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Placebo analgesia: Self-report measures and preliminary evidence of cortical dopamine release associated with placebo response

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ABSTRACT

Placebo analgesia is measured by self-report, yet current, expected, and recalled efficacy may be differentially related to brain function. Here we used a human thermal pain model to compare self-reports of expected, concurrent, and recalled efficacy of a topical placebo analgesic, and tested associations of the three measures of efficacy with changes in dopamine D2/D3 receptor availability in brain using [^{18}F]fallypride with positron emission tomography (PET). Participants (15 healthy women) were assessed on three test days. The first test day included a laboratory visit, during which the temperature needed to evoke consistent pain was determined, placebo analgesia was induced via verbal and experience-based expectation, and the placebo response was measured. On two subsequent test days, PET scans were performed in *Control* and *Placebo* conditions, respectively, in counterbalanced order. During Visit 1, concurrent and recalled placebo efficacy were unrelated; during the *Placebo* PET visit, expected and recalled efficacy were highly correlated ($\rho = 0.68$, $p = 0.005$), but concurrent efficacy was unrelated to expected or recalled efficacy. Region of interest analysis revealed dopamine D2/D3 receptor availability was lower in left ventrolateral prefrontal cortex in the *Placebo* condition ($p < 0.001$, uncorrected), and greater change in this measure was associated with higher levels of recalled analgesic efficacy ($\rho = 0.58$, $p = 0.02$). These preliminary findings underscore the need to consider how self-reported symptom improvement is assessed in clinical trials of analgesics and suggest that dopaminergic activity in the ventrolateral prefrontal cortex may promote recalled efficacy of placebo.

1. Introduction

Clinical outcomes across a broad range of disorders are influenced by placebo effects. Self-reported symptom improvement is a common measure of the placebo response, particularly among patients with chronic pain disorders, which often lack biologically based measures of disease severity (Farrar et al., 2001; Von Korff et al., 1992). In chronic pain patients, subjective symptoms of pain are the leading cause for health care utilization (Andersson et al., 1999; Von Korff et al., 1991) and the basis for perceived success of treatment (Dworkin et al., 2008; Turk et al., 1993). Isolating biological mechanisms that mediate discrete forms of self-reported placebo analgesia may help minimize placebo effects in the context of clinical trials, or maximize them in the context of clinical management of chronic pain.

The subjective experience of pain is shaped by many factors, including mood and affect, expectations, prior sensory information, and the subsequent appraisal of this information (Senkowski et al., 2014). Neuroimaging studies have suggested that placebo analgesia involves

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increased functional activity in medial, lateral, and orbitofrontal aspects of prefrontal cortex (PFC), brain regions commonly implicated in regulating expectations and reappraising outcomes (see meta-analysis by Amanzio et al., 2013). This heightened engagement in brain regions that may inhibit the experience of pain through cognitive mechanisms, is often coupled with diminished activity in the insula and striatum, brain regions commonly implicating in indexing the actual experience of pain (see meta-analysis by Amanzio et al., 2013). Using positron emission tomography (PET), we have previously shown that, among patients with a pain disorder, placebo analgesia is associated with heightened functional activity in ventrolateral PFC (vlPFC) (Lieberman et al., 2004). Other PET studies have shown that endogenous opioid release in regions of the PFC and striatum also mediate placebo analgesia (Pecina et al., 2014; Wager et al., 2007; Zubieta et al., 2005, 2006). More recently, dopamine release in the striatum has been linked to placebo effects in Parkinson's disease (de la Fuente-Fernández et al., 2002, 2001; Kim et al., 2008; Lidstone et al., 2010; Strafella et al., 2006) and placebo analgesia (Scott et al., 2007, 2008). Such studies of dopamine release have not been extended to extrastriatal brain regions, leaving open the question of how extrastriatal dopaminergic function may contribute to placebo analgesia. Moreover, despite the role of dopamine in shaping expectations, concurrent experience, and memory (Schultz, 1998; Wise, 2004), whether distinct aspects of self-report are differentially related to subjective efficacy of placebo and to dopaminergic function has not been fully explored (Pecina et al., 2014). Finally, overlapping psychological processes, related to expectation, concurrent experience and memory, have important roles in shaping a wide range of placebo effects (e. g., Benedetti et al., 2003; Leuchter et al., 2014; Price et al., 1999). Thus, distinct self-reported measures of placebo analgesia may vary in magnitude, which in turn may be related to dopaminergic function.

To address these issues, we assessed self-reports of expected, concurrent, and recalled placebo analgesia using a thermal pain model. We used [^{18}F]fallypride, a high-affinity D2/D3 dopamine receptor ligand (Mukherjee et al., 1995, 2002), with PET to quantify striatal and extrastriatal receptor binding as participants underwent a sustained pain challenge with and without a topical placebo analgesic. We hypothesized that placebo effects would vary in magnitude, depending on type of self-report measurement. The dopamine system has consistently been linked with pain processing and placebo effects; therefore, we hypothesized that D2/D3 dopamine-receptor availability in the striatum and vlPFC would be lower in the placebo condition, reflecting enhanced endogenous dopamine release. As distinct brain regions that comprise the dopamine system may influence a variety of mechanisms implicated in the appraisal subjective experiences, we also hypothesized that dopamine release would be differentially related to discrete self-reported measures of placebo analgesia.

2. Materials and methods

2.1. Subjects

Fifteen young women (mean ± SD: 24.33 ± 3.11 years) completed the study. Participants were medication-free, right-handed, nonsmokers with no current or lifetime major medical illnesses. The SCID-I/NP was administered to confirm the absence of current and lifetime psychiatric disorders (DSM-IV-TR, Axis I or II). Participants underwent a urine drug screening at the beginning of each visit to confirm that they were drug-free. Visits were scheduled to occur during the follicular phase of each participant's menstrual cycle, and were re-scheduled as needed to accommodate cycle irregularity. On each testing visit, participants reported the first day of her last cycle, and provided a saliva sample to test if estradiol and progesterone levels were consistent with the follicular phase of her cycle. Participants gave written informed consent prior to enrollment, and at the conclusion of the study, were fully debriefed regarding the use of deception. The institutional review board of the University of California, Los Angeles approved all aspects of the study.

2.2. Experiment overview

Procedures were modified from a well-established paradigm in which placebo analgesia is induced via verbal and experience-based expectations of pain relief (Wager et al., 2004). Participants were told that the goal of the study was to evaluate how the brain responds to thermal stimulation when it is paired with topical application of either a pain-relief medication or a control liquid that does not contain medication. The *Placebo* was identified as Lidocaine, a powerful topically active, liquid analgesic. The *Control* was identified as water, which would not affect pain but otherwise would provide a sensory experience similar to that of the purportedly active medication. In actuality, both *Placebo* and *Control* liquids were water; no active medication was used. The experimenter wore a white coat, applied the *Placebo* and *Control* liquids with sterile, cotton-tipped applicators, from amber vials marked “LIDOCAINE” and “WATER”, respectively. The investigator wore examination gloves while applying the *Placebo* liquid but not the *Control* liquid. During a laboratory visit, the temperature required to evoke a subjective rating of moderate pain was determined, and placebo analgesia was induced via an expectancy paradigm, as described below. On two separate days, PET scans were performed using [^{18}F]fallypride to quantify D2/D3 receptor availability and how it may differ following application of the *Placebo* and *Control* liquids, respectively.

2.3. Laboratory visit

The laboratory visit (Test day 1) had two parts: part 1, to identify the temperature of thermal stimulus needed to evoke consistent pain and induce placebo analgesia via a verbal and experience-based expectancy procedure; part 2, to measure the placebo response during a painful thermal stimulation.

2.3.1. Define thermal stimulus profile (Fig. 1A)

The *Control* solution, which was truthfully identified to the participant as water, was applied to the left upper or lower volar forearm (location counterbalanced with that of *Placebo* across subjects). A thermal stimulus was then delivered continuously for 12 min to the same location using a temperature contact device (Yale University Bioengineering Department; Eisenberger et al., 2006; Jarcho et al., 2013). Stimulation started at 40 °C, and pain was rated at 15-sec intervals. Ratings were made by finger press on a button box according to a 0-to-100 (no pain to most pain imaginable) visual analog scale (VAS), which was displayed on a computer screen in front of the participant. During each interval, a red bar on the VAS began at 0 and increased by 1 point every 150 ms. The participant was instructed to make a button press when the bar reached the point on the VAS that described her current level of pain. The bar remained at that point on the VAS for the remainder of the 15-sec interval before being reset to 0. Temperature was adjusted at each interval to maintain a moderate level of pain, defined as 30–40 on the 0 to 100 VAS scale, with 35 as a target rating. Ratings 15 points above or below the target rating resulted in a 1.5 °C increase or decrease in temperature; parametrically smaller adjustments were made as ratings approached 35 VAS. To avoid tissue damage, the maximum temperature was set to 46 °C.

2.3.2. Expectancy procedure to induce placebo analgesia (Fig. 1B)

The *Placebo*, characterized as Lidocaine, was applied to a distinct location of the upper or lower volar forearm (opposite location as the control). A 3-min continuous thermal stimulus, purportedly at the average temperature required to evoke moderate pain (i.e., the average temperature for all intervals with a rating between 30 and 40 VAS), was then delivered to the same location. To simulate the sensation of analgesia, the thermal stimulus was surreptitiously decreased by 3 °C from the average temperature actually required to evoke moderate pain. This procedure was performed to reinforce the expectation of analgesia.

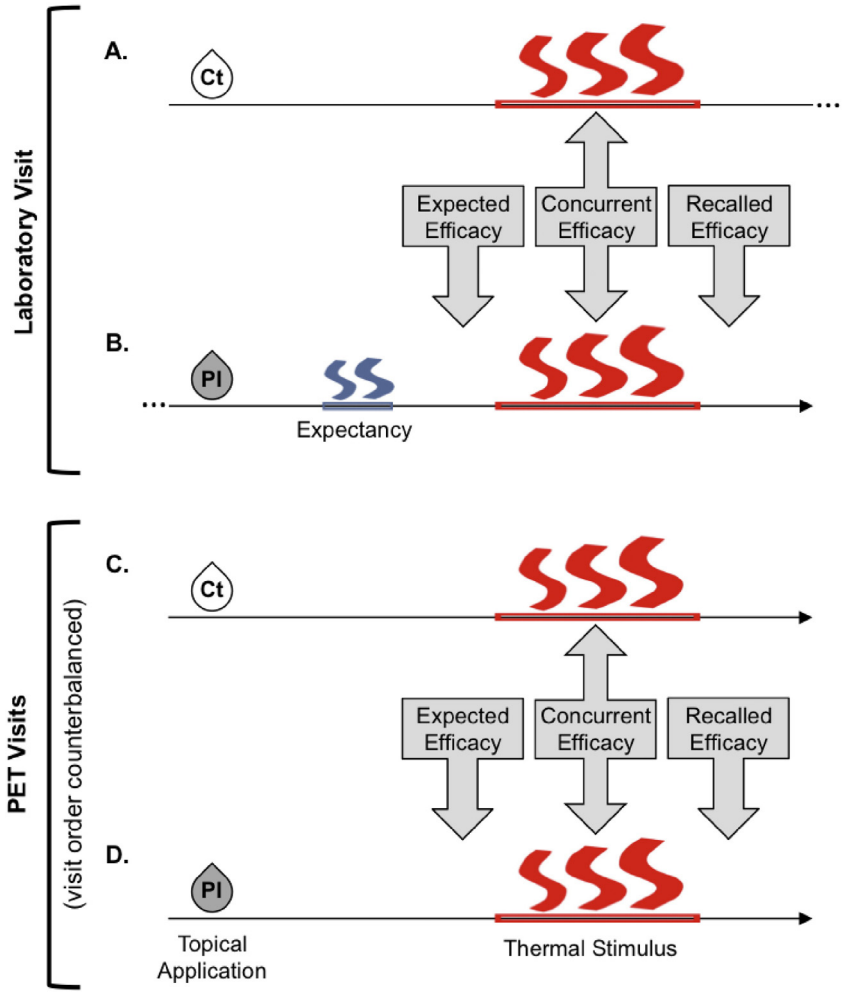

Fig. 1. Depiction of experimental methods. An initial laboratory visit included 2 phases, depicted in Panels A and B. (A) Define thermal stimulus profile. A 12-min continuous thermal stimulus was delivered to the same location of the volar forearm where the *Control* liquid had been applied. Stimulation started at 40 °C, and pain was rated at 25-sec intervals using an electronic visual analog scale. Temperature was adjusted at each interval to maintain a moderate level of pain. (B) Expectancy procedure and measurement of placebo analgesia. The *Placebo*, characterized as Lidocaine, was applied to a distinct location of the volar forearm. To produce the sensation of analgesia, a 3-min continuous thermal stimulus, purportedly the average temperature required to evoke moderate pain, was then delivered to the same location, but surreptitiously decreased by 3 °C. Prior to receiving the 12-min thermal stimulus profile paired with *Placebo*, participants rated how effective they expected the analgesic treatment would be. Thermal stimulation was delivered to the location where the experienced-based expectancy procedure had been carried out. Although participants rated their pain at 25-sec intervals, these ratings were now independent of the temperature. Thus, the temperature was held constant across *Control* and *Placebo* conditions while the ratings were allowed to vary. Once the thermal stimulus concluded, participants were asked to report their recalled efficacy of the analgesic treatment. After their laboratory visit, participants received two PET scans: for one scan the 12-min thermal stimulus profile was paired with the *Control* (Panel C), for the other it was paired with the *Placebo* (order counterbalanced; Panel D). As with the laboratory visit, participants rated expected and recalled efficacy of the *Placebo* prior to and following thermal stimulation, respectively. They used the electronic visual analog scale to rate their pain at 25-sec intervals during each thermal stimulus.

2.3.3. Measurement of placebo analgesia (Fig. 1B)

Prior to receiving the 12-min thermal-stimulus profile paired with *Placebo*, participants rated how effective they expected the analgesic treatment would be on a 0 to 100 ("not at all" to "entirely") VAS scale. Thermal stimulation was delivered to the location on the arm that was involved in the prior experience-based expectation induction. Although participants rated their pain at 15-sec intervals, the temperature of the stimulus was no longer adjusted on the basis of these ratings. Instead, the temperature at each interval was set to the temperature determined by the initial thermal-stimulus profile. Thus, the temperature during each interval was identical during the *Control* and *Placebo* conditions, while ratings were allowed to vary. Once the thermal stimulus was removed, participants were asked to rate the efficacy of the analgesic treatment on a 0-to-100 (not at all to entirely) VAS scale.

2.4. PET scanning visits

After the laboratory visit (13.13 ± 14.77 days), each participant received two PET scans on separate test days: for one scan, the 12-min thermal-stimulus profile was paired with the *Control* condition (Fig. 1C); for the other, it was paired with the *Placebo* condition (Fig. 1D). The order of scans for *Control* and *Placebo* conditions was counterbalanced. For all participants, scans were performed between 1 and 7 days apart (0.47 ± 3.42 days). One each of the two scan days, the participant was aware of the test condition (*Placebo* or *Control*) before entering the scanning room. As with the laboratory visit, participants rated expected and recalled efficacy of the *Placebo* prior to and following thermal stimulation, respectively. They used the same VAS and button box to rate their pain at 25-sec intervals during each thermal stimulus.

2.5. PET and MR imaging

D2/D3 receptor availability was quantified with the radioligand [-^{18}F]fallypride, in order to compare the effects of the stimulus complex, consisting of the label on the vial of purported medication or control solution, and the fact that the investigator was wearing gloves (*Placebo*) or not (*Control*). Images were acquired using a Siemens ECAT EXACT HR+ scanner (in-plane resolution full-width at half-maximum

(FWHM) = 4.6 mm, axial FWHM = 3.5 mm, axial field of view = 15.52 cm) in 3D mode. A 7-min transmission scan was acquired using a rotating $^{68}Ge/^{68}Ga$ rod source to obtain data for measured attenuation correction. Dynamic data were acquired in list mode following a bolus injection of [^{18}F]fallypride (~5 mCi ± 5% in 30 s; specific activity ≥ 1 Ci/μmol). After 70-min of data acquisition, participants had a 15-min break, and then returned to the scanner bed. After a second transmission scan, dynamic data were collected for another 80-min. The total dynamic scanning sequence consisted of 76-frames acquired during the first scanning block (twelve 30-sec frames followed by sixty-four 1-min frames) and 80-frames (eighty 1-min frames) acquired during the second block of scanning. The *Placebo* or *Control* liquid was applied 5-min prior to delivery of the thermal stimulus (100-min following injection). The thermal stimulus was applied after the radioligand reached an approximate steady state in the brain (105-min following injection). Data were reconstructed using ECAT v7.3 software using the OSEM algorithm (Ordered Subset Expectation Maximization; 6 iterations, 16 subsets), correcting for decay, attenuation, and scatter.

On the same day as one of the PET scans, participants underwent structural magnetic resonance imaging (MRI) with a 1.5-T Siemens SONATA scanner. A high-resolution sagittal T1-weighted 3D volumetric scan was acquired using a whole-brain MPRAGE sequence (repetition time/echo time = 25/11-ms, number of excitations = 1, slice thickness = 1.2 mm contiguous, in-plane resolution = 1×1 mm^2). This anatomical scan was used for data registration in preprocessing, to improve anatomical localization of PET data.

2.6. Quantification of placebo response

Three aspects of the placebo response were measured by self-report during the laboratory visit and the PET scans. 1) Expected efficacy was defined as effectiveness of the analgesic treatment, just before delivery of the 12-min thermal stimulus paired with *Placebo* (immediately after verbal and experience-based procedures during the Laboratory visit). Participants used a scale from 0 (not at all effective) to 100 (completely effective) to rate their expectations. 2) Concurrent efficacy was defined as the difference in average pain ratings provided at 25-sec intervals during the 12-min thermal stimulation paired with the *Placebo* relative to *Control* conditions. 3) Recalled efficacy was defined by ratings about the effectiveness of the analgesic treatment immediately following the 12-min thermal stimulus paired with *Placebo*. Participants used a 0- (not at all effective) to 100-point (completely effective) scale to rate the efficacy of the purported treatment.

Separate one-sample t-tests were used to determine whether expected efficacy and recalled efficacy differed significantly from a rating of 0 (not at all effective). Concurrent efficacy was tested using a paired sample t-test to assess the difference in average pain ratings when the thermal stimulus was paired with *Placebo* vs. *Control*. Separate paired sample t-tests were used to determine whether the magnitude of placebo response differed during the laboratory visit and PET assessments. The relationship among expected efficacy, concurrent efficacy, and recalled efficacy were assessed with Spearman's Rho (ρ) tests due to the small size of the sample.

Statistical analyses for all behavioral data relied on 2-tail tests, and were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp).

2.7. Quantification of D2/D3 receptor availability

Preprocessing for PET data was carried out with PMOD software v3.2 (PMOD Technologies Ltd, Zurich, Switzerland). Short-duration frames were binned together to generate a series of 10-min frames. Thus, the first scanning block comprised frames 1–7, and the second scanning block comprised frames 8–15. For scans in both the *Placebo* and *Control* conditions, thermal stimulation was initiated during the second scanning block, at the start of frame 10. A mean image was then generated using all 15 averaged frames. To correct for motion, each of the averaged frames was then realigned to a mean image. Motion-corrected PET data from each participant were co-registered to those from her structural MRI scan.

Whole-brain BP_{ND} maps were used to quantify D2/D3 dopamine receptor availability (i.e., binding potential, BP_{ND}) in the *Placebo* and *Control* conditions. These maps were generated for each participant using a two-step process implemented with the Pixel-wise Kinetic Modeling Tool in PMOD (PMOD Technologies Ltd). In the first step, a simplified reference-tissue model (SRTM) (Lammertsma and Hume, 1996), was used to determine k2′ estimates and generate time-activity curves (TACs) from one region of interest (ROI) with a high level of receptor availability, in this case the striatum (comprised of nucleus accumbens, caudate, and putamen), and another with negligible receptor expression, in this case the cerebellum (Mukherjee et al., 2002), to serve as a reference tissue. Bilateral striatal ROIs were delineated on each participant's anatomical MRI using FMRIB [functional MRI of the brain] Integrated Registration and Segmentation Tool [FIRST], a template-based method in FSL [FMRIB Software Library] (Oxford University, Oxford UK). Unlike the striatum, the cerebellum has negligible and homogeneous D2/D3 dopamine receptor availability (Mukherjee et al., 2002). As such, cerebellar TACs can be derived from several consecutive slices, which reflect D2/D3 dopamine receptor binding in the structure as a whole. Bilateral cerebellar ROIs were manually delineated with cylindrical volumes (diameter = 15 mm; height = 5 mm) placed in the middle of the cerebellum to avoid potential artifacts introduced at CSF/grey matter intersections. In the second step, ROIs were transferred to the co-registered PET data, where TACs were extracted and entered, along with the fixed k2′ estimate obtained in step one, into an SRTM2 (Wu and Carson, 2002) pixel-wise analysis that produced a whole-brain BP_{ND} map for each participant. This analysis assumed that BP_{ND} was constant throughout the scan, with negligible effects of the thermal stimulation, which was applied 105 min after injection. Indeed, no change in TACs was observed in response to thermal stimulation in any of the subcortical regions assessed (caudate nucleus, putamen, nucleus accumbens, amygdala, hippocampus, and thalamus; data not shown). As such, the analysis tested the effect of the stimulus complex, including knowledge that PET scans would be acquired in the *Placebo* or *Control* conditions, respectively.

Structural MRI data were normalized into the MNI (Montreal Neurological Institute) template space using SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm), and the transformation parameters were then applied to the coregistered whole-brain BP_{ND} maps. BP_{ND} maps were then smoothed with a Gaussian filter to 8-mm FWHM.

2.8. Dopamine D2/D3 receptor availability and the placebo response

A whole-brain analysis was performed with SPM8. Main effects of *Placebo* on dopamine D2/D3 receptor BP_{ND} were first assessed with a paired t-test; scan order was included as a covariate. Since few prior studies have tested the relationship between extrastriatal dopaminergic markers and the placebo response, we used a relatively liberal statistical threshold for testing these effects. We took this approach so that results from this preliminary study can be used to help generate hypotheses for future work on the relationship between placebo analgesia and dopaminergic function. Statistical significance was therefore set using a combined uncorrected height threshold of $p < 0.005$ with a 100-voxel extent threshold.

Clusters with significant differences in BP_{ND} were subjected to exploratory correlation analyses with measures of placebo response. To do this, a sphere with a 5-mm radius was drawn around the peak voxel of clusters with significant differences in BP_{ND}. Average BP_{ND} values across this sphere were extracted for each participant's MNI-space data, and imported to SPSS. Spearman's Rho (ρ) tests were used to determine whether changes in BP_{ND} were correlated with expected, concurrent, or recalled placebo efficacy. A threshold of $p = 0.017$ was needed to reach significance after Bonferroni correction for performing three tests.

Main effects of placebo on dopamine D2/D3 receptor BPND were also assessed using effect-size maps, which provide a comparison of differences in BPND that did not reach the prescribed statistical threshold. Effect-size maps (Cohen's d) with a threshold of d > 0.20 (which corresponds with a small effect size) were created by taking the square root of the mean difference in intensity of whole-brain BPND maps obtained in *Control* scans to whole-brain BPND maps obtained in *Placebo* scans, divided by the pooled standard deviation of the difference values.

3. Results

3.1. Placebo response (see Table 1)

The average temperature required to maintain moderate pain across the 12-min thermal stimulus was 44.57 °C (SD = 1.08 °C).

3.1.1. Expected efficacy

Participants expected the placebo to be highly effective during both Laboratory and PET testing visits. A paired sample t-test showed no difference in expected efficacy during Laboratory versus PET visits ($t(14) = 1.03$, $p = 0.32$), but self-reports of expected efficacy during Laboratory and PET visits were not significantly correlated ($\rho = 0.31$, $p = 0.26$).

3.1.2. Concurrent efficacy

During the Laboratory visit, average on-line pain ratings were lower when the thermal stimulus was paired with the placebo relative to the control, indicating a significant placebo analgesic effect ($t(14) = 3.33$, $p = 0.005$). There was no difference in concurrent efficacy across PET visits ($t(14) = -1.07$, $p = 0.31$). Further analyses were completed to help clarify whether the absence of concurrent placebo effects across PET visits was due to ratings obtained during the *Control* condition or *Placebo* condition. Paired sample t-tests showed while there was no difference in average pain ratings during Laboratory and PET testing visits when the thermal stimulus was paired with placebo ($t(14) = 0.14$, $p = 0.89$), pain ratings were significantly lower during the PET, relative to Laboratory, visit when the thermal stimulus was paired with control ($t(14) = 3.91$, $p = 0.002$). Concurrent efficacy during Laboratory and PET visits were positively correlated ($\rho = 0.69$, $p = 0.006$).

3.1.3. Recalled efficacy

Participants recalled the placebo as being highly effective during both Laboratory and PET visits. A paired sample t-test showed no difference in recalled efficacy during Laboratory or PET visits ($t(14) = 0.16$, $p = 0.88$); and recalled efficacy during Laboratory and PET visits were significantly positively correlated ($\rho = 0.63$, $p = 0.02$).

3.1.4. Relationship between three forms of placebo response

During the Laboratory visit, concurrent, and recalled placebo efficacy were unrelated. During the *Placebo* PET visit, expected and recalled efficacy were highly correlated ($\rho = 0.68$, $p = 0.005$), but concurrent efficacy was not related either to expected or to recalled efficacy. Notably, the more days that elapsed from the laboratory visit, the lower were the levels of expected efficacy during the *Placebo* PET visit ($\rho = -0.62$; $p = 0.01$). Exploratory analyses determined that none of the three forms of placebo response during the Laboratory visit were associated with expected efficacy during the subsequent *Placebo* PET visit.

Table 1
Placebo response across Laboratory and PET visits.

	Laboratory		PET	
	Mean	SD	Mean	SD
Predicted efficacy[a]	53.67	32.81***	43.33	32.16***
Concurrent Efficacy (*Placebo–Control*)[b]	−10.38	12.11**	2.93	10.56[ns]
Average ratings with *Placebo*	23.38	11.01	22.82	17.95
Average ratings with *Control*	33.70	3.91	19.9	13.4
Recalled efficacy[a]	47.50	29.40***	45.13	38.55**

[ns] p > 0.05 not significant.
[a] One-sample t-tests: reported efficacy of placebo compared with 0 (not effective at all).
[b] Paired sample t-tests: average ratings for stimulus paired with placebo vs. control.
** p < 0.005.
*** p < 0.001.

3.2. Dopamine release and the placebo response

In a whole-brain analysis, there was higher BPND (less DA) in left vlPFC for *Control* relative to *Placebo* scans (x, y, z coordinates: −29, 30, −14; ke = 507; $t(14) = 3.12$, $p = 0.001$ uncorrected) (Fig. 2A). This effect did not retain statistical significance after familywise correction for number of comparisons. No differences were observed for the contrast of *Placebo* > *Control*.

Exploratory analyses revealed that the greater change in left vlPFC BPND for *Control*, relative to *Placebo* scans, the greater the recalled placebo efficacy ($\rho = 0.58$, $p = 0.022$; Fig. 2B). However, results did not remain significant after Bonferroni correction for the three types of self-reported efficacy. There was no significant relationship between the change in BPND with expected or concurrent efficacy, nor was there a relationship between BPND, measures obtained during the laboratory visit, or number of days that elapsed between laboratory and PET visits.

Effect size maps (Cohen's d > 0.2) demonstrated that while differences in striatal BPND for *Control* relative to *Placebo* scans did not reach the prescribed statistical threshold, there were medium-size effects in this region. Medium to large effects also emerged in the thalamus, hippocampus, insula, and dorsal anterior cingulate (Fig. 3).

4. Discussion

In this study, three forms of placebo response were measured during laboratory and PET scanning. Expected and recalled placebo efficacy occurred at equally high levels across both visits. Concurrent efficacy was only observed during the laboratory visit. Dopamine D2/D3 receptor availability was lower in left vlPFC when the stimulus complex for a topical placebo analgesic was present during noxious thermal stimulation compared to a control stimulus complex. The degree to which receptor availability was higher in left vlPFC in the *Control* than the *Placebo* condition was associated with higher levels of recalled analgesic efficacy. While derived from a small sample, these results support research that suggests the dopamine system plays important role in mediating placebo effects (e. g., Boileau et al., 2007; Brody et al., 2009; de la Fuente-Fernández et al., 2001, 2002; Haltia et al., 2008; Kaasinen et al., 2004; Kim et al., 2008; Lidstone et al., 2010; Martikainen et al., 2005; Oswald et al., 2005; Scott et al., 2007, 2008; Strafella et al., 2006), and provide further insight into the psychological and neuropharmacological mechanisms that promote placebo analgesia.

Pain is a subjective experience. Thus, the method used to measure placebo analgesia may affect the magnitude of self-reported placebo effects. In this study, relatively high levels of placebo analgesia were obtained with measures of expected and recalled efficacy. However, expected efficacy during the *Placebo* PET scan was negatively correlated with the number of days that had elapsed from the laboratory visit. This suggests that temporal factors related to prior experience may influence some measures of placebo response. Hints of other temporal influences on placebo effects also emerged. For instance, there was a lack of continuity between all three forms of placebo response during the initial laboratory visit, yet high levels of continuity for expected and recalled efficacy during PET scanning. Thus, some form of experience-related consolidation may occur during the initial laboratory visit that influences the subsequent experience of placebo analgesia.

Concurrent efficacy, calculated as the difference between online pain ratings when the 12-min thermal stimulus was paired with placebo, relative to control, was only observed during the laboratory visit. Closer inspection of the data shows that when the thermal stimulus was paired

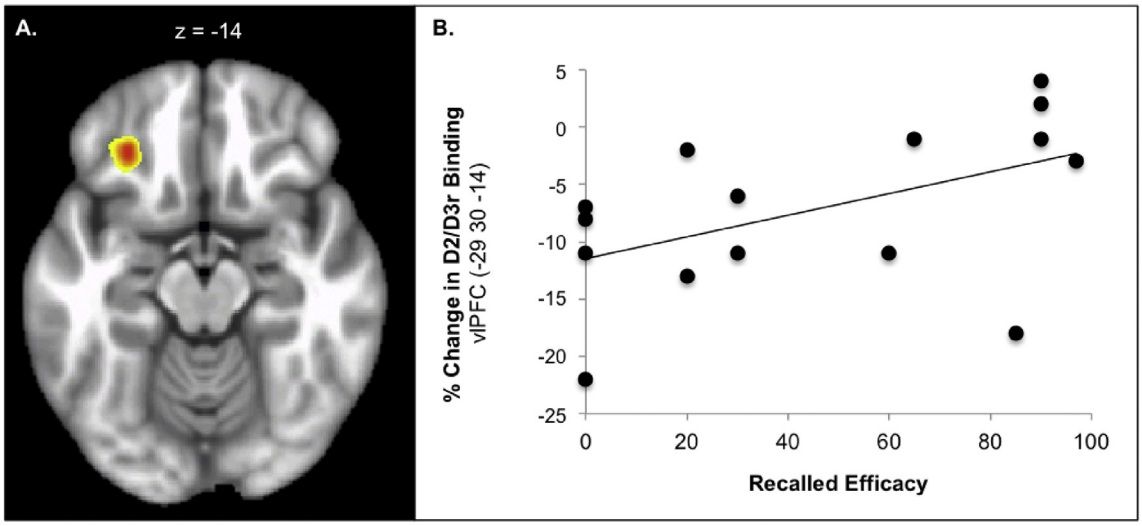

Fig. 2. Dopaminergic changes related to placebo effects. (A). A whole brain analysis demonstrated significantly greater binding potential (less DA) in left vlPFC (−29, 30, −14) for *Control*, relative to *Placebo*, scans. (B). A positive slope on the scatter plot reflects greater recalled placebo efficacy is associated with higher BP (less DA) in left vlPFC for *Control*, relative to *Placebo*, scans.

with placebo, participants made equally low ratings during clinic and PET visits. However, when the thermal stimulus was paired with the control condition, significantly higher ratings were provided in the laboratory than in the PET environment. This suggests that factors unrelated to placebo analgesia may have modulated pain during the control scan (e.g., anxiety for painful stimulations).

There was weak evidence for a role of prefrontal cortical dopaminergic transmission in placebo analgesia. Specifically, dopamine D2/D3 receptor availability was lower in left vlPFC when analgesia was anticipated, suggesting that prefrontal cortical dopamine release occurred. These findings correspond with fMRI studies that, using similar experimental methods, show the vlPFC is engaged by placebo analgesia and is related to placebo efficacy (Wager et al., 2004, 2011; Watson et al., 2009). In that work, as with in the current study, the memory of placebo efficacy was established during an initial testing session, and then retrieved and evaluated in light of stimuli delivered during the neuroimaging phase of the experiment. This reflects one of the primary functions of dopaminergic transmission in PFC, which is to maintain memory representations and update them at appropriate times (reviewed by Seamans and Robbins, 2010). Thus dopaminergic transmission in PFC may help promote placebo analgesia by maintaining memory of treatment efficacy and updating beliefs about that efficacy.

An effect-size analysis demonstrated that dopamine D2/D3 BP_{ND} was reduced in a widespread network of brain regions often implicated in nociception and placebo analgesia (Apkarian et al., 2005; Atlas and Wager, 2014; Garcia-Larrea and Peyron, 2013; Peyron et al., 2000), including striatum, dorsal anterior cingulate, thalamus, hippocampus and insula along with vlPFC. Failure to reach prescribed statistical significance, particularly in the striatum, may be related to the small sample size, methodological differences with prior work, and/or limitations in the design of the current study. For instance, in prior PET studies that find a relationship between placebo analgesia and striatal dopamine transmission (Scott et al., 2007, 2008), participants learned about the effectiveness of the placebo while undergoing PET scanning, without the opportunity to form experience-based expectations about the placebo's efficacy. Given that the striatum plays an integral role in learning, these findings are not unexpected. In the present study, participants formed experience-based expectations about the placebo's efficacy during their initial laboratory visit. Thus, unlike prior work, participants had already learned about the effectiveness of the placebo before to

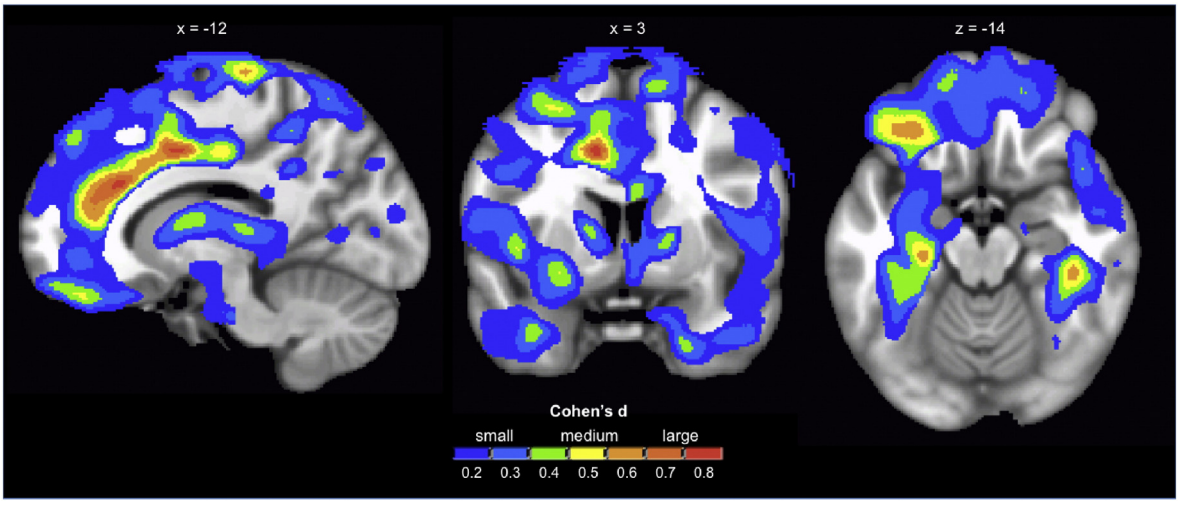

Fig. 3. Effect size of dopaminergic changes related to placebo effects. Whole brain maps depict effect size (Cohen's d) for change in binding potential during PET scans where thermal stimulation was paired with *Control* relative to *Placebo*. Overall lower levels of binding, suggestive of greater endogenous DA, are observed throughout the brain for the *Placebo* condition.

undergoing PET scanning. Because of this, dopamine transmission may have been more closely related to the implicit or explicit *recall* of previously learned relationships, which is commonly associated with engagement of vlPFC (Badre and Wagner, 2007; Long et al., 2010; Murray and Ranganath, 2007). This suggests that the vlPFC may play a critical role in promoting placebo analgesia, once the relationship between a placebo and the experience of analgesia has been learned. Future work that differentiates the neural mechanisms implicated in promoting suggestion and learning-based analgesia as they differ from the recall of learned associations is critical.

Alternatively kinetics of the radioligand used in the present study in conjunction with the length of PET scanning may have contributed to a failure to observe statistically significant effects in the striatum. Prior PET studies assessed the relationship between DA system function and placebo effects using [^{11}C]raclopride (Scott et al., 2007, 2008). This radiotracer has relatively rapid kinetics and uptake/washout properties that make it well suited to measure BP in brain regions with a high density of D2/D3 receptors, such as the striatum, but largely precludes the reliable measurement of BP in brain regions with a low density of D2/D3 receptors, such as the cortex (Farde et al., 1987; Kohler et al., 1985). [^{18}F]fallypride has relatively slow kinetics and uptake/washout properties that make it well suited to measure BP in brain regions with both high and low density D2/D3 receptors (Zald et al., 2010). However, the rate of uptake and washout of [^{18}F]fallypride varies across brain regions depending on D2/D3 receptor density. In regions with low D2/D3 receptor density, uptake and washout occur more rapidly than in regions with high D2/D3 receptor density. Thus, the duration of scanning (165 min from tracer injection to the end of scanning) may have been sufficient to obtain a reliable signal in vlPFC (low D2/D3 receptor density), it may have been insufficient to obtain a reliable signal in the striatum (high D2/D3 receptor density). Some argue that a scan duration of 3–4 h is necessary for [^{18}F]fallypride to achieve maximal stability in the striatum (Kegeles et al., 2008; Mukherjee et al., 2002), while others suggest such long-duration scans are optimal for studies that include a task-based experimental manipulation (Ceccarini et al., 2012). Follow-up studies may be better able to simultaneously detect effects of placebo analgesia on DA function in cortical and striatal regions by implementing longer [^{18}F]fallypride PET scans.

The study had two additional limitations. First, only women were assessed. Although a preponderance of evidence demonstrates gender differences in nociceptive processing, the mechanisms driving this difference remain unclear (Mogil, 2012). Given the limited sample size of this preliminary study, it was not possible to assess a sufficient number of men and women to make meaningful conclusions about potential gender effects. Since more women than men suffer from chronic pain syndromes (Mogil, 2012), we sought to maximize the potential clinical impact of this work by specifically studying women. Follow-up studies with a larger sample size should include men and women to determine whether results are generalizable, or if gender-based differences emerge. A second limitation is that the thermal stimulus profile was defined in the context of the *Control* condition. This replicates well-tested methods used in prior studies relating brain function to placebo analgesia (Wager et al., 2004); however, defining the thermal stimulus profile independently, during a separate laboratory visit, may optimize this design. By implementing this change, order of *Control* and *Placebo* conditions could then be counterbalanced during the laboratory visit in which the expectation manipulation is performed.

Despite these limitations, taken together, these findings are consistent with an important role of cortical dopaminergic transmission in modulating specific forms of placebo analgesia. They provide initial evidence that dopamine transmission in vlPFC modulates learning-based placebo analgesia. Further work is needed to determine whether learned, compared with verbally induced expectation of placebo analgesia is associated with distinct pathways of DA transmission. Finally, these results underscore the need to carefully consider how self-reported symptom improvement is assessed in clinical settings.

Conflict of interest

The authors have no conflicts of interest to report.

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