

Original Investigation

Association Between Placebo-Activated Neural Systems and Antidepressant Responses

Neurochemistry of Placebo Effects in Major Depression

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IMPORTANCE High placebo responses have been observed across a wide range of pathologies, severely impacting drug development.

OBJECTIVE To examine neurochemical mechanisms underlying the formation of placebo effects in patients with major depressive disorder (MDD).

DESIGN, SETTING, AND PARTICIPANTS In this study involving 2 placebo lead-in phases followed by an open antidepressant administration, we performed a single-blinded 2-week crossover randomized clinical trial of 2 identical oral placebos (described as having either active or inactive fast-acting antidepressant-like effects) followed by a 10-week open-label treatment with a selective serotonin reuptake inhibitor or, in some cases, another agent as clinically indicated. The volunteers (35 medication-free patients with MDD at a university health system) were studied with positron emission tomography and the μ -opioid receptor-selective radiotracer [^{11}C]carfentanil after each 1-week inactive and active oral placebo treatment. In addition, 1 mL of isotonic saline was administered intravenously within sight of the volunteer during positron emission tomographic scanning every 4 minutes over 20 minutes only after the 1-week active placebo treatment, with instructions that the compound may be associated with the activation of brain systems involved in mood improvement. This challenge stimulus was used to test the individual capacity to acutely activate endogenous opioid neurotransmission under expectations of antidepressant effect.

MAIN OUTCOMES AND MEASURES Changes in depressive symptoms in response to active placebo and antidepressant. Baseline and activation measures of μ -opioid receptor binding.

RESULTS Higher baseline μ -opioid receptor binding in the nucleus accumbens was associated with better response to antidepressant treatment ($r = 0.48$; $P = .02$). Reductions in depressive symptoms after 1 week of active placebo treatment, compared with the inactive, were associated with increased placebo-induced μ -opioid neurotransmission in a network of regions implicated in emotion, stress regulation, and the pathophysiology of MDD, namely, the subgenual anterior cingulate cortex, nucleus accumbens, midline thalamus, and amygdala (nucleus accumbens: $r = 0.6$; $P < .001$). Placebo-induced endogenous opioid release in these regions was associated with better antidepressant treatment response, predicting 43% of the variance in symptom improvement at the end of the antidepressant trial.

CONCLUSIONS AND RELEVANCE These data demonstrate that placebo-induced activation of the μ -opioid system is implicated in the formation of placebo antidepressant effects in patients with MDD and also participate in antidepressant responses, conferring illness resiliency, during open administration.

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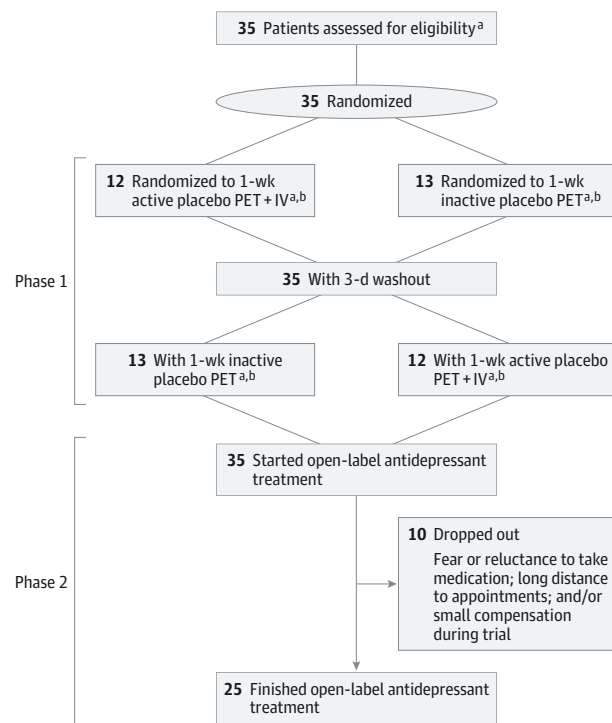
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High rates of placebo responses are consistently reported across medical conditions, notably mood disorders, Parkinson disease, and pain, but also schizophrenia, substance use disorders, and surgical procedures.¹⁻⁵ Placebo response rates in antidepressant trials average 31% to 45% compared with approximately 50% responses to antidepressants, and they have increased over the last 30 years.^{4,5} The failure of antidepressant responses to separate from placebo has contributed to the reduction or discontinuation of research on new treatments for depression and other neuropsychiatric illnesses,⁶ hindering the development of novel neuropsychiatric treatments.⁷

In conditions such as pain, where the neurobiological bases of placebo analgesic effects were first described,⁸ substantial headway has been made to identify their neural and molecular basis. Neural circuits involved in placebo analgesia⁹⁻¹⁴ include the rostral anterior cingulate cortex (ACC), dorsolateral prefrontal cortex and orbitofrontal cortex, insula, nucleus accumbens (NAc), amygdala (AMYG), midline thalamus (THA), and periaqueductal gray. Opioid and dopamine neurotransmissions in these areas are known to modulate various elements of the analgesic placebo effect, including the representation of its subjective value, updates of expectations over time,¹⁵ the recall of pain and placebo experiences,¹⁶ and the changes in affective state and pain ratings.^{12,17,18} Furthermore, genetic variants have shown to modulate these neurotransmitter systems and placebo-associated symptom improvements.¹⁹⁻²¹

In the only study examining the neural correlates of placebo effects in MDD,²² to our knowledge, overlapping changes in metabolism were observed for placebo and selective serotonin reuptake inhibitor (SSRI) arms of a randomized clinical trial (RCT), albeit more extensively with the active agent. In addition, metabolic increases were noted in the ventral striatum and orbitofrontal regions at 1 week, regardless of treatment, regions implicated in reward expectation and monitoring, even in the absence of clinical effects.²³ Here, we investigated μ -opioid receptor (MOR)-mediated neurotransmission as a potential candidate mechanism for the formation of placebo effects in MDD, given the MOR system's involvement in the regulation of emotion, stress and social rewards,^{24,25} and placebo analgesia.^{8,9,12,18,26} The study design incorporated a commonly used placebo lead-in phase with the administration of 2 identical placebos: 1 described as having fast-acting antidepressant effects (active) and 1 described as being a placebo with no antidepressant effects (inactive) (Figure 1). This was done to simulate common trial designs and to appropriately control for other statistical biases, such as the regression to the mean or response biases associated with study participation. In addition to evaluating the effects of sustained placebo pills, an intravenous (IV) placebo administration followed the 1-week active placebo to investigate the effects of acute placebo administration on μ -opioid neurotransmission. Following each placebo intervention, patients underwent a 10-week open-label trial with a common SSRI treatment. We hypothesized that placebo-induced improvement in depressive symptoms would be associated with the capacity to activate endogenous MOR-mediated neurotransmission in brain areas involved in stress

Figure 1. Experimental Design



IV indicates intravenous; PET, positron emission tomography.

^a The 16-Item Quick Inventory of Depression Symptomatology-Self-report.

^b Patient's Impression of Depression Severity.

and mood regulation²⁷⁻³² (ie, subgenual [sg] ACC, NAc, and AMYG). In addition, we hypothesized that learning mechanisms involved during the administration of placebos would reinforce the response to common antidepressants, which might result in interactions between placebo and antidepressant effects.

Methods

Patients and Trial Design

Thirty-five right-handed unmedicated participants with a DSM-5 diagnosis of MDD (23 women; age range, 19-59 years; mean [SD], 35 [13] years) were recruited via advertisement (eAppendix 1 in the Supplement). Written informed consent was obtained in all cases. 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. The study had 2 phases; a 2-week placebo single-blind RCT (starting 3-5 days after the screening interview) and a 10-week open-label flexible-dose antidepressant treatment (Figure 1).

Placebo Phase

During the first phase, patients were randomized to (1) 1-week active oral placebo treatment (2 pills per day), with expectations that it represented a fast-acting antidepressant agent, or

(2) 1-week inactive oral placebo, with disclosure that it was an inactive control. After a 3-day washout period without pills, participants were crossed over into the group to which they were not previously assigned. After each placebo week, participants underwent a positron emission tomographic (PET) scanning session (for data acquisition and statistical analysis, see eAppendix 1 and eFigure 1 in the Supplement). As a challenge to induce endogenous opioid system activation and determine acute placebo effects, the PET session following the 1-week active oral placebo included the administration of an IV active placebo. This consisted of 1 mL of 0.9% isotonic saline-introduced IV every 4 minutes over 20 minutes, starting at minute 42 and lasting for 15 seconds each time. Patients were aware that the study drug was to be administered through a computer-generated human voice recording, followed by a second-by-second count of the infusion timing (15 seconds). No IV placebo followed the inactive placebo condition.

Depression symptoms were assessed using the 16-Item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16)³³ before (baseline) and after each placebo treatment. A single measure of sustained placebo response was created by subtracting the changes in QIDS-SR16 reductions from active and inactive placebo treatments ([QIDS-SR16 pre and post] active placebo – [QIDS-SR16 pre and post] inactive placebo). Positive numbers then reflected reductions in depression symptoms as a result of oral placebo, and this variable was used for correlational analysis and to dichotomize patients into placebo responders (positive values, $n = 14$) and nonresponders (0 or negative values, $n = 21$) (mean [SD], 1.2 [5.4]; range, –10 to 16).

The IV placebo treatment was only administered during the scanning session that followed the active placebo. Patients' impression of severity (PIDS) ratings ("From 0 to 100, how depressed do you feel now?") were acquired every 4 minutes during the 2 PET scans in the presence and absence of the IV placebo. Acute, IV placebo responses were assessed by the subtraction: PIDS and no IV – PIDS and active IV.

Antidepressant Phase

Following the placebo phases and the 2 PET sessions, patients were invited to participate in an unblinded 10-week open-label trial with a commercially available SSRI, in most cases citalopram (starting at 20 mg per day and up to 40 mg per day in 77% of cases). An alternative agent was used if clinically indicated (eg, history of prior nonresponse to citalopram). Other treatments included sertraline hydrochloride ($n = 1$), mirtazapine ($n = 1$), fluoxetine hydrochloride ($n = 3$), and bupropion hydrochloride ($n = 2$). Participants were evaluated at weeks 0, 2, 4, 8, and 10 using the QIDS-SR16 to evaluate symptom change.

Nonaggregated depression symptoms during the 10-week open-label treatment were assessed using linear mixed-effects models^{34,35} (Stata version 11; StataCorp). The longitudinal measurements of QIDS-SR16 during the open trial were the repeated-measures outcomes. Baseline QIDS-SR16 scores and week of the trial were included as covariates, which were also fit with random intercepts. Two continuous measures of placebo response were examined: sustained (oral) and acute (IV)

placebo effects. By including a main effect and an interaction term with time for each predictor, the main effect was interpreted as the effect of the predictor on QIDS-SR16 scores at the beginning of the open-label trial, and the interaction term was interpreted as the degree to which the trajectory of QIDS-SR16 score over the 10-week trial varied by level of the predictor.

We also ran mixed-effects models using a categorical variable that grouped participants as placebo responders or nonresponders (as described here). A χ^2 test was used to evaluate the effect of placebo responsiveness group on remission rates. All statistical analyses were controlled by sex, order effects, and QIDS-SR16 prerandomization scores.

Results

Placebo-Induced Changes in Depression Symptoms

The patients' characteristics are reported in eAppendix 2 in the Supplement. As expected, no significant differences were observed between the 2 pretreatment QIDS scores (mean [SD], QIDS baseline for inactive placebo: 13.3 [4.9] and QIDS baseline for active placebo: 14.2 [4.7]; $t = -1.2$; $P = .24$). The administration of 1 week of active placebo, compared with inactive, was associated with significant reductions in depression symptoms (mean [SD] Δ , QIDS-SR16 pre- and post-active placebo: 1.75 [3.39] and QIDS-SR16 pre- and post-inactive placebo: –0.15 [3.36]; $F = 5$; $P = .03$). The IV acute placebo administration was also associated with a significant reduction in the average PIDS scores (mean [SD], PIDS with active IV, 42 [26] and PIDS with no IV, 49 [22.4]; $F = 4.3$; $P = .04$).

Oral placebo-induced improvement of depression symptoms (measured with Δ QIDS-SR16) was significantly correlated with the changes in PIDS scores after IV placebo administration ($r = 0.35$; $P = .04$). Conversely, placebo-induced changes in QIDS-SR16 and PIDS scores were not correlated with QIDS-SR16 scores at baseline, patients' age, or initial expectations of recovery rated prior to the placebo treatments (for all, $P > .05$). Women showed greater oral placebo-induced reductions in depression symptoms compared with men (mean [SD]: women, 2.7 [5.3] and men, –1.6 [4.4]; $t = 2.3$; $P = .02$), but not after the IV placebo administration. Finally, patients who received the active oral placebo first in order reported greater oral placebo-induced reductions in depressive symptoms than those who received the active oral placebo second (mean [SD]: first, 3.4 [5.7] and second, 0 [3.3]; $t = -2.1$; $P = .04$). Therefore, sex and order were introduced as covariates in subsequent analyses, together with depression severity.

Baseline MOR Binding Potential and Placebo-Induced Activation of MOR-Mediated Neurotransmission

We first evaluated the relationship between baseline MOR binding potential nondisplaceable (BP_{ND}) (postinactive placebo condition measures of MOR BP_{ND}), depression severity prerandomization scores, acute and sustained placebo responses, and antidepressant responses using BP_{ND} measures acquired 5 to 40 minutes posttracer administration. While these postinactive placebo condition measures of MOR BP_{ND} may not represent a true baseline, no significant differences in MOR BP_{ND}

Figure 2. Voxel-by-Voxel μ -Opioid Receptor Availability at Baseline Positively Correlated With Depression Severity (A) and With Antidepressant Treatment Response (B)

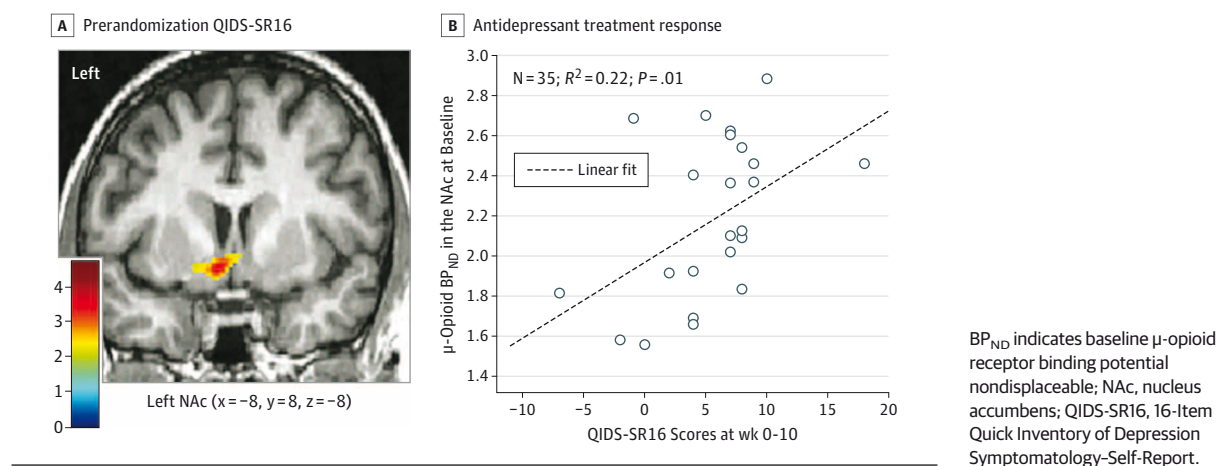


Table. μ -Opioid BP_{ND} at Baseline and Placebo-Induced Reductions in μ -Opioid BP_{ND}—Correlations With Depression Improvement After Placebo and Antidepressant Treatment

					Effects of Regional Placebo-Induced Opioid Release on Antidepressant Response	
Region	Hemisphere	x, y, z, mm ^a	Cluster Size, mm ³	z ^b	Estimate	SE (95% CI)
Baseline μ-Opioid BP _{ND} Correlation With QIDS-SR16 at Screening						
NAC	Left	-8, 8, -8	200	3.76	-0.71	0.18 (-1.05 to -0.36)
Placebo-Induced μ-Opioid BP _{ND} Decrease						
NAC	Left	-8, 2, -4	552	4.72	-0.43	0.22 (-0.85 to -0.004)
Placebo-Induced μ-Opioid BP _{ND} Decrease Correlation With Improvement of Depression Symptoms Measure With the QIDS-SR16						
THA	Left	-4, -8, -4	4888	6.4	-1.02	0.23 (-1.47 to -0.56)
NAC/sgACC	Left	-14, 10, -8	1064	4.49	-0.8	0.2 (-1.18 to -0.41)
	Right	8, 8, -12	1136	4.43	-0.68	0.23 (-1.14 to -0.22)
AMYG	Left	-36, -4, -18	352	3.84	-0.38	0.28 (-0.93 to 0.17)
Placebo-Induced μ-Opioid BP _{ND} Decrease Correlation With Improvement of Depression Symptoms Measure With the PIDS						
sgACC	Left	-4, 10, -6	256	4.19	-0.61	0.2 (-1.01 to -0.22)
AMYG	Left	-22, -2, -24	272	4.19	-0.39	0.2 (-0.79 to 0.01)
Placebo-Induced μ-Opioid BP _{ND} Decrease Correlation With Improvement of Depression Symptoms After 10 wk of Antidepressant Treatment						
THA	Right	0, -8, -2	3584	5.41	-0.98	0.23 (-1.44 to -0.52)
NAC/sgACC	Right	6, 8, -8	1136	4.49	-1.12	0.23 (-1.58 to -0.66)
AMYG	Left	-26, -10, -16	392	3.99	-0.6	0.2 (-1.0 to -0.2)

Abbreviations: AMYG, amygdala; BP_{ND}, binding potential nondisplaceable; NAC, nucleus accumbens; PIDS, patients' impression of depression severity; QIDS-SR16, 16-Item Quick Inventory of Depression Symptomatology-Self-report; sgACC, subgenual anterior cingulate cortex; THA, thalamus.

^a Montreal Neurological Institute coordinates of peak voxel.

^b 2-Sided voxel-level z score at peak voxel and $P < .001$, uncorrected for AMYG, sgACC, and NAC; familywise error corrected for all other regions.

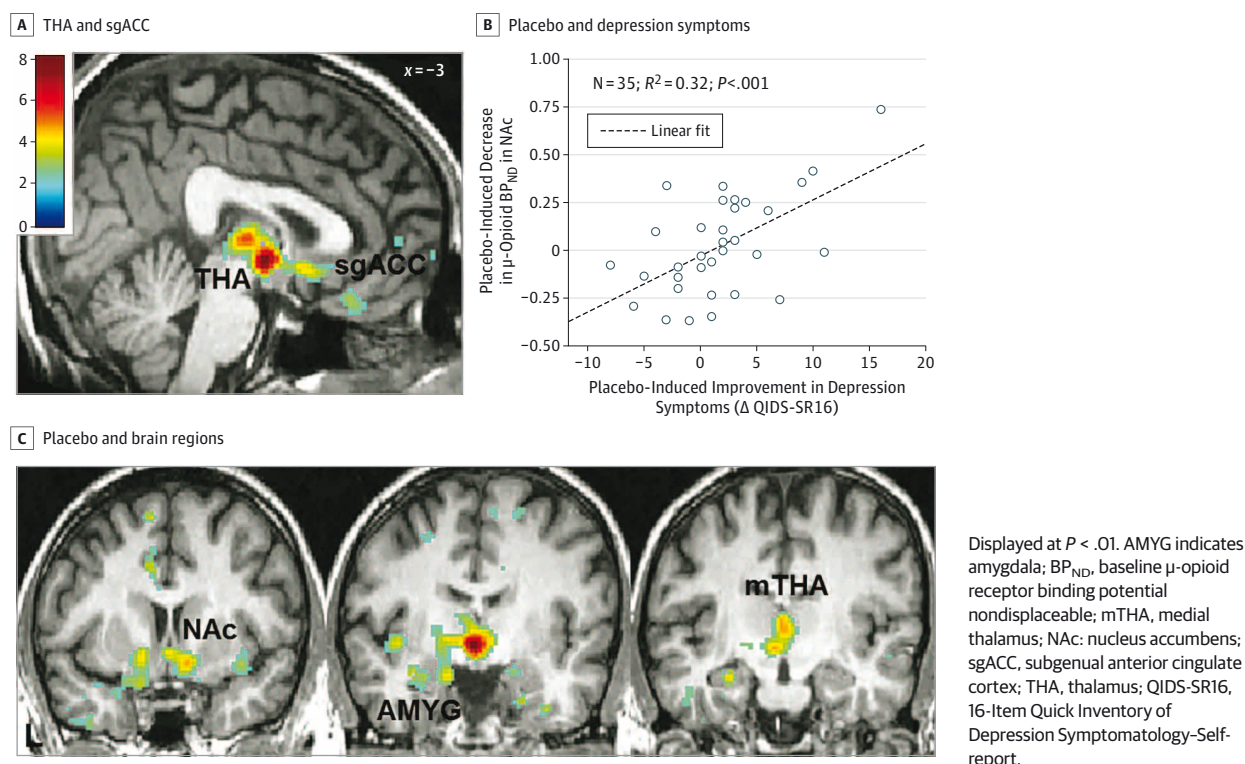
were observed between the active and the inactive conditions during the early scan measures (5-40 minutes), when no IV placebo was administered, which confirms the stability of the BP_{ND} values in the absence of an acute challenge. A whole-brain voxel-by-voxel analysis showed a significant positive relationship between QIDS-SR16 prerandomization scores and baseline MOR BP_{ND} in the NAC (Figure 2; Table). The NAC MOR BP_{ND} was also significantly correlated with improvement in QIDS-SR16 score after 10 weeks of antidepressants ($n = 25$; NAC: $r = 0.48$; $P = .02$). Instead, baseline MOR BP_{ND} was not associated with depression symptom improvements in response

to 1-week oral or IV placebo administration; therefore, imaging analyses examining the effect of placebo on neurotransmitter release were not controlled for baseline BP_{ND}.

Second, we examined the main effect of IV placebo administration on μ -opioid system activation (reductions in BP_{ND} when compared with no IV placebo). Significant activation of μ -opioid neurotransmission after IV placebo was localized in the NAC (Table).

Third, we investigated the relationship between changes in MOR BP_{ND} in response to IV placebo and the sustained and acute placebo responses. Improvement in QIDS-SR16 score af-

Figure 3. Association Between Voxel-by-Voxel Placebo-Induced Activation of μ -Opioid Receptor-Mediated Neurotransmission and Placebo-Induced Improvement in Depression Symptoms



ter the active oral placebo, compared with the inactive, was positively associated with placebo-induced opioid release in multiple brain areas, including the sgACC, NAC, AMYG, and the midline THA, the latter peak extending to the hypothalamus (Figure 3; Table). Reductions in PIDS score during scanning after IV placebo administration were also associated with greater placebo MOR system activation in the sgACC and AMYG (Table).

Last, we examined the relationship between IV placebo activation of endogenous opioid neurotransmission and depression improvement after 10 weeks of antidepressant use. Reductions in QIDS-SR16 scores ($n = 25$) after open-label trial were significantly associated with placebo-induced MOR system activation in the same network of regions associated with placebo antidepressant effects: sgACC, NAC, AMYG, and midline THA (Figure 4; Table).

Placebo-Induced Δ in QIDS-SR16, Δ PIDS, and Δ in μ -Opioid BP_{ND} as Predictors of Antidepressant Treatment Response

The mixed-model analyses revealed that sustained oral placebo responses were associated with significant reductions in QIDS-SR16 scores during antidepressant treatment over time but not acute IV placebo responses (eTable in the Supplement).

The categorical analysis showed that the sustained oral placebo responder group showed larger reductions in QIDS-SR16 scores during antidepressant treatment compared with nonresponders; however, this effect was only present after 4 weeks of its administration (eFigure 2 in the Supplement). By weeks 8 and 10, the mean QIDS-SR16 score was roughly twice as high among placebo nonresponders compared with pla-

cebo responders. Achievement of remission (QIDS-SR16 score ≤ 5) was also significantly higher in placebo responders, with 60% of those categorized as placebo responders and only 20% of nonresponders being considered in remission ($\chi^2 = 3.9$; $P = .048$).

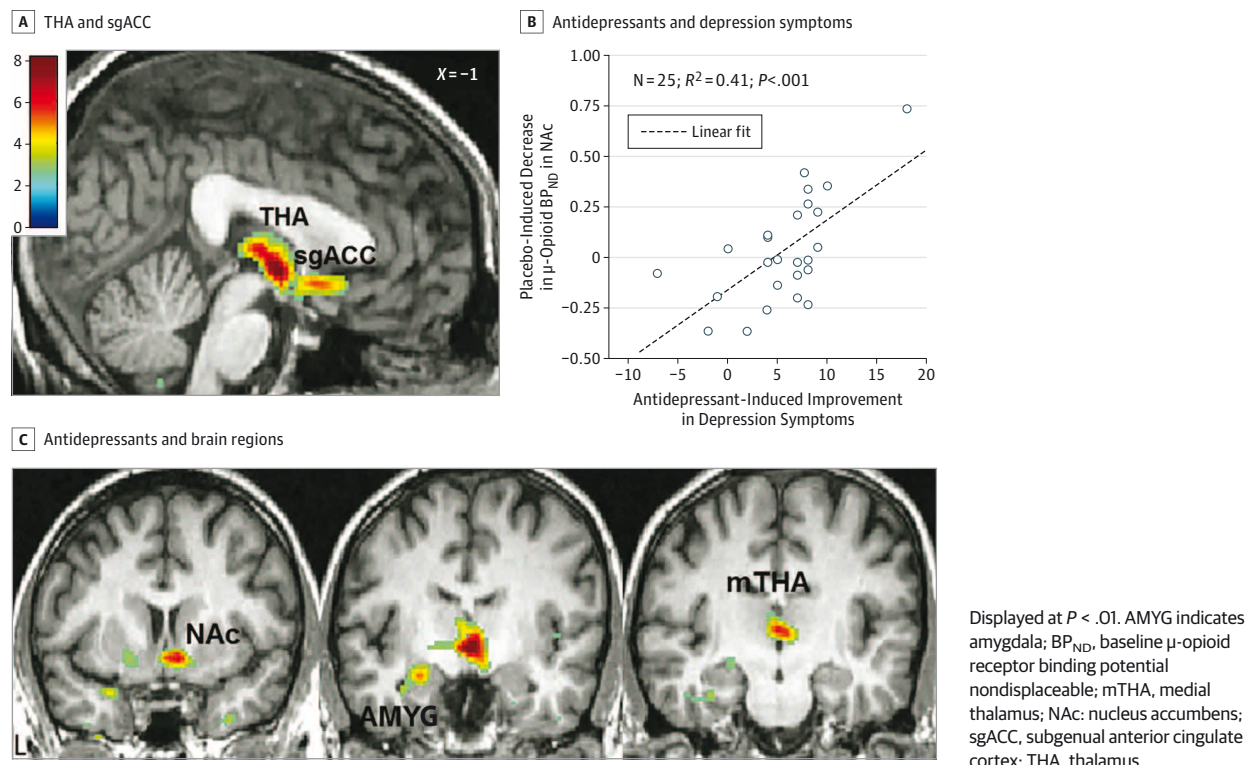
Furthermore, the capacity to activate the MOR system during placebo administration was associated with greater reductions in QIDS-SR16 score over the 10-week trial (Table; Figure 4). A simple regression model that included objectively measured placebo-induced opioid release in the sgACC, NAC, THA, and AMYG as regressors accounted for 43% of the variance in the response to open-label antidepressant treatment (adjusted $R^2 = 0.43$). Similarly, subjective clinical placebo responsiveness itself predicted 46% of the variance in the response to 10 weeks of antidepressant treatment (adjusted $R^2 = 0.46$), while the combination of both the clinical and the opioid release measures predicted 57% of the variance in the response to 10 weeks of antidepressant treatment (adjusted $R^2 = 0.57$).

Discussion

To our knowledge, the present study is the first direct demonstration of the role of a specific neurotransmitter system, namely MOR-mediated neurotransmission, in the formation of placebo effects in MDD and provides an explanation of the variability in antidepressant treatment responses.

Substantial evidence supports the possible implication of the endogenous opioid system in the modulation and regula-

Figure 4. Association Between Voxel-by-Voxel Placebo-Induced Activation of μ -Opioid Receptor-Mediated Neurotransmission and Open-Label Antidepressant Treatment Response



tion of emotional states as well as in the pathophysiology of various psychiatric illnesses, including MDD.^{36,37} Here, we described that in patients with MDD, higher baseline MOR BP_{ND} in the NAc was associated with both higher depression symptoms and antidepressant, but not placebo, responsiveness. Alterations in MOR BP_{ND} and function have been previously described in MDD and linked to both dysfunctions in the neuroendocrine hypothalamic-pituitary-adrenal axis and treatment nonresponsiveness.³⁸

The activation of the MOR system has also been implicated in the formation of placebo effects in pain,^{9,12,17,18,39,40} suggesting that similar neurobiological mechanisms can contribute to the formation of clinical placebo effects across pathologies. By comparison, one single previous neuroimaging study aimed to define the neuroanatomy of placebo responses in MDD²² using metabolic PET imaging in a group of men with depression during an RCT with an SSRI. This study showed overlapping metabolic changes with both SSRI and placebo at 6 weeks and early (1-week) increases in activity in the NAc and orbitofrontal cortex regardless of treatment. Here, we observed a similar pattern of activation in the NAc, but also the sgACC, midline THA, and AMYG, in response to 1 week of placebo, but within a specific neurochemical system, the endogenous opioid and MORs. While not a priori hypothesized, the midline THA has strong and specific connections with the AMYG, NAc, and sgACC as shown in rodent and nonhuman primate studies.⁴¹ These connections represent pathways by which the midline THA, known to be strongly activated by a

wide variety of stressors, may influence structures that regulate motivation and mood.⁴¹

Importantly, placebo-induced MOR system activation in stress and emotion regulatory regions (ie, sgACC, THA, NAc, and AMYG)⁴²⁻⁴⁶ predicted 43% of the variance in the response to antidepressant treatment after 10 weeks. Similarly, subjective clinical placebo responsiveness itself predicted 46% of the response to antidepressant treatment, while the combination of both predicted 57% of the total antidepressant response. Still, by weeks 8 and 10, depression severity scores were roughly twice as high among placebo nonresponders compared with placebo responders. This observation may indicate that the endogenous opioid system, through MORs, reinforces treatment responses over time, a form of positive reward learning, as has been suggested by data acquired in the field of pain and Parkinson disease^{15,47,48} and in animal models of reward learning.⁴⁹ Alternatively, it could be possible that this effect is explained by the patient expectations of delayed response to common antidepressant treatments, disclosed prior to the initiation of the active treatment. Furthermore, achievement of remission was also significantly higher among placebo responders compared with nonresponders, an observation that potentially challenges a common tenant that eliminating placebo responders in clinical trials with placebo lead-in phases or novel sequential parallel comparison designs⁵⁰ would help to more clearly interpret RCT results.

Several hypotheses could explain these findings. First, it is possible that mechanisms involved in placebo responding are

also engaged during antidepressant treatment. In this regard, a number of studies have shown that the analgesic effects of tricyclic antidepressants are reversed by opioid receptor antagonists⁵¹⁻⁵⁵ and that tricyclic antidepressants potentiate morphine-induced analgesia both in animals⁵⁶ and in humans.⁵⁷ From another perspective, compounds such as buprenorphine, a partial μ -opioid agonist, exhibit antidepressant properties in treatment-refractory patients with depression,⁵⁸ leading to studies examining the modulation of opioid mechanisms in MDD.⁵⁹ If aminergic and opioid interactions synergistically improve depressive symptoms, greater placebo-like (eg, opioid-mediated) responses would be expected within active treatment arms, compared with the placebo arm, compromising the interpretation of RCTs. A different possibility would be that the overall reduction of depressive symptoms in an open-label treatment could be explained by a combination of specific and non-specific effects, which, in addition to placebo neurobiological effects, may include variations in the natural history of illness, regression to the mean, reporting biases, or lack of adherence

to the treatment (which was not assessed in this study beyond the patients' reports). However, these nonspecific effects are not likely to be linked to placebo-activated neurotransmission or be represented differentially in placebo responders or nonresponders.

Conclusions

Our results show that placebo administration impacts homeostatic, resiliency mechanisms that can facilitate recovery from illness and could be seen as a probe for the development of new therapeutic targets that regulate those biological processes. In clinical trials, this evidence could help inform decisions regarding patient stratification and drug-specific or nondrug-specific effects. In clinical practice, placebo responsiveness could potentially indicate the likelihood of responsiveness to enhanced patient-clinician interactions or psychosocial or cognitive approaches.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Peciña, Zubieta.

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