ORIGINAL ARTICLE

Placebo and Nocebo Effects Are Defined by Opposite Opioid and Dopaminergic Responses

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Context: Placebo and nocebo effects, the therapeutic and adverse effects, respectively, of inert substances or sham procedures, represent serious confounds in the evaluation of therapeutic interventions. They are also an example of cognitive processes, particularly expectations, capable of influencing physiology.

Objective: To examine the contribution of 2 different neurotransmitters, the endogenous opioid and the dopaminergic (DA) systems, to the development of placebo and nocebo effects.

Design and Setting: Using a within-subject design, subjects twice underwent a 20-minute standardized pain challenge, in the absence and presence of a placebo with expected analgesic properties. Studies were conducted in a university hospital setting.

Participants: Twenty healthy men and women aged 20 to 30 years recruited by advertisement.

Main Outcome Measures: Activation of DA and opioid neurotransmission by a pain stressor with and without placebo (changes in the binding potential of carbon 11 [^{11}C]–labeled raclopride and [^{11}C] carfentanil with positron emission tomography) and ratings of pain, affective state, and anticipation and perception of analgesia.

Results: Placebo-induced activation of opioid neurotransmission was detected in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter. Dopaminergic activation was observed in the ventral basal ganglia, including the nucleus accumbens. Regional DA and opioid activity were associated with the anticipated and subjectively perceived effectiveness of the placebo and reductions in continuous pain ratings. High placebo responses were associated with greater DA and opioid activity in the nucleus accumbens. Nocebo responses were associated with a deactivation of DA and opioid release. Nucleus accumbens DA release accounted for 25% of the variance in placebo analgesic effects.

Conclusions: Placebo and nocebo effects are associated with opposite responses of DA and endogenous opioid neurotransmission in a distributed network of regions. The brain areas involved in these phenomena form part of the circuit typically implicated in reward responses and motivated behavior.

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RECENT YEARS HAVE SEEN A renewed interest in understanding the placebo effect. From the perspective of drug development and therapeutics, placebo effects confound the effects of active compounds. Similarly, nocebo effects, the development of adverse events or worsening of a condition after the administration of a placebo, are reported in a sizable proportion of individuals participating in clinical trials.[1,2]

Historically, placebo and nocebo effects have been thought of as the result of biases in subjective symptom reporting.[3] However, this interpretation has now been challenged by increasing evidence that these effects are mediated by specific neural mechanisms.[4] Clarifying these mechanisms would aid in the development of strategies to reduce response variability in clinical trials, with considerable implications for new drug development. Furthermore, placebo and nocebo effects represent an example in which cognitive-emotional assessments of a potentially therapeutic agent or intervention confer resiliency or vulnerability to allostatic challenges to the organism.

There is an emerging literature examining the neurobiologic features of placebo effects across a variety of domains such as mood and affective regulation[5,6] and motor control in Parkinson disease.[7,8] However, most studies in this area have used pain models in the assessment of placebo-induced analgesia. Through the use of blood flow measures with positron

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emission tomography (PET) or functional magnetic resonance imaging (MRI), changes in neural activity have been detected during placebo administration. Depending on the studies, placebo-induced increases[9,10] and reductions[11] have been reported in the metabolic activity of the rostral anterior cingulate, a cognitive-emotional integrative region. In addition, the introduction of the placebo has been associated with increased correlations between anterior cingulate and periaqueductal gray matter (PAG) activity, the latter being an area centrally involved in opioid-mediated antinociception. Reductions in the activity of other pain-responsive regions, such as the thalamus and orbitofrontal and insular cortices, were also observed in one of these reports.[11] In these studies, the authors postulated that the antinociceptive effects of the placebo could be mediated through the activation of endogenous opioid mechanisms. This assertion was based on a localization of placebo-associated blood flow effects in opioid peptide and receptor-rich regions involved in pain and cognitive-affective integration.[12-14] In addition, a number of pharmacological challenge studies have shown that placebo-induced analgesia is blocked or diminished by the administration of opioid receptor antagonists.[15-17]

A single study[18] has directly monitored the activity of the endogenous opioid system and μ-opioid receptors with molecular imaging techniques. In that work, placebo-induced μ-opioid system activation was observed in the rostral anterior cingulate, insular cortex, and nucleus accumbens.[18] The experimental design used an adaptive pain induction system to maintain pain at similar levels between individuals and conditions. Physiological placebo effects were evaluated by changes in algesic input tolerance, an objective measure that participants were not aware of. The placebo effect has been attributed to assessments of potential benefit (expectations) and perceived outcomes (subjective assessments of efficacy). In this context, minimizing differences in the pain experience between conditions could have resulted in lesser effects and differences between control and placebo studies.[19]

It has also been hypothesized that placebo effects represent a form of reward expectation processing.[20-22] Mesolimbic dopamine (DA) neurons are thought to be centrally involved in reward expectation and variations from expected outcomes in animal models.[23,24] Placebo-induced nucleus accumbens DA release has been described in Parkinson disease when a DA agent was expected. It was further related to the individual expectations of improvement but not to the actual placebo effects on motor function.[25] Increases in nucleus accumbens metabolic activity have additionally been shown in healthy subjects and in cocaine abusers when a psychostimulant was expected instead.[26,27] However, it is presently unknown whether nucleus accumbens DA activation participates in the formation of placebo effects or simply reflects attention to a salient stimulus (the placebo) without physiological consequences. In addition, the more general involvement of this neurotransmitter system in placebo effects not associated with the administration of psychostimulant agents (eg, analgesia) has not been explored.

We studied these mechanisms using the development of placebo analgesia, a prototypical form of placebo effect, during a sustained pain challenge. Molecular imaging techniques were used to determine the response of nucleus accumbens DA neurotransmission to a placebo with potential analgesic properties. Furthermore, we examined the relationship between the nucleus accumbens DA and endogenous opioid systems because the latter has been linked to placebo analgesia in pharmacological challenge studies.[15-17] To eliminate confounds, control and placebo conditions used the same algesic stimulus in a within-subject design. The pain stimulus was calibrated so that pain was maintained at similar levels between individuals. This also allowed for control of motivational factors related to varying levels of experimental pain.[28] The reduction in the in vivo availability of DA D_2/D_3 and μ-opioid receptors (ie, binding potential [BP]) was used to determine placebo-induced activation of DA and opioid neurotransmission. It was hypothesized that a positive relationship would exist between placebo-induced nucleus accumbens DA activity and regional μ-opioid neurotransmission, thereby reducing pain reporting. We also examined whether similar or different mechanisms and brain circuits were involved in nocebo effects.

METHODS

SUBJECTS

Volunteers included 20 healthy, medication-free, right-handed men (n=9) and women (n=11) with a mean (SD) age of 24 (3) years. Subjects had no personal history of medical or psychiatric illness or substance abuse or dependence and no family history of inheritable illnesses. Volunteers were included who had not used any psychotropic medications or hormone treatments for at least 1 year, had no history of smoking, and did not exercise in excess of 1 hour 3 times a week. Women had regular menstrual cycles of 26 to 32 days' duration and had not used hormonal birth control drugs for at least 1 year. The women were studied during the midfollicular phase of the menstrual cycle (4-9 days after the onset of menses). This was determined by menstrual diaries and confirmed by plasma levels of progesterone immediately before scanning (progesterone levels, <3 ng/mL [to convert progesterone to nanomoles per liter, multiply by 3.18]). Written informed consent was obtained in all cases.

A separate sample of 18 men with similar characteristics (age range, 20-30 years) was studied twice with the same pain challenge. These studies were designed to examine whether there were order effects in reported pain levels during consecutive studies that could account for differences between the control and placebo conditions. All of the procedures used were approved by the University of Michigan Investigational Review Board for Human Subject Use and the Radioactive Drug Research Committee of the US Food and Drug Administration.

NEUROIMAGING METHODS

Four 90-minute PET images per subject were acquired (HR^+ scanner; Siemens, Knoxville, Tennessee) in 3-dimensional mode (reconstructed full-width/half-maximum resolution, approximately 5.5 mm in plane and 5.0 mm axially), with the septa retracted and scatter correction. Participants were positioned

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in the PET scanner gantry, and 2 intravenous (antecubital) lines were placed. A light forehead restraint was used to eliminate intrascan head movement. Radiotracer administrations were separated by at least 2 hours to allow for radiotracer decay.

Carbon 11 (^{11}C)–labeled carfentanil was synthesized at high specific activity (>2000 Ci/mmol [the conversion factor for 1 Ci is 3.7×10^{10} Bq]) by the reaction of [^{11}C]methyl iodide and a normethyl precursor as previously described.[29] [^{11}C]Raclopride was synthesized at high specific activity (>2000 Ci/mmol) by the reaction of *O*-desmethyl raclopride with [^{11}C]methyl triflate. Ten to 15 mCi was administered in each of the imaging procedures, with a mean (SD) mass of carfentanil injected of 0.028 (0.013) µg/kg per image and of raclopride of 0.20 (0.15) µg/kg per image. These levels ensured that the compounds were administered in tracer quantities, that is, subpharmacological doses occupying less than 1% of the available receptors. Fifty percent of the radiotracer doses were administered as an initial bolus and the remaining 50% by continuous infusion for the remainder of the study. This procedure compensates for the metabolism of the radiotracer, leading to constant plasma concentrations over time and more rapid equilibration between kinetic compartments. For each study, 21 sets of scans (frames) were acquired over a 90-minute period with an increasing duration (four 30-second frames, three 1-minute frames, two 2.5-minute frames, eight 5-minute frames, and four 10-minute frames).

Images were reconstructed using iterative algorithms (brain mode; Fourier rebinning algorithm with ordered-subsets expectation maximization, 4 iterations, and 16 subsets; no smoothing) into a 128×128-pixel matrix in a 28.8-cm-diameter field of view. Attenuation correction was performed through a 6-minute transmission scan (germanium 68 source) obtained before the PET study and with iterative reconstruction of the blank/transmission data, followed by segmentation of the attenuation image. Small head motions during PET were corrected by an automated computer algorithm for each subject before analysis, and the images were coregistered with the same software.[30] Time points were then decay corrected during reconstruction of the PET data.

Image data were then transformed on a voxel-by-voxel basis into 2 sets of parametric maps, a tracer transport measure (K_1 ratio) and a receptor-related measure (distribution volume ratio [DVR] at equilibrium), using data from 45- to 90-minute posttracer administration. To avoid the need for arterial blood sampling, these measures were calculated by means of a modified Logan graphical analysis[31] using the following reference regions: the occipital cortex (an area devoid of µ-opioid receptors) for [^{11}C]carfentanil scans and the cerebellum (an area with negligible DA D_2/D_3 receptors) for [^{11}C]raclopride scans. The slope of the Logan plot is equal to the receptor concentration divided by its affinity for the radiotracer (f_2 Bmax/K_d) + 1 for this receptor site) and has been referred to as the DVR; f_2Bmax/K_d (or DVR – 1) is the "receptor related" measure (also termed BP)[32] or receptor availability in vivo. Bmax is the receptor concentration and K_d, the receptor-ligand dissociation constant. The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value.

Anatomic MRI studies were acquired before PET on a 3-T scanner (General Electric, Milwaukee, Wisconsin). Acquisition sequences were axial spoiled gradient recall inverse recovery-prepared magnetic resonance [echo time, 3.4 milliseconds; repetition time, 10.5 milliseconds; inversion time, 200 milliseconds; flip angle, 25°; number of excitations, 1; using 124 contiguous images, 1.5-mm thickness). The K_1 and DVR images for each experimental period and the MRIs were coregistered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation.[33] Statistical parametric maps of differences between conditions (pain vs pain + placebo) were generated by anatomically standardizing the T1-weighted spoiled gradient recall MRI of each subject to the ICBM stereotactic atlas coordinates, with subsequent application of this transformation to the DA D_2/D_3 and µ-opioid receptor binding maps. The accuracy of coregistration and nonlinear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images with each other and with the ICBM atlas template.

EXPERIMENTAL DESIGN

Subjects were placed in the scanner gantry as described in the preceding section. Needles (25G11/2) were placed in both masseter muscles approximately 30 minutes before radiotracer administration. Starting 45 minutes after radiotracer administration, 5% hypertonic saline was introduced in the left masseter muscle via a closed infusion system. Subjects were asked to rate pain intensity every 15 seconds using an electronic 0 to 100 visual analog scale (VAS) placed in front of the scanner gantry, as previously described in detail.[34,35] Subjects were informed that the lower end of the scale denoted "no pain" and that the upper bound represented the "most pain imaginable." The pain challenge was maintained for 20 minutes.

Initially, the subject-specific settings of the closed-loop system for maintaining muscle pain were established. This consisted of measuring each subject's response to a standard 0.15-mL bolus of 5% sodium chloride injected over a 15-second period as an impulsive input while recording the subject's pain intensity response every 15 seconds. A suitable infusion rate for the maintenance of pain over time was then estimated by comparing the subject's response to the mean response of 65 subjects of the same age range exposed to the same bolus. From that point on, the adaptive controller depended on feedback from subjects. The subject ratings of pain intensity every 15 seconds were fed back to the computer via an analog-digital board, which then changed the infusion rate to maintain pain at similar levels over time. The same individual infusion profiles generated during the pain challenges were used for the studies with placebo administration.

Subjects were given clinical trial–type instructions before administration of the placebo so that the conditions of the study would be similar to those encountered in typical placebo-controlled drug trials. Subjects consented to participate in a study examining the analgesic effects of a novel substance against placebo. We provided the following further detail to the possible mechanisms underlying the analgesic effect of the substance: "We are studying the effect of a pain relief medication. This medication is thought to have analgesic effects through the activation of natural brain systems that suppress pain." Possible adverse effects of the substance in question were then described, but it was indicated that we did not typically observe significant adverse effects. Actual pharmacological agents were not administered in these studies.

The placebo condition consisted of the introduction of 1 mL of 0.9% isotonic saline into 1 of the intravenous ports every 4 minutes, starting 2 minutes before the pain challenges, and lasting for 15 seconds each time. Subjects were aware that the study drug was to be administered because they were alerted by a computer-generated human voice recording, followed by a second-by-second count of the infusion timing (15 seconds). Subjects were asked to estimate the expected analgesia before the introduction of the placebo. After the pain challenges, they were asked to subjectively estimate the efficacy of the placebo using a VAS ranging from 0 (no analgesic effect) to 100 (maximum analgesia) and any possible adverse effects.

The [^{11}C]carfentanil and [^{11}C]raclopride studies were randomized and counterbalanced in order. We performed 2 stud-

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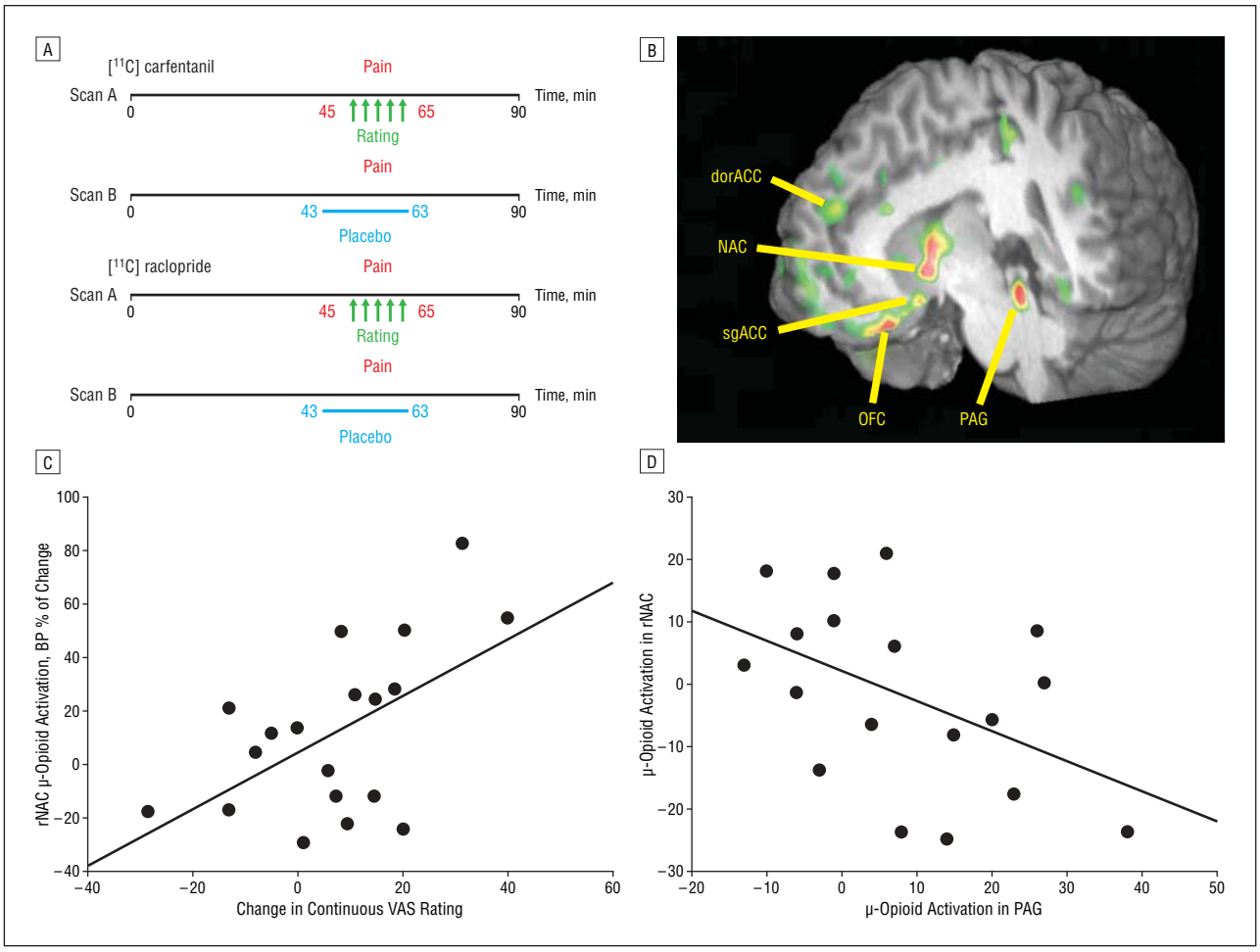

Figure 1. Placebo-induced activation of regional μ-opioid receptor–mediated neurotransmission. A, Experimental design. Four scans were obtained in each subject, 2 with administration of carbon 11 [^{11}C]–labeled carfentanil (without and with placebo) and 2 with administration of [^{11}C]raclopride (without and with placebo). Pain images (scan A) preceded placebo administrations (scan B). Images obtained with [^{11}C]carfentanil and [^{11}C]raclopride were randomized and counterbalanced in order in each scan series. B, Some of the areas in which significant activation of μ-opioid neurotransmission during sustained pain were observed after the introduction of a placebo with expectation of analgesia. The *z* scores of statistical significance are superimposed over an anatomically standardized magnetic resonance image in a 3-dimensional view. C, Positive correlation between placebo-induced μ-opioid system activation in the right nucleus accumbens (rNAC) (y-axis) and reductions in pain report (x-axis). D, Negative correlation between periaqueductal gray matter (PAG) placebo-induced μ-opioid activity (x-axis) and that in other supraspinal regions (the rNAC is shown) (y-axis). BP indicates binding potential; dorACC, dorsal area of the rostral anterior cingulate (Brodmann area [BA] 24); OFC, orbitofrontal cortex; sgACC, subgenual area of the rostral anterior cingulate (BA 25); and VAS, visual analog scale.

ies with [^{11}C]carfentanil and 2 with [^{11}C]raclopride, with and without placebo administration. Tracer administrations were separated by at least 2 hours to allow for radiotracer decay. Based on our prior experience using a fully randomized design,[18] the 2 placebo administrations followed the 2 pain challenges without placebo; this provided the subjects with a frame of reference for the expectation of analgesic effects. Nociceptive input for pain maintenance was defined in pain studies and repeated during the pain + placebo studies.

Immediately after the pain challenges, subjects completed the Positive and Negative Affectivity Scale (PANAS)[36] and the Perceived Pain Intensity (PPI) index of the McGill Pain Questionnaire.[37] The McGill Pain Questionnaire uses weighted word descriptors for the pain. This measure, together with the average pain intensity ratings acquired every 15 seconds during the studies, provided the measures of the pain experience.

The timing of the experimental procedures is summarized as follows: radiotracer administration, 0 minutes (start of imaging experiment); placebo administration, 43 minutes; pain challenge, 45 minutes; end of placebo administration, 63 minutes; end of pain challenge, 65 minutes; completion of ratings scales (effectiveness, PANAS, and McGill Pain Questionnaire), 75 minutes; and end of scanning, 90 minutes. Rating scales at baseline (PANAS and expectation of analgesia) were obtained before the radiotracer administration. Momentary ratings of pain intensity were obtained every 15 seconds for the 20-minute challenges. A schematic representation of the experimental design is shown in **Figure 1**A.

DATA ANALYSES

Differences between conditions were mapped into stereotactic space with *t* maps of statistical significance using a modification of SPM2 (Welcome Department of Cognitive Neurology, University College, London, England) and Matlab (MathWorks, Natick, Massachusetts) software, with a general linear model and correction for multiple comparisons. No global normalization was applied to the data, and therefore the calculations presented herein are based on absolute BP (f_2 Bmax/K_d) estimates. Only regions with specific μ-opioid or DA D_2/D_3 receptor binding were included in the analyses (voxels with DVR > 1.1 or BP > 0.1).[38] To compensate for small residual anatomic variations across subjects and to improve signal to noise ratios, a 3-dimensional gaussian filter (full-width/half-

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maximum resolution, 6 mm) was applied to each scan. Subtraction analyses were performed on μ-opioid and DA D_2/D_3 BP images separately to assess main effects. For each subtraction analysis, 1-sample, paired *t* test values were calculated for each voxel using the pooled variance across voxels. Significant differences and correlations were detected using a statistical threshold of $P<.0001$ for regions hypothesized to mediate placebo effects (PAG, rostral anterior cingulate, prefrontal cortex, insula, thalamus, nucleus accumbens, and amygdala).[11,18] Statistical thresholds for any other regions were calculated using a statistical threshold that controls a type I error rate at $P=.05$ for multiple comparisons. These statistical thresholds were estimated on the basis of the number of voxels in the gray matter, image smoothness, and the extent of local changes.[39,40] The BP values for percentage of change calculations were extracted from image data by averaging the values of voxels contained in an area where significant differences were obtained in the voxel-by-voxel analysis down to a threshold of $P<.01$. Using SPSS statistical software (version 14.0; SPSS Inc, Chicago, Illinois), these values were then used to plot the data and perform correlation and regression analyses and to confirm the voxel-by-voxel results for all analyses. Data are expressed as the mean (SD) in the text and as mean (SEM) in the Figures. Planned analyses included correlations between placebo-induced effects on neurotransmission with ratings of expectation and placebo-induced analgesia (as measured by the change in the 2 pain rating scales used, average pain intensity, and PPI word descriptors). Therefore, these correlations were not corrected for multiple comparisons.

Recent data from other authors[41] have shown that increases in positive affect were associated with nucleus accumbens activity during reward expectation. Therefore, we also examined the relationship between positive affect and regional neurotransmitter responses to the placebo.

RESULTS

PSYCHOPHYSICS

The anticipated placebo analgesic effect before placebo administration was rated at 48 (23) (0 indicates completely ineffective, and 100, completely effective), with a range of 0 to 95 VAS units. Eleven subjects rated an anticipated effectiveness of more than 50%. After placebo administration, subjects reported a perceived analgesia of 42 (29) VAS units. Anticipated analgesic effectiveness correlated significantly with the subjectively perceived efficacy of the placebo ($r=0.55$ [$P=.008$]).

Across all experimental conditions, subjects rated pain intensity every 15 seconds for the duration of each challenge using a 0 to 100 VAS. Average ratings for the pain condition were 31 (11) and 24 (10) for pain with placebo ($t=2.6$ [$P=.009$]). The PPI index also declined significantly after placebo administration (pain, 2.2 (0.6); pain + placebo, 1.8 (0.6); $t=1.8$ [$P=.04$]).

The median change in pain intensity ratings after placebo administration was 50%. This threshold was then used to divide the sample into equal groups of low (lower median) and high placebo responders.

Within the low placebo analgesia group, 5 subjects showed increases in pain report during placebo administration (average increase in pain ratings over a 20-minute period, 7 [1] VAS intensity units). This change was significantly different from that of placebo responders who showed a 15 (8)–unit reduction in VAS scores ($t=4.6$ [$P<.001$]). Placebo and nocebo responders did not differ in their ratings of expected effectiveness (54 [29] and 44 [21], respectively; $t=0.7$ [$P=.45$]).

A mixed-effects analysis of variance was used to rule out placebo effects that could be attributable to the scan order confounds. This analysis confirmed an effect of placebo on pain ratings ($F_{79,3}=17.1$ [$P<.001$]), but no effects of scan order ($F_{79,3}=0.5$ [$P=.80$]) or interactions ($F_{79,3}=0.4$ [$P=.80$]). No significant effects of placebo were obtained for PANAS negative affect ratings ($F_{79,3}=1.1$ [$P=.30$]), order effects on this measure ($F_{79,3}=0.6$ [$P=.40$]), or interactions between them ($F_{79,3}=0.1$ [$P=.70$]). Similar results were obtained for PANAS positive affect ratings (effects of placebo, $F_{79,3}=1.7$ [$P=.20$]; effect of scan order, $F_{79,3}=0.3$ [$P=.60$]; interaction term, $F_{79,3}=0.6$ [$P=.80$]).

In addition, a separate control experiment was conducted with a different sample of 18 healthy male subjects to rule out order effects on pain or affective ratings. These subjects were studied twice with the same pain challenge but without placebo or other interventions and without scanning. Average VAS pain intensity ratings over a 20-minute period were 32 (13) for studies conducted first in order and 31 (13) for those second in order ($t=0.6$ [$P=.30$]). Similarly, no significant differences were obtained as a function of scan order for PANAS negative affect ($t=0.94$ [$P=.40$]), positive affect ($t=0.18$ [$P=.90$]), or fear ratings ($t=0.81$ [$P=.40$]).

PLACEBO-INDUCED ACTIVATION OF μ-OPIOID AND DA D_2/D_3 NEUROTRANSMISSION

Placebo administration was associated with significant reductions in μ-opioid receptor BP, reflecting the activation of endogenous opioid neurotransmission and μ-opioid receptors in several brain regions. These included the subgenual (Brodmann area [BA] 25) and rostral (BA 24) anterior cingulate, orbitofrontal cortex (BA 11), anterior and posterior insular cortex, nucleus accumbens bilaterally, right amygdala, and PAG (Figure 1 and **Table 1**). Reductions in the BP measure ranged from 10% to 26% across these regions. In view of the central role of the PAG in regulating pain transmission to supraspinal regions, we also examined the relationship between PAG and other regional μ-opioid system activity during the placebo condition (Figure 1). Significant negative correlations were obtained between placebo-induced PAG activation and both the right nucleus accumbens ($r=-0.47$ [$P=.02$]) and right amygdala ($r=-0.43$ [$P=.03$]), with trends in the same direction for the subgenual anterior cingulate (BA 25) ($r=-0.41$ [$P=.08$]). No significant positive correlations were obtained in any region.

Placebo-induced activation of DA D_2/D_3 neurotransmission was observed bilaterally in the nucleus accumbens, ventral putamen, and right ventral caudate nucleus (Table 1). The reductions in the DA D_2 receptor BP in the ventral caudate and putamen ranged from 9% to 10%, whereas those in the nucleus accumbens were 16% and 10% in the right and left side, respectively (**Figure 2**).

Correlations were then performed to examine the biological implications on these changes. We examined the relationship between placebo-induced DA and μ-opioid system activation in the regions described in the 2 previous

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Table 1. Placebo-Induced Activation of Regional μ-Opioid and DA D_2/D_3 Neurotransmission During Pain

System	Region	x, y, z Coordinates, mm	*z* Score	Cluster Size, mm^3	BP Change, Mean (SD), %[a]
μ-Opioid	sgACC	3, 9, –12	4.6	128	15 (5)
	rosACC	10, 14, 34	3.0	241	11 (4)
	OFC	6, 27, –23	5.4	134	12 (8)
	Left aINS	–26, 25, 3	3.8	424	26 (8)
	Right pINS	37, –8, –14	4.4	722	22 (7)
	Right NAC	12, 3, –3	5.9	338	12 (7)
	Left NAC	–4, 5, –3	5.9	211	13 (5)
	Right PUT	23, 14, –9	3.6	258	10 (7)
	Right AMY	35, –5, –29	3.3	272	17 (7)
	PAG	2, –31, –18	5.5	568	19 (9)
DA D_2/D_3	Right CAU	16, 2, 10	5.3	406	9 (3)
	Right PUT	22, 4, –11	3.9	170	9 (5)
	Left PUT	–26, 6, –7	5.4	522	10 (5)
	Right NAC	9, 14, –10	3.6	255	10 (5)
	Left NAC	–10, 9, –14	4.4	135	16 (5)

Abbreviations: aINS, anterior insular cortex (INS); AMY, amygdala; BP, binding potential; CAU, caudate; DA, dopaminergic; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray matter; pINS, posterior INS; PUT, putamen; rosACC, rostral anterior cingulate cortex (ACC); sgACC, subgenual ACC.
[a] Indicates significant regional activation of opioid and DA neurotransmission.

paragraphs and analgesic expectations and the update of these expectations during the studies, as well as with actual analgesic effects (average reductions in continuous pain ratings and PPI score). Opioid system activation during placebo in the PAG (r=0.49 [P=.03]) and the right nucleus accumbens (r=0.48 [P=.04]) was positively correlated with anticipated analgesia. Placebo-induced DA activation was positively correlated with anticipated analgesia in the right nucleus accumbens (r=0.42 [P<.01]).

Functional MRI data have shown that the nucleus accumbens and amygdala are involved in the updating of reward expectations based on environmental information.[23,42] The ratio of subjectively perceived to anticipated effectiveness was used as a measure of update of analgesic expectations. It was positively correlated with placebo-induced μ-opioid system activation in the right nucleus accumbens (r=0.55 [P=.01]) and right amygdala (r=0.47 [P=.02]), as well as with DA activation in the right nucleus accumbens (r=0.44 [P=.03]). This is therefore consistent with a role of DA and opioid systems in these regions in modulating responses to changing environmental information (in this case, perceived pain).

For analgesic effects, positive correlations between the activation of μ-opioid neurotransmission and the change in continuous pain ratings were obtained in the nucleus accumbens bilaterally (left, r=0.47 [P=.02]; right, r=0.62 [P=.008]) (Figure 1), with trends in the same direction for the orbitofrontal cortex (r=0.41 [P=.07]). Similar effects were obtained for DA activation, with a positive correlation in the right nucleus accumbens (r=0.48 [P=.02]) (Figure 2). Significant positive correlations were also obtained between placebo analgesic effect using the PPI rating and μ-opioid system activation in the subgenual anterior cingulate (r=0.48 [P=.02]) and with DA activation in the right (r=0.68 [P=.003]) and left nucleus accumbens (r=0.48 [P=.02]), as well as the adjacent left ventral putamen (r=0.51 [P=.02]).

In view of previous data linking changes in positive affect and nucleus accumbens responses to reward,[41] we also tested whether positive affect during placebo administration would be related to neurotransmitter responses. Significant positive correlations were obtained between the increases in PANAS positive affective ratings during placebo administration and left nucleus accumbens μ-opioid (r=0.64 [P=.004]) and DA activation (r=0.47 [P=.02]).

OPIOID AND DA NEUROTRANSMISSION IN HIGH AND LOW PLACEBO RESPONDERS

These series of analyses examined the brain regions and changes in neurotransmission differentiating high and low placebo effects. Significant differences between high and low placebo responders were obtained in the nucleus accumbens but not other brain regions. High placebo responders demonstrated greater placebo-induced μ-opioid activation in the right nucleus accumbens (t=2.2 [P=.04]) and DA D_2/D_3 activation in the same region, bilaterally (right, t=2.2 [P=.04]; left, t=2.4 [P=.02]) (**Figure 3**).

We also examined the proportion of the variance in placebo analgesia accounted for by the various regions involved. We used a stepwise regression model in which the reduction in average pain ratings was examined against placebo-induced changes in regional neurotransmission. Regions were introduced in the model and removed if they did not contribute significantly to the variance explained by the model. Among all regions activated in [^{11}C]carfentanil and [^{11}C]raclopride studies, the most significant predictor was the activation of DA neurotransmission in the right nucleus accumbens, accounting for 25% of the variance in placebo analgesia (r=0.5 and r^2=0.25 [P=.02]).

Nucleus accumbens DA has been involved in the regulation of endogenous opioid transmission in the striatopallidal pathway.[43,44] We hypothesized that the magnitude of placebo-induced DA activation in the right nucleus accumbens would also determine the activity of the pain and affect the regulatory μ-opioid system.

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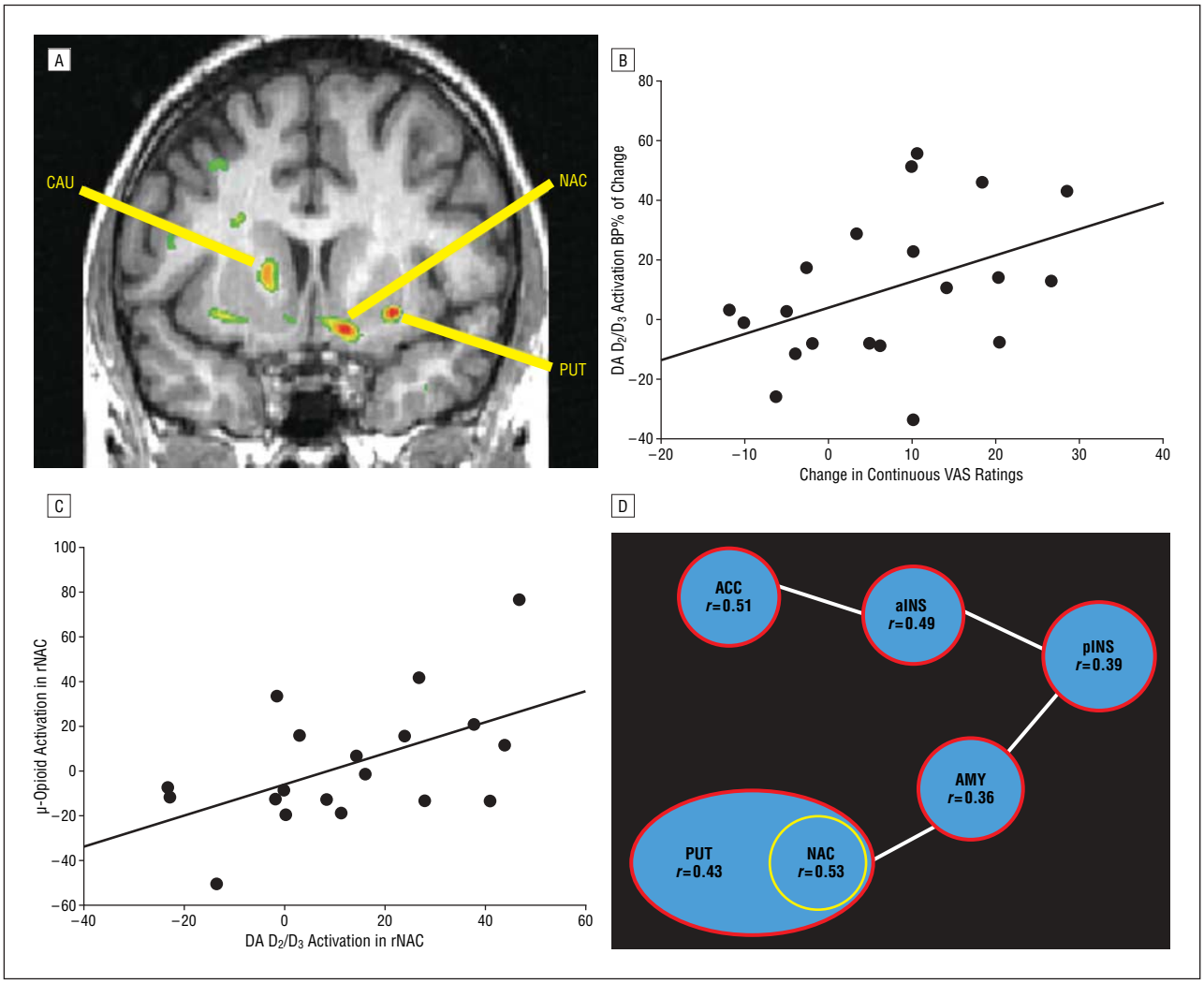

Figure 2. Placebo-induced activation of regional dopaminergic (DA) D_2/D_3 receptor–mediated neurotransmission. A, Areas in which significant activation of DA neurotransmission during sustained pain were observed after the introduction of a placebo with expectation of analgesia. The *z* scores of statistical significance are superimposed over an anatomically standardized magnetic resonance image in a coronal view. B, Positive correlation between placebo-induced DA D_2/D_3 activation in the right nucleus accumbens (rNAC) (y-axis) and reductions in intensity of pain, reported by means of a visual analog scale (VAS) (x-axis). C, Positive correlations observed between the activation of DA D_2/D_3 (x-axis) and opioid (y-axis) systems in response to placebo administration in the rNAC. D, Schematic representation shows some of the connectivity between the regions in which μ-opioid system activation was detected during placebo administration. The yellow circle represents DA activation; the red circles, endogenous opioid activation. The *r* values represent the correlation between DA activation in the nucleus accumbens and regional μ-opioid system activation. ACC indicates anterior cingulate; aINS, anterior insular cortex; AMY, amygdala; CAU, caudate; pINS, posterior insular cortex; and PUT, putamen.

Placebo-induced DA activation in the right nucleus accumbens was positively correlated with the activation of the μ-opioid system in most regions where placebo effects had been detected (Figure 2 and **Table 2**). Dopamine D_2/D_3 neurotransmission in the right nucleus accumbens explained 13% to 30% of the variance in regional μ-opioid system responses to the placebo.

OPIOID AND DA NEUROTRANSMISSION IN NOCEBO RESPONDERS

Placebo-induced changes in μ-opioid and DA D_2/D_3 neurotransmission were compared between high placebo (n=10) and nocebo (n=5) responders. Significant differences between groups in μ-opioid activity during placebo were observed in the subgenual anterior cingulate, orbitofrontal cortex, anterior insular cortex, mediodorsal area of the thalamus, nucleus accumbens bilaterally, and amygdala bilaterally (Figure 3). Placebo responders showed activation of μ-opioid neurotransmission in these regions, but nocebo responders demonstrated the opposite response, a deactivation of opioid neurotransmission, with increases in BP ranging from 2% to 25% (Figure 3). Similar effects were obtained for the DA system, with significant differences between the groups in the right nucleus accumbens and left ventral putamen. Again, a deactivation of DA neurotransmission was observed in nocebo responders. Increases in the BP measure were 6% and 8%, respectively, for these 2 regions (Figure 3).

COMMENT

Herein we have demonstrated the involvement of 2 neurotransmitter systems in the production of placebo an-

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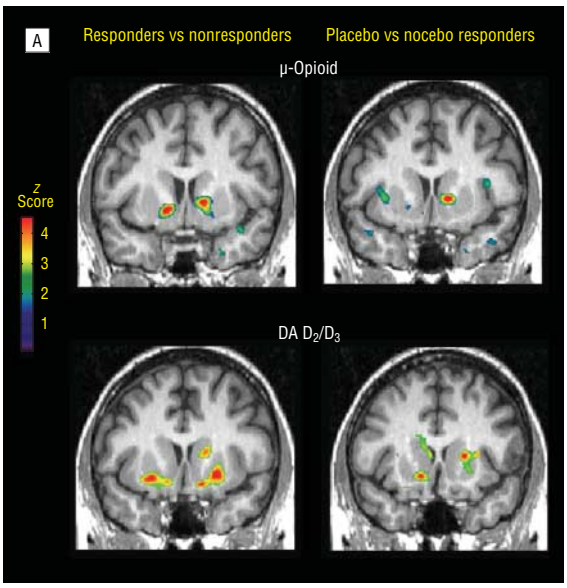

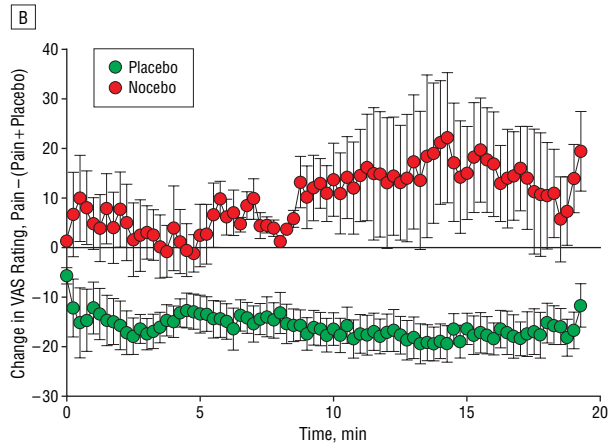

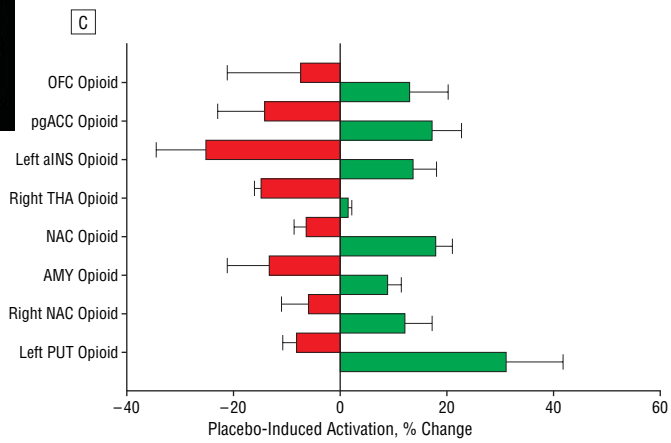

Figure 3. A, Differences in placebo-induced dopaminergic (DA) and opioid system activation between placebo and nocebo responders. Coronal magnetic resonance images (MRIs) in the left-hand column show areas in which μ-opioid and DA D_2/D_3 neurotransmission during placebo administration were significantly different between high placebo (>50% decline in pain intensity ratings) and low placebo responders (<50% decline in pain intensity ratings). Coronal MRIs in the right-hand column show the data for the comparisons between high placebo and nocebo responders. The *z* scores of statistical significance are represented by the pseudocolor scale on the left side of the image and are superimposed over an anatomically standardized MRI. B, The visual analog scale (VAS) pain intensity ratings in high placebo and nocebo responders (y-axis), acquired every 15 seconds for the 20-minute duration of the pain challenge. C, The magnitude of activation (placebo responders) and deactivation (nocebo responders) in regional μ-opioid and DA D_2/D_3 neurotransmission. Data are the mean (SEM) of the changes in the binding potential measure as a positive numeral, depicting system activation (pain – [pain + placebo] contrast). Data are averaged for bilateral regions. aINS indicates anterior insula; AMY, amygdala; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PUT, ventral putamen; pgACC, subgenual anterior cingulate; and THA, thalamus.

Table 2. Significant Correlations Between Placebo-Induced NAC DA D_2/D_3 Activation and Regional μ-Opioid System Responses

Region	x, y, z Coordinates	*z* Score	Cluster Size, mm^3	*r* Values[a]
sgACC	–4, 18, –8	3.4	392	0.51
Left aINS	–34, 16, –24	3.9	268	0.49
Left pINS	–57, 5, –12	3.5	134	0.39
Right NAC	8, 2, 2	4.3	399	0.53
Left PUT	–20, 10, –10	4.0	518	0.43
Right AMY	24, –6, –17	7.1	504	0.36

Abbreviations: aINS, anterior insular cortex (INS); AMY, amygdala; DA, dopaminergic; NAC, nucleus accumbens; pINS, posterior INS; PUT, putamen; sgACC, subgenual anterior cingulate cortex.

[a]Voxel-by-voxel analyses were conducted between the magnitude of placebo-induced activation of NAC DA neurotransmission and that of the endogenous opioid system. Data were then extracted for the calculation of *r* values.

algesia: the mesolimbic DA system, involving the activation of DA D_2/D_3 receptors in the ventral basal ganglia, and the endogenous opioid/μ-opioid receptor system, involving the rostral and subgenual anterior cingulate, orbitofrontal cortex, anterior and posterior insulae, medial thalamus, nucleus accumbens, amygdala, and PAG. Both neurotransmitter systems were activated during the administration of a placebo with expected analgesic prop-

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erties. Regional magnitudes of activation correlated with the subjects' anticipated analgesia, with the update of these expectations by the subjectively perceived efficacy of the placebo, as well as with placebo-induced changes in pain intensity and positive affective state.

Furthermore, it was demonstrated that high and low placebo responsiveness was predicted by the placebo-induced activation of the DA and opioid systems in the nucleus accumbens. The activation of DA neurotransmission in the nucleus accumbens was additionally associated with the magnitude of μ-opioid system responses in placebo responsive regions. This is consistent with the involvement of DA D_2 receptors in the activation of endogenous opioid pathways in animal models.[45-47] Although the involvement of the reward and saliency responsive mesolimbic DA system in placebo responses has been postulated on theoretical grounds,[20,21] this is, to our knowledge, the first study to demonstrate its central involvement in placebo analgesia through interactions with the endogenous opioid system.

We used an experimental design similar to those of clinical randomized controlled trials (no preconditioning or subject preselection, no deception, subjects who were aware that either an active or an inactive drug could be administered), allowing for a full range of expectations and placebo effects. Hyperalgesia during placebo administration was detected in 25% of the sample studied (nocebo effect). These subjects showed reductions in placebo-associated regional DA and endogenous opioid activity. These data then demonstrated a dynamic, bidirectional response of DA D_2/D_3 and μ-opioid neurotransmission to placebo administration, eliciting placebo analgesic and hyperalgesic (nocebo) responses. The regions and neurotransmitter systems involved in the development of placebo and nocebo effects fully overlapped. The opposite psychophysical effects were defined by the directionality of change in neurotransmission and not by the recruitment of additional brain regions.

Previous work addressing changes in regional blood flow or metabolism in response to placebo administration has shown increases in rostral anterior cingulate and PAG activity in the context of expectation of analgesia,[9,10] as well as a reduction in the activity of the anterior cingulate, orbitofrontal cortex, insula, and thalamus during placebo administration.[11] In the latter report, these changes were correlated with subjective analgesic effects.[11] Significant covariation of synaptic activity in the PAG and in the rostral anterior cingulate was also observed and interpreted as reflecting an interaction between pain modulatory (eg, PAG) and cognitive-integrative (anterior cingulate) brain regions. Those authors suggested that placebo-induced modulation of brain regional synaptic activity could be mediated by the endogenous opioid system, as it involved regions with high endogenous opioid concentrations and has been implicated in pain suppression in animal models[48] and humans.[13] In addition, a behavioral literature has shown a blockade of placebo analgesia by opioid receptor antagonists when there is expectation of analgesia.[15-17]

In a previous study examining these processes using molecular imaging to monitor endogenous opioid activity on μ-opioid receptors, placebo-induced activation of this neurotransmitter system was observed in the rostral anterior cingulate, prefrontal and insular cortices, and nucleus accumbens.[18] The experimental design used in that work involved the use of an adaptive pain delivery system that minimized differences in pain intensity between conditions (placebo vs no placebo). This procedure provided an objective measure of pain sensitivity (changes in algesic substance requirements before and after placebo administration) modified by the placebo, additionally related to other subjective measures (pain report and affective state). However, the minimization of perceptually experienced differences between conditions could have reduced motivational factors related to perceived changes in the pain experience.[18,19,49] Consistent with that possibility, herein we observe that in some brain regions (eg, nucleus accumbens, amygdala), placebo-activated DA and endogenous opioid release were associated with the updating of expectations by the subjectively perceived analgesic effect (expressed as the ratio of perceived to anticipated analgesic effects).

The present work resolved these questions by using the same stimulus in studies with and without placebo in a larger sample. As a result of these modifications, we observed a greater number of regions where μ-opioid neurotransmission was activated by the placebo. The relationship between endogenous opioid and mesolimbic DA neurotransmission and their respective contributions to individual variations in placebo effects were also demonstrated. This was also the case for nocebo responses.

The regions implicated in the biological effects of the placebo largely overlap with those in which placebo effects have been obtained using brain regional blood flow measures.[9-11] In addition, we directly demonstrate, through the use of molecular imaging techniques, the involvement of endogenous opioid, μ-opioid receptor–mediated neurotransmission in the effects of placebo when there is a natural expectation of analgesia. The mediation of placebo analgesic effect by the μ-opioid system is further supported by the positive correlations obtained between the magnitude of regional μ-opioid system activation and the reductions in individual pain report. These data explain the findings of blockade of placebo-induced analgesia by the administration of nonselective opioid receptor antagonists in the absence of preconditioning[17] while further involving the μ-opioid receptor type and specific brain regions in this process.

A finding of note is the identification of the PAG as participating in placebo-induced endogenous opioid activation because this is a region centrally involved in the modulation of ascending pain signaling into telencephalic regions (see Fields[20] for a recent review). We report a negative relationship between PAG opioid activity during placebo and that of the nucleus accumbens and the amygdala. Similar effects were observed for the subgenual anterior cingulate at trend levels of statistical significance. Contrary to these findings, positive interrelationships between the activity of the PAG and subgenual anterior cingulate and amygdala have been noted in studies examining blood flow responses to placebo administration.[9,10] However, these measurements reflect the metabolic demands associated with synaptic activity irrespective of its cause[50,51] and lack neurochemical speci-

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ficity. As an example, both μ-opioid receptor agonists and antagonists can increase and decrease cerebral blood flow as a function of brain region and baseline tone of this neurotransmitter system.[52-54]

The nucleus accumbens has been identified as part of an ascending pain responsive and regulatory pathway in animal[55,56] and human studies.[13,57,58] It is further interconnected with the amygdala and prefrontal cortical regions as part of a "motive" or "motivational" network responding to salient rewarding and aversive environmental stimuli.[59,60] The finding of a negative relationship between placebo-induced PAG opioid activity and that of supraspinal regions involved in pain and stress suppression suggests the progressive engagement of ascending, endogenous opioid-modulated pathways as a protective mechanism against allostatic burden. Thus, an effective opioid-mediated nociceptive suppression at the level of the PAG would not require the engagement of antinociceptive supraspinal regions, in agreement with the gating role of the PAG in pain regulation.[48,61] An alternative hypothesis would involve a disinhibition of an opioid-mediated suppression of nucleus accumbens, amygdala, and subgenual anterior cingulate activity that would engage descending pathways into the PAG, eliciting more efficient pain suppression at that level. However, positive relationships have been consistently found between endogenous opioid activity in these supraspinal regions and analgesia in the absence[13,57,58] and presence[18] of placebo administration (including the present report), therefore not supporting this scenario.

Together with the PAG, opioid responses in the nucleus accumbens were correlated with the anticipated analgesic effects of the placebo. Nucleus accumbens and amygdala opioid responses to the placebo were also related to the ratio of perceived analgesic to anticipated analgesic effects (addressing the update of expectations during the receipt of the placebo). Both of these regions have been implicated in the updating of reward expectations based on observed environmental information in nonhuman primates[23] and humans,[42] in addition to their known involvement in endogenous opioid antinociception in animal models[55,62] and humans.[13,57,58]

Dopaminergic activity in the nucleus accumbens is activated during both rewarding and aversive environmental events,[24,63] providing a mechanism that responds to salience across valences. These effects have also been observed during pain challenges in which this physical and emotional stressor activated DA D_2/D_3 receptor–mediated neurotransmission in the nigrostriatal (dorsal caudate and putamen) and mesolimbic (nucleus accumbens) terminal fields.[64] In animal models, the tonic firing of mesolimbic DA cells increases with the expectation of a positive outcome (the receipt of a reward larger than expected) and is reduced when the expected outcome is less prominent than that predicted by initial cues.[23] Similar effects have been observed in recent work examining the human response to potential gains and losses in a gambling task using functional MRI as a measure of synaptic activity.[65] Potential gains increased the neural activity of the dorsal and ventral striatum, orbitofrontal cortex, and rostral and subgenual anterior cingulate, whereas potential losses reduced the level of activity in these brain regions. Herein we demonstrate a bidirectionality of placebo and nocebo responses on DA and opioid neurotransmission in these same reward-responsive regions.

The development of placebo analgesia was most strongly predicted by the activation of DA neurotransmission in the nucleus accumbens, accounting for one-fourth of its variance. Dopaminergic activation in this region was further correlated with the regional activation of the μ-opioid system. Nucleus accumbens DA and μ-opioid activity also differentiated high and low placebo and nocebo responders. This brain region is thought to be part of a critical pathway that, through the activation of DA D_2 receptors, responds to the novelty and saliency of a stimulus,[43,44] then engaging a series of interconnected regions regulating motivated behavior.[59,60] Herein we have demonstrated that individual variations in the response of this motivational circuit underlie the development of placebo analgesia and nocebo hyperalgesia. The definition of the pathways, and more specifically the neurotransmitter systems involved in these processes, permits not only the understanding of the neurobiological mechanisms underlying placebo and nocebo responding but also opens the possibility of an exploration of the factors contributing to individual variations in these phenomena.

Motivated behavior has been successfully framed in the context of prospect[66] and decision affect theories,[67,68] whereby decision making and behavior under uncertainty can be predicted by the emotional response to positive and negative expectations and their comparison with observed outcomes (counterfactual comparisons). We observe an overlap between the regions implicated in the assessment of potential gains and losses (eg, nucleus accumbens and medial orbitofrontal cortex)[41,65,69,70] and those engaged in the development of placebo and nocebo effects. Placebo-induced expectations and their update during administration of the placebo were further related to DA and opioid system activity in the nucleus accumbens. This suggests that placebo and nocebo effects represent the physiological counterpart of decision-making processes under conditions of risk or uncertainty.

CONCLUSIONS

We have herein demonstrated that placebo and nocebo effects engage specific neurotransmitter systems as a consequence of cognitive-emotional assessments of their efficacy. Dopaminergic and opioid systems modulate a number of processes, including the regulation of reward and affective states, cardiovascular, immunological, and neuroendocrine functions, as well as the effects of substances of abuse and the development of drug dependence. This line of inquiry offers the possibility that nonpharmacological interventions exploiting these systems may affect the capacity of the organism to adapt to allostatic challenges, modifying risk for various illnesses or their progression.

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