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Distraction and Placebo: Two Separate Routes to Pain Control

Jason T. Buhle[1], Bradford L. Stevens[1], Jonathan J. Friedman[1], and Tor D. Wager[2]

[1]Columbia University and [2]University of Colorado, Boulder

Abstract

An explosion of recent research has studied whether placebo treatments influence health-related outcomes and their biological markers, but almost no research has examined the psychological processes required for placebo effects to occur. This study tested whether placebo treatment and cognitive distraction reduce pain through shared or independent processes. We tested the joint effects of performance of an executive working memory task and placebo treatment on thermal pain perception. An interactive effect of these two manipulations would constitute evidence for shared mechanisms, whereas additive effects would imply separate mechanisms. Participants (N = 33) reported reduced pain both when they performed the working memory task and when they received the placebo treatment, but the reductions were additive, a result indicating that the executive demands of the working memory task did not interfere with placebo analgesia. Furthermore, placebo analgesia did not impair task performance. Together, these data suggest that placebo analgesia does not depend on active redirection of attention and that expectancy and distraction can be combined to maximize pain relief.

Keywords

executive function, working memory, *n*-back task, pain, placebo, distraction, attention, cognition, cognitive neuroscience, frontal lobe

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Placebo effects have long been both a nuisance to clinical researchers and a therapeutic adjuvant to medical practitioners, and they are thought to affect diverse treatment outcomes (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Placebo effects have been most commonly documented in pain research (Vase, Petersen, Riley, & Price, 2009), and placebo analgesia has been demonstrated in both laboratory and clinical contexts (Hróbjartsson & Gøtzsche, 2004). Whereas many early theories assumed that placebo effects simply reflect response bias on the part of participants (Clark, 1969), more recent neuroimaging studies have demonstrated that placebo analgesia involves modulation of pain-related responses in the brain (Petrovic, Kalso, Petersson, & Ingvar, 2002; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Wager et al., 2004; Wager, Scott, & Zubieta, 2007; for a review, see Wager & Fields, in press), and spinal cord (Eippert, Finsterbusch, Bingel, & Buchel, 2009).

Although much research has focused on whether placebo effects exist, there has been almost no research on the constituent psychological processes that are required for placebo analgesia. In particular, although most current theories emphasize the role of people's expectations in the analgesic effects of placebos (Stewart-Williams & Podd, 2004), it is unclear how expectations relate to other cognitive processes, such as attention, and what conditions are required for their creation and maintenance. One possibility is that reduced expectations of pain lead people to redirect attention away from pain, a strategy known to have analgesic effects (Buhle & Wager, 2010; Legrain et al., 2009; Valet et al., 2004). If this account is correct, expectations might function as a form of cognitive control, and executive processes that control attention might be necessary for expectations to influence pain. In support of this view, a number of neuroimaging studies have reported placebo- and expectancy-related activity in the dorsolateral prefrontal cortex (DLPFC; Atlas, Bolger, Lindquist, & Wager, 2010; Eippert, Bingel, et al., 2009; Kong et al., 2006; Pariente, White, Frackowiak, & Lewith, 2005; Wager et al., 2004; Wager et al., 2007; Zubieta et al., 2005), an area known to be involved in executive working memory (Smith & Jonides, 1999).

Corresponding Author:
Jason T. Buhle, Department of Psychology, Columbia University, 406 Schermerhorn Hall, 1190 Amsterdam Ave., Mail Code 5501, New York, NY 10027
E-mail: jtb2102@columbia.edu

Furthermore, fronto-parietal activity predicts the magnitude of placebo analgesia (Wager, Atlas, Leotti, & Rilling, 2011) and has been shown to be correlated with performance on tasks requiring executive control (Benedetti et al., 2006). However, this evidence for the role of executive working memory in placebo analgesia is indirect, as the prefrontal cortex is involved in a number of cognitive and emotion-related processes that are not specifically related to the control of executive attention and working memory.

Alternatively, expectations may influence placebo analgesia primarily though noncognitive state changes. For example, the belief that one has been given an analgesic may reduce anxiety (Evans, 1985), which is known to enhance pain (Weisenberg, Aviram, Wolf, & Raphaeli, 1984), or may engage descending antinociceptive systems that release pain-reducing neurotransmitters, such as endogenous opioids (Amanzio & Benedetti, 1999; Wager et al., 2007), without mediation by cognitive processes.

To directly test whether executive resources mediate placebo analgesia, we designed a novel experimental paradigm that combined thermal pain, a difficult working memory task, and placebo drug treatment. In previous work, we confirmed that performing a task that places demands on multiple aspects of executive attention and working memory (the *n*-back task; Kane & Engle, 2002; Kirchner, 1958; Smith & Jonides, 1999) substantially reduces pain (Buhle & Wager, 2010). In the research reported here, we tested whether this cognitive demand interferes with analgesia produced by a placebo treatment or whether the two manipulations have independent analgesic effects.

When interference between two concurrently performed tasks is observed, it may be inferred that the mental resources engaged by the tasks overlap and that the processing capacity of these resources is limited (Norman & Bobrow, 1975). We applied this logic of limited resources to the relationship between attention-driven analgesia (caused by performance of the working memory task) and expectation-driven analgesia (caused by the placebo). If the executive-attention and working memory processes engaged by the working memory task also support placebo analgesia, then we would expect concurrent placebo treatment and performance of the working memory task to inhibit placebo analgesia, such that they would have an underadditive interactive effect on ratings of pain. Alternatively, if placebo analgesia does not involve these executive processes, then the effects of the placebo and performance of the working memory task would be additive.

Method

Participants

Thirty-three right-handed volunteers (mean age = 27.2 years, range = 18–55 years; 14 male, 19 female) completed the experiment. Participants were compensated at a rate of $12 per hour and received additional performance bonuses (up to $10 for Day 1 and up to $20 for Days 2 and 3). All participants gave informed consent in a manner approved by Columbia University's institutional review board.

Procedure

Each participant was tested on 3 days. On Day 1, participants completed 3-back-task and thermal-pain calibration procedures similar to those we used in a previous study (for details, see Buhle & Wager, 2010). The 3-back calibration consisted of a single block of 16 trials (20.16 s each). Participants viewed a series of letters one at a time; on each trial, participants indicated whether the letter was the same as or different from the letter presented 3 trials before. Performance was assessed in a signal detection framework, using A, a nonparametric measure of target sensitivity (J. Zhang & Mueller, 2005). The presentation duration of the letter in a given trial was reduced if the participant demonstrated good performance on the previous 2 trials (i.e., $A \geq .95$). The final letter duration achieved in the calibration procedure was then used for the remainder of the experiment.

For the thermal-pain calibration, pain was delivered using a 16-mm TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat Yishai, Israel). The calibration procedure consisted of 24 trials; the duration of each trial was 20.16 s (including a 4-s ramp-up and a 2-s ramp-down). Ratings were made on a 100-unit visual analog scale with anchors of *no pain* and *worst imaginable pain* (Price, McGrath, Rafii, & Buckingham, 1983).

Thermal pain was administered over eight skin sites on the left volar forearm in a fixed order. On each trial after the initial three trials, the temperature applied was taken from a linear regression model predicting the temperature that would result in a pain rating of 10 (low), 50 (moderate), or 90 (high). This model was based on results from all the preceding trials. We ran trials in a fixed, counterbalanced order to maximize predictive power and avoid confounds between temperature and time; this method ensured that thermal pain was applied once at each of the three levels at each of the eight skin sites. Thus, the order of skin sites and targeted pain levels (low, medium, or high) was always the same, but the temperatures applied varied across trials and participants. The final temperature levels derived from this procedure were then used for the remainder of the experiment (for participants completing the study—low: $M = 41.5$ °C, $SD = 1.83$; moderate: $M = 44.9$ °C, $SD = 1.99$). Participants were not permitted to advance to Days 2 and 3 if the relationship between their ratings of pain and the applied temperatures was inconsistent ($R^2 < .7$; $n = 13$), if they could not perform the 3-back task ($n = 2$), or if their calibrated moderate temperature was higher than 50 °C (for safety reasons; $n = 1$).

On each of Days 2 and 3, participants completed two counterbalanced sessions: a placebo session and a control session (see Fig. 1a). At the beginning of both types of sessions, an emollient cream was applied to participants' skin. In placebo sessions, participants were told that this cream contained a

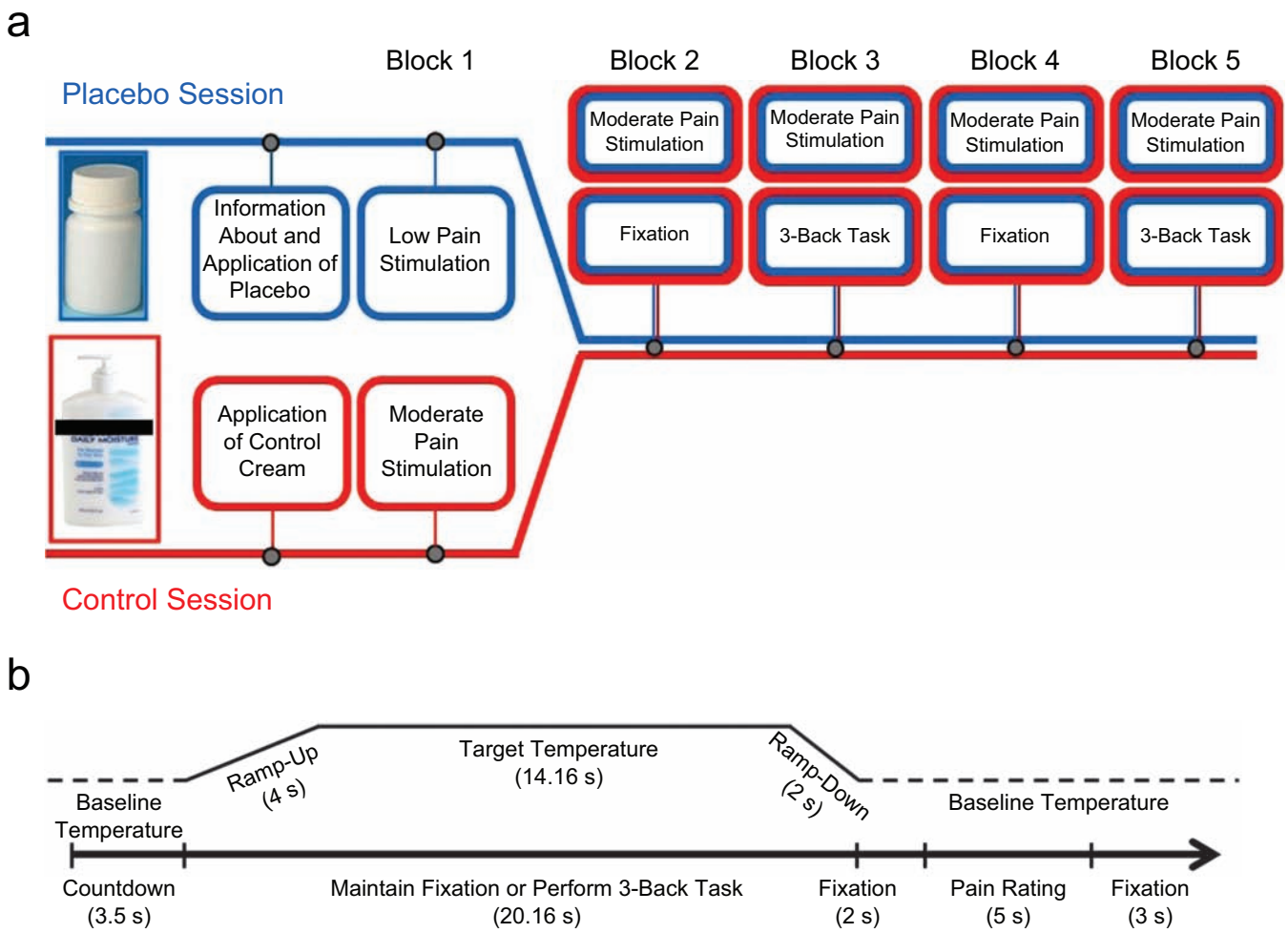

Fig. 1. Experimental design and trial structure on Days 2 and 3. On both days, thermal-pain stimuli were applied to participants in a placebo session and a control session (a); both types of sessions consisted of five blocks of 16 trials. In Block 1 of the placebo sessions, a placebo cream was administered to participants, who were told it was an analgesic cream, before low thermal pain was applied; in Block 1 of the control sessions, a cream was administered to participants, who were told it was a nonanalgesic cream, before moderate thermal pain was applied. In Blocks 2 and 4, participants fixated a cross while moderate thermal pain was administered; in Blocks 3 and 5, participants performed the 3-back task while moderate thermal pain was administered. On each trial (b), heat was applied for 20.16 s, including a 4-s ramp-up and a 2-s ramp-down; when the applied heat reached its target level, participants maintained fixation (in Blocks 2 and 4) or performed the 3-back task (in Blocks 3 and 5). After the heat stimulus returned to the baseline temperature, participants maintained fixation, rated the pain they had experienced, and then maintained fixation until the start of the next trial.

powerful analgesic; in control sessions, they were told that it was a nonanalgesic control cream. In each session, participants then rated pain that was administered in five blocks of 16 trials (20.16 s each; see Fig. 1b). In control sessions, only moderate-pain stimuli were administered. In placebo sessions, we covertly administered low-pain stimuli in the first block in order to strengthen participants' expectation of analgesia; moderate-pain stimuli identical to those applied during the control session were applied during the four remaining blocks. In both the placebo and control sessions, participants were told to fixate a centrally located cross during the pain stimulation in Blocks 2 and 4 and performed the 3-back task for the duration of pain stimulation in Blocks 3 and 5. We compared pain ratings during the 3-back task with pain ratings during fixation rather than pain ratings during a cognitive task with lower executive demand, such as a 2-back task, in order to best estimate the total effect of distraction.

At the end of Day 3, participants were asked to rate the effectiveness of the analgesic cream, using a 10-point scale (1 = *not at all effective*, 10 = *extremely effective*). Participants were then asked how much they would pay to use the cream in a hypothetical fourth session identical to the sessions on Days 2 and 3.

Analyses

In all analyses, session order was used as a between-subjects predictor. Only data from the experimental blocks (Blocks 2 through 5) of each session were used.

In our first set of analyses, we used general linear models (GLMs) to test for effects of task (3-back vs. fixation) and placebo (placebo cream vs. control cream) on pain. Model 1a was a mixed-effects GLM that included within-subjects effects of placebo and task, the Placebo × Task interaction, and mean-centered trial number and the square of mean-centered trial number (to model habituation). Participant was modeled as a random effect. To account for variability in mean pain reports and scale use across participants, we first normalized trial-by-trial ratings within participants by converting the ratings to *z* scores. We calculated Cohen's *d* to estimate the sizes of the main effects and their interaction. Because conventional statistics cannot provide evidence about the likelihood of null hypotheses (in this case, no Placebo × Task interaction), we used Gallistel's (2009) Bayesian procedure on condition averages to estimate the odds in favor of the null hypothesis.

For Models 1b, 1c, 1d, and 1e, we entered condition averages in repeated measures analyses of variance. In Model 1b, the dependent variable was normalized trial-by-trial pain rating. In Model 1c, to account for between-subjects variability in another way, we entered nonnormalized pain ratings as the outcome variable and each participant's average pain rating as a between-subjects covariate. Results might have been influenced by nonlinear habituation effects across blocks, such that pain ratings were higher in Block 2 (the first experimental fixation block in each session) than in Blocks 3 through 5 (the second experimental fixation block and both 3-back blocks); to account for this possibility, in Models 1d and 1e, we repeated the analyses of Models 1b and 1c with data from Block 2 removed.

Models 2 and 3 concerned the relations among placebo treatment, pain, and 3-back task performance. As during the calibration procedure, 3-back task performance was assessed using *A*. Model 2 tested whether performance differed as a function of placebo treatment, using a mixed-effects GLM. We again used Gallistel's (2009) Bayesian procedure to examine the strength of evidence for effects of the placebo on performance of the 3-back task. We used Model 3 to confirm that pain ratings predicted performance on a trial-by-trial basis. First, we converted pain ratings made by each participant in Blocks 3 and 5 to *z* scores. Next, pain was used as a continuous, within-subjects predictor in a mixed-effects GLM, with participant entered as a random effect; placebo, mean-centered trial number, and the square of mean-centered trial number entered as within-subjects covariates of no interest; and performance entered as the outcome variable.

Results

On average, participants rated the effectiveness of the placebo as 6.6 (*SD* = 1.9) on the 10-point scale and said they would pay $16.69 (*SD* = $9.23) to use it again.

Results from Model 1a confirmed both a main effect of task, $t(31) = 9.82$, $p < .001$, $d = 1.71$, indicating that performing the 3-back task reduced pain, and a main effect of placebo, $t(31) = 4.10$, $p < .001$, $d = 0.71$, indicating that the placebo treatment also reduced pain. There was no Task × Placebo interaction, $t(31) = -0.33$, $p = .746$, $d = -0.06$; this result indicated that the strength of the placebo analgesia was unaffected by the concomitant working memory load (see Fig. 2a). Gallistel's (2009) Bayesian procedure yielded 6.44:1 odds in favor of the null hypothesis; in this framework, such odds are considered substantial. The fact that Models 1b, 1c, 1d, and 1e yielded qualitatively identical findings confirms that these results were not dependent on the scaling of pain reports or driven by habituation.

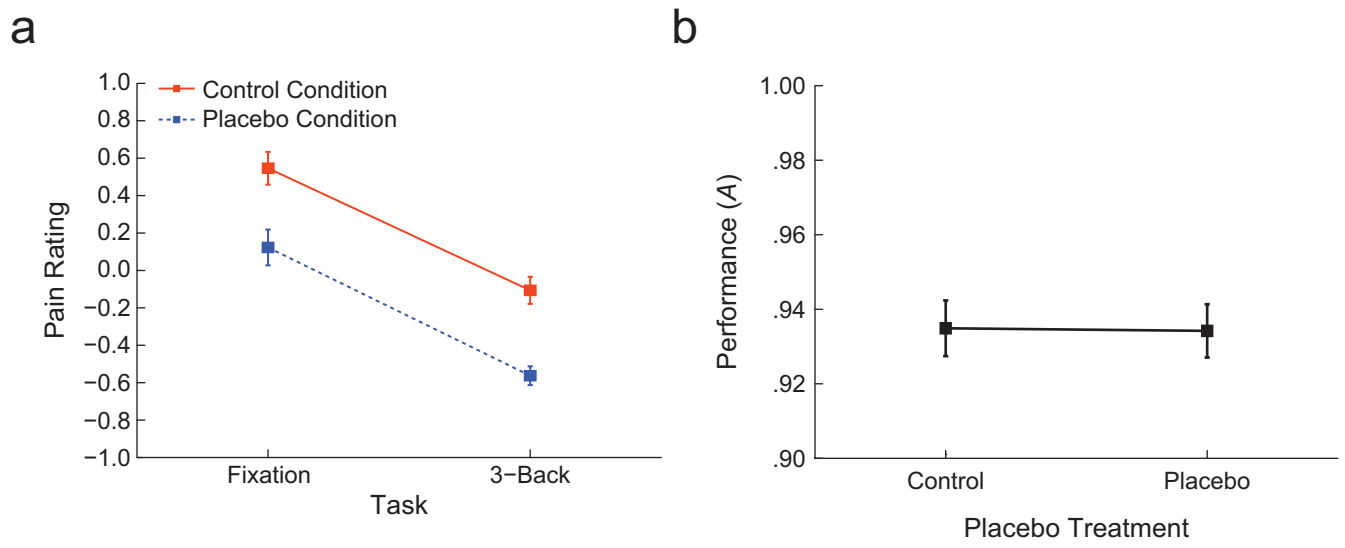

Fig. 2. Experimental results: (a) mean pain rating as a function of task (3-back task vs. fixation) and placebo treatment (placebo vs. control) and (b) mean performance (*A*) as a function of placebo treatment. Error bars represent between-subjects standard errors.

Results from Model 2 showed no effect of placebo treatment on 3-back task performance, $t(31) = -0.48$, $p = .63$, $d = -0.08$ (see Fig. 2b). Thus, although placebo analgesia was effective in relieving pain, it did not improve 3-back task performance. Gallistel's (2009) Bayesian procedure yielded substantial odds (7.97:1) in favor of the null hypothesis that the effects of performance of the working memory task and placebo treatment were additive. Results from Model 3 showed a significant effect of trial-by-trial pain reports on 3-back task performance, with higher pain reports predicting lower performance, $t(31) = -2.42$, $p < .05$, $d = -0.43$.

Discussion

Recent theories of placebo analgesia have posited that executive processes are involved in the transformation of expectations into pain relief (Benedetti, 2010; Benedetti et al., 2006; Krummenacher, Candia, Folkers, Schedlowski, & Schonbachler, 2010; Wager et al., 2004). However, these theories have largely relied on indirect, neural evidence of DLPFC involvement. To test this hypothesis directly, we used an experimental design in which we independently manipulated executive demand and placebo treatment. If placebo analgesia requires executive attention and working memory, then the performance of a task that places high demands on these limited resources should inhibit placebo analgesia.

We found that both placebo treatment and executive demand reduced pain substantially, but that their effects were nearly perfectly additive; moreover, Bayesian odds substantially favored the null hypothesis that the performance of the working memory task and placebo treatment had additive effects. Furthermore, placebo analgesia had no effect on working memory performance, even though performance was influenced by trial-by-trial fluctuations in pain. Together, these data suggest that placebo analgesia does not require executive attention or working memory. It is therefore unlikely that placebo-related expectations cause relief by altering cognitive processes related to the perception and on-line interpretation of the nociceptive stimuli (e.g., the redirection of attention from pain; Buhle & Wager, 2010).

These findings might appear to contradict those of Benedetti and his colleagues (2006), who found that placebo analgesia was reduced in patients with Alzheimer's disease. In that study, placebo analgesia was reduced most for participants whose performance on a frontal-lobe task battery and functional connectivity between prefrontal and posterior brain sites were impaired. Given the profound impairments in executive function and the frontal atrophy in Alzheimer's patients, these findings imply that executive function is involved at some point in the analgesic process. However, it is also possible that impairments in processes other than executive attention or working memory, such as long-term memory, might be responsible for people's failure to recall context information and generate appropriate expectations regarding pain.

Given the present results, one plausible explanation for the findings of Benedetti et al. (2006) is that executive function is important for understanding context and constructing meaning during placebo administration (Benedetti, 2002; Moerman, 2002), but that neither executive attention nor working memory is critical for actively maintaining placebo responses once the context has been established. Other evidence for the role of executive function in placebo analgesia is suggestive but still indirect; such evidence has come from studies demonstrating that neural regions believed to support executive function are involved during placebo analgesia (Eippert, Bingel, et al., 2009; Kong et al., 2006; Krummenacher et al., 2010; Pariente et al., 2005; Wager et al., 2004; Wager et al., 2007; Zubieta et al., 2005). Our results suggest that the involvement of the frontal cortex in placebo analgesia does not imply the engagement of executive attention and working memory.

The DLPFC is a broad, heterogeneous area containing neurons that subserve a number of different functions. The DLPFC-dependent processes that support placebo analgesia may be different from the DLPFC-dependent processes that support working memory. In a recent analysis of individual differences in placebo analgesia, for example, Wager and his colleagues (2011) found that DLPFC and superior parietal activity strongly predicted the magnitude of placebo analgesia. However, the placebo-predictive areas did not overlap with DLPFC and superior parietal areas that a meta-analysis identified as involved in working memory. Furthermore, a formal test of whether placebo analgesia could be predicted by activity in either areas involved in working memory or areas involved in emotional appraisal, including regions in the DLPFC in both cases, showed that only activity in the appraisal-related regions predicted the magnitude of placebo effects.

The same ambiguity complicates the interpretation of findings from a recent study in which repetitive transcranial magnetic stimulation (TMS) to the DLPFC eliminated placebo analgesia (Krummenacher et al., 2010). Although this study implicated the DLPFC in placebo analgesia, it did not test whether TMS influenced cognitive performance as well. In a commentary on the study, Benedetti (2010) noted that the use of a standard reference system rather than individual functional localization of the DLPFC raised the possibility that the effect was due to suppression of adjacent tissue, rather than of the DLPFC itself. Future TMS studies could reduce this ambiguity by demonstrating a selective deficit of executive function at the stimulated regions. However, although such a demonstration would resolve the ambiguity of localization, it would not resolve the question of functional specificity. Swaths of cortex as large as those influenced by TMS or measured by current neuroimaging techniques likely support a great diversity of functions (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009).

Thus, the possibility remains that the DLPFC is important for placebo analgesia in ways unrelated to cognitive control. In fact, extensive evidence suggests that DLPFC regions are

also involved in the descending opioidergic system that mediates placebo analgesia (Eippert, Bingel, et al., 2009; Wager et al., 2007; Zubieta et al., 2005) and that may be relatively independent of executive control. The lateral and medial prefrontal cortices project directly to the brainstem periaqueductal gray, a major site of opioid production that modulates descending analgesia in the spinal cord, and stimulation of the lateral prefrontal cortex in rats evokes analgesia that is reversed by blocking opioids in the periaqueductal gray (Y. Q. Zhang, Tang, Yuan, & Jia, 1997). Thus, the frontal cortex might play a role in affective appraisal and direct regulation of brainstem systems that is conceptually and functionally distinct from its role in cognitive control. The present findings bear on this hypothesis because they suggest that expectancy-based placebo analgesia, which is believed to rely on this descending opioidergic system, is independent of cognitive processes that underlie distraction-based analgesia. The dissociation implied by our results constitutes a step toward establishing the existence of multiple, independent systems for the regulation of pain.

Given that trial-by-trial pain reports predicted performance on the working memory task, both in the data reported here and in previous work (Buhle & Wager, 2010), it is noteworthy that there was no significant effect of placebo treatment on performance. This finding could possibly be due to a lack of statistical power, given the small sample size in combination with the small magnitude of the effect, or insufficient sensitivity of the performance measures to resource demands (e.g., because of floor or ceiling effects; Norman & Bobrow, 1975). However, four pieces of evidence are inconsistent with these possibilities. First, the effect was in the direction opposite the predicted direction. Second, Bayesian odds substantially favored the null hypothesis that placebo treatment does not affect performance. Third, we calibrated the 3-back task so that performance would be well below ceiling. Finally, there was a negative relation between pain and performance on a trial-by-trial basis, which implies that performance was sensitive to pain. Thus, these two potential explanations are less likely than a theoretically interesting alternative possibility: that placebo treatment and executive working memory influence different aspects of pain. This interpretation is in line with our main findings showing separable effects of placebo treatment and performance of the 3-back task; if this interpretation is correct, then placebo treatment may influence affective aspects of pain that are separable from those driven by cognitive elaboration. In addition, pain-related cognitive impairment may be a functional outcome measure that is not affected by the same treatments that influence reported pain.

In addition to helping illuminate the mechanisms that underlie placebo analgesia, the results of the present study may have important clinical implications. If placebo analgesia and distraction-related analgesia do not rely on overlapping resources, then the two types of treatment provide separate routes to pain relief, and combining them may be an efficient way for physicians to maximize analgesia without the use of drugs. To further explore this possibility, future work should test the interactive effect of placebo treatment and distraction on neural correlates of pain. Such work would be important not only because it could confirm the additive effects on pain reported here, but also because it could reveal important distinctions in the ways in which placebos (and related expectancy-based interventions) and distraction influence pain. For example, placebos and distraction may exert their influence during different stages of pain processing, on distinct anatomical systems (as discussed earlier in this section), or on distinct neurochemical systems. An intriguing possibility is that expectancy effects are mediated mainly by medial-prefrontal, striatal, and brainstem regions, with strong involvement of the opioid system and only peripheral involvement of lateral frontal and parietal cortices (Atlas et al., 2010; Wager et al., 2007; Zubieta et al., 2005), whereas the effects of cognitive distraction are mediated mainly by direct frontal-cortical somatosensory interactions, without the engagement of brainstem pain-control systems.

The present results also raise the possibility that placebo treatments may work in patients with impaired executive function. We suggested earlier in this section that the disrupted placebo response observed in Alzheimer's patients (Benedetti et al., 2006) might reflect the importance of executive function or mnemonic processes at the time of placebo induction. In some cases, it might be possible either to strengthen the induction procedures, and thereby counteract the effect of weakened executive function, or to use conditioning-based methods that may not require executive function (Atlas et al., 2010; Colloca et al., 2008; Stewart-Williams & Podd, 2004). In other cases, life experiences prior to the development of the deficit may provide the needed therapeutic expectation, obviating the need for a specific induction procedure (Colloca & Benedetti, 2006). Future research examining the placebo response in different patient groups and different treatment contexts will be critical to resolve this important clinical issue.

Finally, it is important to note that there exist several alternative explanations for our results. Executive function encompasses a complex set of cognitive processes. It remains possible that placebo analgesia does involve executive processes other than those required for the performance of the 3-back task. Although the present results cannot exclude this possibility, we used the 3-back task because it is complex and places a relatively continuous demand on an array of executive functions that load on general fluid intelligence, including the maintenance of working memory in the face of distraction, the scheduling of sequences of cognitive operations, the monitoring of working memory control, and updating, attention shifting, and task switching (Kane & Engle, 2002; Smith & Jonides, 1999). The involvement of multiple executive working memory components is thought to underlie the beneficial effects of training on the *n*-back task on general fluid intelligence (as assessed using Raven's Advanced Progressive Matrices; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008).

Another alternative explanation is that placebo analgesia involves the same executive processes as the 3-back task, but

that in the present experiment the combined requirements of placebo analgesia and 3-back task did not exceed available executive resources. However, this alternative is unlikely because task difficulty was titrated for each participant, pushing performance well below ceiling. In addition, the task had a strong impact on pain ratings, even in comparison with the effects of other distraction tasks used in previous research (see Buhle & Wager, 2010); this result suggests that demand on executive attention and working memory was high and continuous during 3-back task performance.

In sum, the present data suggest that placebo analgesia does not require executive attention or working memory during the processing of painful stimuli, and that distraction and placebo treatment provide two separate routes to pain relief. Previous data suggesting the involvement of the DLFPC likely reflect the involvement either of adjacent regions or of nonexecutive functions subserved by the DLPFC. If executive function does play a role in placebo analgesia, its involvement is probably limited to the development of appropriate expectations, rather than to the ongoing, active redirection of attention or reappraisal of painful events.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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