered to allow for the initial habituation of the skin site to contact heat. This "washout" stimulus was not used in the analyses. During pre-scan training and prior to each run the participant was reminded that they could stop the task at any time if the pain became intolerable or for any other reason.

Pain rating. During each stimulation, participants were asked to continuously rate the intensity of the pain (not heat) they perceived on a 100-point generalized labeled magnitude scale (gLMS) [67] using an MRI compatible trackball (Current Designs Inc.). The scale anchors were 0 (No Experience) - 100 (Strongest Imaginable Experience). Intermediate labels were placed as follows: 1.4 (Barely Detectable), 6 (Weak), 17 (Moderate), 35 (Strong), 53 (Very Strong), though only labels and not numbers were visible to participants. The general anchors on the scale have been found to allow for effective comparison of sensory and affective experiences across modalities and people, and the labels spacing has been found to provide the scale with ratio properties [67]. The area under the curve (AUC) of the continuous within-trial pain intensity rating was used in the present analyses and is referred to as the *within-trial pain intensity rating*. We

have previously validated the use of continuous pain rating during the noxious stimulation period[30,33]. After a subset of stimulations (one stimulus at each temperature-duration combination), participants were also asked to rate the overall pain intensity and pain unpleasantness (order counterbalanced across trials) experienced on the previous trial using the same labeled magnitude scale as used for the continuous rating, referred to as the *post-trial pain intensity* and *post-trial pain unpleasantness* ratings. During pre-scan task training we carefully described the distinction between intensity and unpleasantness ratings using the standard language developed by Price, et al. [68], which describes the intensity ratings as rating "how strong the pain feels" and the unpleasantness ratings as "how unpleasant or disturbing the pain is". As in Price et al.[61], we also used an analogy to the volume versus pleasantness of music, and emphasized that pain intensity and unpleasantness should be rated independently.

Additional task conditions. In addition, 24, 8-second trials of aversive sounds in two conditions were interspersed with the heat stimuli. The first aversive sound condition consisted of a physically aversive recording of nails on a chalkboard from a study of the psychoacoustics of aversive sounds [69] played at three different levels of intensity (5 Db steps). The second aversive sound condition consisted of a subset of emotionally aversive sounds (attacks, screaming, and crying) from the International Affective Digital Sounds database (IADS)[70] with the highest arousal and lowest pleasure. Intensity levels for aversive sounds were determined using the arousal-pleasure difference scores. Occurrences of the sound conditions were evenly distributed between and randomly distributed within the thirds of each run. These stimuli were not used in the present analysis and thus will not be described further here.

Pre-scan task training. Prior to the scanning session, participants were familiarized with the task by practicing each condition without actual heat or sound stimulation. Instead, the experimenter asked the participant to imagine that the heat or sound was occurring as he/she practiced making continuous ratings. In the scanner, participants were given an additional opportunity to practice the task (with imagined rather than real stimulation) to reinforce their understanding of the task and rating procedure within the scanner environment. Thus, it was not until the first trial of the actual MRI task that participants first experienced the heat or sound stimuli.

fMRI Acquisition and Preprocessing

Data acquisition. Data were collected on a 3 Tesla Siemens Trio MRI scanner at the University of Colorado Boulder Center for Innovation and Creativity. A high-resolution T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) structural scan (1×1×1 mm voxels, TR: 2530 ms, TE 1: 1.64 ms, Flip angle: 7°, Tl: 1200 ms, FoV Read: 256 mm, echo spacing 12.2 ms, bandwidth: 651 hz/px, time: 6:03) was performed on each participant to allow for normalization and display of functional data. During the four runs of the thermal pain task either a multiband (8-simultanious slices) or standard (1 slice at a time) echo-planar imaging (EPI) sequence was performed. On the first 25 participants, the multiband sequence was used (3×3×3 mm voxels, TR: 460 ms, TE: 29 ms, slices: 56, multiband factor=8, flip angle: 44°, FoV read: 248 mm, echo spacing: 0.51 ms, bandwidth: 2772 Hz/Px, time: 10:15). Due to interference problems between the multiband sequence and the thermal stimulator that arose after an update to the thermal stimulator software, the remaining 63 participants were scanned with a standard sequence (3.4×3.4×3.4 mm voxels, TR: 1300 ms, TE: 25 ms, slices: 26,

flip angle: 50°, FoV read: 220 mm, echo spacing: 0.55 ms, bandwidth: 2170 Hz/Px, time: 10:15). To control for the potential effects of the difference in scanning sequence, scanning sequence is included as a covariate in brain imaging analyses.

Missing data. Several participants had partial fMRI data for the following reasons: thermode failed to deliver heat (1/4 runs (9 pain trials) for two participants, and a single trial for 8 additional participants), scanning cessation due to finding pain intolerable (1/4 runs for one participant and 3/4 runs for another), scanning cessation due to claustrophobia (2/4 runs for one participant, and 3/4 runs for another), and missing data due to scanner error (1/4 runs for one participant). These omissions resulted in a total of 11/352 (3.13%) runs being dropped from a total of 6/88 participants.

Preprocessing. The following preprocessing steps were applied to the brain imaging data prior to statistical analysis. First, the structural T1-weighted MPRAGE was co-registered to mean functional image using an iterative mutual information algorithm in SPM8 with manual adjustment of the registration starting point. The MPRAGE was subsequently normalized to the MNI-152 template using SPM8. The initial images of every functional scan (standard sequence: 7, multiband sequence: 20) were discarded to allow for stabilization of signal intensity. Image intensity outliers resulting from gradient and motion-related artifacts were identified and removed from the data set prior to statistical analyses using the following procedure. First, we calculated the mean and standard deviation of image intensity values across all voxels within each slice. We then created a matrix of these values concatenated across slices within a volume x volumes across time. Next, the Mahalanobis distance of this matrix was calculated and images with a significant chi-square value (multiple comparison correction using the more strict of FDR

or Bonferroni) were identified as outliers and included as nuisance covariates in first level statistical analysis (% motion outliers: *M* = 4.80, *SD* = 1.97, Range = 1.92-12.05). Functional images were corrected for timing differences in slice acquisition (only for standard sequence) and realigned to the first image to correct for head motion using SPM8. Functional images were warped to the MNI-152 template using warping parameters from the co-registered structural images. Finally, functional images were interpolated to 2x2x2 mm, and smoothed with 8 mm FWHM Gaussian kernel.

In order to calculate a summary statistic of head motion we calculated average geometric displacement on each trial across the six motion parameters (X, Y, Z, pitch, roll, yaw) using the following procedure: 1) calculate the mean for each of the 6 motion parameters across all images included, 2) subtract the mean from each motion parameter, square each difference, and sum results across all six to obtain one value per image, 3) take square root of the result from step 2 (this gives the distance from the mean for each image), and 4) calculate a mean across all images included. Average geometric displacement per heat pain trial across all participants was .14mm (SD = .17). We tested for ethnic group differences in geometric displacement both on average and in response to increases in temperature using a linear mixed effects model in R with the same parameters as the models used to test for group differences in pain rating described below. We found that AA participants (*M* = .21mm, *SD* = .21mm) moved significantly more on average ($\hat{\beta}$ = .09, t_{84} = 2.51, *p* = .01) and in response to increases in temperature ($\hat{\beta}$ = .04, t_{84} = 2.53, *p* = .01) than did WA (*M* = .11mm, *SD* = .15 mm) and HA (*M* =

.12mm, *SD* = .12mm) participants. No movement differences existed between HA and WA participants (average: $\hat{\beta} = .007$, $t_{84} = .34$, $p = .73$; temperature: $\hat{\beta} = .005$, $t_{84} = .59$, $p = .56$).

African-American participants both moved more and reported higher levels of pain on average, which was the phenomenon under study. Furthermore, in the single trial data used for analysis (see details below) we found that participants who reported experiencing more pain also moved more ($\hat{\beta} = .0006$, $t_{84} = 1.90$, $p = .06$), likely as a result of that pain. Therefore, we felt it was more appropriate to control for movement in our analyses and only exclude the portion of data from each participant which actually showed evidence of movement contamination rather than to completely exclude participants with higher levels of movement as the latter strategy would have resulted in excluding more African-American participants than participants in the other groups, creating a confound to the interpretation of any findings of group differences.

To minimize the influence of head movement on our results, we realigned images and removed image intensity outliers as described above and included the six motion parameters as well as their mean-centered squares, derivatives, and squared derivatives as nuisance regressors in the first level fMRI analysis described below. In order to further rule out group differences in head motion as a confounding factor in our fMRI analyses, we repeated all analyses reported on single trial fMRI data controlling for single trial average geometric displacement. Results, reported in Supplementary Tables 4-7, were largely unchanged when controlling for trial-by-trial geometric displacement.

Behavioral Data Analysis

644 **Pain rating analysis.** Tests for ethnic group differences in pain rating were carried out
645 using linear mixed effects models in R [71] with the command lmer from the package lme4.
646 Degrees of freedom for all effects in lmer models throughout the paper were estimated by
647 subtracting the number of between-person model parameters from the number of subjects as
648 in[72], which were then used to calculate corresponding p values (2-tailed) using the *t* distribution
649 (pt function in R). Each of the three pain rating variables were used as dependent measures in
650 separate models. One model used post-trial ratings of pain intensity (9 per participant) as the
651 dependent variable; another used post-trial ratings of pain unpleasantness (9 per participant);
652 and the third model used the area under the curve (AUC) of continuous within-trial pain
653 intensity rating (36 per participant). The following factors were included in each model: 1)
654 participant as a random effect, 2) participant ethnicity as two fixed effect orthogonal contrasts
655 based on hypothesized group differences in pain report: African Americans (coded as .68)
656 compared to Hispanic and non-Hispanic whites (each coded as -.32) and Hispanics (coded as 1)
657 compared to non-Hispanic whites (coded as -1), as these contrasts represent hypothesized
658 group differences in pain report based on prior studies[4-6], 3) the linear effect of temperature as
659 a fixed effect (47 ^{o}C (L) , 48 ^{o}C (M), and 49 ^{o}C (H) coded as -1, 0, 1) with a random slope to
660 account for between subject differences in temperature response, 4) interactions of
661 temperature with each ethnicity contrast to test for group differences in the temperature effect
662 on pain rating, and 5) participant gender as a fixed effect to control for previously documented
663 effects of gender on pain rating [73].

664 **Psychological mediator analyses.** We tested for potential psychological and
665 sociocultural mediators of ethnic group differences in pain report using a two-stage process.

The first stage was an exploratory analysis in which we tested for ethnic group differences in each of the 19 psychological and sociocultural self-report measures that paralleled ethnic group differences in pain rating, "candidate mediators". For these analyses we used linear models in R (command lm) with each participant's score on a given self-report measure as the dependent variable and the two orthogonal ethnicity contrasts used in the pain rating analyses as the predictors. We corrected for the 19 statistical tests by adjusting *p* values using Bonferroni correction.

In the second stage we tested whether any of the candidate mediators identified in the first stage mediated the observed ethnic differences in pain report using a mediation analysis based on a 3-variable path statistical model [74] using the Mediation Toolbox (https://github.com/canlab) [75-77]. In these analyses, participant ethnicity was the predictor (X) variable coded as .68 for AA participants and -.32 for WA and HA participants as this was the observed difference in pain rating we were trying to explain. Average participant pain rating was the outcome (Y) variable (3 temperature average or H-L temperature average), and the participant scores on the candidate psychological mediators meeting the above criteria served as the mediator (M) variable (one analysis per candidate mediator). We also controlled for participant gender, and the HA (1) vs WA (-1) contrast as second level covariates. We used bootstrapping for significance testing. We estimated distributions of subject-level path coefficients by randomly sampling with replacement 10,000 observations (rows) from the matrix of [*a b c' c (a x b)*] path coefficients. Two-tailed *p*-values were calculated from the bootstrap confidence interval.

fMRI Data Analysis

688 **First level analysis and robust regression.** We tested for group differences in average
689 brain activity during pain (averaged across temperature levels) and brain responses to increases
690 in painful heat (the temperature effect) using a standard general linear model (GLM) analysis.

691 First level GLM analyses were conducted using SPM8 to estimate individual subjects'
692 activation at each voxel. The four runs of the thermal stimulation task were concatenated for
693 each subject. Boxcar functions representing the time courses of the different components of
694 the task were convolved with a canonical hemodynamic response function and included as
695 regressors in the first-level GLM. These task components included: 1) the period of heat or
696 sound stimulation in each condition at each intensity level, 2) the cue period preceding each
697 trial type, 3) the first heat "washout trial" during each run, 4-5) the jittered pre-stimulus and
698 post-stimulus rating periods, 6-7) the post-stimulus overall pain intensity or unpleasantness
699 rating periods, 8) trials on which the thermode mistakenly did not deliver heat, and 9) the
700 screen signaling the end of the task. The fixation cross epochs in between trials, in between trial
701 components, and at the beginning and end of the task were used as the implicit baseline. A
702 high-pass filter of 224 seconds, which is well-suited for longer duration pain [33], was applied. The
703 following regressors of non-interest (nuisance variables) were also included in the first level
704 model: 1) "dummy" regressors representing each run (run intercepts); 2) regressors modeling
705 linear drift across the duration of each run; 3) the six estimated head motion parameters (X, Y,
706 Z, pitch, roll, yaw), their mean-centered squares, their derivatives, and their square derivatives
707 for each run (24 columns total); and 4) indicator vectors for signal intensity outliers (see
708 description of outlier identification above). We entered two contrasts into the first level
709 analysis. The first contrast averaged across heat conditions and temperature levels compared

to the resting baseline, to investigate average brain activity during pain. The second contrast compared average activity across all conditions at the highest temperature to average activity across all conditions at the lowest temperature (H-L), to investigate brain responses to increases in painful heat (the temperature effect).

Second-level (group) analyses were conducted using robust regression [78]. We compared average brain activity during pain and brain responses to increases in painful heat between ethnic groups using the same ethnicity contrasts as in pain rating and psychological mediator analyses. These contrasts were African Americans (coded as .68) compared to Hispanic and non-Hispanic whites (each coded as -.32) and Hispanics (coded as 1) compared to non-Hispanic whites (coded as -1). As in other models, we also controlled for participant gender, and type of scanning sequence (multiband or standard). Results were thresholded using a false discovery rate (FDR) of $q < .05$ ($p < .000047$). For the purposes of display, we included voxels meeting two additional, more liberal, uncorrected voxel-wise thresholds: $p < .0005$ and $p < .001$ that were in contact with voxels meeting the more stringent FDR corrected threshold.

Single trial analysis. In order to estimate single trial response magnitudes for use in NPS pattern expression and brain vs pain rating analyses, we employed a single-trial analysis approach as in [79,80] by constructing a GLM design matrix that included one regressor for each trial. In this model, we included the same boxcar regressors representing each instance of the different task components as included in the standard GLM analysis above as well as the same nuisance covariates. Additionally, we included a trial-specific regressor for the duration of the heat or sound stimulation period in each trial, also convolved with the hemodynamic response function. These single trial beta images were used in NPS pattern expression and brain vs pain

rating analyses. Because of the short duration of individual trials, single trial estimates of brain activity can be strongly influenced by signal intensity artifacts caused by factors such as head motion. Therefore, we calculated trial-by-trial variance inflation factors (VIFs), indices of the increase in variance of estimated regression coefficients due to multicollinearity with other predictor variables (in this case with nuisance regressors). Any trials with VIFs greater than 3.5 were excluded from the single-trial analyses.

In order to test whether significant ethnic group differences in brain responses during pain were related to group differences in pain rating, we extracted single trial parameter estimates from each cluster exhibiting significant group differences in the GLM analysis. We then and tested for group differences in in the relationship between activity in a given cluster and pain rating, with and without controlling for the effects of temperature. We used linear mixed effects models with heat condition, fMRI sequence, gender, within-trial pain intensity rating, the orthogonal ethnicity contrasts, and the interaction between each ethnicity contrast and pain rating as fixed factors, and subject with a random slope and intercept for pain rating as the random factor. Models controlling for temperature also included heat condition, temperature, and the interaction between temperature and each ethnicity contrast as fixed factors and a random slope of the temperature effect for each subject.

Pattern expression analysis. We tested group differences in expression of the NPS pattern on average and in response to temperature. To do so, we calculated the strength of NPS pattern expression for each heat trial. We calculated a dot-product of each vectorized beta image ($\vec{\beta}_{map}$) with the NPS pattern (voxel-wise weight map; $\overrightarrow{W}_{map}$), i.e., $\vec{\beta}^{T}_{map}\overrightarrow{w}_{map}$, yielding a

continuous scalar pattern expression value. We then tested for ethnic group differences in average NPS pattern expression and NPS temperature response using a similar linear mixed effects model to that used for pain rating except with NPS pattern expression values as the dependent variable (fixed factors: temperature, condition, gender, fMRI sequence, orthogonal ethnicity contrasts and their interaction with temperature; random factors: subject with random slope for temperature). We also tested for ethnic group differences in the relationship between the NPS and within-trial pain intensity rating both with and without controlling for temperature using the same models used to test for relationships between pain rating and activity within ROIs from the GLM analysis but with NPS pattern expression as the dependent variable.

Self-report vs brain analyses. Finally, we tested whether self-report measures we identified as candidate mediators of group differences in pain rating were related to 1) activity or the dose-activity relationship within brain regions (ROIs) exhibiting significant group differences in the GLM analysis or 2) NPS pattern expression or the dose-NPS expression relationship. In these analyses we corrected for multiple comparisons across clusters, candidate mediators, and average activation versus dose-activity effect (24 tests total). For any results that survived multiple-comparison correction, we conducted follow-up analyses within each ethnic group separately for which we did not correct for multiple comparisons.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code Availability

775 The Mediation Toolbox (https://github.com/canlab) used to conduct the multilevel mediation
776 analysis between participant race/ethnicity, self-report measures, and pain rating can be freely
777 accessed at https://github.com/canlab.
778

References

1 Trawalter, S. & Hoffman, K. M. Got pain? Racial bias in perceptions of pain. *Social and Personality Psychology Compass* **9**, 146-157 (2015).

2 Hoffman, K. M., Trawalter, S., Axt, J. R. & Oliver, M. N. 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*, 201516047 (2016).

3 (US), N. C. f. H. S. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. (National Center for Health Statistics (US), Hyattsville, MD, 2016).

4 Anderson, K. O., Green, C. R. & Payne, R. Racial and ethnic disparities in pain: causes and consequences of unequal care. *J Pain* **10**, 1187-1204, doi:10.1016/j.jpain.2009.10.002 (2009).

5 Rahim-Williams, B., Riley, J. L., Williams, A. K. & Fillingim, R. B. A quantitative review of ethnic group differences in experimental pain response: Do biology, psychology, and culture matter? *Pain Medicine* **13**, 522-540 (2012).

6 Kim, H. J. *et al.* Racial and ethnic differences in experimental pain sensitivity: systematic review and meta-analysis. *Pain* **158**, 194-211, doi:10.1097/j.pain.0000000000000731 (2017).

7 Anderson, S. R. & Losin, E. A. R. A sociocultural neuroscience approach to pain. *Culture and Brain*, doi:10.1007/s40167-016-0037-4 (2016).

8 Craig, K. D. Social communication model of pain. *Pain* **156**, 1198-1199, doi:10.1097/j.pain.0000000000000185 (2015).

9 Bates, M. S. Ethnicity and pain: a biocultural model. *Soc Sci Med* **24**, 47-50 (1987).

10 Campbell, C. M. *et al.* Ethnic differences in diffuse noxious inhibitory controls. *The Journal of Pain* **9**, 759-766 (2008).

11 Campbell, C. M. *et al.* Ethnic differences in the nociceptive flexion reflex (NFR). *Pain* **134**, 91-96, doi:10.1016/j.pain.2007.03.035 (2008).

12 Gelernter, J., Kranzler, H. & Cubells, J. Genetics of two u opioid receptor gene (OPRM1) exon I polymorphisms: population studies, and allele frequencies in alcohol-and drug-dependent subjects. *Molecular psychiatry* **4** (1999).

13 Williams, D. R. & Mohammed, S. A. Discrimination and racial disparities in health: evidence and needed research. *J Behav Med* **32**, 20-47, doi:10.1007/s10865-008-9185-0 (2009).

14 Williams, D. R. Race, socioeconomic status, and health. The added effects of racism and discrimination. *Ann N Y Acad Sci* **896**, 173-188 (1999).

15 Hatch, S. L. & Dohrenwend, B. P. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: a review of the research. *Am J Community Psychol* **40**, 313-332, doi:10.1007/s10464-007-9134-z (2007).

16 Campbell, C. M., Edwards, R. R. & Fillingim, R. B. Ethnic differences in responses to multiple experimental pain stimuli. *Pain* **113**, 20-26, doi:10.1016/j.pain.2004.08.013 (2005).

17 Cano, A., Mayo, A. & Ventimiglia, M. Coping, pain severity, interference, and disability: the potential mediating and moderating roles of race and education. *J Pain* **7**, 459-468, doi:10.1016/j.jpain.2006.01.445 (2006).

18 Burgess, D. J. *et al.* The effect of perceived racial discrimination on bodily pain among older African American men. *Pain Med* **10**, 1341-1352, doi:10.1111/j.1526-4637.2009.00742.x (2009).

19 Edwards, R. R. The association of perceived discrimination with low back pain. *J Behav Med* **31**, 379-389, doi:10.1007/s10865-008-9160-9 (2008).

20 Goodin, B. R. *et al.* Perceived racial discrimination, but not mistrust of medical researchers, predicts the heat pain tolerance of African Americans with symptomatic knee osteoarthritis. *Health Psychol* **32**, 1117-1126, doi:10.1037/a0031592 (2013).

21 Mathur, V. *et al.* (244) Discrimination in health care settings is associated with greater clinical and laboratory pain in sickle cell disease. *The Journal of Pain* **15**, S37, doi:10.1016/j.jpain.2014.01.151 (2014).

22 Apkarian, A. V., Bushnell, M. C., Treede, R. D. & Zubieta, J. K. Human brain mechanisms of pain perception and regulation in health and disease. *European journal of pain* **9**, 463-463 (2005).

23 Sokol-Hessner, P., Camerer, C. F. & Phelps, E. A. Emotion regulation reduces loss aversion and decreases amygdala responses to losses. *Soc Cogn Affect Neurosci* **8**, 341-350, doi:10.1093/scan/nss002 (2013).

24 Hutcherson, C. A., Plassmann, H., Gross, J. J. & Rangel, A. Cognitive regulation during decision making shifts behavioral control between ventromedial and dorsolateral prefrontal value systems. *J Neurosci* **32**, 13543-13554, doi:10.1523/JNEUROSCI.6387-11.2012 (2012).

25 Borsook, D., Upadhyay, J., Chudler, E. H. & Becerra, L. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. *Mol Pain* **6**, 27, doi:10.1186/1744-8069-6-27 (2010).

26 Baliki, M. N., Geha, P. Y., Fields, H. L. & Apkarian, A. V. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron* **66**, 149-160, doi:10.1016/j.neuron.2010.03.002 (2010).

27 Baliki, M. N. *et al.* Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* **15**, 1117-1119, doi:10.1038/nn.3153 (2012).

28 Dias-Ferreira, E. *et al.* Chronic stress causes frontostriatal reorganization and affects decision-making. *Science* **325**, 621-625 (2009).

29 May, A. Neuroimaging: visualising the brain in pain. *Neurol Sci* **28 Suppl 2**, S101-107, doi:10.1007/s10072-007-0760-x (2007).

30 Wager, T. D. *et al.* An fMRI-based neurologic signature of physical pain. *New England Journal of Medicine* **368**, 1388-1397 (2013).

31 Woo, C. W. *et al.* Quantifying cerebral contributions to pain beyond nociception. *Nature communications* **8**, 14211, doi:10.1038/ncomms14211 (2017).

32 Chang, L. J., Gianaros, P. J., Manuck, S. B., Krishnan, A. & Wager, T. D. A Sensitive and Specific Neural Signature for Picture-Induced Negative Affect. *PLoS Biol* **13**, e1002180, doi:10.1371/journal.pbio.1002180 (2015).

33 Krishnan, A. *et al.* Somatic and vicarious pain are represented by dissociable multivariate brain patterns. *eLife* **5**, doi:10.7554/eLife.15166 (2016).

34 Kross, E., Berman, M. G., Mischel, W., Smith, E. E. & Wager, T. D. Social rejection shares somatosensory representations with physical pain. *Proc Natl Acad Sci U S A* **108**, 6270-6275, doi:10.1073/pnas.1102693108 (2011).

35 Craig, A. D., Krout, K. & Andrew, D. Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. *Journal of Neurophysiology* **86**, 1459-1480 (2001).

36 Woo, C. W. *et al.* Separate neural representations for physical pain and social rejection. *Nature communications* **5**, 5380, doi:10.1038/ncomms6380 (2014).

37 Baliki, M. N. *et al.* Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci* **26**, 12165-12173, doi:10.1523/JNEUROSCI.3576-06.2006 (2006).

38 Woo, C.-W., Roy, M., Buhle, J. T. & Wager, T. D. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biol* **13**, e1002036 (2015).

39 Apkarian, A. V., Hashmi, J. A. & Baliki, M. N. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain* **152**, S49 (2011).

40 Lopez-Sola, M. *et al.* Towards a neurophysiological signature for fibromyalgia. *Pain*, doi:10.1097/j.pain.0000000000000707 (2016).

41 Lampe, A. *et al.* Chronic pain syndromes and their relation to childhood abuse and stressful life events. *Journal of psychosomatic research* **54**, 361-367 (2003).

42 Brascher, A. K., Becker, S., Hoeppli, M. E. & Schweinhardt, P. Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. *J Neurosci* **36**, 5013-5025, doi:10.1523/jneurosci.1954-15.2016 (2016).

43 Williams, D. R. & Rucker, T. D. Understanding and addressing racial disparities in health care. *Health care financing review* **21**, 75 (2000).

44 Woodrow, K. M., Friedman, G. D., Siegelaub, A. B. & Collen, M. F. Pain tolerance: differences according to age, sex and race. *Psychosomatic Medicine* **34**, 548-556 (1972).

45 Edwards, C. L., Fillingim, R. B. & Keefe, F. Race, ethnicity and pain. *Pain* **94**, 133-137 (2001).

46 Han, S. Understanding cultural differences in human behavior: a cultural neuroscience approach. *Current Opinion in Behavioral Sciences* **3**, 68-72, doi:10.1016/j.cobeha.2015.01.013 (2015).

47 Han, S. Cultural Neuroscience. 217-220, doi:10.1016/b978-0-12-397025-1.00182-2 (2015).

48 Losin, E. A. R. Culture, brain, and health: introduction to the special issue. *Culture and Brain* **5**, 1-3, doi:doi: 10.1007/s40167-017-0049-8 (2017).

49 Rahim-Williams, F. B. *et al.* Ethnic identity predicts experimental pain sensitivity in African Americans and Hispanics. *Pain* **129**, 177-184, doi:10.1016/j.pain.2006.12.016 (2007).

50 Portenoy, R. K., Ugarte, C., Fuller, I. & Haas, G. Population-based survey of pain in the United States: differences among white, African American, and Hispanic subjects. *J Pain* **5**, 317-328, doi:10.1016/j.jpain.2004.05.005 (2004).

51 Shavers, V. L., Bakos, A. & Sheppard, V. B. Race, ethnicity, and pain among the U.S. adult population. *J Health Care Poor Underserved* **21**, 177-220, doi:10.1353/hpu.0.0255 (2010).

52 Barratt, W. The Barratt simplified measure of social status (BSMSS): Measuring SES. *Unpublished manuscript, Indiana State University* (2006).

53 Barratt, W. The Barratt simplified measure of social status (BSMSS): Measuring SES. *Terre Haute: Department of Educational Leadership, Administration, and Foundations, Indiana State University* (2005).

54 Gray, M. J., Litz, B. T., Hsu, J. L. & Lombardo, T. W. Psychometric properties of the life events checklist. *Assessment* **11**, 330-341, doi:10.1177/1073191104269954 (2004).

55 Williams, D. R., Yan, Y., Jackson, J. S. & Anderson, N. B. Racial Differences in Physical and Mental Health: Socio-economic Status, Stress and Discrimination. *J Health Psychol* **2**, 335-351, doi:10.1177/135910539700200305 (1997).

56 Melzack, R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* **1**, 277-299 (1975).

57 Freynhagen, R., Baron, R., Gockel, U. & Tolle, T. R. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* **22**, 1911-1920, doi:10.1185/030079906X132488 (2006).

58 Watson, D., Clark, L. A. & Tellegen, A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* **54**, 1063-1070 (1988).

59 Spielberger, C. D., Gorsuch, R. L. & Lushene, R. E. Test manual for the state trait anxiety inventory. (Palo Alto, California, 1970).

60 Meyer, T. J., Miller, M. L., Metzger, R. L. & Borkovec, T. D. Development and Validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy* **28**, 487-495, doi:Doi 10.1016/0005-7967(90)90135-6 (1990).

61 Edwards, L. C., Pearce, S. A., Turner-Stokes, L. & Jones, A. The Pain Beliefs Questionnaire: an investigation of beliefs in the causes and consequences of pain. *Pain* **51**, 267-272 (1992).

62 McNeil, D. W. & Rainwater, A. J., 3rd. Development of the Fear of Pain Questionnaire--III. *J Behav Med* **21**, 389-410 (1998).

63 Kohn, P. M. Sensation-seeking, augmenting-reducing, and strength of the nervous system. *Motivation, emotion, and personality. Amsterdam: Elsevier*, 167-173 (1985).

64 Sullivan, M. J., Bishop, S. R. & Pivik, J. The pain catastrophizing scale: development and validation. *Psychological assessment* **7**, 524 (1995).

65 Street, R. L., O'Malley, K. J., Cooper, L. A. & Haidet, P. Understanding concordance in patient-physician relationships: personal and ethnic dimensions of shared identity. *Ann Fam Med* **6**, 198-205, doi:10.1370/afm.821 (2008).

66 Hall, M. A. *et al.* Measuring patients trust in their primary care providers. *Medical care research and review* **59**, 293, doi:10.1177/1077558702059003004 (2002).

67 Bartoshuk, L. M., Fast, K. & Snyder, D. J. Differences in Our Sensory Worlds: Invalid Comparisons With Labeled Scales. *Current Directions in Psychological Science* **14**, 122-125, doi:10.1111/j.0963-7214.2005.00346.x (2005).

68 Price, D. D., Mcgrath, P. A., Rafii, A. & Buckingham, B. The Validation of Visual Analog Scales as Ratio Scale Measures for Chronic and Experimental Pain. *Pain* **17**, 45-56, doi:Doi 10.1016/0304-3959(83)90126-4 (1983).

69 Reuter, C. & Oehler, M. Psychoacoustics of chalkboard squeaking. *The Journal of the Acoustical Society of America* **130**, 2545-2545, doi:doi:http://dx.doi.org/10.1121/1.3655174 (2011).

70 Bradley, M. M. & Lang, P. J. The International Affective Digitized Sounds (; IADS-2): Affective ratings of sounds and instruction manual. *University of Florida, Gainesville, FL, Tech. Rep. B-3* (2007).

71 R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, 2014).

72 Lindquist, M. A., Spicer, J., Asllani, I. & Wager, T. D. Estimating and testing variance components in a multi-level GLM. *Neuroimage* **59**, 490-501, doi:10.1016/j.neuroimage.2011.07.077 (2012).

73 Greenspan, J. D. *et al.* Studying sex and gender differences in pain and analgesia: a consensus report. *Pain* **132**, S26-S45 (2007).

74 Baron, R. M. & Kenny, D. A. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* **51**, 1173-1182 (1986).

75 Wager, T. D. *et al.* Brain mediators of cardiovascular responses to social threat: part I: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage* **47**, 821-835, doi:10.1016/j.neuroimage.2009.05.043 (2009).

76 Atlas, L. Y., Bolger, N., Lindquist, M. A. & Wager, T. D. Brain mediators of predictive cue effects on perceived pain. *J Neurosci* **30**, 12964-12977, doi:10.1523/JNEUROSCI.0057-10.2010 (2010).

77 Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A. & Ochsner, K. N. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* **59**, 1037-1050, doi:10.1016/j.neuron.2008.09.006 (2008).

78 Wager, T. D., Keller, M. C., Lacey, S. C. & Jonides, J. Increased sensitivity in neuroimaging analyses using robust regression. *Neuroimage* **26**, 99-113, doi:10.1016/j.neuroimage.2005.01.011 (2005).

79 Koyama, T., McHaffie, J. G., Laurienti, P. J. & Coghill, R. C. The single-epoch fMRI design: validation of a simplified paradigm for the collection of subjective ratings. *Neuroimage* **19**, 976-987 (2003).

80 Rissman, J., Gazzaley, A. & D'Esposito, M. Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage* **23**, 752-763, doi:10.1016/j.neuroimage.2004.06.035 (2004).

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977

978 **Author Contributions**

979 E. A. R. L. and T. D. W. designed the study. E. A. R. L., J. A., and H. E. collected the data. E. A. R.

980 L., C. W., T. D. W. and N. A. M. analyzed the data. E. A. R. L. wrote the manuscript and E. A. R. L

981 and C. W. created the figures, both with substantial input from the other authors.

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Supplementary Tables

Table S1. Ethnic group differences in post-trial pain rating

Measure	β	*df*	*t*	*p*	Sig.
Post-trial pain intensity					
Temperature	6.32	84	10.18	< .0001	***
AA - (HA + WA)	5.20	84	1.71	.09	+
HA - WA	-.68	84	-.40	.69	
[AA - (HA + WA)] * Temp	2.09	84	1.55	.13	
[HA – WA] * Temp	.69	84	.92	.36	
Post-trial pain unpleasantness					
Temperature	5.84	84	9.36	< .0001	***
AA - (HA + WA)	8.99	84	2.80	.01	*
HA - WA	-1.74	84	-.97	.34	
[AA - (HA + WA)] * Temp	2.43	84	1.79	.08	+
[HA – WA] * Temp	-.01	84	-.02	.99	

Note: Regressions of pain on temperature and ethnicity. Statistics are from linear mixed effects models in R with single heat trial (n = 36) pain rating values as the dependent variable and participant gender, heat condition, ethnicity contrasts, temperature, and the interaction of each ethnicity contrasts with temperature as fixed factors and subject with a random slope for temperature by subject as random factors. Temperature = linear temperature contrast (H (1), M (0), L (-1)); AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. + = $p < .1$, * = $p < .05$, *** = $p < .001$.

Table S2. Self-report measures of variables that may influence pain report by ethnic group

	African American		White American		Hispanic American		t-test: AA > HA + WA				Corrected	
Measure	N	M(SD)	N	M(SD)	N	M(SD)	β	*t*	*p*	Sig	*p*	Sig
Pain precursors: Stressful experiences												
SES	27	40.36 (7.01)	30	44.1 (9.26)	29	38.21 (11.23)	-0.8	-.37	.72		1	
Discrimination response	24	4.53 (1.5)	28	3.29 (1.7)	29	2.86 (1.75)	1.45	3.6	<.001	***	.01	*
Discrimination frequency	25	16.4 (5.89)	29	7.24 (6.32)	29	8.08 (7.27)	8.74	5.58	<.001	***	<.001	***
Traumatic life events	28	5.68 (5.91)	30	6.37 (4.28)	29	5.76 (3.83)	-.38	-.35	.73		1	
History of pain incidents	28	0.29 (.53)	30	0.93 (1.20)	30	0.97 (1.40)	-.66	-2.59	.01	*	.21	
History of pain severity	28	9.5 (17.81)	30	22.26 (23.95)	30	16.69 (21.23)	-9.98	-2.05	.04	*	.82	
Pain precursors: Mood												
General positive mood	28	39.84 (7.34)	30	37.01 (6.8)	30	35.99 (7.37)	3.31	2.02	<.05	*	.89	
Positive mood day of scan	28	34.75 (6.66)	30	31.03 (6.6)	30	31.37 (7.73)	3.55	2.21	.03	*	.57	
General negative mood	28	16.04 (5.85)	30	16.2 (4.29)	30	17.06 (7.21)	-0.6	-.44	.66		1	
Negative mood day of scan	28	16.18 (4.85)	30	14.93 (2.84)	30	15.53 (2.94)	0.95	1.14	.26		1	
State anxiety day of scan	28	31 (8.43)	30	33.77 (8.72)	30	33.03 (8.18)	-2.40	-1.24	.22		1	
Worry	25	37.52 (14.06)	29	41.34 (15.07)	28	46.07 (13.47)	-6.19	-1.81	.07	+	1	
Pain precursors: Beliefs and expectations												
Fear of Pain	28	68.74 (23.08)	30	69.13 (19.45)	30	70.97 (15.83)	-1.31	-.29	.77		1	
Pain beliefs physical	25	27.49 (6.03)	29	25.28 (6.89)	29	24.09 (7.86)	2.8	1.67	<.1	+	1	
Pain beliefs psychological	25	18.04 (3.4)	29	17.83 (4.04)	29	16.93 (4.22)	0.66	0.7	.48		1	
Pain responses												
Pain catastrophizing trait	26	8.35 (9.83)	30	10.73 (6.96)	29	14.17 (9.26)	-4.11	-2.00	<.05	*	.92	
Physiological reactivity	27	66.97 (11.38)	30	64.76 (11.75)	30	65.2 (12.75)	1.99	.72	.48		1	
Pain context and communication												
Trust in experimenter	28	41.55 (5.4)	28	45.43 (4.37)	30	45.44 (4.73)	-3.89	-3.49	<.001	***	.01	*
Similarity to experimenter	26	22.44 (4.96)	27	21.69 (5.12)	28	22.54 (4.25)	0.32	.28	.78		1	

Note: Ethnicity differences in sociocultural self-report measures. Statistics are from linear models in R (command lm) with each self-report measure listed as the dependent variable and the two orthogonal ethnicity contrasts used in the pain rating analyses as the predictors. Only the AA - (HA + WA) contrast is reported here. *P* values are corrected by adjusting for 19 statistical tests using Bonferroni correction. AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. + = $p < .1$, * = $p < .05$, *** = $p < .001$.

Table S3. Regions more responsive to increases in painful heat in AA participants

Region	x	y	z	Volume (mm^3)	Maxstat
L parahippocampal gyrus	-14	-10	-26	-248	5.81
R amygdala	12	-6	-18	-1144	10.17
R frontal orbital cortex	16	10	-16	-656	9.31
L subcallosal cortex	-6	24	-20	-2072	11.94
R subcallosal cortex	2	18	-20	-496	7.63
L frontal medial cortex	-4	38	-18	-2776	14.04
L frontal orbital cortex	-14	4	-18	-1456	14.60
R frontal medial cortex	6	40	-14	-1616	12.01
L putamen	-20	14	-12	-1296	9.20
L accumbens	-6	0	-8	-912	10.09
R accumbens	10	4	-8	-2136	15.98
R anterior cingulate gyrus	8	32	-6	-240	6.37
R paracingulate gyrus	6	50	-2	-1720	13.20
L paracingulate gyrus	-6	50	2	-960	7.30
R caudate	22	14	12	-872	7.83
R thalamus	18	-18	16	-256	8.93
L frontal pole	-44	42	4	-1848	11.8
L middle frontal gyrus	-34	20	42	-792	8.49
R frontal pole	36	54	18	-1672	11.28

Note: Significant positive clusters and subclusters from an interaction contrast from a second level GLM analysis comparing AA with other participants [AA - (HA + WA)] on the high vs low temperature painful heat contrast. Covariates were participant gender, fMRI sequence (multiband or standard), and the [HA > WA] contrast. Clusters are labeled using the highest probability region from the Harvard-Oxford probabilistic cortical atlas. Only the clusters/subcluster with the highest Maxstat from each region and side of the brain are included. Maxstat = log(1/p). Statistical threshold: FDR corrected $q < .05$ ($p < .000047$). AA = African American, HA = Hispanic American, WA = Non-Hispanic White American.

Table S4. NPS analyses controlling for trial-by-trial head movement (geometric displacement)

Measure	β	*df*	*t*	*p*	Sig.
Group differences in average and temperature effects on NPS					
Temp	4.19	84	8.55	< .0001	***
AA - (HA + WA)[a]	-2.4	83	-.74	.46	
HA - WA[a]	1.28	83	.71	.48	
[AA - (HA + WA)] * Temp[a]	.12	84	.11	.91	
[HA – WA] * Temp[a]	.10	84	.15	.88	
Temp AA	4.35	26	3.40	< .01	**
Temp HA	4.42	28	5.35	< .0001	***
Temp WA	3.93	28	6.94	< .0001	***
Group differences in NPS relationships with pain rating (not controlling for temperature)					
Pain Rating[b]	.17	84	5.33	< .0001	***
[AA - (HA + WA)] * Pain[b]	-.13	84	-1.99	.05	+
[HA – WA] * Pain[b]	-.05	84	-1.20	.23	
Pain AA	.08	26	1.43	.17	
Pain HA	.18	28	4.03	< .001	***
Pain WA	.26	28	4.10	< .001	***
Group differences in NPS relationships with pain rating (controlling for temperature)					
Pain Rating[c]	.07	84	1.86	.07	+
[AA - (HA + WA)] * Pain[c]	-.09	84	-1.44	.15	
[HA – WA] * Pain[c]	-.06	84	-1.63	.11	
Pain AA	-.006	26	-.11	.91	
Pain HA	.05	28	.89	.38	
Pain WA	.19	28	2.63	.01	*

Note: Results mirror those reported in main text with the addition of a covariate for trial-by-trial head movement (geometric displacement in mm, see Online Methods for formula). Statistics are from linear mixed effects models in R with single heat trial (n = 36) NPS pattern expression values as the dependent variable and participant gender, fMRI sequence, and subject as a random factor. Contrasts marked with the same letter ([a-c]) are from the same statistical model. Additional fixed covariates/factors in [a] were heat condition as a random factor and a random slope for temperature by subject. Additional fixed covariates/factors in [b] were a random slope for pain rating by subject. Additional fixed covariates/factors in [c] were temperature, each ethnicity contrast and their interaction with temperature, and random slopes for both temperature and rating by subject. Rows ending in ethnicity abbreviations, e.g., "Pain AA" are parallel models in each ethnic group separately. Temp = linear temperature contrast (H (1), M (0), L (-1)); Pain = area under the curve of single trial, within-trial continuous pain intensity rating / 100; AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. + = $p < .1$, * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

Table S5. Average GLM ROI activity vs pain rating controlling for trial-by-trial head movement (geometric displacement) but not controlling for temperature and heat condition

Measure	β	*df*	*t*	*p*	Sig.
Group differences in vmPFC relationships with pain rating (not controlling for temperature)					
Pain Rating[a]	-.003	84	-1.81	.07	+
[AA - (HA + WA)] * Pain[a]	-.0002	84	-.05	.96	
[HA – WA] * Pain[a]	.0004	84	.21	.83	
Pain AA	-.0006	26	-.25	.80	
Pain HA	-.00006	28	.02	.98	
Pain WA	-.004	28	-1.31	.20	
Group differences in mPFC relationships with pain rating (not controlling for temperature)					
Pain Rating[b]	.002	84	1.38	.17	
[AA - (HA + WA)] * Pain[b]	.0003	84	.08	.93	
[HA – WA] * Pain[b]	-.0003	84	-.17	.87	
Pain AA	.003	26	1.38	.18	
Pain HA	.004	28	1.78	.09	+
Pain WA	.002	28	.55	.59	
Group differences in mFG relationships with pain rating (not controlling for temperature)					
Pain Rating[c]	.002	84	2.15	.03	*
[AA - (HA + WA)] * Pain[c]	.004	84	1.96	.05	+
[HA – WA] * Pain[c]	.0006	84	.47	.64	
Pain AA	.005	26	2.86	< .01	**
Pain HA	.004	28	2.16	.04	*
Pain WA	.002	28	1.06	.30	
Group differences in NAc relationships with pain rating (not controlling for temperature)					
Pain Rating[d]	.004	84	3.12	< .01	**
[AA - (HA + WA)] * Pain[d]	-.002	84	-.91	.37	
[HA – WA] * Pain[d]	.0005	84	.36	.72	
Pain AA	.003	26	1.85	.08	+
Pain HA	.005	28	2.00	.05	+
Pain WA	.003	28	1.48	.15	

Note: Results mirror those reported in main text with the addition of a covariate for trial-by-trial head movement (geometric displacement in mm, see Online Methods for formula). Statistics are from linear mixed effects models in R with single heat trial (n = 36) average values from each of the 4 ROIs (separate models) identified in the whole-brain GLM analysis comparing temperature responsive activity in AA vs HA and WA participants as the dependent variable, participant gender and fMRI sequence as fixed factors, and subject with a random slope for pain rating as random factors. Contrasts marked with the same letter ([a-d]) are from the same statistical model. Rows ending in ethnicity abbreviations, e.g., "Pain AA" are parallel models in each ethnic group separately. Pain = area under the curve of single trial, within-trial continuous pain intensity rating / 100; AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. + = $p < .1$, * = $p < .05$, ** = $p < .01$.

Table S6. Average GLM ROI activity vs pain rating analyses controlling for trial-by-trial head movement (geometric displacement) and controlling for temperature and heat condition

Measure	β	*df*	*t*	*p*	Sig.
Group differences in vmPFC relationships with pain rating (controlling for temperature)					
Pain Rating[a]	-.002	84	-.91	.37	
[AA - (HA + WA)] * Pain[a]	-.002	84	-.75	.45	
[HA – WA] * Pain[a]	.00003	84	.02	.99	
Pain AA	-.003	26	-.83	.41	
Pain HA	.0009	28	.32	.75	
Pain WA	-.002	28	-.54	.60	
Group differences in mPFC relationships with pain rating (controlling for temperature)					
Pain Rating[b]	.001	84	.52	.60	
[AA - (HA + WA)] * Pain[b]	-.002	84	-.49	.62	
[HA – WA] * Pain[b]	-.0005	84	-.24	.81	
Pain AA	.001	26	.53	.60	
Pain HA	.002	28	.71	.48	
Pain WA	.003	28	.80	.43	
Group differences in mFG relationships with pain rating (controlling for temperature)					
Pain Rating[c]	.0004	84	.30	.77	
[AA - (HA + WA)] * Pain[c]	.003	84	1.24	.22	
[HA – WA] * Pain[c]	.0007	84	.46	.64	
Pain AA	.003	26	1.74	.09	+
Pain HA	.001	28	.51	.61	
Pain WA	.00005	28	.02	.99	
Group differences in NAc relationships with pain rating (controlling for temperature)					
Pain Rating[d]	.002	84	1.15	.25	
[AA - (HA + WA)] * Pain[d]	-.003	84	-1.39	.17	
[HA – WA] * Pain[d]	-.00006	84	-.04	.97	
Pain AA	.001	26	.68	.50	
Pain HA	.0002	28	.06	.96	
Pain WA	.004	28	1.53	.14	

Note: Results mirror those reported in main text with the addition of a covariate for trial-by-trial head movement (geometric displacement in mm, see Online Methods for formula). Statistics are from linear mixed effects models in R with single heat trial (n = 36) average values from each of the 4 ROIs (separate models) identified in the whole-brain GLM analysis comparing temperature responsive activity in AA vs HA and WA participants as the dependent variable, participant gender, fMRI sequence, temperature and its interaction with each ethnicity contrast as fixed factors, and subject with a random slope for temperature and pain rating as random factors. Contrasts marked with the same letter ([a-d]) are from the same statistical model. Rows ending in ethnicity abbreviations, e.g., “Pain AA” are parallel models in each ethnic group separately. Pain = area under the curve of single trial, within-trial continuous

pain intensity rating / 100; AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. + = $p < .1$.

Table S7. Average activity in GLM ROIs vs candidate sociocultural mediators controlling for trial-by-trial head movement (geometric displacement)

Measure	β	*df*	*t*	*P unc.*	Sig.	*P cor.*	Sig.
Candidate mediator relationships with average NAc pattern expression							
Discrimination Frequency[a]	.02	74	3.09	< .01	**	.07	+
[AA - (HA + WA)] * Disc. Fr.[a]	.04	74	2.04	.04	*	1	
[HA – WA] * Disc. Fr.[a]	.003	74	.31	.76		1	
AA Disc. Fr.	.05	20	2.67	.01	*		
HA Disc. Fr.	.01	24	1.59	.12			
WA Disc. Fr.	.006	24	.73	.47			
Experimenter Trust[b]	.01	77	1.02	.31		1	
[AA - (HA + WA)] * Trust[b]	-.08	77	-3.50	< .001	***	.02	*
[HA – WA] * Trust[b]	.002	77	.17	.86		1	
AA Trust	-.04	23	-1.88	.07	+		
HA Trust	.03	25	2.11	.04	*		
WA Trust	.004	23	.29	.77			
Candidate mediator relationships with average mPFC pattern expression							
Experimenter Trust[c]	.004	77	.29	.78		1	
[AA - (HA + WA)] * Trust[c]	-.10	77	-3.34	< .01	**	.03	*
[HA – WA] * Trust[c]	.005	77	.25	.81		1	
Trust AA	-.07	23	-2.42	.02	*		
Trust HA	.02	25	.94	.36			
Trust WA	-.02	23	-.78	.44			

Note: Results mirror those reported in main text with the addition of a covariate for average head movement (geometric displacement in mm, see Online Methods for formula). Head movement covariate was either averaged across all three temperatures or the difference between the average for high and low temepratures to match the outcome variable. Because of the large number of models, only models with main effects or interactions with candidate mediators reaching corrected statistical significance (Bonferroni, $p < .05$) are reported in table. Statistics are from linear models in R with average values from each of the 4 ROIs (separate models) identified in the whole-brain GLM analysis as the dependent variable. Separate models were run with activity within each ROI averaged across all three temperatures and average activity from the high minus the low temperature. Participant gender, fMRI sequence, each ethnicity contrast, the candidate sociocultural mediator (discrimination frequency, discrimination response, or experimenter trust demeaned within ethnic group), and the interaction between the sociocultural mediator and each ethnicity contrast were predictors. Contrasts marked with the same letter ([a-c]) are from the same statistical model. Rows ending in ethnicity abbreviations, e.g., "Trust AA" are parallel models in each ethnic group separately. Disc Fr. = Discrimination frequency, Trust = Experimenter Trust; AA = African American, HA = Hispanic American, WA = Non-Hispanic White American. *P* values for tests across groups are corrected by adjusting for 24 statistical tests using Bonferroni correction. + = $p < .1$, * = $p < .05$, ** = $p < .01$, *** = $p < .001$.