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Neural Correlates of Placebo Analgesia and Emotion Regulation: A Coordinate-Based Neuroimaging Meta-Analysis

Javeria Noor & Muhammad Aqeel

Abstract

Background: Placebo analgesia and emotion regulation engage overlapping cognitive and affective mechanisms, yet the extent of shared versus distinct neural circuits remains unclear. This study aimed to: (i) identify brain regions consistently activated during placebo response and emotion regulation, (ii) quantify neural overlap between these processes, and (iii) characterize top-down versus bottom-up network engagement through contrast analyses.

Method: A coordinate-based meta-analysis was performed using Activation Likelihood Estimation (ALE) across published fMRI studies of placebo analgesia and emotion regulation in healthy adults. Conjunction analyses identified shared neural substrates, while contrast analyses isolated process-specific regions reflecting top-down (emotion regulation) versus bottom-up (placebo) mechanisms. Literature was systematically searched using the NeuroSynth Compose tool, applying stringent inclusion/exclusion criteria: only studies with healthy adults (≥18 years), fMRI-based paradigms, sample size ≥15, and direct investigation of placebo analgesia or emotion regulation were included. Data extraction followed a uniform template to ensure consistency. ALE maps of local maxima were generated, and subsequent conjunction and subtraction analyses were conducted to delineate overlapping and distinct activation patterns.

Results: Conjunction analysis revealed bilateral insula activation as a shared hub integrating interoceptive awareness and cognitive appraisal. Contrast analyses demonstrated that emotion regulation preferentially engaged the middle temporal gyrus, hippocampus/amygdala complex, inferior frontal gyrus, and supplementary motor area (SMA), reflecting top-down control, semantic processing, and emotion modulation. In contrast, placebo analgesia elicited stronger activation in the mid-cingulate cortex, Rolandic operculum, basal ganglia, and bilateral insula, consistent with bottom-up expectancy, sensory integration, interoceptive processing, and reward-related learning.

Conclusions: These findings support a dual-process model wherein both placebo response and emotion regulation share salience and interoceptive processing via the insula, but differ in their engagement of top-down versus bottom-up networks. This work advances our understanding of the neural architecture underlying internally generated versus expectancy-driven affective modulation and informs the development of non-pharmacological interventions for pain and emotion regulation.

Keywords: Placebo analgesia, emotion regulation, fMRI, activation likelihood estimation, meta-analysis, neural mechanisms.

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Background

Emotion regulation is a fundamental component of psychological well-being, and impairments in this ability are implicated in a wide range of mental health disorders (Gross, 2015). Within affective neuroscience, two strategies have received the most empirical attention: expressive suppression**,** which involves inhibiting emotional expressions after an emotion has been generated, and cognitive reappraisal**,** which involves reinterpretation of an emotional situation to modify its impact (McRae & Gross, 2020). Cognitive reappraisal—also referred to as adaptive reappraisal is consistently linked to positive psychological outcomes, whereas expressive suppression is typically associated with poorer social functioning and heightened physiological stress (Gross & Levenson, 1997; Aldao et al., 2010; Cutuli, 2014).

Neurobiological models suggest that effective emotion regulation involves prefrontal parietal network that exerts top-down control over subcortical emotion-generative regions (Ochsner et al., 2012). Cortical regions such as the ventrolateral PFC (VLPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and dorsomedial PFC (DMPFC) play a key role in cognitive control functions like attention, inhibition, and goal maintenance. These regions regulate activity in subcortical structures, including the insula, amygdala and ventral striatum, which are involved in affective salience, interoception and reward processing (Berridge & Kringelbach, 2008; Costafreda et al., 2008; Lindquist et al., 2012; Sergerie et al., 2008; Zaki et al., 2012). Additionally, reappraisal consistently reduces amygdala activation, indicating diminished affective reactivity (Buhle et al., 2014; Messina et al., 2015).

Cognitive reappraisal involves domain-general cognitive regions such as bilateral DLPFC, DMPFC and VLPFC posterior parietal cortex. These are the areas which support processes like working memory, mentalizing, semantic re-evaluation, and response inhibition (Buhle et al., 2014; Kalisch, 2009; Kohn et al., 2014; Morawetz et al., 2017; Powers & LaBar, 2019). The left posterior temporal cortex also plays a role in semantic processing by enabling to reinterpret emotionally salient stimuli. Resting-state studies further reveal that individual differences in reappraisal ability are associated with Default Mode Network (DMN) connectivity, which supports cognitive processes such as autobiographical memory and, self-referential thought which are integral to the reappraisal process (Martins & Mather, 2016; Morawetz et al., 2017; Sripada et al., 2014; Xie et al., 2016).

Additionally, placebo effects, especially placebo analgesia, represent how affective and cognitive expectations modulate neural processing. Placebo effects in pain contexts are driven by expectancy treatment, which is the belief in therapeutic benefit after receiving an inert intervention. These effects can be influenced by conditioning, verbal suggestion, and social influence, both with deception and in open-label forms (Colloca & Howick, 2018). Neuroimaging evidence shows that the brain regions activated during placebo analgesia overlap with fronto-cortical regions, including the VLPFC and DLPFC, as well as subcortical structures like the thalamus, amygdala, insula regions and periaqueductal gray. These regions are involved in interoception, pain processing and affective modulation (Koban et al., 2019; Oken, 2008; Wager et al., 2004).

During the placebo effect, both dopamine and opioid systems are activated, which are involve in the brain processes such as rewards and emotional regulation (Theodosis-Nobelos et al., 2021). Therefore, they share common neurochemical basis and require high-level brain activity to influence perception of events. Neuroimaging research also suggests that placebo analgesia and cognitive reappraisal share common neural substrates, especially in frontal-parietal networks that regulate cognition and attention, as well as emotion generative and pain-related areas like the amygdala, insula, and ventral striatum(Bo et al., 2024; Čeko et al., 2022). Although the two processes differ in timing and awareness, placebo responses usually begin before the event through formed expectations and often work unconsciously. On the other hand, reappraisal takes place during the event and involves a conscious effort to rethink the situation (Botvinik-Nezer et al., 2024; Kober et al., 2019; Schafer et al., 2015). Moreover, open-label placebos appear to activate distinct networks, depending more on ventromedial PFC and limbic regions rather than lateral prefrontal regions, emphasizing the roles of belief, awareness, and context (Ashar et al., 2024; Schaefer et al., 2023).

Despite substantial research on each domain independently, no study has yet conducted a direct meta-analytic comparison of the neural correlates of placebo analgesia and cognitive emotion regulation. Existing meta-analyses have delineated their respective neural networks (Buhle et al., 2014; Messina et al., 2015; Morawetz et al., 2017; Zunhammer et al., 2021) but an integrative framework remains lacking.

The present study aims to fill this gap by conducting a coordinate-based Activation Likelihood Estimation (ALE) meta-analysis (Laird et al., 2005) of fMRI studies investigating placebo analgesia and cognitive emotion regulation in healthy adults. The purpose of the study is to explore neural pathways during placebo effects and emotional regulation. This is done by identifying common pattern, through conjunction analysis and distinct pattern, through contrast analysis. Thus, the research provides a comprehensive understanding of functional brain dynamics. It is hypothesized on the basis of existing literature that significant overlap in ACC, DLPFC, and insula suggests common top-down modulatory mechanisms. Furthermore, it is anticipated that multisensory and self-referential regions such as the superior temporal sulcus and precuneus would converge (Beauchamp, 2005; Buckner et al., 2008; Utevsky et al., 2014). This study aims to develop a more unified model of cognitive-affective modulation by addressing the common and distinct neural substrates of emotion regulation and placebo analgesia. This may influence the development of integrated clinical strategies that enhance emotional resilience and therapeutic outcomes (Raio et al., 2013; van der Meulen et al., 2017).

Method

Research Design

In the present study, findings from multiple neuroimaging investigations were synthesized using a coordinate-based meta-analytic framework. This approach enables systematic integration of data across studies that differ in participant characteristics, analytic pipelines, and experimental designs. Specifically, the Activation Likelihood Estimation (ALE) method was employed to identify brain regions consistently implicated in placebo analgesia and emotion regulation. By aggregating peak activation coordinates from independent studies, ALE mitigates common limitations such as small sample sizes, methodological variability, and inconsistent results.

This meta-analytic approach was used to:

i. Identify the core neural substrates underlying placebo responses and emotion regulation.

ii. Quantitatively evaluate neural convergence and divergence through conjunction and subtraction analyses.

iii. Control for methodological heterogeneity, thereby enabling a more reliable and generalizable synthesis of findings across diverse paradigms.

iv. Implement rigorous statistical correction procedures, including false discovery rate (FDR) adjustments, to minimize the likelihood of false-positive results.To examine the neural mechanisms of emotional control and placebo-induced modulation, two separate ALE analyses were first conducted one for placebo analgesia and one for emotion regulation. Conjunction and subtraction analyses were then performed to determine shared and distinct patterns of activation between the two processes.

Following agreement on predefined inclusion criteria, the authors jointly conducted a systematic literature search using established keywords. To minimize selection bias and ensure a high-quality dataset, the full screening procedure was performed independently by the investigators, in accordance with contemporary meta-analytic guidelines (Müller et al., 2018). For the placebo-response analysis, one investigator conducted an independent review of all articles in the agreed dataset, which was subsequently evaluated and approved by all co-authors. For the emotion down-regulation analysis, the dataset of eligible studies was independently compiled by another investigator and validated by the research team.

Study Design and Meta-Analytic Approach

This study performed a coordinate-based meta-analysis to systematically explore the neural bases associated with the placebo response. The main aims were to (i) identify brain areas that are consistently activated in fMRI research on placebo response and emotional regulation (ii) to assess the degree of overlap between the areas activated during placebo response and emotional regulation, thereby delineating top-down versus bottom-up modulatory networks. Additionally, contrast analysis aimed to identify regions concerning bidirectional processing to explore (iii) regions more engaged during emotion regulation compared to placebo (contrast 1), reflecting predominantly top-down control mechanisms (iv) regions more engaged during placebo compared to emotion regulation (contrast 2), reflecting predominantly bottom-up sensory and expectancy-driven processes. The study utilized a coordinate-based Activation Likelihood Estimation (ALE) meta-analysis using the NeuroSynth Compose tool (https://compose.neurosynth.org/) to achieve this aim. ALE meta-analysis was used to map neural processing in healthy individuals, directly comparing emotion regulation and placebo activations, followed by conjunction and subtraction analyses to identify their overlapping and specific patterns. This approach improves the generalizability and reliability of the results by providing coordinates of local maxima, which allowed for the integration and evaluation of data from multiple published fMRI studies. This advanced meta-analytic technique provided a reliable method which made it easier in identifying the brain networks that remain constantly active during the placebo response. Additionally, it investigated common limitations of individual fMRI studies, such as replication issues, small sample sizes, and analytic variation, which could amplify false positives and increase the likelihood of false negatives (Genon et al., 2022; Müller et al., 2018).

Literature Search and Study Selection

Placebo Response Ale Meta-Analysis

A comprehensive literature search was conducted using the NeuroSynth Compose tool (https://compose.neurosynth.org/) to identify eligible studies for the ALE meta-analysis. The search strategy incorporated key terms related to placebo mechanisms combined with neuroimaging terminology :("placebo response in pain" OR "placebo analgesia" OR "placebo pain relief") AND ("fMRI") AND ("healthy adults") NOT ("meta-analysis" OR "review") NOT ("sample size < 15")**.**

The specific inclusion and exclusion criteria were used in the participant selection process to ensure methodological integrity and relevance. Firstly, only studies directly investigating placebo analgesia (i.e., the reduction of pain produced by a placebo) or placebo response related to pain were included. Secondly, the studies needed to use functional magnetic resonance imaging (fMRI) to explore the neural mechanisms of placebo analgesia. Although the primary focus was on fMRI studies, studies were required to include only healthy adults (18 years or older). Thirdly, systematic reviews that included several meta-analyses were included, to provide a wider picture of previous findings. Studies with fewer than 15 participants were excluded, as small sample sizes might have an impact on statistical test power and generalizability. To ensure consistency across data extraction within the analysis, several studies. To ensure consistency throughout data extraction within the analysis, English studies were deliberately selected. Finally, no restrictions were imposed on publication status or the participant's cultural background to reduce publication bias and improve the comprehensiveness of the findings. This method ensured that the meta-analysis encompassed a diverse array of studies, leading to a more thorough understanding of the placebo effect in pain relief.

Screening Procedure

The initial search identified 42 studies. No duplicates were found. After title and abstract screening, 6 studies were excluded as irrelevant, resulting in 36 candidate studies. Eight additional articles were excluded based on full-text evaluation.

Inter-rater agreement during the first screening phase was 78%, indicating acceptable reliability. Discrepancies were resolved through discussion, and full-text review was subsequently conducted for the remaining 28 studies**.** Any uncertainties regarding eligibility were addressed through consensus among the authors. This systematic and collaborative screening approach aligns with contemporary methodological recommendations and ensured a high-quality dataset for the ALE meta-analysis.

Data Extraction

It was conducted for every study that fulfilled the established inclusion criteria. A uniform template was utilized to maintain consistency throughout the entries. The key information is documented from each study. This method enabled a concise and structured integration of findings from various techniques.

Coordinate-Based Meta-Analysis

Table 1 summarizes 28 functional neuroimaging studies examining the neural substrates of placebo responses. For each study, the following information is provided: study identifier (serial number, authors, and year), sample size (healthy adults), task or experimental condition, reported brain regions, neuroimaging modality, and principal findings. Additionally, the original contrasts used in each study for the ALE meta-analysis are indicated, along with the number of reported foci and the stereotactic space (MNI coordinates).

All studies reported results in normalized stereotactic space (Montreal Neurological Institute; MNI). For the ALE meta-analysis, relevant parameters including sample size and activation coordinates were extracted. The analysis incorporated brain regions exhibiting both increased and decreased activation under placebo conditions. For visualization purposes, ALE maps were projected onto a standardized MNI152 anatomical template using MRICroGL (see Table 1 and Figure 1).

Emotional regulation ale meta-analysis

A parallel ALE meta-analysis was conducted to examine the neural correlates of emotion regulation. Relevant studies were identified using the NeuroSynth Compose tool (https://compose.neurosynth.org/) with the following search query:("emotion regulation" OR "affective control") AND ("fMRI" OR "neuroimaging") AND ("MNI" OR "Talairach") AND ("healthy participants" OR "healthy controls") AND ("explicit emotion modulation tasks") NOT ("meta-analysis" OR "Activation Likelihood Estimation" OR "Seed-based d Mapping" OR "MKDA").

The same methodological selection criteria as for the placebo meta-analysis were applied. The initial search yielded 947 studies. After removing duplicates and screening for relevance, 286 studies were evaluated in detail. Following title and abstract screening by two independent blinded reviewers, 210 studies were deemed potentially relevant. Of these, 9 studies were excluded for insufficient methodological details, 30 studies for limited rigor, and 37 studie**s** for being outside the scope.

Given the large number of eligible studies (n = 210), a representative sample of 14 high-quality studies is presented in Table 2, selected based on methodological rigor, sample size, geographic diversity, and relevance to primary outcomes.

Coordinate-Based Meta-Analysis of Placebo

Table 2 presents an overview of the 14 studies included in the quantitative ALE meta-analysis examining the neural bases of emotion regulation. The table reports, from left to right, the study number (N), authors and publication year, number of subjects (healthy adults), type of task used (with conditions), brain regions, imaging technique, main findings, and the original contrasts included in each ALE analysis, along with their respective number of foci and standard anatomical space.

This study investigates a specific neural phenomenon using a meta-analytic approach to integrate and analyze findings from multiple studies. Activation Likelihood Estimation (ALE) was employed to examine consistent patterns of brain activity across these studies (Samartsidis et al., 2017). The process began with a comprehensive literature review to identify high-quality studies. Key activation coordinates from these studies were compiled into a database, allowing the spatial distribution of activations to be assessed while accounting for variability across experiments (Farah et al., 2014; Samartsidis et al., 2017).Statistical thresholds and significance testing were then applied to identify brain regions that were consistently active across studies. This meta-analytic approach provides a robust and comprehensive overview of the neural mechanisms underlying emotion regulation by combining results from independent research (see Table 2 and Figure 2).

Results

In the Table 3, the ALE meta-analysis identified seven significant clusters that survived cluster-level FDR correction at $p \leq 0.05$, associated with brain regions consistently activated during placebo responses. A threshold of $Z \geq 3.28267$ and a minimum cluster size of 32 voxels were applied. Clusters were observed in both cortical and subcortical regions. Cluster 1 displayed significantly higher activation in the right middle cingulate cortex (6.8, 8.0, 43.3) with a strong activation value ($Z = 4.26$, $p = 0.00003$). This brain region emphasizes its function in processing pain, controlling cognition, and regulating emotions. This region is often involved in placebo analgesia and is crucial for assessing both internal and external stimuli.

Cluster 2 demonstrated significantly increased activation in the right rolandic operculum (54.8, –25.2, 23.4), with a robust value ($Z = 3.89$, $p = 0.00010$). This region is engaged in processing sensorimotor activities and integrating somatosensory information. This area contributes to bodily awareness and is associated with emotional reactions and pain perceptions. Cluster 3 revealed a significant increase in activation in the left insular cortex (–35.2, 13.9, 7.1), with a robust value ($Z = 3.72$, $p = 0.00020$). This area plays a key role in controlling emotions, regulating pain, and identifying internal body signals. This region is vital to the brain's salience network as it identifies significant stimuli like pain and placebo signals. In contrast, Cluster 4 demonstrated statistically significant activation in right cerebellar lobule VI, (6.8, –26.7, –18.7), with a value ($Z = 3.29$, $p = 0.00100$). This region plays a key role in cognitive and emotional processes and involved in coordinating movement. Also, this area is recognized for expectancy-related placebo effects and helps in pain processing and emotion regulation.

Cluster 5 exhibited moderate but significant activation vermis lobule VI (0.2, –30.4, –9.1), with a value

(Z = 2.81, p = 0.00200). This area maintains equilibrium, regulates emotions, and overseeing autonomic functions. The emotional components of pain and the changes in emotional states induced by placebo effects have been linked to this region. Cluster 6 revealed moderate but significant activation in the left striatum including caudate and putamen (–7.9, 7.2, –7.6), with a value (Z = 2.81, p = 0.00300). It is a key structure in the reward system and is involved in motivation, habit formation, and emotional processing. This area engages in expectancy-driven placebo responses, especially through its role in reward prediction and dopaminergic signaling. Moreover, Cluster 7 showed relatively low activation of the right insula and putamen (31.9, 19.8, 1.2), with a value (Z = 2.58, p = 0.00100). This region integrates interoceptive (bodily) and emotional information and is involved in salience detection. The putamen contributes to motor control and reward-based learning; together, they support placebo effects via emotional and reward circuits.

These results show consistent activation in significant brain areas associated with placebo effects, highlighting a coordinated interplay. These include the right middle cingulate cortex, right rolandic operculum, left insular cortex, right cerebellar lobule VI, vermis lobule VI, left striatum including caudate and putamen, and right insula and putamen. It reveals a coordinated interplay of top-down control, bottom-up sensory processing, and integrative prediction signals. The right middle cingulate cortex is important for expectation and cognitive regulation. This region enhances the anticipated pain relief by influencing pain circuits from the top-down. The right Rolandic operculum interprets sensory input via the bottom up, sending basic sensory and visceral information for further cognitive analysis. The left insular cortex is a center hub for adaptively modifying perceptual sensitivity, integrating contextually significant cues with interoceptive signals. Similarly, the right cerebellar lobule VI is involved in predictive (top-down) timing and error-correction processes and compares anticipated analgesic outcomes with incoming feedback. From a bottom-up perspective, the vermis lobule VI regulates affective and autonomic regulation affecting posture and emotional tone in response to placebo cues. In the basal ganglia, the left caudate–putamen complex is responsible for encoding signals related to reward expectation and prediction errors, which enhance the belief in pain relief. Meanwhile, the right insula–putamen network integrates significant interoceptive changes with motor functions and translates feelings of relief into adaptive behaviors. Collectively, these regions form a bidirectional loop where bottom-up signals shape expectations, and top-down regulation affects sensory processing, establishing the neural basis of the placebo effect (see Table 3 and Figure 3).

In the Table 4, the ALE meta-analysis identified eight notable clusters that survived after applying cluster-level FDR correction at $p \leq 0.05$. These clusters are associated with brain regions that consistently activated across studies on placebo responses. A threshold was applied at $Z \geq 3.28267$ and $p \leq 0.05$, along with a minimum cluster size of 32 voxels. This study's findings showed significant clusters in both cortical and subcortical brain regions. This study's findings showed significant clusters in both cortical and subcortical brain regions. Cluster 1 displayed significantly higher activation in the left middle temporal gyrus (–59.5, –38.5, –1.0). This brain area exhibited a strong activation value (Z = 3.50, p = 0.00023), underscoring its role in semantic processing and the retrieval of emotional memories during regulation tasks. The integration of sensory and contextual information is frequently linked to the middle temporal gyrus, which is responsible for modifying affective responses. Cluster 2 demonstrated notably high activation in the left mid-cingulate cortex (–2.0, 19.0, 33.7) with a robust activation value (Z = 3.50, p = 0.00023). It emphasized its role in cognitive regulation and conflict monitoring in emotionally salient conditions. Cluster 3 revealed a significant increase in activation in the right amygdala ((23.8, –4.6, –17.2), with a robust value (Z = 3.50, p = 0.00023). It highlights that it processes emotional salience and produces affective responses. Cluster 4 demonstrated significantly higher activation in the left insula (–43.3, 18.3, –1.0) with a marked activation value (Z = 3.50, p = 0.00023). It promotes its role in internal emotional state awareness and interoceptive perception. Through the integration of bodily sensations and emotional processing, the insula supports effective adaptive behavioral responses.

Cluster 5 exhibited significantly higher activation in the left supplementary motor area (–3.5, 9.4, 58.0). This motor-related region revealed a significant activation value (Z = 3.50, p = 0.00023), reflecting its involvement in the preparation and initiation of regulatory behaviors. The SMA coordinates the planning of voluntary actions in response to emotional cues. Cluster 6 displayed significantly higher activation in the right inferior frontal gyrus, pars triangularis (46.7, 18.3, 19.7). This prefrontal area exhibited a strong activation value (Z = 3.50, p = 0.00023), highlighting its role in inhibitory control and reappraisal strategies during emotion regulation. Cluster 7 showed significantly higher activation in the left hippocampus (–21.9, –5.3, –15.7). This medial temporal structure showed a robust activation value (Z = 3.50, p = 0.00023), which indicated its critical role in contextual memory of emotional events. The hippocampus supports the integration of past events in the regulation of current mood. Cluster 8 displayed significantly higher activation in the right insula (37.1, 18.3, 1.2). This region exhibited an activation value (Z = 3.50, p = 0.00023), indicating its role in interoceptive processing and emotional awareness. This region is involved in mapping physiological states onto conscious feelings, supporting adaptive regulation.

These results show consistent activation in significant brain areas associated with emotional regulation, highlighting a coordinated interplay. These include the middle temporal gyrus, middle cingulate gyrus, amygdala, insula, supplementary motor area (SMA), inferior frontal gyrus, pars triangularis, hippocampus and insula. These results show that there are both top-down regulatory mechanisms and bottom-up emotional and sensory processes that work together to regulate emotions. The left supplementary motor area and the right inferior frontal gyrus (pars triangularis) exhibit typical top-down activation. Left SMA initiates deliberate regulatory behaviors while right IFG displays reappraisal and inhibitory regulation of emotional states. Conversely, the bilateral insulae, right amygdala, and left hippocampus all reflect bottom-up signaling; they receive and send interoceptive signals, contextual memory traces, and affective salience that bias and influence regulatory demands. The left middle temporal gyrus further links various sources and allows higher-order systems to truly understand incoming signals by integrating semantic and contextual information. The left mid-cingulate cortex appears to mediate the processes like flexible allocation of resources and monitor the conflicts between goal-directed control and automatic emotional reactions, The network operates as a bidirectional loop in which bottom-up inputs drive the demand for regulation, while top-down cognitive control structures shape the evaluation and control of bottom-up affective and sensory inputs (see Table 4 and Figure 4).

To identify shared neural substrates between emotion regulation and placebo response, a conjunction ALE meta-analysis was conducted. Individual ALE maps were thresholded at Z > 3.5, and conjunction analysis was performed using the FMRIB Software Library (FSL**)** to assess cluster-wise spatial overlap (fslmaths emotional_regulation.nii -mas placebo.nii conjunction.nii). This procedure generated a conjunction map highlighting brain regions consistently activated across both domains.

The analysis revealed two significant clusters of convergent activation, suggesting a common functional network supporting higher-order cognitive and affective processes underlying both placebo response and emotion regulation. Cluster 1: Right insula (MNI: 31.9, 21.2, –1.0), Z = 3.5, p = 0.00023, with 35% probability of insular localization (65% overlap with adjacent opercular regions). This region integrates expectations with bodily signals, contributing to both placebo analgesia and emotional down-regulation. Cluster 2: Left insula (MNI: –34.5, 11.7, 5.7), Z = 3.5, p = 0.00023, 100% insular probability. This cluster monitors and interprets internal bodily states, tagging them for salience and integrating them into conscious emotional and socio-cognitive processing, reflecting its dual role in placebo and emotion regulation.

The bilateral insular engagement indicates a shared neural substrate, consistent with the insula's role in interoceptive awareness and affective processing, supporting the integration of bodily signals with cognitive and emotional control mechanisms (see Table 5 and Figure 5).

The analysis revealed significant activation in eight clusters for emotional regulation relative to placebo response. Cluster 1, middle temporal gyrus (MNI coordinates: -59.5, -38.5, -1.0) in the left hemisphere demonstrated strong engagement, with a 100% probability overlap in the left middle temporal gyrus. This activation suggests the involvement of these region in semantic processing, social cognition, and emotional appraisal. Cluster 2, cingulate cortex (MNI coordinates: -2.0, 19.0, 33.7), in the left anterior and middle cingulate cortices and extending into the right middle cingulate cortex, reflecting bilateral cingulate involvement. The activation reveals its essential role in emotional conflict monitoring, cognitive control and error detection during emotion regulation. Cluster 3, bilateral regions of hippocampus and amygdala (MNI coordinates: 23.8, -4.6, -17.2) revealed their crucial role in emotional modulation. In the right hemisphere, the activation was mainly localized to the hippocampus (55%), amygdala (30%), and parahippocampal gyrus (13%). It reveals that amygdala is central to emotional salience detection, especially fear and threat-related processing. However, the hippocampus supports contextual memory and emotional memory encoding. Cluster 4 left insula and adjacent inferior frontal regions (MNI coordinates: -43.3, 19.0, -1.0), predominantly overlapping with the left insula (40%) and the left inferior frontal gyrus, orbital (29%), triangular (17%), and opercular (8%) parts. These regions suggests that insula is critical for interoceptive awareness (perception of internal bodily states) and integration of emotional and bodily signals. Additionally, inferior frontal gyrus, which is involved in inhibitory control and reappraisal strategies during emotional regulation. Cluster 5, the supplementary motor area SMA (MNI coordinates: -3.5, 9.4, 58.0) localized to the left hemisphere, with 95% overlap in the left SMA and minor extension into the right SMA. This area associates with motor planning but also plays a role in voluntary initiation of regulation strategies and response inhibition. Cluster 6, inferior frontal gyrus (MNI coordinates: 46.7, 18.3, 19.7), mainly overlapping the triangular (64%) and opercular (26%) parts, with some involvement of the right precentral gyrus (10%). This region specializes in response inhibition and emotional suppression. Cluster 7, bilateral hippocampal and amygdalar regions (MNI coordinates: -21.9, -5.3, -15.7), the left hemisphere showed activation in the hippocampus (49%) and amygdala (41%). Similar to Cluster 3, but localized to the left hemisphere, the amygdala here involves in emotional memory and contextual processing.

Cluster 8, inferior frontal gyrus IFG and insula (MNI coordinates: 37.8, 17.6, 1.2) in the right hemisphere, with maximal overlap in the right insula (84%). The right insula involves in awareness of emotional states and subjective feeling states and right IFG supports inhibition of automatic emotional responses. Finally, these results supported a distributed network which involves frontal, temporal, limbic, insular, and cingulate areas, supporting the neural differentiation between emotional regulation and the placebo effect. The repeated bilateral engagement of the hippocampus, amygdala, insula, and cingulate cortex highlights their crucial role in regulating emotional processes (see Table 6 and Figure 6 & 7).

The analysis revealed significant activation in eleven clusters for emotional regulation relative to placebo response. Cluster 1, mid-cingulate cortex and supplementary motor area (SMA) (MNI coordinates: approximately 2, 15, 44) in the right hemisphere showed strong engagement, with peak activation (Z = 14.0) and 100% probability overlap in regions linked to motor planning, action monitoring, and cognitive control. This implies that these regions play a significant part in the voluntary regulation of emotional responses. Cluster 2, Rolandic operculum (MNI coordinates: approximately 50, -8, 13) in the right hemisphere, showed notable activation (Z = 13.0), with the majority of overlap in the right Rolandic operculum (69%) and adjacent supramarginal gyrus (31%). These areas have been shown to promote sensorimotor integration, especially facial and oral motor activity, which can be stimulated during emotional expression or suppression. Cluster 3, unclassified based on AAL labeling (MNI coordinates: approx. -32, -20, -15), appeared to include limbic or temporal areas, potentially suggesting deeper affective processing pathways, but could not be conclusively assigned. Cluster 4, similarly unlabeled by AAL (MNI coordinates: approx. -40, -60, 30), may be located in the posterior or parietal temporal regions, maybe

Figure 1

PRISMA flow diagram illustrating the literature search, screening, eligibility assessment, and final study selection process for the placebo response Activation Likelihood Estimation (ALE) meta-analysis.

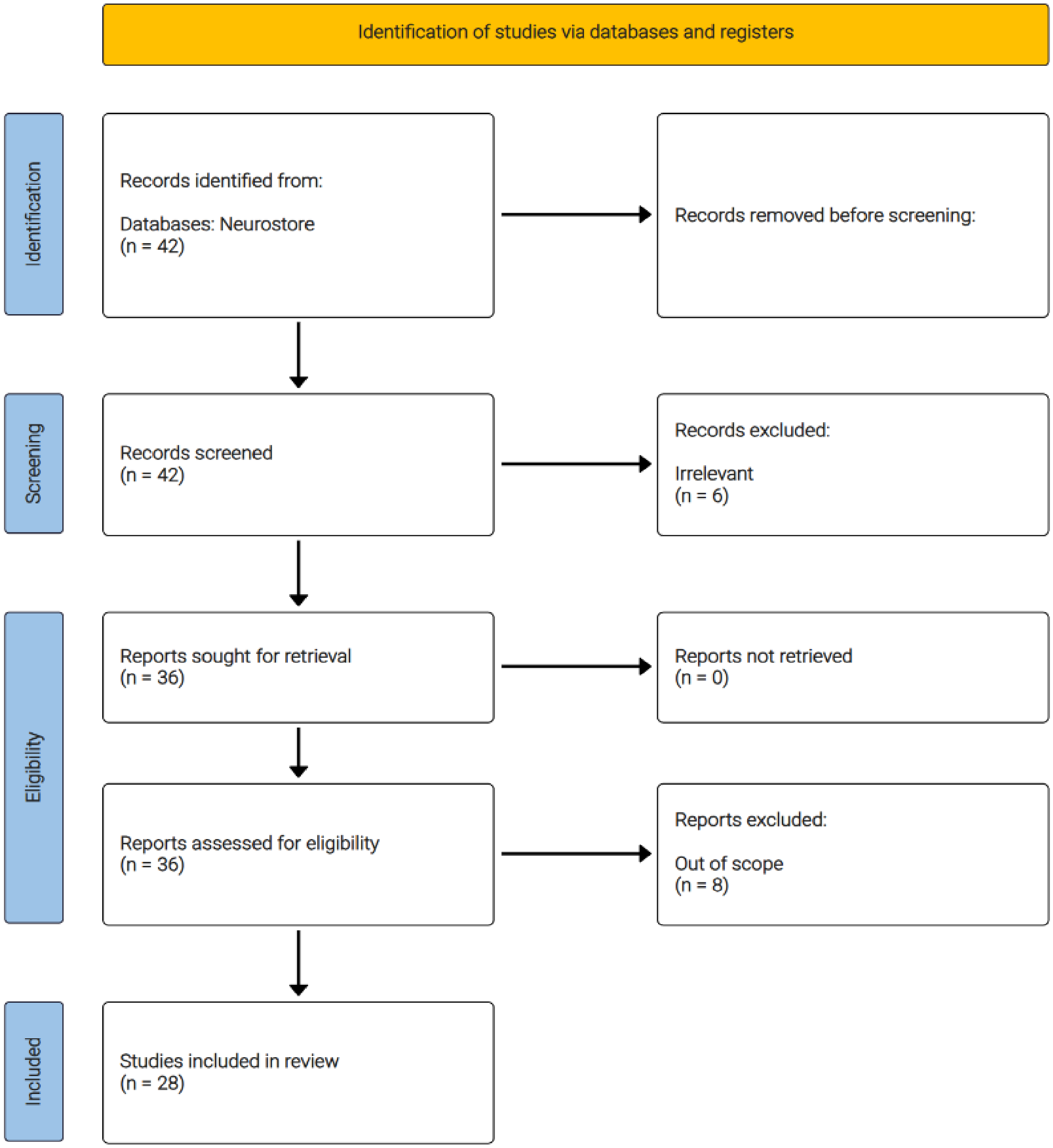

Figure 2

PRISMA flowchart of the literature search and selection process for the 'emotional regulation' ALE meta-analysis.

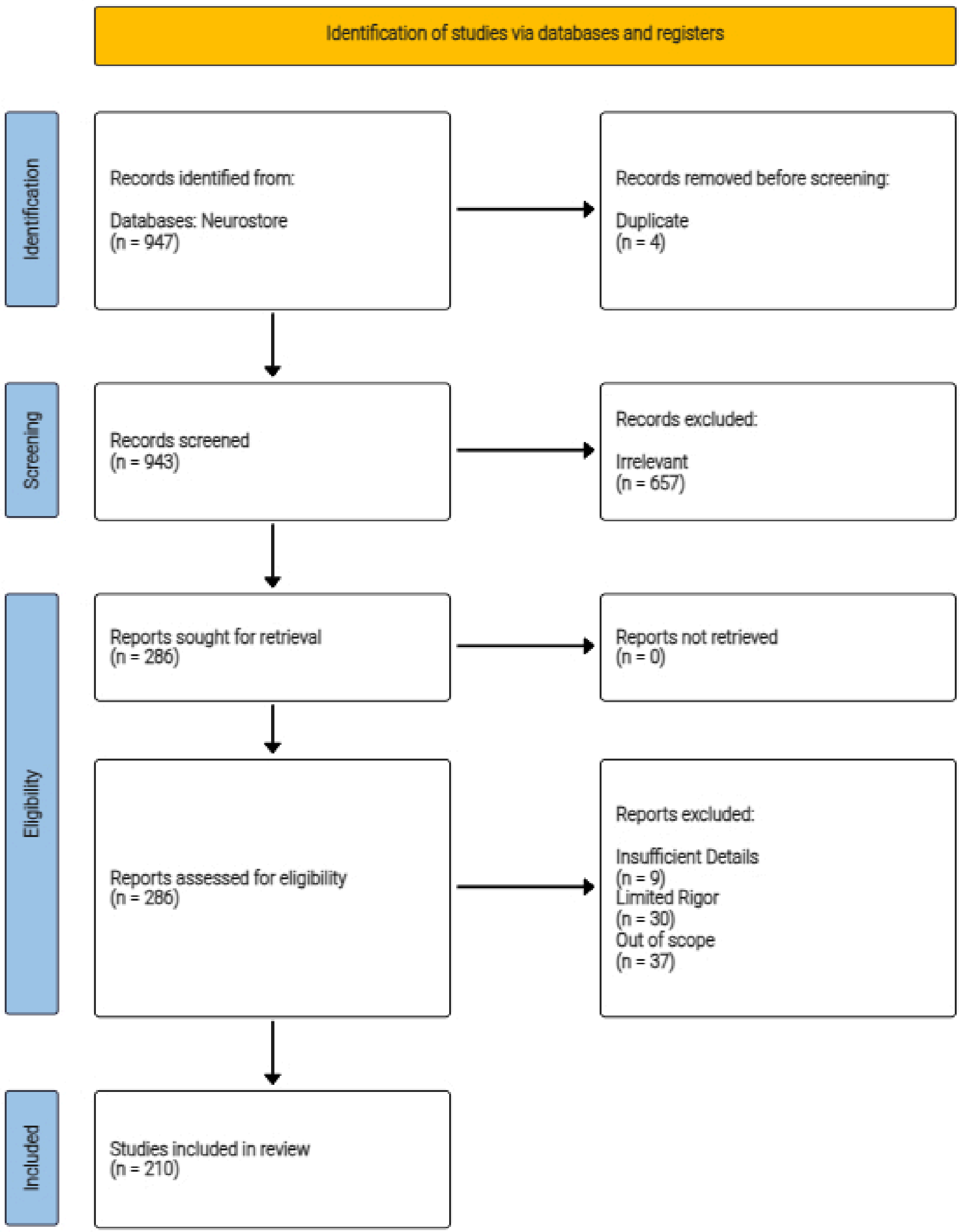

Table 1

Overview of the 28 studies included in the quantitative ALE meta-analysis on the neural bases of 'placebo response'

Serial No.	Author (Year)	Sample Size	Task / Condition	Brain Regions Reported	Imaging Technique	Main Findings
1	Elsenbruch et al. (2012)	36	Cued anticipation and painful rectal stimulation with expectancy of receiving an analgesic (0%, 50%, 100%)	DLPFC; somatosensory cortex; thalamus; PCC	fMRI (BOLD)	Expectation of pain relief reduced pain and urge to defecate; responders showed decreased PFC, somatosensory, and thalamic activation during anticipation and stimulation compared to nonresponders.
2	Geuter et al. (2013)	40	Two creams ("high-priced" vs "low-priced") with surreptitious temperature lowering, followed by fMRI test (5 s anticipation, 20 s heat pain, pain rating)	rACC; ventral striatum; anterior insula; thalamus; SII; PAG; dACC	fMRI (BOLD, SPM8)	Strong placebo induced greater pain relief (21.8% vs 8.2%; p = 0.002) and willingness-to-pay; neural effects included rACC and ventral striatum activation scaling with efficacy, plus insula/PAG activations and thalamus/SII deactivations.
3	Petrovic et al. (2005)	15	Viewing neutral and unpleasant IAPS pictures under placebo (saline described as anxiolytic) vs control	rACC; lateral orbitofrontal cortex (vlPFC)	fMRI (BOLD, event-related)	Expectations of anxiety relief reduced unpleasantness ratings by ~29 %; fMRI showed a modulatory network—rostral ACC and lateral OFC—activated during placebo, correlating with individual response magnitude.
4	Lu et al. (2010)	14	Esophageal balloon distension under placebo intervention (saline described as analgesic) vs no-treatment control	Thalamus; somatosensory cortices; insula; ACC; PFC; bilateral amygdala; VLPFC	fMRI (3 T BOLD)	Placebo reduced pain extent, VAS, and McGill scores, with decreased activation in the visceral pain matrix and amygdala; VLPFC increased during anticipation, indicating top-down modulation.
5	Kong et al. (2009)	24	Calibrated heat-pain sequences under verum or sham acupuncture paired with high vs low expectancy conditioning, followed by fMRI testing	Insula; putamen; claustrum; STG; frontal gyri; ACC; M1; IPL; operculum/IFG	fMRI (3 T BOLD, SPM2)	Verum acupuncture produced greater decreases in pain-related signals (insula, cingulate, frontal) than sham, especially on the high-expectancy side, dissociating acupuncture from expectancy-driven placebo networks.
6	Kong et al. (2006)	24	Expectancy-enhanced placebo analgesia	Dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), periaqueductal gray (PAG), thalamus	fMRI (3T scanner)	Expectancy-enhanced placebo analgesia was associated with increased brain activation in DLPFC, ACC, and PAG during both pain anticipation and experience.
7	van der Meulen et al. (2017)	30	Cognitive reappraisal task (reappraise vs watch negative pictures) followed by placebo-analgesia fMRI: thermal stimuli applied to "analgesic" vs "control" cream patches (anticipation, pain)	Left DLPFC; PAG	fMRI (3 T BOLD, SPM8)	Placebo-induced left DLPFC activation correlated with pain reductions and individual reappraisal scores; DLPFC–PAG connectivity increased, supporting cognitive reappraisal in pain control.
8	Bingel et al. (2006)	19	Painful laser stimuli to both hands preceded by auditory cue; one hand treated with fake analgesic cream	rACC; bilateral amygdalae; PAG	fMRI (event-related BOLD; PPI analysis)	Placebo analgesia enhanced rACC connectivity with amygdala and PAG, recruiting a subcortical antinociceptive network and suggesting a top-

			(placebo) vs no-cream control			down, opioid-dependent pain inhibition mechanism.
9	Eippert et al. (2009)	48	Placebo analgesia induced via suggestion and conditioning; naloxone vs saline comparison to assess opioid role	rACC; PAG; RVM; hypothalamus	Functional MRI (fMRI)	Naloxone disrupted both behavioral and neural placebo analgesia; abolished placebo-induced rACC→PAG connectivity and RVM activation, confirming endogenous opioidergic descending modulation's role in placebo pain relief.
10	Wrobel et al. (2014)	50 Healthy volunteers	Heat pain calibration and two-phase placebo paradigm with double-blind 2 mg oral haloperidol (D_2/D_3 antagonist) vs placebo; conditioning (covert temperature lowering) and test (identical supra-threshold stimuli with "analgesic" cream)	Dorsal striatum; insula; thalamus; ACC	fMRI (event-related BOLD)	Haloperidol reduced the correlation between dorsal striatum activity and individual placebo analgesic response but did not alter behavioral placebo analgesia magnitude or modulate activity in core pain-processing regions.
11	Sevel et al. (2015)	30	Thermal pain stimuli applied randomly to four foot sites (two placebo cream, two baseline) after expectation conditioning, during fMRI scanning	DLPFC; dACC; periaqueductal gray (PAG)	fMRI (BOLD) with Dynamic Causal Modeling	Placebo increased descending connectivity among pain-modulatory regions, modulating dACC→PAG and reducing DLPFC→PAG coupling, indicating network-level pain modulation.
12	Huber et al. (2013)	36	Conditioned placebo analgesia: red-cue "analgesic" vs green-cue control, with separate anticipation and pain-perception fMRI phases	Right DLPFC, anterior mid-cingulate cortex/medial PFC, bilateral anterior thalamus, left caudate, left precuneus, bilateral posterior temporal cortices	fMRI BOLD (3T) with multiple-regression interaction and seed-based functional connectivity analyses	Hypnotic susceptibility modulated placebo networks: high-HS individuals showed ↑ anticipatory right DLPFC activity and ↓ DLPFC connectivity with emotional regions; during pain, placebo magnitude negatively correlated with thalamus, caudate, precuneus, and temporal activity.
13	Wagner et al. (2020)	99	Resting-state fMRI after pain induction; placebo (analgesic cream + conditioning) vs. control (no expectation manipulation)	Bilateral somatosensory cortex, posterior insula, brainstem, thalamus, striatum, dACC, rACC, anterior insula	Resting-state fMRI with independent component analysis	Placebo analgesia induced inverse coupling between somatosensory/posterior-insula network and a pain-modulatory network; stronger negative coupling linked to lower pain intensity, unrelated to expectancy ratings.
14	Crawford et al. (2023)	47	Thermal noxious stimuli at sites treated with control (vaseline) vs. placebo (lidocaine-described) cream; ongoing and event-related connectivity compared	Stimulus-independent: lPAG, posterior hypothalamus, medial amygdala, dlPFC, rACC; Stimulus-dependent: S1, anterior insula, NAc, rACC, dACC, MCC	fMRI (3 T BOLD), seed-based FC, PPI, DCM analyses	Placebo responders showed dual-network modulation: reduced hypothalamus-PAG & enhanced dlPFC/rACC-PAG coupling (stimulus-independent), and increased rACC-PAG & NAc-rACC connectivity (stimulus-dependent), mediating analgesia responses.
15	Hartmann et al. (2020)	45	fMRI during placebo analgesia induction (own pain: "analgesic" vs. control) + empathy-for-pain task (observing painful/nonpainful stimuli)	Left anterior insula (AI), anterior midcingulate cortex (aMCC), somatosensory cortices (S1/S2)	Event-related fMRI (BOLD)	Placebo analgesia reduced activity in affective regions (AI, aMCC) during both self-pain and empathy-for-pain but spared sensory (S1/S2) empathy processing.
16	Linnman et	9 migraine	Placebo analgesia in episodic migraine	Insula, anterior cingulate cortex,	PET-fMRI	The study found that placebo analgesia modulates

	al. (2018)	patients + 9 healthy controls		thalamus		activity in brain regions associated with pain perception and emotional regulation. Increased connectivity was observed in the pain network.
17	Jensen et al. (2015)	24	Within-subject fMRI with conscious and nonconscious (masked) visual cues predicting high pain (nocebo), low pain (placebo), or control; moderate heat stimuli	Placebo (both conscious & nonconscious): OFC ↑; Nocebo (both): thalamus, amygdala, hippocampus ↑	3T fMRI (BOLD)	Both conscious and nonconscious cues triggered placebo and nocebo effects; nonconscious placebo activated reward-related OFC, while nonconscious nocebo engaged threat-processing subcortical areas.
18	Zeidan et al. (2015)	75	Mindfulness meditation vs. placebo and sham meditation	Prefrontal cortex, anterior cingulate cortex, insula	fMRI	Mindfulness meditation engages distinct neural mechanisms for pain relief compared to placebo and sham meditation, indicating different paths of analgesic effects.
19	Lui et al. (2010)	31	Conditioned placebo analgesia	Anterior cingulate cortex, insula, thalamus	fMRI	The study identified neural correlates of conditioned placebo analgesia, showing that placebo responses involve specific brain regions associated with pain modulation and processing.
20	Hartmann et al. (2021)	45 (final)	Placebo analgesia and empathy for others' pain	Insula, anterior cingulate cortex, mirror neuron system	fMRI	The study found that placebo analgesia does not significantly reduce empathy for the pain of others, indicating that placebo effects are not somatosensory specific in nature.
21	Shi et al. (2021)	20 healthy volunteers (12 male, aged 20–33)	ALBP induction; placebo or nocebo intervention in pseudo-random order; fMRI and VAS scores collected	Placebo: DLPFC, S2, ACC, IC, thalamus, SMA, VMPFC, parahippocampal gyrus, hippocampus, TP, caudate, S1, PCC; Nocebo: DLPFC, S1, SMA, caudate, IC, TP, hippocampus	3T fMRI with Multivariate Granger Causality Analysis (GCA)	Granger Causality Analysis (GCA) Placebo engaged reward circuits and inhibited pain networks; nocebo activated pain networks and deactivated emotional control regions, with shared and distinct areas.
22	Shi et al. (2021)	31	ALBP induced via saline; two fMRI sessions: (a) placebo patch, (b) nocebo patch; resting-state and VAS ratings	Placebo (males): vmPFC, parahippocampal gyrus, PCC; females: dlPFC, hippocampal gyrus, insula	3T resting-state BOLD fMRI with seed-based FC (rACC ROI)	Placebo analgesia activated reward circuits in sex-specific patterns: males showed vmPFC-parahippocampal-PCC increases; females showed dlPFC-hippocampal-insula increases.
23	Sacca et al. (2023)	81 (final)	Repeated tDCS effects on placebo and nocebo responses	Dorsal attention network, frontal-parietal network	fMRI and behavioral assessments	Repeated tDCS modulated dorsal attention and frontal-parietal networks, enhancing placebo effects and reducing nocebo, indicating a neurophysiological mechanism.
24	Watson et al. (2009)	11 healthy right-handed adults (6 F, 5 M; 19–36 yrs)	Three-block laser paradigm: pre-conditioning, conditioning (sham cream), post-conditioning; measured anticipation and pain phases	Anticipation: left DLPFC, medial frontal cortex, aMCC, OFC; Pain: aMCC, postcentral gyrus, posterior cingulate	3T event-related fMRI (BOLD, TR=3000 ms, TE=30 ms)	Placebo analgesia involved fronto-cingulate network during anticipation; pain reduction mainly linked to aMCC and sensory regions, suggesting anticipation reduction drives effect.
25	Jensen et al. (2015)	24 healthy participants (10 F, mean age 25 ± 5 yrs)	Within-subject fMRI: conditioning (faces + high/low pain), test (conscious and nonconscious cues) with pain ratings on 0–20 NRS	Placebo: rACC; Nonconscious placebo: OFC; Nonconscious nocebo: thalamus, amygdala, hippocampus	3T event-related fMRI (BOLD EPI; TR=2000 ms, TE=40 ms)	Nonconscious placebo activated OFC; nonconscious nocebo engaged thalamus, amygdala, hippocampus—showing pain modulation without conscious awareness.
26	Sevel et al. (2015)	24 healthy subjects (13 F, mean age 22.6	Visit 1: fMRI during thermal pain; Visit 2: placebo conditioning (lowered temperature) and fMRI with original	PAG, thalamus, rACC, DLPFC effective connectivity parameters	3T event-related fMRI (BOLD EPI)	Baseline thalamus→DLPFC and DLPFC→PAG connectivity predicted 82% of placebo analgesia variance; thalamus→DLPFC was the strongest

		± 2.9 yrs)	temperature to assess placebo			predictor.
27	Shi et al. (2020)	30 healthy subjects	Saline-induced back pain; fMRI during baseline, pain, and placebo (analgesic patch) vs. nocebo (algetic patch) blocks after conditioning	Placebo: ↓ rACC connectivity with amygdala, hippocampus, OFC, DLPFC, S2, SMA, precuneus; Nocebo: ↑ rACC–cerebellum, ↓ rACC–brainstem, OFC, DLPFC, S1	3T event-related fMRI (BOLD) with rACC-seed PPI	Extroverts showed greater placebo-related rACC connectivity reductions; introverts showed distinct DLPFC and anxiety-related changes during nocebo hyperalgesia.
28	Crawford et al. (2023)	38 healthy controls recruited	3 sessions: Day 1 conditioning, Day 2 reinforcement (thermal stimuli with placebo vs. control cream), Day 2 test (7T MRI with VAS during fMRI)	Placebo > control: rACC, PCC, vlPFC, mPFC, ipsilateral dlPFC; Placebo < control: contralateral S1, parahippocampal gyrus	7T MRI: T1, ^1H-MRS (dlPFC), BOLD fMRI (1×1×1.2 mm voxels, TR=2.5s)	Greater conditioning precision predicted placebo effect; responders showed ↑dlPFC activation, ↑dlPFC–PAG connectivity, dlPFC glutamate ↓ pain variability.

Note. From left to right, the table reports the progressive study number (N), the authors and publication year of each study, the number of subjects (healthy adults), type of task used (with conditions), brain regions, imaging technique, and main findings Finally, the original contrasts included in each ALE meta-analysis are reported, together with their respective number of foci and standard anatomical space.

Table 2

Key Characteristics of Studies Included in the ALE Meta-Analysis

Serial No.	Author (Year)	Sample Size	Task / Condition	Brain Regions	Imaging Tech	Main Findings
1	Berthold-Losleben et al. (2018)	32	Aversive vs. neutral odors + music	SMA, TP, SFG	Task fMRI (BOLD)	Positive music attenuated multisensory/attentional activity.
2	Kuang et al. (2022)	28 SZ; 33 HC	Resting fALFF + emotion recognition under load	Amygdala, Hippocampus, Fusiform	Resting fMRI (fALFF)	Fusiform ↓ activity linked to poorer fearful-face recognition.
3	Wang et al. (2022)	19	Experiential vs. defusion vs. watch of negative images	ACC, IFG, Insula, Amygdala	Task fMRI	Experiential ups PFC/insula-amygdala coupling; defusion downregulates subcortical nodes.
4	Zhu et al. (2019)	20	Real-time NF to downregulate hippocampus while viewing negative images	Hippocampus, PFC, ACC	Real-time fMRI NF	Learned hippocampal downregulation with increased PFC/ACC engagement.
5	Li et al. (2021)	50	Resting-state FC + reappraisal questionnaire	IFG ↔ Amygdala/ACC	Resting fMRI (rs-FC)	Medium reappraisers show optimal IFG–amygdala/ACC connectivity.
6	Nicholson et al. (2017)	30 PTSD; 30 HC	Real-time NF downregulating PCC during trauma vs. neutral scripts	PCC, DLPFC, ACC	Real-time fMRI NF	PTSD group's PCC–PFC/ACC coupling linked to symptom improvement.
7	Outhred et al. (2013)	Review	Meta-analysis SSRI vs. NRI on emotion tasks	Amygdala, sgACC, Insula	fMRI meta-analysis	SSRIs ↓ amygdala/sgACC reactivity; NRIs modulate insula/thalamus.
8	Hallam et al. (2015)	30	"If–then" reappraisal vs. watch negative images	LatPFC, MedPFC, dACC, Amygdala	Task fMRI	"If–then" plans recruit PFC/ACC to downregulate amygdala.
9	Dolcos et al. (2014)	24 young; 24 older	Passive vs. spontaneous regulation of high/low-arousal negatives	Amygdala, vlPFC	Task fMRI	Older adults show greater amygdala/vlPFC modulation during spontaneous ER.
10	Yamamoto et al. (2017)	20 ELS; 20 controls	Viewing negative faces vs. shapes	Amygdala, rPFC	Task fMRI	Early-life stress ↑ amygdala reactivity and PFC coupling.
11	Vanderhasselt et al. (2011)	22	Disengagement from negative vs. neutral words (emotional Stroop)	IFG, ACC, Parietal	Event-related fMRI	Better disengagers↑ IFG/parietal activation.
12	Akitsuki & Decety (2009)	18	Empathy for pain: painful vs. non-painful hands	Insula, ACC	Event-related fMRI	Agency/context modulate insula/ACC during pain empathy.
13	Vrticka et al. (2013)	25	Imitation vs. suppression of dynamic facial expressions	SMA, STS, Insula, LatPFC	Task fMRI	Imitation engages mirror/emotion circuits; suppression engages lateral PFC/ACC.
14	Hallam et al. (2014)	28	Reappraisal of others' distress videos vs. watch	dmPFC, TPJ, LatPFC, Amygdala	Task fMRI	Mentalizing + reappraisal regions reduce others' distress-related amygdala activity.

Note. From left to right, the table lists the study number (N), authors and publication year, number of healthy adult subjects, task type (with conditions), brain regions, imaging technique, and main findings. The original contrasts included in each ALE meta-analysis are also reported, along with their number of foci and standard anatomical space.

Figure 3
Brain Regions Activated During Placebo Response

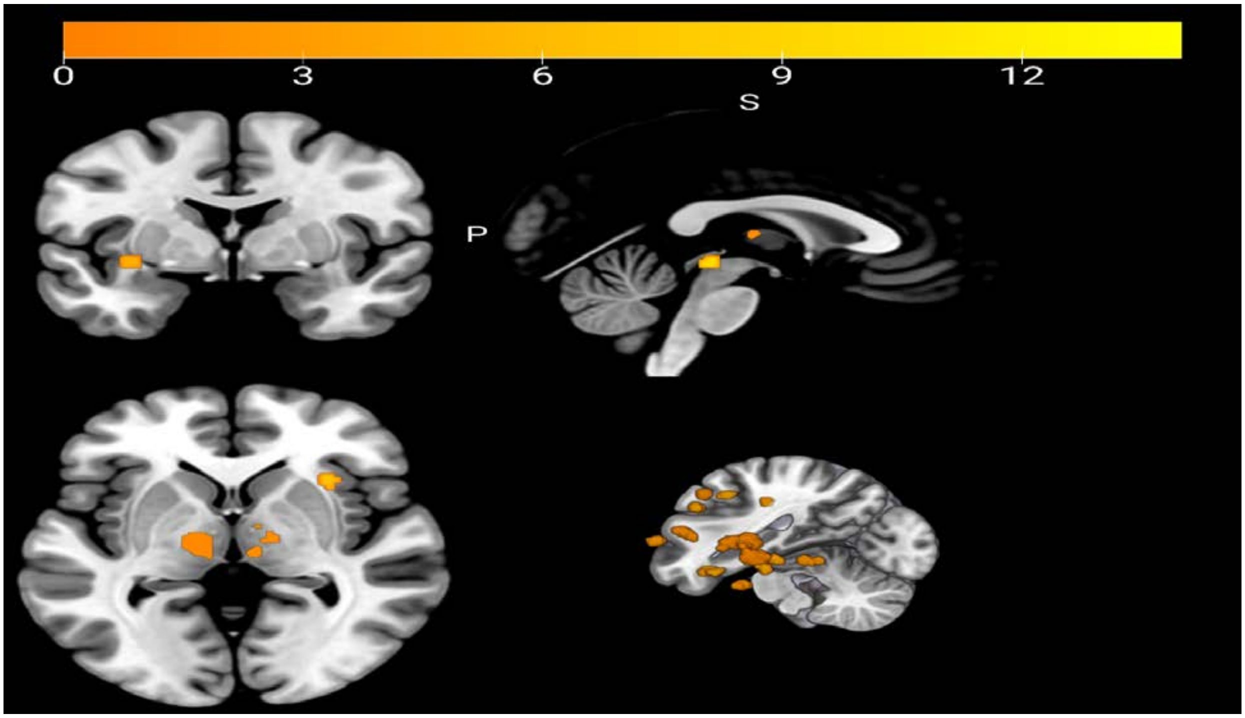

Figure 4
Emotion Regulation Brain Activations

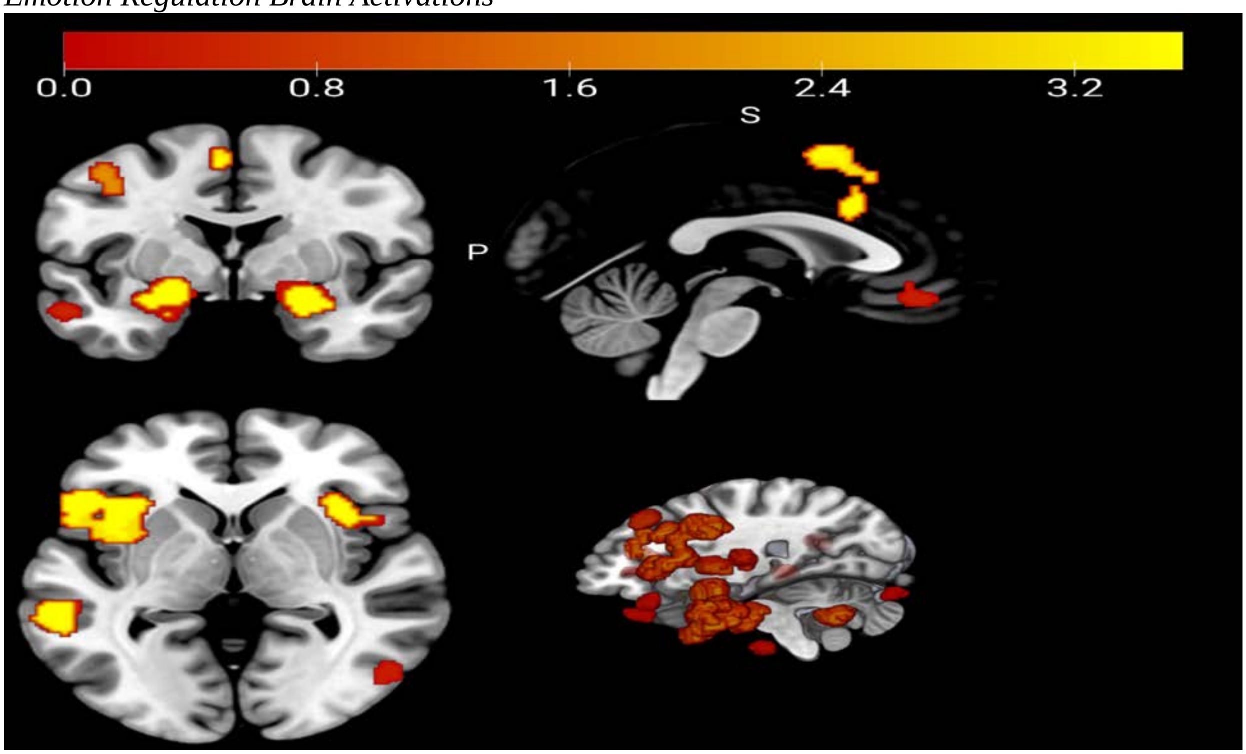

Figure 5

Shared Neural Substrates: Placebo & Emotion Regulation

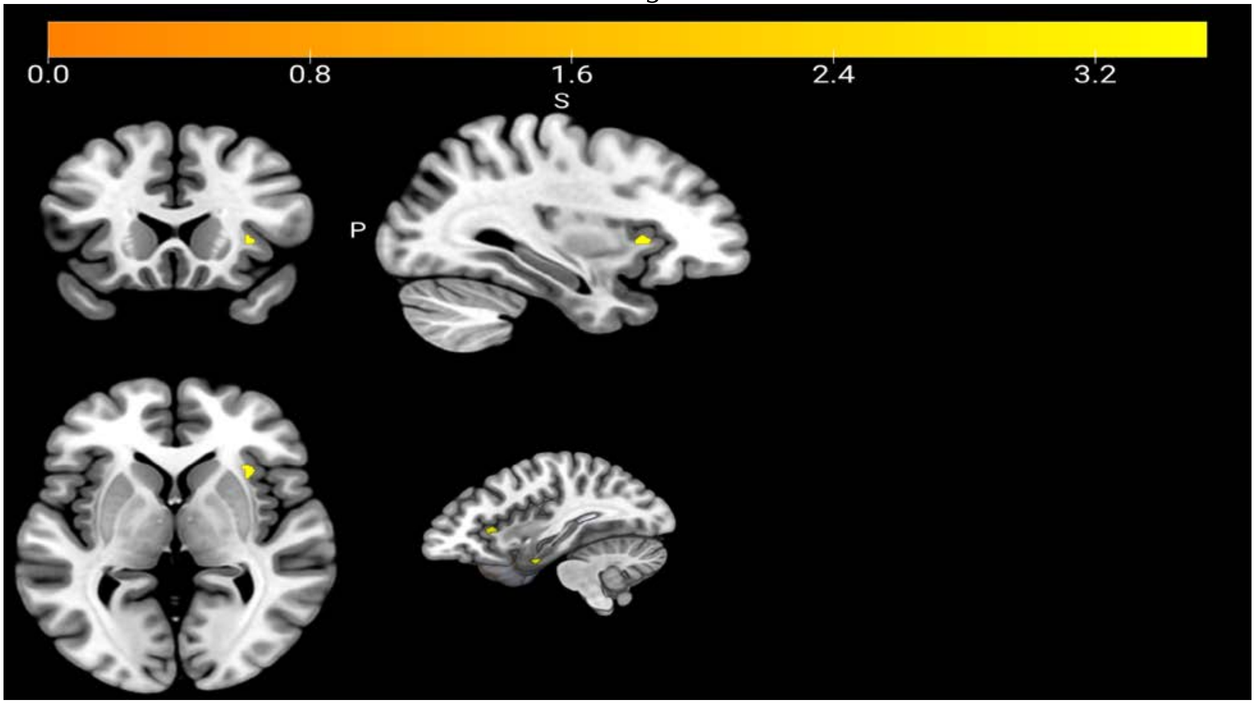

Figure 6

Distinct Neural Mechanisms: Placebo vs Emotion

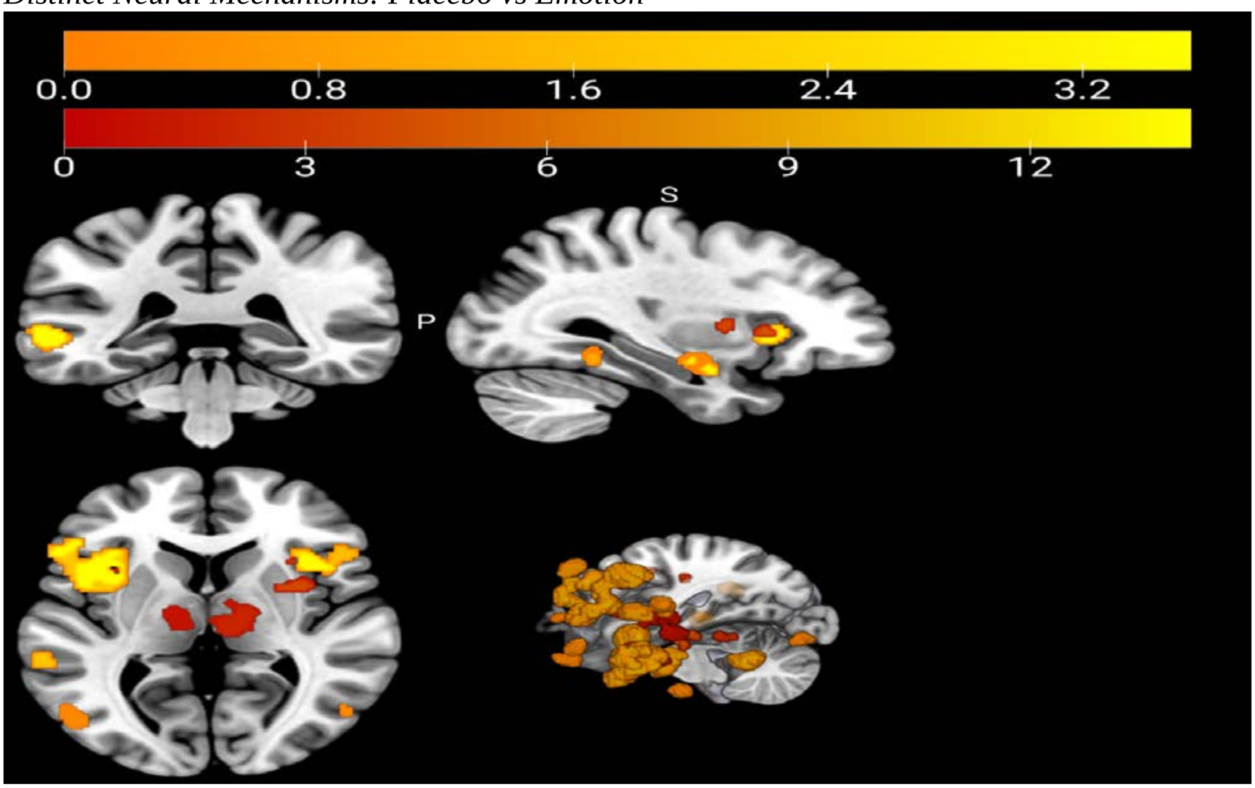

Figure 7

Brain Regions: Emotion vs Placebo

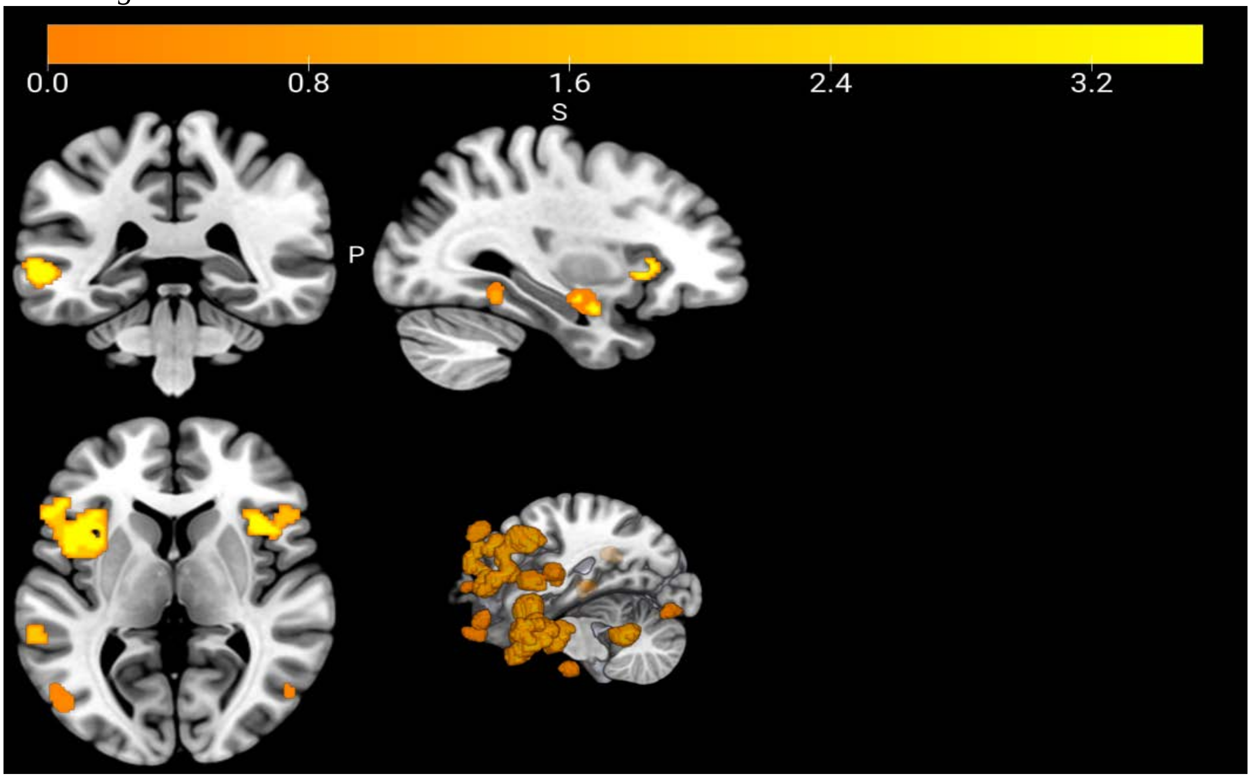

Figure 8

Differential Brain Networks: Placebo vs Emotion

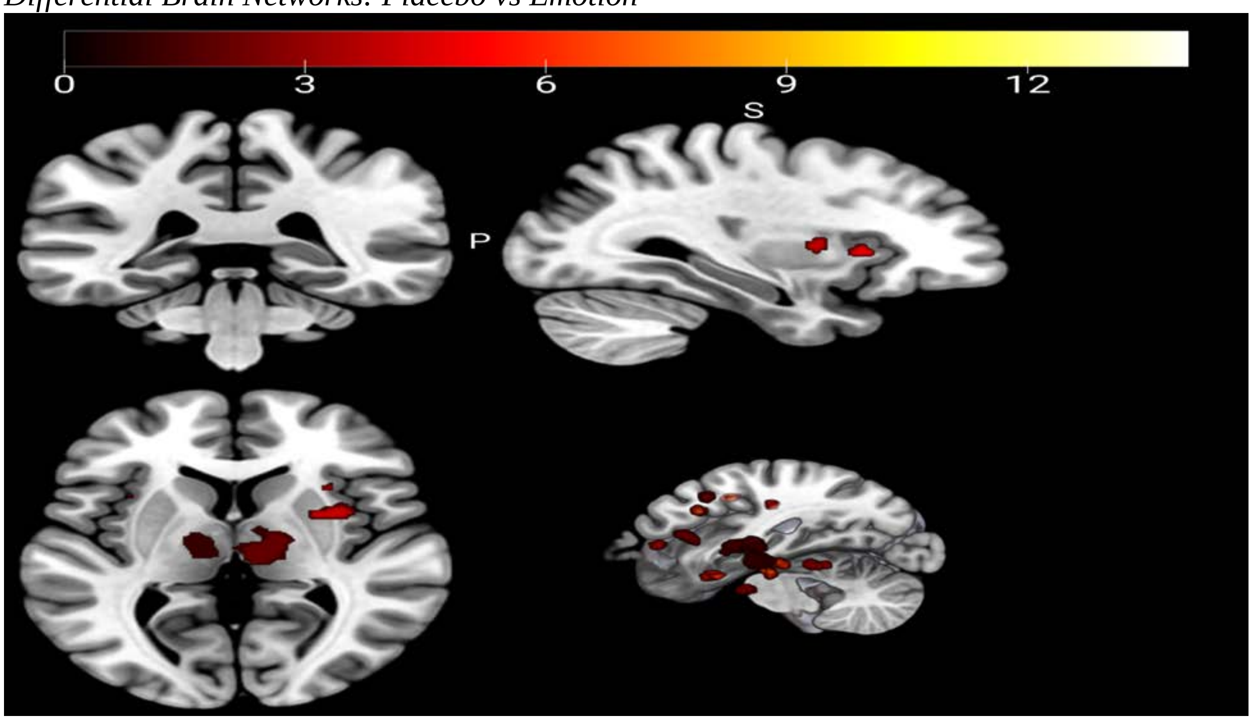

Table 3

Brain Regions Activated by Placebo Response (ALE Meta-Analysis)

Cluster No.	Brain Region	Hemisphere	MNI Coordinates	Volume Voxels)	Z score	P value	ALE values
1	Cingulum_Mid_R	R	(6.8, 8.0, 43.3)	132	4.26	0.00003	High
2	Rolandic_Oper_R	R	(54.8, –25.2, 23.4)	56	3.89	0.00010	High
3	Insula_L	L	(–35.2, 13.9, 7.1)	49	3.72	0.00020	High
4	Cerebellum_6_R	R	(6.8, –26.7, –18.7)	82	3.29	0.00100	Moderate
5	Vermis_6	Midline	(0.2, –30.4, –9.1)	98	3.01	0.00200	Moderate
6	Caudate_L; Putamen_L	L	(–7.9, 7.2, –7.6)	71	2.81	0.00500	Low
7	Insula_R; Putamen_R	R	(31.9, 19.8, 1.2)	54	2.58	0.01000	Low

Note. The table lists cluster number, brain region, hemisphere (L/R), MNI coordinates (X, Y, Z) of local maxima, cluster volume (voxels), Z score, p value, and ALE values indicating activation likelihood. All seven clusters were consistently associated with the placebo condition and survived cluster-level FDR correction at P ≤ 0.005. Z-map threshold ≥ 3.28267, p-map ≤ 0.005, minimum cluster size = 32 voxels. ALE activation strength is categorized as Low, Moderate, or High. Abbreviations: R = Right, L = Left, Cingulum_Mid_R = Right Middle Cingulate Cortex, Rolandic_Oper_R = Right Rolandic Operculum, Cerebellum_6_R = Right Lobule VI of Cerebellum, Vermis_6 = Lobule VI of Vermis, Caudate_L = Left Caudate, Putamen_L = Left Putamen, Insula_R = Right Insular Cortex, Putamen_R = Right Putamen.

Table 4

Brain Regions Activated by Emotional Regulation (ALE Meta-Analysis)

Cluster No.	Brain Region	Hemisphere	MNI Coordinates (x, y, z)	Volume (voxels)	Z-score	P-value	ALE value
1	Middle Temporal Gyrus	L	−59.5, −38.5, −1.0	831	3.5	0.00023	High
2	Middle Cingulate Gyrus	L	−2.0, 19.0, 33.7	815	3.5	0.00023	High
3	Amygdala	R	23.8, −4.6, −17.2	1 893	3.5	0.00023	High
4	Insula	L	−43.3, 18.3, −1.0	5 868	3.5	0.00023	High
5	SMA	L	−3.5, 9.4, 58.0	1 734	3.5	0.00023	High
6	Inferior Frontal Gyrus, pars triangularis	R	46.7, 18.3, 19.7	855	3.5	0.00023	High
7	Hippocampus	L	−21.9, −5.3, −15.7	2 027	3.5	0.00023	High
8	Insula	R	37.1, 18.3, 1.2	929	3.5	0.00023	High

Note. The table lists cluster number, brain region, hemisphere (L/R), MNI coordinates (X, Y, Z) of local maxima, cluster volume (voxels), Z score, p value, and ALE values indicating activation likelihood. All seven clusters were consistently linked to emotional regulation and survived cluster-level FDR correction at P ≤ 0.005. Z-map ≥ 3.28267, p-map ≤ 0.005, minimum cluster size = 32 voxels. ALE activation strength is classified as Low, Moderate, or High. Abbreviations: R = Right, L = Left, SMA = Supplementary Motor Area.

Table 5

Overlapping Brain Regions: Placebo & Emotion

Cluster	Brain Region	Hemisphere	MNI Coordinates (X, Y, Z)	Volume (voxels)	Z-score	p-value	ALE value	Overlapping region (% probability)
1	Insula	Right	31.9, 21.2, –1.0	109	3.5	0.00023	High	-(65) Insula_R (35%)
2	Insula	Left	–34.5, 11.7, 5.7	58	3.5	0.00023	High	Insula_L (100%)

Note. The table lists cluster number, brain region, hemisphere (L/R), MNI coordinates (X, Y, Z), cluster volume (voxels), Z score, p value, ALE values (activation likelihood), and overlapping region (% probability). Both clusters were consistently linked to placebo and survived cluster-level FDR correction at $p \leq 0.005$. Z-map threshold ≥ 3.28267, minimum cluster size = 32 voxels. ALE strength is classified as Low, Moderate, or High. Overlap probabilities are based on AAL atlas labels in MRIcroGL. Abbreviations: Insula_R = Right Insula, Insula_L = Left Insula.

Table 6

Distinct Neural Mechanisms: Placebo vs Emotion Regulation

Serial No.	Brain Region	Hemisphere	MNI Coordinates (X, Y, Z)	Volume (Voxels)	Z	p	Overlapping Region (% probability)
1	Temporal Middle Gyrus	Left	(-59.5, -38.5, -1.0)	831	3.5	0.0005	Temporal_Mid_L (100%)
2	Cingulate Cortex (Mid/Ant)	Left	(-2.0, 19.0, 33.7)	815	3.5	0.0005	Cingulum_Ant_L (37%), Cingulum_Mid_L (37%), Cingulum_Mid_R (23%), Cingulum_Ant_R (2%), Frontal_Sup_Medial_L (1%)
3	Amygdala / Hippocampus	Right	(23.8, -4.6, -17.2)	1893	3.5	0.0005	Hippocampus_R (55%), Amygdala_R (30%), ParaHippocampal_R (13%)
4	Insula / Inferior Frontal	Left	(-43.3, 19.0, -1.0)	5684	3.5	0.0005	Insula_L (40%), Frontal_Inf_Orb_L (29%), Frontal_Inf_Tri_L (17%), Frontal_Inf_Oper_L (8%), Temporal_Pole_Sup_L (2%), Rolandic_Oper_L (1%)
5	Supplementary Motor Area	Left	(-3.5, 9.4, 58.0)	1734	3.5	0.0005	Supp_Motor_Area_L (95%), Supp_Motor_Area_R (5%)
6	Inferior Frontal Gyrus	Right	(46.7, 18.3, 19.7)	855	3.5	0.0005	Frontal_Inf_Tri_R (64%), Frontal_Inf_Oper_R (26%), Precentral_R (10%)
7	Hippocampus / Amygdala	Left	(-21.9, -5.3, -15.7)	2027	3.5	0.0005	Hippocampus_L (49%), Amygdala_L (41%), ParaHippocampal_L (2%)
8	Insula / Inferior Frontal	Right	(37.8, 17.6, 1.2)	744	3.5	0.0005	Insula_R (84%), Frontal_Inf_Oper_R (7%)

Note. From left to right, the table reports the cluster number, anatomical brain region, MNI coordinates (X, Y, Z) of local maxima, cluster volume in voxels, Z score, and p-value, which shows the strength of activation likelihood and overlapping region (% probability).

Table 7

Distinct Neural Mechanisms: Placebo vs Emotion

Serial No	Brain Region(s)	Hemisphere	Peak MNI Coordinates (X, Y, Z)	Volume (Voxels)	Z-score	p-value	Activation Level	Overlapping Region (% probability)
1	Cingulate Mid, Supp Motor Area	Right	(5.4, 8.7, 44.0)	236	14.0	<0.00001	Very High	Cingulum_Mid_R(93%), Supp_Motor_Area_R(7%)
2	Rolandic Operculum, Supramarginal	Right	(54.0, -26.0, 22.6)	113	13.0	<0.00001	Very High	Rolandic_Oper_R(69%), SupraMarginal_R(31%)
3	Unlabeled (likely limbic/temporal area)	-	(6.8, -27.4, -19.4)	184	11.0	<0.00001	Very High	None (100%)
4	Unlabeled (likely limbic/subcortical)	-	(-1.3, -31.1, -9.8)	201	10.0	<0.00001	Very High	None (100%)
5	Caudate, Putamen, Pallidum	Left	(-8.7, 6.5, -7.6)	185	9.0	<0.00001	Very High	Caudate_L(38%), Putamen_L(10%), Pallidum_L(4%), None(48%)
6	Insula	Left	(-34.5, 13.9, 7.9)	54	8.4	<0.00001	Very High	Insula_L(100%)
7	Putamen, Insula	Right	(30.4, 18.3, 0.5)	95	7.2	<0.00001	Very High	Putamen_R(21%), Insula_R(14%), None(65%)
8	Temporal Superior (partial)	Right	(42.2, -41.4, 18.2)	89	7.0	<0.00001	Very High	Temporal_Sup_R(18%), None(82%)
9	Supramarginal, Temporal Superior	Left	(-58.1, -26.0, 22.6)	167	6.0	<0.00001	High	SupraMarginal_L(96%), Temporal_Sup_L(4%)
10	Insula, Putamen	Left	(-33.7, -1.6, -7.6)	140	5.0	<0.00001	High	Insula_L(28%), Putamen_L(4%), None(68%)
11	Putamen, Insula	Right	(29.7, 2.8, 4.2)	175	4.0	<0.00001	High	Putamen_R(58%), Insula_R(18%), None(24%)

Note. From left to right, the table reports the cluster number, anatomical brain region, MNI coordinates (X, Y, Z) of local maxima, cluster volume in voxels, Z score, and p-value, which shows the strength of activation likelihood and overlapping region (% probability).

associated with context-based or visuospatial regulation strategies. Cluster 5, basal ganglia regions (MNI coordinates: approx. -13, 10, 4) in the left hemisphere, revealed significant overlap across the caudate (38%), putamen (10%), and pallidum (4%), with the remaining portion unclassified. This subcortical cluster emphasizes that motor-emotional coordination and reward circuits play a role in regulation process. Cluster 6, insular cortex (MNI coordinates: approx. -38, -2, 4) in the left hemisphere, showed full activation within the left insula (100%). The insula plays a crucial role in emotional regulation as it is necessary for interoceptive awareness and the integration of physiological and emotional cues.

Cluster 7, putamen and insula (MNI coordinates: approx. 28, 6, 0) in the right hemisphere, showed partial overlap with the right putamen (21%) and insula (14%), with 65% unclassified.These areas could facilitate the detection of affective salience and motor readiness. Cluster 8, unlabeled (MNI coordinates: approx. 50, -15, 20), could not be confidently localized, although its proximity to temporal-parietal junctions suggests a possible role in social-emotional integration. Cluster 9, supramarginal gyrus (MNI coordinates: approx. -56, -38, 28) in the left hemisphere, showed dominant overlap with the left supramarginal gyrus (96%), and minor with superior temporal areas (4%).This area is associated with empathy, social cognition, and the integration of emotional tone in speech. Cluster10, left insula (MNI coordinates: approx. -35, -5, 3), overlapped primarily with the insula (28%) and adjacent putamen (4%), though a majority remained unlabeled (68%). This activation supports the insula's continued role in emotion regulation. Cluster 11, right putamen and insula (MNI coordinates: approx. 30, 4, 0), had highest overlap in the putamen (58%) and insula (18%), with some undefined areas. These results suggest that motor-affective hubs are recruited bilaterally.

These findings all suggest a distributed neural network comprising sensorimotor, limbic, frontal, subcortical, and insular regions. This gives idea to the notion that emotional regulation relies on an integrated system for controlling emotional experience and expression rather than being limited to distinct cortical regions, as often observed in placebo-related activations (see Table 7 and Figure 8).

Discussion

A coordinate-based meta-analysis of prior fMRI studies was conducted to identify brain regions consistently associated with placebo response and emotion regulation. Given the conceptual overlap between emotion regulation and related affective processes, we further examined the degree of shared versus domain-specific neural substrates underlying these phenomena.

Shared Neural Substrates: Placebo & Emotion

Consistent with our hypotheses, conjunction analysis revealed overlapping activations in the bilateral insula for both cognitive reappraisal in emotion regulation and placebo response (Figure 5). These findings align with prior evidence of salience network involvement in placebo analgesia (Atlas & Wager, 2012; Ashar et al., 2017; Zunhammer et al., 2021), providing quantitative confirmation that the insula acts as a central hub for integrating anticipatory signals with interoceptive input, thereby modulating both pain perception and the cognitive down-regulation of emotional arousal.

Bilateral insular activation underscores its established role in interoceptive awareness, salience tagging, and the integration of sensory and affective information. The right insula mediates the integration of expectations with bodily feedback, a mechanism crucial for placebo-induced analgesia (Ashar et al., 2017) and for reframing emotional responses in cognitive reappraisal paradigms (Buhle et al., 2014). The left insula contributes to the monitoring and gating of internal states into conscious socio-cognitive processes (Menon & Uddin, 2010; Wager & Barrett, 2017).

These insular processes likely operate in concert with nodes of the fronto-parietal control network, including the dorsolateral prefrontal cortex (DLPFC) and superior parietal cortices, transmitting interoceptive and salience signals to top-down modulatory regions (Bo et al., 2024; Hutcherson & Tusche, 2022; Ochsner et al., 2012; Zunhammer et al., 2021). Collectively, these findings provide a neurobiological basis for the conceptual similarity between placebo response and emotion regulation, which until now has been largely theoretical.

Emerging evidence from open-label placebo (OLP) paradigms indicates that the recruitment of neural circuits may shift from lateral prefrontal regions to subcortical and ventromedial prefrontal cortex (VMPFC) areas depending on awareness and belief framing (Ashar et al., 2024; Schaefer et al., 2023). This highlights the need for contrast analyses to dissociate different placebo types in terms of insular connectivity. While both cognitive reappraisal and deceptive placebos rely on DLPFC-mediated top-down control, OLP effects appear to bypass these executive regions.

Additionally, convergent evidence implicates the dorsal precuneus and superior temporal sulcus—regions associated with multisensory integration and self-referential processing—as potential loci of shared engagement across placebo and emotion regulation tasks (Beauchamp, 2005; Buckner et al., 2008; Utevsky et al., 2014). Overall, these results emphasize the insula’s pivotal role in balancing bottom-up sensory integration with top-down appraisal, supporting a unified neural framework for both placebo response and emotion regulation.

Top-Down Networks in Emotion Regulation

The present results revealed distinctive activations for emotion regulation compared to the placebo response. A distributed network of cortical and subcortical regions was engaged in the emotional regulation vs. placebo response. These include the hippocampus, amygdala, right inferior frontal gyrus, bilateral cingulate cortex, fronto-insular control regions, supplementary motor areas, and left middle temporal gyrus. These results correlate with previous meta-analytic studies that have consistently shown the activation of these prefrontal regions (Buhle et al., 2014; Frank et al., 2014; Messina et al., 2015; Morawetz et al., 2017). For instance, activation of the left middle temporal gyrus emphasizes the role of the lateral temporal cortex in socio-cognitive evaluation and semantic reappraisal (Dörfel et al., 2014; Morawetz et al., 2017). The bilateral cingulate cortex plays a part in cognitive control and conflict monitoring during reappraisal (Buhle et al., 2014; Morawetz et al., 2017). The strong activity in the hippocampus and amygdala suggests that top-down emotional regulation involves subcortical mnemonic and affective mechanisms, such as salience detection and contextual memory encoding, which extend beyond the cerebral emphasis of the previous meta-analyses (Buhle et al., 2014). Additionally, the frontoinsular control regions were also emphasized; the left insula/IFG supports interoceptive awareness and inhibitory reappraisal procedures, while the right IFG/insula promotes the suppression of automatic emotional reactions (Buhle et al., 2014; Morawetz et al., 2017). Lastly, supplementary motor area activity highlights the role of the SMA in initiating attempts at volitional modulation (Morawetz et al., 2017).

These findings correlate with previous meta-analytic studies (Buhle et al., 2014; Dörfel et al., 2014; Morawetz et al., 2017), which also discovered that the "emotion regulation network" is comprised of up of lateral temporal cortex, midline evaluative structures, fronto-parietal control regions, and insula prefrontal interactions. Furthermore, the high activation of the hippocampus and amygdala nodes supports a deeper understanding of subcortical contributions to cognitive reappraisal, suggesting that effective emotion regulation involves dynamic integrating of the affective, executive, and semantic memory systems.

Bottom-Up Networks in Placebo Response

The findings showed unique activations for emotion regulation and placebo response. The placebo response vs. emotional regulation involved the right mid-cingulate cortex and supplementary motor area, right rolandic operculum, left caudate, putamen, and pallidum, bilateral insula, right putamen clusters, and left supramarginal gyrus.

These findings uniquely recruited key nodes of bottom-up sensory and expectancy-driven networks. The ventral attention/salience network's involvement in coordinating action monitoring and cognitive regulation of pain expectations is highlighted by the right mid-cingulate cortex and supplementary motor region (Ashar et al., 2017; Atlas & Wager, 2012). Activation of the right Rolandic operculum further implicates sensorimotor integration mechanisms that underlie the modulation of nociceptive and orofacial responses (Zunhammer et al., 2021). In addition to basal ganglia involvement in both motor regulation and the reinforcement learning of analgesic expectancies, subcortical clusters in the left caudate, putamen, and pallidum expand earlier findings of ventral striatum engagement in placebo analgesia (Koban et al., 2021; Roy et al., 2012). Bilateral insular activations (Clusters 6 & 10), which emphasize interoceptive awareness and the tagging of salient body signals, are compatible with the down-regulation of mid-insula activity during placebo analgesia (Ashar et al., 2017; Zunhammer et al., 2021).

Additional right putamen clusters and left supramarginal gyrus activation point to enhanced sensorimotor integration and empathy-related processes during analgesic expectancy. Although several clusters could not be definitively labeled, they likely represent adjacent limbic, temporal, or parietal regions implicated in somatosensory signaling and self-referential processing within the default mode network analgesia (Koban et al., 2021; Roy et al., 2012).

These results are consistent with previous meta-analytic studies (Ashar et al., 2017; Koban et al., 2021; Zunhammer et al., 2021) that also found that placebo analgesia modulates the default mode/limbic systems, somatosensory circuits, basal ganglia, and VAN/salience network. These results mainly highlight bottom-up expectancy-driven pain management strategies.

Novel Contributions

This meta-analysis provides quantitative evidence delineating both shared and distinct neural substrates underlying placebo response and emotion regulation. A key finding is the bilateral insula as a central hub integrating interoceptive awareness with top-down cognitive appraisal, highlighting its role in coordinating salience and executive control mechanisms. Direct comparisons revealed that emotion regulation primarily engages cortical and subcortical regions including the hippocampus, amygdala, middle temporal gyrus, and fronto-insular control areas reflecting reliance on cognitive and semantic reappraisal processes. In contrast, placebo response predominantly activates regions associated with bottom-up anticipatory processes**,** such as the mid-cingulate cortex, somatosensory-related structures, and basal ganglia, consistent with reinforcement learning and expectancy-based pain modulation. These findings elucidate how internally generated regulatory strategies differ from externally cued, expectancy-driven analgesic mechanisms, offering a neural framework for understanding affective modulation.

The results also underscore overlapping engagement of salience and control networks across both processes, suggesting that shared circuits may support integrative functions while divergent activation patterns reflect distinct regulatory strategies—cognitive reappraisal versus expectancy-based modulation. This insight provides a foundation for refining therapeutic interventions targeting emotional and pain regulation.

Limitations and Future Directions

Despite its contributions, several limitations warrant consideration. First, the ALE meta-analysis relies on published coordinates, which may exclude subtle activations or network-level dynamics captured in full statistical maps. Second, variations in experimental paradigms, task design, and sample characteristics across studies may influence convergence patterns. Third, current analyses do not differentiate the effects of open-label versus deceptive placebo paradigms**,** which may recruit distinct neural circuits.

Future research should aim to:

1. Examine moderators of neural engagement, including individual differences, expectancy, and environmental factors.
2. Combine neurostimulation techniques (e.g., TMS, tDCS) targeting DLPFC/VLPFC with placebo or emotion regulation paradigms to enhance cognitive control and emotional resilience.
3. Investigate **s**ynergistic effects of placebo-like cues and structured cognitive reappraisal in clinical populations to optimize therapeutic outcomes with minimal cognitive effort.
4. Explore overlap with pharmacological interventions**,** as antidepressants and placebo responses share mechanisms (e.g., insula and amygdala modulation), to better understand expectancy-driven affective regulation.

These directions may help develop scalable, low-cost interventions for individuals with chronic affective dysregulation or limited cognitive resources, bridging expectancy-based mechanisms and structured cognitive control strategies.

Conclusions

This study provides robust meta-analytic evidence that placebo response and emotion regulation engage a shared neural network centered on the bilateral insula**,** while also recruiting distinct cortical and subcortical circuits reflecting their unique regulatory mechanisms. Emotion regulation relies on top-down cognitive control and semantic reappraisal, whereas placebo responses involve bottom-up anticipatory and reinforcement processes.

Integrating these findings enhances our understanding of the neural basis of affective and pain modulation and offers a framework for novel therapeutic strategies that combine expectancy, cognitive reappraisal, and neural modulation. Such approaches have the potential to improve outcomes in pain management and mental health interventions by leveraging both cognitive and belief-driven mechanisms to optimize emotional and sensory regulation.

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Ethical Consideration

The study was approved by Department of Psychology, Cognitive and Neuroscience Laboratory, Foundation University Islamabad, Pakistan. Consent Form was taken before taking data and participants were asked to take voluntary participation.

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Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions/Author details

Javeria Noor conducted this study under the supervision of Dr.Muhammad Aqeel

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References

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004

Ashar, Y. K., Chang, L. J., & Wager, T. D. (2017). Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annual Review of Clinical Psychology*, *13*(1), 73–98. https://doi.org/10.1146/annurev-clinpsy-021815-093015

Ashar, Y. K., Sun, M., Knight, K., Flood, T. F., Anderson, Z., Kaptchuk, T. J., & Wager, T. D. (2024). Open-Label Placebo Injection for Chronic Back Pain With Functional Neuroimaging. *JAMA Network Open*, *7*(9), e2432427. https://doi.org/10.1001/jamanetworkopen.2024.32427

Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*(2), 140–148. https://doi.org/10.1016/j.neulet.2012.03.039

Beauchamp, M. S. (2005). See me, hear me, touch me: multisensory integration in lateral occipital-temporal cortex. *Current Opinion in Neurobiology*, *15*(2), 145–153. https://doi.org/10.1016/j.conb.2005.03.011

Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology*, *199*(3), 457–480. https://doi.org/10.1007/s00213-008-1099-6

Bo, K., Kraynak, T. E., Kwon, M., Sun, M., Gianaros, P. J., & Wager, T. D. (2024). A systems identification approach using Bayes factors to deconstruct the brain bases of emotion regulation. *Nature Neuroscience*, *27*(5), 975–987. https://doi.org/10.1038/s41593-024-01605-7

Botvinik-Nezer, R., Petre, B., Ceko, M., Lindquist, M. A., Friedman, N. P., & Wager, T. D. (2024). Placebo treatment affects brain systems related to affective and cognitive processes, but not nociceptive pain. *Nature Communications*, *15*(1), 6017. https://doi.org/10.1038/s41467-024-50103-8

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). *The Brain's Default Network. Annals of the New York Academy of Sciences*, *1124*(1), 1–38. https://doi.org/10.1196/annals.1440.011

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex*, *24*(11), 2981–2990. https://doi.org/10.1093/cercor/bht154

Čeko, M., Kragel, P. A., Woo, C.-W., López-Solà, M., & Wager, T. D. (2022). Common and stimulus-type-specific brain representations of negative affect. *Nature Neuroscience*, *25*(6), 760–770. https://doi.org/10.1038/s41593-022-01082-w

Colloca, L., & Howick, J. (2018). *Placebos Without Deception: Outcomes, Mechanisms, and Ethics* (pp. 219–240). https://doi.org/10.1016/bs.irn.2018.01.005

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. Y. (2008). Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews*, *58*(1), 57–70. https://doi.org/10.1016/j.brainresrev.2007.10.012

Cutuli, D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. *Frontiers in Systems Neuroscience*, *8*. https://doi.org/10.3389/fnsys.2014.00175

Dörfel, D., Lamke, J.-P., Hummel, F., Wagner, U., Erk, S., & Walter, H. (2014). Common and differential neural networks of emotion regulation by Detachment, Reinterpretation, Distraction, and Expressive Suppression: A comparative fMRI investigation. *NeuroImage*, *101*, 298–309. https://doi.org/10.1016/j.neuroimage.2014.06.051

Farah, M. J., Hutchinson, J. B., Phelps, E. A., & Wagner, A. D. (2014). Functional MRI-based lie detection: scientific and societal challenges. *Nature Reviews Neuroscience*, *15*(2), 123–131. https://doi.org/10.1038/nrn3665

Feeser, M., Prehn, K., Kazzer, P., Mungee, A., & Bajbouj, M. (2014). Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. *Brain Stimulation*, *7*(1), 105–112. https://doi.org/10.1016/j.brs.2013.08.006

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., Hussein, A. A., Smart, L. M., & Sabatinelli, D. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neuroscience & Biobehavioral Reviews*, *45*, 202–211. https://doi.org/10.1016/j.neubiorev.2014.06.010

Genon, S., Eickhoff, S. B., & Kharabian, S. (2022). Linking interindividual variability in brain structure to behaviour. *Nature Reviews Neuroscience*, *23*(5), 307–318. https://doi.org/10.1038/s41583-022-00584-7

Grillon, C., Quispe-Escudero, D., Mathur, A., & Ernst, M. (2015). Mental fatigue impairs emotion regulation. *Emotion*, *15*(3), 383–389. https://doi.org/10.1037/emo0000058

Gross, J. J. (2015). Emotion Regulation: Current Status and Future Prospects. *Psychological Inquiry*, *26*(1), 1–26. https://doi.org/10.1080/1047840X.2014.940781

Gross, J. J., & Levenson, R. W. (1997). Hiding feelings: The acute effects of inhibiting negative and positive emotion. *Journal of Abnormal Psychology*, *106*(1), 95–103. https://doi.org/10.1037/0021-843X.106.1.95

Hutcherson, C. A., & Tusche, A. (2022). Evidence accumulation, not 'self-control', explains dorsolateral prefrontal activation during normative choice. *ELife*, *11*. https://doi.org/10.7554/eLife.65661

Kalisch, R. (2009). The functional neuroanatomy of reappraisal: Time matters. *Neuroscience & Biobehavioral Reviews*, *33*(8), 1215–1226. https://doi.org/10.1016/j.neubiorev.2009.06.003

Koban, L., Gianaros, P. J., Kober, H., & Wager, T. D. (2021). The self in context: brain systems linking mental and physical health. *Nature Reviews Neuroscience*, *22*(5), 309–322. https://doi.org/10.1038/s41583-021-00446-8

Koban, L., Jepma, M., López-Solà, M., & Wager, T. D. (2019). Different brain networks mediate the effects of social and conditioned expectations on pain. *Nature Communications*, *10*(1), 4096. https://doi.org/10.1038/s41467-019-11934-y

Kober, H., Buhle, J., Weber, J., Ochsner, K. N., & Wager, T. D. (2019). Let it be: mindful acceptance down-regulates pain and negative emotion. *Social Cognitive and Affective Neuroscience*, *14*(11), 1147–1158. https://doi.org/10.1093/scan/nsz104

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *NeuroImage*, *87*, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001

Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., Turkeltaub, P. E., Kochunov, P., & Fox, P. T. (2005). ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*, *25*(1), 155–164. https://doi.org/10.1002/hbm.20136

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., &

Barrett, L. F. (2012). The brain basis of emotion: A meta-analytic review. *Behavioral and Brain Sciences*, *35*(3), 121–143. https://doi.org/10.1017/S0140525X11000446

Martins, B., & Mather, M. (2016). Default mode network and later-life emotion regulation: Linking functional connectivity patterns and emotional outcomes. In *Emotion, aging, and health.* (pp. 9–29). American Psychological Association. https://doi.org/10.1037/14857-002

McRae, K., & Gross, J. J. (2020). Emotion regulation. *Emotion*, *20*(1), 1–9. https://doi.org/10.1037/emo0000703

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Messina, I., Bianco, S., Sambin, M., & Viviani, R. (2015). Executive and semantic processes in reappraisal of negative stimuli: insights from a meta-analysis of neuroimaging studies. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.00956

Morawetz, C., Bode, S., Derntl, B., & Heekeren, H. R. (2017). The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. *Neuroscience & Biobehavioral Reviews*, *72*, 111–128. https://doi.org/10.1016/j.neubiorev.2016.11.014

Müller, J. M., Kiel, D., & Voigt, K.-I. (2018). What Drives the Implementation of Industry 4.0? The Role of Opportunities and Challenges in the Context of Sustainability. *Sustainability*, *10*(1), 247. https://doi.org/10.3390/su10010247

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, *1251*(1). https://doi.org/10.1111/j.1749-6632.2012.06751.x

Oken, B. S. (2008). Placebo effects: clinical aspects and neurobiology. *Brain*, *131*(11), 2812–2823. https://doi.org/10.1093/brain/awn116

Powers, J. P., & LaBar, K. S. (2019). Regulating emotion through distancing: A taxonomy, neurocognitive model, and supporting meta-analysis. *Neuroscience & Biobehavioral Reviews*, *96*, 155–173. https://doi.org/10.1016/j.neubiorev.2018.04.023

Raio, C. M., Orederu, T. A., Palazzolo, L., Shurick, A. A., & Phelps, E. A. (2013). Cognitive emotion regulation fails the stress test. *Proceedings of the National Academy of Sciences*, *110*(37), 15139–15144. https://doi.org/10.1073/pnas.1305706110

Rebstock, L., Schäfer, L. N., Kube, T., Ehmke, V., & Rief, W. (2020). Placebo prevents rumination: An experimental study. *Journal of Affective Disorders*, *274*, 1152–1160. https://doi.org/10.1016/j.jad.2020.06.010

Roy, M., Shohamy, D., & Wager, T. D. (2012). Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends in Cognitive Sciences*, *16*(3), 147–156. https://doi.org/10.1016/j.tics.2012.01.005

Samartsidis, P., Montagna, S., Johnson, T. D., & Nichols, T. E. (2017). The Coordinate-Based Meta-Analysis of Neuroimaging Data. *Statistical Science*, *32*(4). https://doi.org/10.1214/17-STS624

Schaefer, M., Kühnel, A., Schweitzer, F., Enge, S., & Gärtner, M. (2023). Neural underpinnings of open-label placebo effects in emotional distress. *Neuropsychopharmacology*, *48*(3), 560–566. https://doi.org/10.1038/s41386-022-01501-3

Schafer, S. M., Colloca, L., & Wager, T. D. (2015). Conditioned Placebo Analgesia Persists When Subjects Know They Are Receiving a Placebo. *The Journal of Pain*, *16*(5), 412–420. https://doi.org/10.1016/j.jpain.2014.12.008

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *32*(4), 811–830. https://doi.org/10.1016/j.neubiorev.2007.12.002

Sripada, C., Angstadt, M., Kessler, D., Phan, K. L., Liberzon, I., Evans, G. W., Welsh, R. C., Kim, P., & Swain, J. E. (2014). Volitional regulation of emotions produces distributed alterations in connectivity between visual, attention control, and default networks. *NeuroImage*, *89*, 110–121. https://doi.org/10.1016/j.neuroimage.2013.11.006

Theodosis-Nobelos, P., Filotheidou, A., & Triantis, C. (2021). The placebo phenomenon and the underlying mechanisms. *Hormones*, *20*(1), 61–71. https://doi.org/10.1007/s42000-020-00243-5

Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus Is a Functional Core of the Default-Mode Network. *The Journal of Neuroscience*, *34*(3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014

van der Meulen, M., Kamping, S., & Anton, F. (2017). The role of cognitive reappraisal in placebo analgesia: an fMRI study. *Social Cognitive and Affective Neuroscience*, *12*(7), 1128–1137. https://doi.org/10.1093/scan/nsx033

Wager, T. D., & Barrett, L. F. (2017). *From affect to control: Functional specialization of the insula in motivation and regulation*. https://doi.org/10.1101/102368

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. *Science*, *303*(5661), 1162–1167. https://doi.org/10.1126/science.1093065

Xie, X., Mulej Bratec, S., Schmid, G., Meng, C., Doll, A., Wohlschläger, A., Finke, K., Förstl, H., Zimmer, C., Pekrun, R., Schilbach, L., Riedl, V., & Sorg, C. (2016). How do you make me feel better? Social cognitive emotion regulation and the default mode network. *NeuroImage*, *134*, 270–280. https://doi.org/10.1016/j.neuroimage.2016.04.015

Zaki, J., Davis, J. I., & Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. *NeuroImage*, *62*(1), 493–499. https://doi.org/10.1016/j.neuroimage.2012.05.012

Zunhammer, M., Spisák, T., Wager, T. D., Bingel, U., Atlas, L., Benedetti, F., Büchel, C., Choi, J. C., Colloca, L., Duzzi, D., Eippert, F., Ellingsen, D.-M., Elsenbruch, S., Geuter, S., Kaptchuk, T. J., Kessner, S. S., Kirsch, I., Kong, J., Lamm, C., … Zeidan, F. (2021). Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nature Communications*, *12*(1), 1391. https://doi.org/10.1038/s41467-021-21179-3

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