Is placebo analgesia for heat pain a sensory effect? An exploratory study on minimizing the influence of response bias

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ABSTRACT

We explored the ongoing question of whether placebo analgesia alters afferent nociceptive processing in a novel paradigm designed to minimize the role of response bias in placebo measurement. First, healthy adult participants received a standard heat placebo induction and conditioning procedure using a topical "analgesic" cream applied to one arm. During a subsequent placebo testing procedure, participants rated stimuli on the placebo-treated arm and untreated arm, using a task that minimized subjects' ability to guess the expected response, thus reducing experimenter demand. Retrospectively participants reported moderate analgesia effectiveness (mean = 5.3/10), but for individual temperature ratings, only 2 subjects exhibited a perceptual placebo response > 5 points. Next, these subjects completed a novel, exploratory task designed to measure changes in inter-arm in discriminative accuracy that would be expected from changes in afferent nociception. Both placebo responders (but no non-responders) showed reduced discriminative ability when the hotter stimulus occurred on the placebo arm, an effect consistent with alterations in nociceptive afferent flow and unlikely to be caused by response bias.

1. Introduction

Placebo analgesia occurs when a person experiences a reduction in pain from a pharmacologically inert substance they believe to be an effective pain reliever. Placebo effects have been demonstrated in clinical trials as well as in laboratory studies of healthy volunteers (Vase, Petersen, Riley, & Price, 2009). Yet the mechanism underlying the placebo response remains controversial. One unresolved question is whether placebos actually alter sensory perception, or whether they merely bias reporting of pain (e.g. (Allan and Siegel, 2002; Clark, 1969; Wager et al., 2006)). Placebo analgesia is almost always demonstrated using subjects' numerical estimates of perceptual experience. This makes them susceptible to response bias related to demand characteristics of the experiment (Zellner et al., 2004). In other words, subjects may report their pain to be reduced because they believe it should have been.

Placebo treatments have been shown to suppress activity in pain-related brain areas (e.g. (Wager et al., 2004, 2007)), and two studies show suppression of early nociceptive responses argued to occur before the onset of evaluative and decision processes (Wager et al., 2006, 2007). However, a behavioral measure of placebo analgesia that is robust to response bias has not been available. Signal detection theory (SDT) has been applied to placebo analgesia (Clark 1969; Feather 1972) to assess the potential for changes in response bias. However, numerous concerns have been raised about its relationship with pain judgments and whether it can actually measure analgesia, as discussed in (Rollman, 1977, 1979).

To test whether placebo analgesia alters sensory discrimination, we modified standard placebo manipulation procedures to reduce effects of experimenter demand (described in detail in Methods Section). We then conducted exploratory testing of a novel sensory discrimination task in two subjects who exhibited a perceptual placebo response (reduction in pain ratings) as well as in six subjects without a placebo response. Our task was statistically powered for within-subject analysis in order to determine whether, in subjects with a strong placebo response, there is evidence of altered afferent nociception.

Our novel, exploratory assay of the sensory component of placebo analgesia was an inter-arm sensory discrimination task in which

subjects compared the intensity of painful heat applied to an arm treated with a topical placebo analgesic to heat applied to an arm treated with a control moisturizer cream. The ability to discriminate differences in heat pain intensity is better for larger differences than small differences (Bushnell et al., 1983). We therefore hypothesized that if placebo analgesia alters sensory processing, it should become *more difficult* to discriminate accurately between two heat stimuli if the *hotter* stimulus is applied to the arm treated with the placebo analgesic. In this case, the processing of the hotter stimulus should be reduced and the perceptual distance between the stimuli would be narrower (and vice versa when the hotter stimulus is applied to the control arm). Participants were asked to identify which arm had the hotter stimulus on each trial, avoiding the response bias involved in numerical ratings.

2. Materials and Methods

2.1. Participant recruitment and screening

This study was approved by the NIH CNS Institutional Review Board. Volunteer participants were included if they were English-speaking adults ages 18–50 and excluded for major medical conditions, third trimester pregnancy, chronic pain, conditions that could affect touch perception, allergies to topical treatments, or recent use of caffeine, tobacco, alcohol, narcotics, recreational drugs, pain-relieving medications, or centrally acting medications. All participants provided informed consent and were financially compensated for their time. Participants were instructed to abstain from caffeinated beverages for two hours prior to testing (Keogh and Witt, 2001) and were informed that they would receive some inaccurate information (see Supplementary Methods) during the study ("authorized deception" (Miller, Wendler, & Swartzman, 2005).

2.2. Heat stimuli

Heat stimuli were delivered using a 1-cm-diameter computer-controlled contact thermode (Medoc Pathway Model CHEPS, Medoc Ltd Advanced Medical System, Israel) and lasted approximately 1.5 sec, with a rise-time of 70 °C/sec.

2.3. Placebo analgesic and control creams

The placebo analgesic cream was packaged in an NIH Pharmacy bottle labeled NIH Compound 812C Cream 15G FOR EXTERNAL USE ONLY and was applied using gloves. The control moisturizing cream was packaged in a commercial jar labeled as a generic moisturizer. Unbeknownst to participants, both creams were the same inert moisturizing cream.

2.4. Procedures

As described below, Day 1 testing involved five sequential procedures designed to identify robust placebo responders: 1) screening, 2) heat pain range calibration, 3) pain intensity discrimination, 4) placebo induction, 5) perceptual placebo test (see Fig. 1).

Day 1 Screening ($N = 40$) (Figs. 1-A1): Subjects were told that they would be in a study further investigating characteristics of an established topical analgesic cream. Participants completed a clinical exam and review of exclusion criteria and were screened for drug use and psychotic disorders (MINI International Neuropsychiatric Interview, (Sheehan et al., 1998)). Two participants failed to meet medical criteria.

Day 1 Heat Pain Range Calibration ($N = 38$) (Figs. 1-A2): Moisturizing cream was applied to four test regions on the volar surface of each forearm. Subjects were (truthfully) informed that this was to control for the effect of having a cream on the testing region. An ascending series of stimuli ranging from 35 °C to 50 °C was manually

delivered; trials alternated arms and skin sites. Participants rated each stimulus on an 80-point numeric/verbal descriptor scale to determine individual pain range (Fig. 1-C). After this initial ascending series, a random sequence of stimuli spanning the individual's pain range was presented to both arms in alternation to confirm pain threshold and tolerance. Ten subjects were dismissed after calibration because their ratings did not exhibit ordinal consistency with physical temperatures (using Kendall's tau (τ)), their pain range did not span at least 4 °C, or they exhibited "arm bias" (rated the pain on one arm, on average, five points higher than on the other arm).

Day 1 Pain Intensity Discrimination ($N = 28$) (Figs. 1-A3): To test baseline inter-arm temperature discrimination ability, participants were presented with predetermined pairs of heat stimuli in a random sequence within their pain range and asked to report which was more painful. The first stimulus was applied to one arm and then the thermode was quickly transferred to the second arm and the second stimulus was applied. Arm order was switched halfway through the task and stimulus order (higher or lower stimulus first) was counterbalanced within each task. Pairs rotated through the 4 test locations. Twenty-four pairs were 2 °C apart and 24 pairs were identical temperatures. Any subject exhibiting arm bias (binomial test comparing responses to the identical temperature pairs) or with a discriminative accuracy of < 70% for 2 °C pairs were to be dismissed at this stage, but no participant met these exclusion criteria.

Day 1 Placebo Induction ($N = 28$) (Figure 1.4): (see Figs. 1-A4). Participants were asked to rate how effective they expected the cream to be ("Expected Effectiveness") using a 0 ("Not at all effective") to 10 ("Completely effective") scale. Then the placebo analgesic cream was applied to the volar surface of one forearm and the control moisturizing cream to the other arm (counterbalanced across participants). The experimenter timed 5 min for the placebo analgesic to be "absorbed." See Script in Supplementary Methods. Participants then received 4 pairs of temperatures that they were told were identical in order to "make sure the cream was working." Consistent with other placebo induction procedures (Laverdure-Dupont, Rainville, Montplaisir, & Lavigne, 2009; Wager et al., 2004; Wager, Scott, & Zubieta, 2007), the temperature administered to the control arm was actually 4 °C higher than that administered to the placebo arm. For three pairs the participant reported which stimulus was more painful and for the fourth pair they rated each stimulus on the rating scale.

Day 1 Perceptual Placebo Test ($N = 28$) (Figs. 1-A5): To identify perceptual placebo responders, a random sequence of 20 single stimuli spanning the pain range was presented with successive stimuli alternating arms. Participants were told that a variety of temperature levels would be presented in random order. Sixteen of the 20 trials were the same temperature at the middle of the subject's pain range. In the remaining 4 trials, hotter stimuli were presented to the control arm and less-hot stimuli to the placebo arm; this was intended to reinforce the placebo induction. Data analysis did not include the ratings of these latter stimuli.

Participants rated the pain after each trial. A subject was declared a placebo responder if he or she rated the stimuli on the placebo arm, on average, at least 5 points less painful than the control arm. Two placebo responders were identified. At the end of the session all subjects were asked to rate how effective they found the analgesic cream to be ("Perceived Effectiveness"), using the same 0 – 10 effectiveness scale on which they previously had rated expected effectiveness.

Day 2 Sensory Placebo Test ($N = 2$ placebo responders and 6 nonresponder controls) (Fig. 1B: Both Day 1 placebo responders completed Day 2. In addition, the 6 final subjects in the study (who were not placebo responders) were tested, in order to assess whether any observed sensory effects would be restricted to placebo responders.
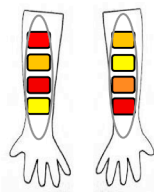
After the participant arrived on Day 2, the placebo induction was repeated. Next, the subject received pairs of heat stimuli spanning their pain range with one temperature presented to either arm and was asked to report which was more painful. There were 140 trials presented in 10
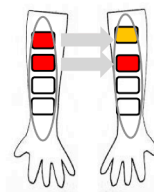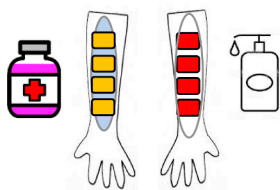
A) Day 1

1. Screening
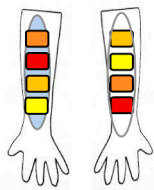
2. Heat pain range calibration
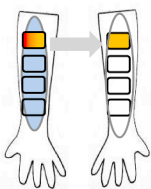
3. Pain Intensity Discrimination

4. Placebo Induction

5. Perceptual Placebo Test

C) Rating Scale

B) Day 2

Repeated Placebo Induction, then performed Sensory Placebo Test

No Sensation Warm Hot Weakly Painful Moderately Painful Strongly Painful Extremely Painful Intolerable Pain
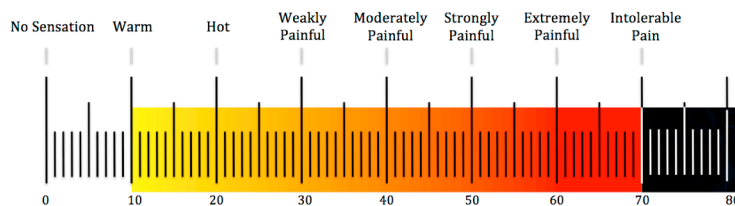
0   10   20   30   40   50   60   70   80

Fig. 1. Study Flow. A: 1) Participants underwent medical screening. 2) Participants rated single trials of heat on the pain rating scale (Fig. 1-C) to identify their pain range. 3) Participants discriminated pairs of heat pain stimuli on four sites across the arms to measure baseline 2 °C discrimination ability as well as arm bias (from equal temperature trials). 4) Placebo analgesic cream was applied to one arm and moisturizer to the other. Stimulus pairs were described as having equal temperatures, but the stimuli were in fact 4°hotter on the control arm. 5) A perceptual placebo test was administered to check whether the placebo analgesic cream reduced the perceived painfulness of single trial heat stimuli. B: $N = 2$ perceptual placebo responders and $N = 6$ non-responders completed the novel inter-arm sensory discrimination placebo test. If placebo analgesia (blue) alters sensory perception, it should be more difficult to discriminate between heat stimuli if the hotter stimulus is applied over the placebo analgesic, as the processing of the painful heat should be reduced, narrowing the perceptual distance between the stimuli. C: Participants rated the pain of heat stimuli on a 0–80 pain rating scale according to descriptors of heat and pain levels. The pain range was defined as 30–70 ("weakly painful" to "intolerable pain"). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Effectiveness Ratings

Cream Effectiveness

Perceptual Placebo

Pain Ratings Before and After Placebo Induction
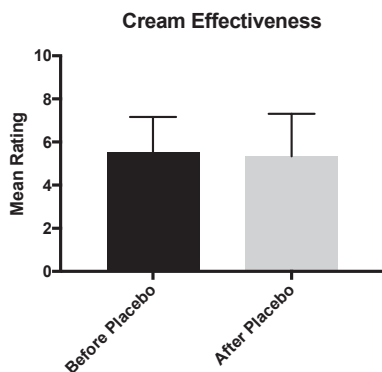
■ All Subjects Before Placebo
▨ All Subjects After Placebo
▲ PR 1 Before Placebo
△ PR 1 After Placebo
● PR 2 Before Placebo
● PR 2 After Placebo
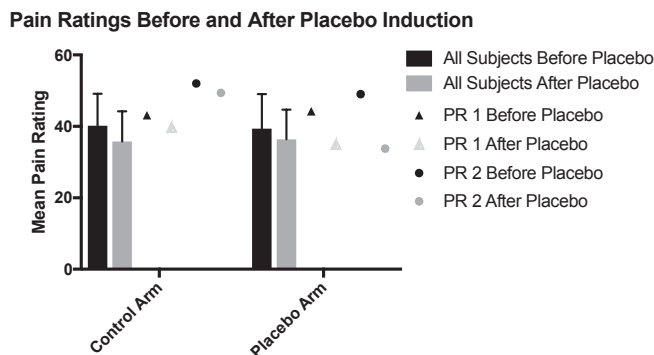
Fig. 2. Effectiveness Ratings and Perceptual Placebo Ratings. Left: "Effectiveness Ratings." Participants were asked to rate how effective they expected the cream to be (before placebo induction) and how effective they experienced the cream to be (after placebo induction) using a 0 to 10 scale (0 = "Not at all effective" and 10 = "Completely effective")("Expected Effectiveness"). Right: "Perceptual Placebo." Participants rated the painfulness of a series of stimuli on the placebo and control arms during the placebo testing task on the scale presented in Fig. 1-C.

blocks of 14 randomly sequenced trials. Each block included 10 trials in which the stimuli differed by 2° (five with the hotter stimulus applied to the placebo arm and five the reverse), two in which the stimuli were equal, and two in which they differed by 4° (one in each direction). Thus of the 140 trials, 100 had a 2 °C separation (half with the hotter stimulus on the placebo arm), which allowed us to test whether the placebo alters discrimination. Twenty trials had equal temperatures, which tested whether placebo reduces pain on the placebo arm. Ten trials presented a stimulus 4 °C hotter to the placebo arm to ensure that the placebo arm would sometimes feel more painful. Finally, 10 presented a stimulus 4 °C hotter to the control arm, which allowed us to reinforce the placebo induction throughout the session. After each of these last type of trials subjects were told that the temperatures were equal, "to confirm the cream is still working."

The 100 trials of discriminating 2 °C differences (50 in each direction) had power of .84 to detect a difference between binomial proportions of 0.75 (pilot-data-based predicted accuracy when stimuli differ by 2 °C) and 0.50 (predicted accuracy after placebo induction based on a 2 °C decrease in perceived pain intensity of stimuli delivered to the treated arm) (G* Power 3; (Faul, Erdfelder, Lang, & Buchner, 2007).

3. Results

Twenty-eight participants (ages 21–47, 15 female) met all medical and psychophysical criteria and completed the full Day 1 testing session.

3.1. Sensory discrimination accuracy (Day 1)

Average baseline sensory discrimination accuracy for trials with 2 °C separation was 92.4% ($SD = 7.4\%$; **$Mdn = 95.5\%$; range = 71–100%).**

3.2. Effectiveness ratings (Day 1)

Participants consistently expected the cream to be moderately effective ($M = 5.5$, $SD = 1.6$). Following the manipulation, participants found the cream to be moderately effective ($M = 5.3$, $SD = 2.0$). There was no difference between expected effectiveness and perceived effectiveness ($t(27) = 0.39$, $p = 0.70$, see Fig. 2) (**Mdn after = 5, Mdn before = 5, $Z = 0.55$, $p = 0.58$).**

3.3. Perceptual placebo effect (Day 1)

On average the 28 participants rated the heat on Day 1 as less painful after placebo induction ($M = 36.1$) than before ($M = 40.4$, $t(27) = 3.33$, $p < 0.01$) (**Mdn before = 42.1, Mdn after = 36.9, $Z = 2.91$, $p = 0.004$).** However, pain was not reduced more on average on the placebo arm ($M = -3.7$, $SD = 7.8$) than on the control arm ($M = -5.0$, $SD = 6.5$), indicating no group level placebo effect ($t(27) = 1.53$, $p = 0.14$, Cohen's $d = -0.16$, see Fig. 2). Two participants (henceforth "perceptual placebo responders") showed the perceptual placebo effect on Day 1, as defined by our *a priori* criterion of a 5-point rating difference between arms. These subjects showed 5.8 and 12.6 greater reduction in pain ratings on the placebo arm, respectively. This effect remained after subtracting initial arm bias. Individual Day 1 placebo effects for participants tested on Day 2 are presented in Table 1.

3.4. Sensory placebo effect (Day 2)

Unequal temperatures: The first placebo responder was significantly more accurate discriminating temperatures separated by 2 °C when the hotter stimulus was on the control arm than when it was on the placebo arm. The second placebo responder showed a similar but weaker effect (**see** Table 2). One non-responder showed a difference in discrimination

Table 1
Day 1 Pain Ratings Before and After Placebo Induction for Day 2 Participants Participants rated the painfulness of a series of stimuli on the placebo and control arms during the Day 1 placebo testing task on the scale presented in Fig. 1-C. Pain ratings before placebo induction were subtracted from pain ratings after placebo induction and the Placebo Effect was calculated as the difference between the two arms. Average placebo effect for the full study sample is presented in Fig. 2. A higher indicates a greater placebo effect (greater reduction in pain ratings on the placebo arm).

Participant	Day 1: Mean Change in Pain Rating for Placebo Arm	Day 1: Mean Change in Pain Rating for Control Arm	Placebo Effect (Change on Placebo Arm – Change on Control Arm)
PL-responder 1	9.3	3.5	5.8
PL-responder 2	15.3	2.6	12.6
No-PL 1	0.3	8.0	-7.8
No-PL 2	3.1	1.4	1.7
No-PL 3	5.4	5.0	0.4
No-PL 4			
	6.5	9.0	-2.5
No-PL 5	12.9	15.7	-2.8
No-PL 6	-3.3	-0.2	-3.1

in the opposite direction but this pattern was also present at baseline, before the placebo induction (another showed a trend in this same direction).

Equal temperatures: On trials with equal temperatures, 1 placebo responder and 1 non-responder showed a significant shift in arm bias from Day 1 (before induction) to Day 2 (after induction), such that after placebo induction they significantly more frequently identified the stimulus on the control arm as more painful (**see** Table 3). One non-responder showed a significant shift in the other direction.

4. Discussion

Using a standard heat placebo analgesia induction procedure that we modified to reduce response bias, we minimized overall placebo response but identified two individuals with a robust perceptual placebo analgesic response. In our exploratory novel inter-arm heat discrimination task, these subjects showed changes in heat discrimination accuracy, suggesting an alteration in sensory processing of afferent pain signals. Non-responders did not show this effect.

Although we observed a moderate placebo analgesic effect when subjects rated the perceived effectiveness of the cream, we did not observe a placebo effect at the group level for single numerical ratings of painful heat. We believe this is due to our efforts to minimize response bias in our measurement of perceptual placebo analgesia, making our paradigm quite different from most studies of placebo analgesia. First, our sensory placebo test used a short inter-stimulus interval between the two stimuli in each pair to avoid temporal bias in ratings (Geertsma, 1958; Rainville, Doucet, Fortin, & Duncan, 2004). Second, participants compared stimuli on a placebo site to a control site on every trial, while most studies test the placebo and control arm in different blocks – or in a separate control session or control group (see Table 4, Supplementary Methods) – making direct sensory comparison difficult. Third, we used short-duration pain stimuli; long-duration pain stimuli yield larger placebo responses (Vase et al., 2009), possibly due to degradation of sensory memory. Fourth, we used multiple heat intensities in our study; most studies test only one temperature, making it easier for subjects to develop expectations about the stimuli and perhaps report what they think the experimenter wants. Finally, we weakened subjects' expectations by ensuring that some stimuli presented to the placebo arm clearly exceeded some presented to the control arm. Thus, the fact that we did not see significant placebo effects across all participants when we added these additional safeguards raises the possibility that response bias may underlie a portion of the placebo

Table 2

Sensory Discrimination on 2 °C- Separated Trials Before and After Placebo Induction. During the sensory discrimination test 24 trials (before placebo) and 100 trials (after placebo) presented pairs of temperatures separated by 2 °C. We hypothesized that if placebo analgesia alters sensory processing, it should be *easier* to discriminate between two heat stimuli if the *lower* stimulus is applied over the placebo analgesic, but *more difficult* to discriminate if the *hotter* stimulus is applied over the placebo analgesic. The number of trials on which a given arm was perceived as more painful is reported below. Accuracy when the hotter stimulus was placed on the placebo arm versus control arm was compared for each participant with a chi-square test. * indicates a significant change from before to after placebo, $p < 0.05$.

	Before Placebo		After Placebo			
Participant	Correct when hotter stimulus on Placebo Arm	Correct when cooler stimulus on Placebo Arm	Correct when hotter stimulus on Placebo Arm	Correct when cooler stimulus on Placebo Arm	χ2(1)	p-value
PL-responder 1	11/12 91.7%	12/12 100%	34/50 68.0%	49/50 98.0%	15.9	0.00007 **
PL-responder 2	9/12 75.0%	10/12 83.3%	41/50 82.0%	47/50 94.0%	3.4	0.06 * (trend)
No-PL 1	10/12 83.3%	7/12 58.3%	48/50 96.0%	38/50 76.0%	8.3	0.004 * (but same bias on Day 1, before placebo induction)
No-PL 2	11/12 91.7%	12/12 100%	47/49 95.9%	46/49 93.9%	0.2	0.65
No-PL 3	12/12 100%	11/12 91.7%	48/50 96.0%	43/50 86.0%	3.1	0.08
No-PL 4	12/12 100%	10/12 83.3%	46/48 95.8%	46/49 93.9%	0.2	0.66
No-PL 5	12/12 100%	10/12 83.3%	34/36 94.4%	33/34 97.1%	0.3	0.59
No-PL 6	12/12 100%	12/12 100%	46/50 92.0%	44/50 88.0%	0.4	0.50

Table 3

Sensory Discrimination on Equal Trials Before and After Placebo Induction. During the sensory discrimination test 24 trials (before placebo) and 20 trials (after placebo) presented equal temperatures. The number of trials on which a given arm was perceived as more painful is reported below. These tallies were compared before and after placebo induction for each participant to determine whether placebo induction decreased the number of times the stimulus was perceived as more painful on the placebo arm. * indicates a significant change from before to after placebo, $p < 0.05$.

Participant	Before Placebo: Placebo arm LESS painful	After Placebo: Placebo arm LESS painful	χ2(1)	p-value
PL-responder 1	9/24 37.5%	17/20 85.0%	10.18	.0014 * (less painful)
PL-responder 2	12/24 50.0%	7/20 35.0%	1.00	.317
No-PL 1	9/24 37.5%	8/20 40.0%	0.03	.862
No-PL 2	16/23 69.6%	15/20 75.0%	0.16	.689
No-PL 3	8/24 33/3%	6/20 30.0%	0.06	.807
No-PL 4	11/23 47.8%	8/19 42.1%	0.14	.708
No-PL 5	9/22 40.9%	13/15 86.7%	7.75	.005 * (less painful)
No-PL 6	18/23 21.7%	12/20 60.0%	6.55	.01 * (more painful)

effect reported in other studies.

It is clear from our study that there are multiple types of responses that suggest placebo analgesia. For example, the majority of our subjects rated our cream as having been moderately effective, even though they did not show a placebo effect in rating the heat pain after each trial, suggesting a role of response bias in that placebo analgesia assessment. However, the two participants that exhibited a perceptual placebo effect – under stringent conditions designed to reduce response bias- also showed a sensory placebo effect on nociceptive processing, suggesting that placebo analgesia can exert a robust effect on sensory processing for some people, or some of the time.

On trials separated by 2 °C, both placebo responders, but no non-responders, showed a trend or significantly poorer ability to discriminate heat pairs when the hotter stimulus was presented on the placebo arm- but not on 2 °C trials when the hotter stimulus was presented on the control arm. This indicates not an overall shift in performance but a specific difference in processing hotter temperatures originating from the placebo arm: as the processing of pain from the placebo arm is decreased, the perceptual difference between the stimuli become narrower and more difficult to discriminate. Global changes in pain processing would affect sensory discrimination in both directions.

On equal-temperature trials, placebo induction significantly decreased the number of times than the placebo arm felt hotter for one PL-responder and one non-responder, and increased the number of times

the placebo arm felt hotter for one non-responder. This confirms that placebo induction can alter the perception of pain, as previously known. Since the temperatures on these trials are equal, however, providing no difference in sensory input. a change in performance on these trials could reflect either a change in afferent processing or in response bias.

An observation of altered heat intensity discrimination would suggest a corresponding change in pain-related activation in primary somatosensory processing areas. Several brain imaging studies of placebo analgesia using experimental heat stimuli have found reductions in pain-related activation within brain regions with nociceptive neurons, including thalamus, primary somatosensory cortex, insula, and cingulate cortex, e.g. (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2013; Atlas & Wager, 2014; Bingel et al., 2011; Eippert et al., 2009; Wager et al., 2004). Nevertheless, findings differed substantially among studies, and a recent *meta*-analysis of placebo effects on pain and brain responses to noxious stimuli (Zunhammer et al., 2018) revealed large effects on reported pain, but minute effects on the neurological pain signature pattern, a brain-based classifier that is highly specific to acute pain perception (Wager et al., 2013). This suggests that placebo analgesia is primarily mediated by regions outside primary pain processing regions, and much of the perceptual placebo responses may reflect cognitive processes related to response bias. Indeed, in addition to the insula, discrimination of pain intensity involves prefrontal brain areas outside the primary processing regions (Oshiro, Quevedo, McHaffie, Kraft, & Coghill, 2009). Our current findings are consistent with this conclusion. The large majority of subjects who said they perceived the cream to be effective did not show alterations in pain ratings or in sensory discrimination. The observation that a small minority of subjects have a true sensory change could underlie the sporadic reports of placebo-related alterations in afferent pain processing, whereas perceptual placebo analgesia without sensory change could be mediated by other brain regions. Future experiments should pair discrimination tasks such as the one presented here with phenotyping and characterization of individual differences to determine whether there are identifiable factors that predict these sensory placebo responders.

5. Declarations of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynpai.2018.09.001.

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