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Neural Mechanisms of Cognitive Behavioral Therapy for Depression: A Multimodal Systematic Review

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Abstract

Major depressive disorder involves disturbances in neural systems supporting emotion regulation, cognitive control, reward processing, and self-referential thought. Cognitive behavioral therapy (CBT) is an established treatment for depression, yet the neural mechanisms through which different CBT modalities exert therapeutic effects remain unclear. This review aimed to synthesize multimodal neuroimaging evidence to identify consistent and modality-specific neural changes associated with CBT for depression. A systematic search was conducted in a major biomedical database using predefined keywords. Eligible studies included peer-reviewed human research examining a CBT-based intervention and reporting pre- or posttreatment neural outcomes measured using functional magnetic resonance imaging, resting-state imaging, structural magnetic resonance imaging, or diffusion imaging. Study characteristics and neural results were extracted using a structured template. Findings were organized by CBT modality to compare neural outcomes across intervention types. Eleven studies met inclusion criteria. Across modalities, CBT was associated with changes in prefrontal, limbic, cingulate, and striatal systems. Standard CBT produced changes in prefrontal activation, limbic gray-matter volume, and connectivity between cognitive control and reward-related regions. Internet-based CBT was linked to enhanced reward-circuit engagement, reduced dominance of default-mode network states, and greater transitions toward central-executive network states. Rumination-focused CBT influenced posterior midline regions involved in repetitive negative thinking. Computer-assisted CBT increased connectivity between cognitive control and limbic circuits. Neurofeedback delivered prior to CBT enhanced amygdala activation to positive imagery and strengthened downstream reward-related engagement. Structural and diffusion findings demonstrated therapy-related gray- and white-matter plasticity consistent with functional reorganization. Across modalities, CBT produced convergent effects within neural systems aligned with the cognitive and emotional processes targeted by each intervention. These findings underscore the importance of large-scale network integration, reward sensitivity, and reduced self-focused rumination in symptom improvement. CBT influences neural systems at multiple organizational levels, with modality-specific patterns reflecting distinct therapeutic mechanisms. These results support the potential usefulness of neural markers in guiding personalized psychological treatment and highlight the value of considering intervention modality when interpreting neural outcomes.

Keywords: cognitive behavioral therapy; depression; neuroimaging; functional magnetic resonance imaging; structural magnetic resonance imaging; diffusion imaging; neural mechanisms; emotion regulation; reward processing

Introduction

Major depressive disorder (MDD) is among the most prevalent and disabling psychiatric conditions worldwide, affecting mood, cognition, and daily functioning across the lifespan [1]. Although many individuals benefit from psychotherapy or pharmacological treatments, a substantial proportion experience recurrent or persistent symptoms despite adequate care [2]. Cognitive Behavioral Therapy (CBT) is a first-line psychological intervention for depression and is supported by extensive clinical evidence demonstrating its efficacy across diverse populations and treatment settings [3]. However, the specific neural mechanisms through which CBT alleviates depressive symptoms remain incompletely understood. Clarifying these mechanisms is important for advancing precision mental health care, improving prediction of therapeutic response, and guiding the development of personalized interventions [4].

Neuroimaging techniques such as functional and structural magnetic resonance imaging (MRI) allow researchers to observe how CBT influences brain systems implicated in depression. These systems include circuits supporting emotional processing, cognitive control, self-referential thought, and reward sensitivity, which frequently show dysregulation in depressive disorders [5]. Functional MRI studies have demonstrated that CBT can modify activity within the dorsolateral prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, and striatum [6, 7]. Resting-state imaging studies show that CBT may normalize connectivity patterns between prefrontal and limbic networks,

including the default mode network (DMN), which is implicated in rumination and maladaptive self-focus [8]. Structural MRI and diffusion imaging have identified therapy-related changes in gray matter volume and white matter integrity, suggesting that CBT may promote neuroplasticity at both macro- and microstructural levels [9, 10]. Together, these findings support the possibility that CBT engages a diverse set of neural pathways across the brain.

Despite these advances, existing reviews typically focus on isolated imaging modalities or specific task paradigms. Some emphasize task-based fMRI results, whereas others concentrate on resting-state connectivity or predictors of treatment response [11]. Few reviews integrate across structural, functional, and diffusion modalities, and none synthesize results across all major CBT formats, including internet-based, rumination-focused, computer assisted, and neurofeedback-augmented CBT. For instance, König et al. [11] was restricted to task-based fMRI studies of predominantly standard CBT formats and did not incorporate resting-state fMRI, structural MRI, or diffusion tensor imaging, nor did it include emerging modalities such as rumination-focused, computer-assisted, or neurofeedback-augmented CBT [12]. These limitations restrict the ability to identify consistent patterns of neural change across treatment approaches and across multiple levels of neural organization.

A comprehensive multimodal synthesis is needed to clarify how CBT influences neural mechanisms across major brain systems implicated in depression. Organizing findings according to CBT modality provides a systematic, clinically intuitive framework for identifying modality-specific and cross-cutting neural effects that may underlie symptom improvement. To guide this synthesis, a systematic literature search was conducted to identify eligible neuroimaging studies examining CBT-related neural changes in depression.

The aim of this review is to examine the multiscale neural mechanisms associated with CBT for depression across functional, structural, and diffusion MRI studies. The review synthesizes evidence across different CBT modalities to identify consistent patterns of neural change and highlight mechanisms that may contribute to therapeutic response. The research question guiding this review was: What consistent and modality-specific neural changes are associated with cognitive behavioral therapy for depression across functional, structural, and diffusion MRI studies?

Methods

A systematic literature search was conducted in PubMed using a strategy adapted from König et al. [11]. The search included all records published up to February 8, 2023, using the Boolean combination: (“depressive disorder” OR “depression”) AND (“fMRI” OR “functional MRI” OR “functional magnetic resonance imaging”) AND (“psychotherapy” OR “psychotherapeutic” OR “cognitive-behavioral therapy” OR “cognitive-behavioural therapy” OR “CBT”). Records were imported into Covidence for duplicate removal, screening, and full-text evaluation. Titles and abstracts were screened first, followed by full-text review. Additional studies were identified through hand-searching of reference lists in included articles and related reviews.

Eligibility criteria followed PRISMA guidelines and the framework described by König et al. [11]. Studies were eligible if they were empirical, peer-reviewed human investigations published in English and available in full text. Eligible samples included adolescents or adults (approximately ages 13–70) with major depressive disorder, persistent depressive disorder, dysthymia, or clinically significant depressive symptoms. Studies were required to include a CBT-based intervention, such as standard CBT, cognitive therapy, behavioral activation, rumination focused CBT (RF-CBT), mindfulness-based CBT, group CBT, computerized CBT, or internet-based CBT (iCBT). Adjunctive approaches such as neurofeedback were eligible if CBT constituted a core therapeutic component.

Eligible neuroimaging modalities included task-based fMRI, resting-state fMRI, structural MRI, and diffusion imaging. Studies needed to report at least one neural outcome relevant to CBT (e.g., pre- to post-treatment activation or connectivity change, baseline neural predictors of treatment response). Both whole-brain and region-of interest analyses were eligible. Studies were excluded if they involved bipolar or psychotic disorders, focused exclusively on geriatric depression, lacked extractable neural data, omitted CBT, or were case reports, conference abstracts, trial protocols, or narrative reviews.

The search identified 440 records. After duplicate removal, 26 full-text articles were screened. Fifteen were excluded for lacking a CBT component, omitting pre-/post-treatment imaging, focusing exclusively on resting-state fMRI without meeting other criteria, or lacking extractable neural data. Eleven studies met inclusion criteria and were retained for synthesis. The study identification, screening, and inclusion process is illustrated in Figure 1.

Data extraction followed König et al. [11] using a structured Excel template. Extracted information included sample characteristics, intervention type, treatment duration, imaging modality, acquisition parameters, analytic methods, and all reported neural outcomes. No interpretation occurred during extraction. Neural findings were later synthesized according to CBT modality to align with the structure required by review objectives and mentor guidance.

Results

Across the 11 included studies, the total combined sample comprised 682 participants, with available demographic data indicating 60.4% female and 39.6% male. Age ranges across studies spanned approximately 14 to 65 years, representing both adolescent and adult clinical populations. Participants included individuals with current MDD, adolescents with remitted depression, and healthy controls. Treatment protocols ranged from 6 to 20 sessions delivered over approximately 8 to 16 weeks, with modality-specific differences described

below. Across the 11 studies, the combined sample by imaging modality was as follows: task-based fMRI studies contributed a total of 200 participants, resting-state fMRI studies (including dynamic functional connectivity) contributed 255 participants, structural MRI contributed 30 participants, and diffusion tensor imaging contributed 65 participants. Note that some participants were drawn from overlapping samples within the same research group, and modality totals therefore reflect reported N values per study rather than unique individuals across the review. Characteristics of the included studies, including sample, intervention type, imaging modality, and key neural findings, are summarized in Table 1.

Standard CBT

Standard CBT was examined in four studies that assessed neural changes across functional, structural, and connectivity-based measures. Strege et al. [13] reported response-related activation changes in prefrontal and parietal regions during an emotional word processing task following standard CBT. Wei et al. [14] found that higher pre-treatment regional homogeneity in the left dorsolateral prefrontal cortex predicted post-treatment symptom severity. Structural MRI results from Zwiky et al. [15] demonstrated increased gray matter volume in the bilateral amygdala and right anterior hippocampus, with decreased volume in the right posterior hippocampus after treatment. Katayama et al. [16] reported that standard CBT increased frontopolar–nucleus accumbens resting-state connectivity compared with a talking control condition.

Internet-based CBT

Three studies investigated internet-based CBT and its neural correlates. Hanuka et al. [17] reported increased activation in the nucleus accumbens and subgenual anterior cingulate cortex, along with strengthened NAcc–sgACC connectivity during reward feedback. Thai et al. [18] found that baseline inhibitory control performance and resting-state connectivity among the dorsal ACC, bilateral anterior insula, and temporoparietal junction predicted treatment response. Katayama et al. [19] reported that CBT reduced dominance of default mode network states centered on medial prefrontal cortex and anterior cingulate cortex while increasing transitions toward central executive network states.

Rumination-focused CBT

Two studies examined RF-CBT. Westlund Schreiner et al. [20] reported increased activation in the posterior cingulate cortex, precuneus, and angular gyrus during rumination-induction tasks in adolescents with a history of depression. Katayama et al. [19] observed that CBT-related reductions in DMN dominance occurred in participants receiving RF-CBT and pharmacotherapy, with increases in transitions toward central executive network states.

Computer-assisted CBT

Two studies evaluated CCBT and its neural correlates. Sheline et al. [21] reported increased functional connectivity between the dorsolateral prefrontal cortex and subcortical emotion-related regions, including the amygdalae, hippocampi, nucleus accumbens, and sgACC. This study also showed broader increases in frontoparietal–limbic connectivity following treatment. Additional connectivity analyses in Katayama et al. [16] identified increased frontopolar–striatal coupling in participants receiving CBT compared with a talking control group.

Neurofeedback-augmented CBT

One study examined CBT delivered following real-time amygdala neurofeedback. Compère et al. [22] reported that neurofeedback increased amygdala activation during positive memory recall prior to CBT initiation. These changes were followed by improved engagement of reward-related pathways during CBT and greater reductions in depressive symptoms.

Structural and Diffusion MRI Findings

Two studies used structural MRI or diffusion tensor imaging to assess CBT-related anatomical plasticity. Zwiky et al. [15] identified gray matter increases in bilateral amygdala and anterior hippocampus and decreases in posterior hippocampus following standard CBT. Flinkenflügel et al. [23] reported increased fractional anisotropy in the corpus callosum, corona radiata, and superior longitudinal fasciculus, with FA changes predicting symptom improvement and partially mediating the relationship between early life adversity and depressive symptoms.

Across CBT modalities, findings converged on changes in prefrontal, cingulate, limbic, and striatal systems. Task-based fMRI demonstrated alterations in emotional, cognitive, and reward-processing networks, while resting-state studies showed increased connectivity among prefrontal and limbic circuits and reduced dominance of DMN states. Structural and diffusion findings indicated gray and white matter plasticity consistent with functional reorganization.

Table 1. Characteristics of Included Neuroimaging Studies Examining Cognitive Behavioral Therapy for Depression

Study	CBT Modality	Sample (N, age)	Sessions / Duration	Imaging Modality	Key Neural Findings
Strege et al. (2024)	Standard CBT	Adults, N not specified	16 sessions (~12–16 weeks)	Task-based fMRI	↑ DLPFC & parietal activation during emotional word processing
Wei et al. (2023)	Standard CBT	Adults with MDD	12–16 weeks	Resting-state fMRI	Left DLPFC ReHo predicted post-CBT severity
Zwiky et al. (2025)	Standard CBT	Adults with MDD	20 sessions	Structural MRI	↑ amygdala & anterior hippocampus GM; ↓ posterior hippocampus GM
Katayama et al. (2023)	Standard CBT	Adults with MDD	16 sessions	Resting-state fMRI	↑ frontopolar–NAcc connectivity vs. talking control
Hanuka et al. (2023)	iCBT	Adults with MDD	10-week online program	Task-based fMRI	↑ NAcc & sgACC activation; ↑ NAcc–sgACC connectivity during reward
Thai et al. (2024)	iCBT	Adults with MDD	10-week program	Resting-state fMRI	Inhibitory-control network connectivity predicted response
Katayama et al. (2025)	iCBT / RF-CBT	Adults with MDD	Varied	Dynamic FC modeling	↓ DMN dominance; ↑ transitions to CEN states
Westlund Schreiner et al. (2025)	RF-CBT	Adolescents w/ remitted depression	10–14 sessions	Task-based fMRI	↑ PCC, precuneus, angular gyrus activation during rumination
Sheline et al. (2025)	CCBT	Adults with MDD	12-week program	Resting-state fMRI	↑ DLPFC–limbic connectivity (amygdala, hippocampus, NAcc, sgACC)
Katayama et al. (2023)	CCBT (comparison)	Adults with MDD	12–16 weeks	Resting-state fMRI	↑ frontopolar–striatal connectivity
Compère et al. (2023)	Neurofeedback-augmented CBT	Adults with MDD	Neurofeedback + CBT	Task-based fMRI	↑ amygdala activation during memory recall; downstream reward activation

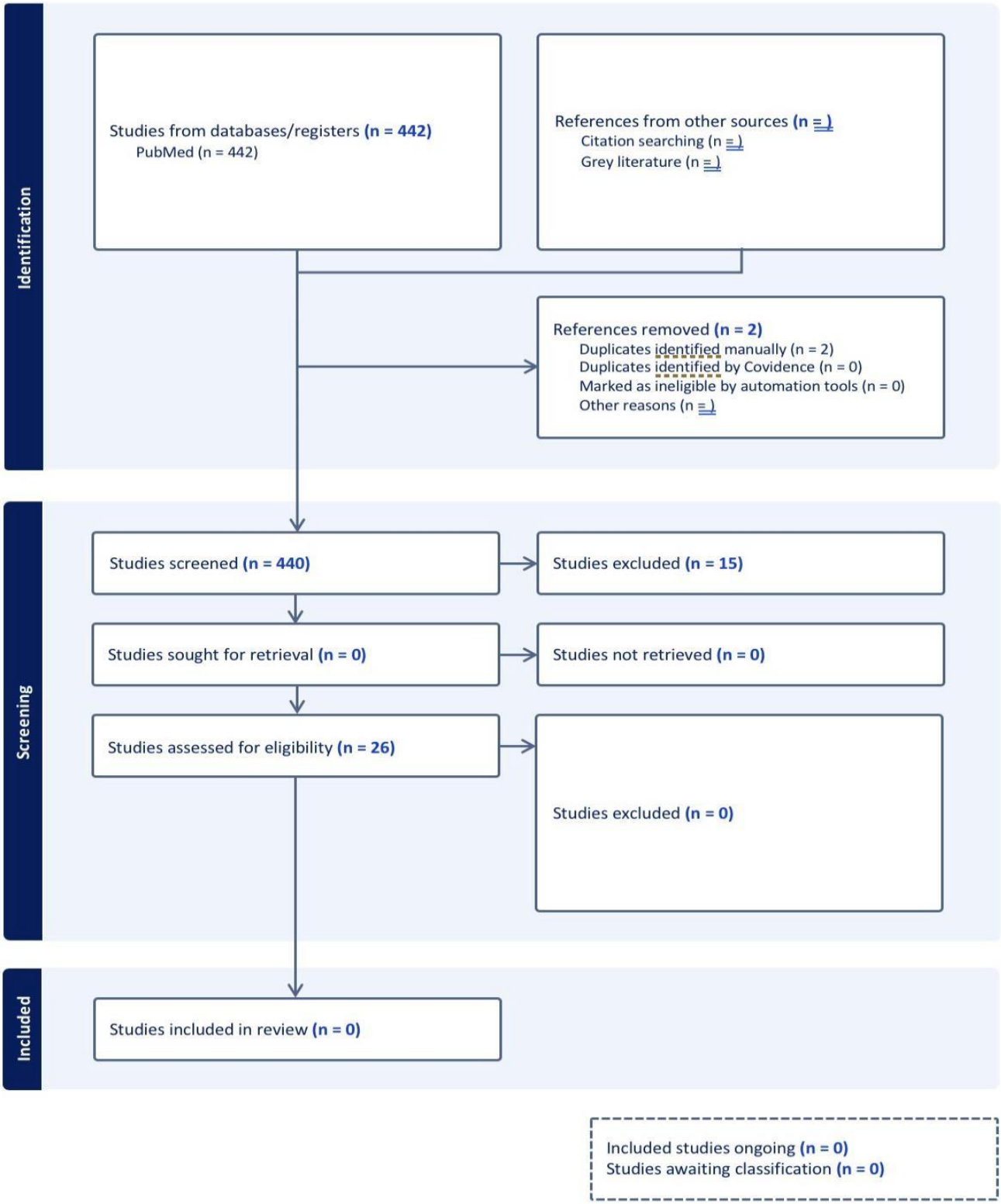

Figure 1. PRISMA flow diagram of study identification, screening, and inclusion. Generated using Covidence systematic review software.

Discussion

This multimodal review synthesized structural, functional, and diffusion MRI evidence examining the neural mechanisms associated with different CBT modalities for major depressive disorder. By organizing findings according to modality, the review identified modality-specific neural profiles as well as cross-cutting effects across major brain systems involved in emotion regulation, cognitive control, and reward processing.

Standard CBT produced changes in regions supporting cognitive control and emotional processing. Increased activation in dorsolateral and medial prefrontal regions during emotional tasks was observed following treatment [13], while higher pre-treatment DLPFC regional homogeneity predicted symptom outcomes [14]. Structural changes in limbic regions, including increased amygdala and anterior hippocampal volume, further suggest that standard CBT may influence affective and memory-related circuits [15]. Increased frontopolar–striatal connectivity following CBT [16] suggests engagement of reward-related pathways during cognitive restructuring. iCBT studies consistently demonstrated changes in reward and cognitive control networks. Increased NAcc and sgACC activation and strengthened NAcc–sgACC connectivity during reward feedback were observed following treatment [17]. Baseline inhibitory control network organization predicted treatment response [18], indicating that prefrontal inhibitory control systems may support CBT engagement. Reductions in DMN dominance and increased transitions toward central executive states following treatment [19] highlight the role of network-level shifts in improving self-referential processing.

RF-CBT primarily influenced posterior midline regions involved in rumination and self-referential thought. Increased activation in the PCC, precuneus, and angular gyrus during rumination-induction tasks [20] aligns with the intervention's focus on altering repetitive negative thinking. Dynamic functional connectivity evidence showing reduced DMN dominance following CBT [19] further supports the idea that RF-CBT targets neural systems associated with maladaptive self-focus.

CCBT was associated with increased functional connectivity between prefrontal control regions and limbic structures, including the amygdala, hippocampus, and sgACC [21]. These findings suggest enhanced integration between cognitive control and emotional processing networks following treatment. Increases in frontopolar–striatal connectivity observed in related CBT conditions [16] support the role of frontostriatal mechanisms in symptom improvement.

Neurofeedback before CBT increased amygdala activation during positive memory recall [22], which was followed by downstream engagement of reward-related circuits during CBT. These findings suggest that targeting specific neural circuits prior to treatment may amplify CBT-related neural changes.

Structural MRI demonstrated limbic gray matter changes following CBT [15], while diffusion imaging revealed increases in white matter integrity across frontoparietal and interhemispheric pathways [23]. These structural findings complement functional results and support the hypothesis that CBT may influence neural systems at multiple organizational levels.

Clinical Implications

Across modalities, findings illustrate that CBT influences neural systems in ways that reflect the therapeutic focus of each modality. Reward-focused interventions shaped limbic and striatal circuits [16, 17], rumination-focused interventions modulated posterior midline regions [19, 20], and cognitive restructuring approaches engaged prefrontal systems [13, 14, 18, 21]. These modality-specific neural signatures underscore the value of matching therapeutic strategies to a patient's neural and cognitive profile and highlight the potential utility of neuroimaging biomarkers for informing precision psychotherapy.

More explicitly, the observed neural changes may translate to symptom improvement through several interconnected pathways. Enhanced prefrontal activation and front limbic connectivity likely strengthens top-down cognitive control over limbic reactivity, dampening maladaptive emotional responses and facilitating the cognitive restructuring that is central to CBT. Increased reward circuit engagement, particularly in the nucleus accumbens and subgenual anterior cingulate cortex, may restore sensitivity to positive reinforcement and reduce anhedonia. Reductions in default mode network dominance are consistent with decreased self-referential rumination, a key maintenance factor in depression. These mechanistic pathways are broadly consistent with the cognitive model of depression, in which CBT is proposed to exert its effects by modifying dysfunctional cognitive patterns through engagement of prefrontal regulatory systems [5].

The neural patterns identified in this review extend and refine the findings of König et al., who synthesized neural correlates of CBT across a narrower set of modalities and primarily emphasized task-based and resting-state fMRI. Several trends observed in the previous review remained consistent, including CBT-related modulation of prefrontal, cingulate, and limbic systems. However, the present synthesis incorporates additional imaging modalities. Specifically, structural MRI and diffusion tensor imaging, which reveal evidence of macro- and microstructural plasticity not captured in König et al. Furthermore, this review integrates emerging CBT subtypes that were not included in König et al., such as neurofeedback-augmented CBT and newer internet-delivered CBT programs targeting inhibitory control or reward processing. Methodological advancements were also evident, with more recent studies using dynamic functional connectivity modeling, individualized connectivity predictors, and multimodal imaging pipelines. Together, these expansions demonstrate

both continuity with and progression beyond the earlier review, highlighting meaningful advances in the methodological and conceptual landscape of CBT neuroimaging research.

Limitations

This review has several limitations. Only eleven studies met inclusion criteria, and the heterogeneity of imaging modalities, analytic approaches, and CBT protocols limited the ability to identify specific causal mechanisms. Sample sizes across studies were modest, reducing statistical power and generalizability. Few studies directly compared CBT modalities within the same design, limiting inferences about modality-specific effects. Most studies lacked longitudinal follow-up imaging, preventing conclusions about the durability of neural changes. Concurrent pharmacotherapy was handled inconsistently across studies: some explicitly excluded psychotropic medications [13, 17, 18, 21], while others permitted stable antidepressant use [15, 22] or incorporated pharmacotherapy as routine clinical care [16, 19, 23], and one focused specifically on treatment-naive patients [14]. This heterogeneity limits the extent to which observed neural changes can be attributed exclusively to CBT. Despite these limitations, converging multimodal findings support the conclusion that CBT influences neural systems across multiple levels.

Conclusions

This multimodal systematic review synthesizes evidence across functional, structural, and diffusion MRI modalities to clarify the neural mechanisms associated with CBT for major depressive disorder. Results demonstrate that CBT influences limbic, prefrontal, cingulate, and striatal systems, with modality-specific patterns reflecting the cognitive and emotional targets of each intervention. Reward-oriented, rumination-focused, computer-assisted, and neurofeedback-augmented forms of CBT each produced distinct neural changes aligned with their therapeutic goals. Structural and diffusion findings provided additional evidence of neuroplasticity accompanying functional reorganization. These findings highlight the importance of considering CBT modality when interpreting neural outcomes and point toward the potential for neuroimaging markers to guide personalized treatment selection in clinical practice. Future research should evaluate whether modality-specific neural signatures can reliably predict treatment outcomes across diverse populations and whether combining multimodal imaging approaches can enhance the identification of biomarkers for personalized psychotherapy.

List of Abbreviations

ACC: anterior cingulate cortex
BA: behavioral activation
CBT: cognitive behavioral therapy
MRI: Magnetic resonance imaging
DLPFC: dorsolateral prefrontal cortex
DMN: default mode network
fMRI: functional magnetic resonance imaging
GM: gray matter
MDD: major depressive disorder
PFC: prefrontal cortex
RF-CBT: rumination-focused cognitive behavioral therapy
ROI: region of interest
WM: white matter

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This review did not use or collect data requiring ethical approval or participant consent.

Authors' Contributions

AD: made substantial contributions to the design of the study, the collection of data, interpretation, and analysis of the data, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements

I would like to express my sincere gratitude to my mentor, Frank Nicholas Mazza, for his guidance throughout the writing of this review. His expertise, encouragement, and detailed feedback were instrumental in refining the study's ideas and final manuscript.

Funding

This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Frank Mazza, Miray Youssef
Article Dates: Received Nov 28 25; Accepted Apr 11 26; Published Jun 09 26

Citation
Please cite this article as follows:
Dimopoulos A. Neural mechanisms of cognitive behavioral therapy for depression: A multimodal systematic review. URNCST Journal. 2026 Jun 09: 10(6). https://urncst.com/index.php/urncst/article/view/1015
DOI Link: https://doi.org/10.26685/urncst.1015