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**Personalizing PTSD Psychotherapy: A Circuit-Based Framework Linking Symptom
Profiles to Neuroimaging Markers of Treatment**

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Abstract

Posttraumatic stress disorder (PTSD) is characterized by substantial variability in symptom presentation and treatment outcomes. Although trauma-focused psychotherapies such as Prolonged Exposure Therapy (PE) and Cognitive Processing Therapy (CPT) are effective for many individuals, treatment response remains highly heterogeneous. The present study replicates and extends a systematic review and meta-analysis examining predictors of response to trauma-focused psychotherapy for PTSD. Findings from over 100 studies were synthesized to evaluate demographic, clinical, and biological factors associated with treatment outcomes. Consistent with the original analysis, pretreatment symptom severity, psychiatric comorbidities, demographic characteristics, and fear-related biological variables were associated with variability in psychotherapy response. To extend these findings, predictors were reorganized according to neural systems implicated in PTSD, including fear-regulation, contextual-memory, and cognitive-control circuits. Evidence from neuroimaging studies suggests that reduced hippocampal volume is associated with PTSD (Logue et al., 2018), while greater hippocampal integrity and increased ventromedial prefrontal cortex activation predict stronger psychotherapy outcomes (Rubin et al., 2016; Fonzo et al., 2017). Together, these findings support a circuit-based framework for understanding treatment heterogeneity and highlight the potential of neurobiologically informed approaches to PTSD treatment.

Keywords

posttraumatic stress disorder (PTSD); psychotherapy response; neuroimaging; precision psychiatry; hippocampus; ventromedial prefrontal cortex (vmPFC); treatment prediction; neural circuits

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition that develops following exposure to traumatic events and is characterized by intrusive memories, avoidance behaviors, negative alterations in cognition and mood, and heightened physiological arousal. PTSD affects approximately 6.8% of individuals during their lifetime and remains associated with substantial personal, social, and economic burden (McLean et al., 2019). Although evidence-based psychotherapies such as Prolonged Exposure Therapy (PE) and Cognitive Processing Therapy (CPT) have demonstrated efficacy across numerous clinical trials, treatment outcomes remain highly variable. Approximately 30–50% of patients fail to achieve full remission, suggesting that important determinants of treatment response remain poorly understood.

Identifying predictors of psychotherapy response has therefore become a major focus of PTSD research. Recent systematic reviews and meta-analyses have examined a broad range of demographic, clinical, and biological variables associated with treatment outcomes. Factors including pretreatment symptom severity, psychiatric comorbidities, age, sex, and fear-related biological characteristics have all been investigated as potential predictors of therapeutic success. Understanding these predictors may improve treatment selection and ultimately contribute to more personalized interventions for individuals with PTSD.

Despite these efforts, PTSD remains a highly heterogeneous disorder. Individuals meeting diagnostic criteria often exhibit markedly different symptom profiles, levels of functional impairment, and treatment trajectories. Some patients primarily experience hyperarousal and fear-related symptoms, whereas others exhibit disturbances in memory, emotional regulation, or

executive functioning. This variability suggests that individuals sharing the same diagnosis may differ substantially in the underlying neurobiological mechanisms contributing to their symptoms.

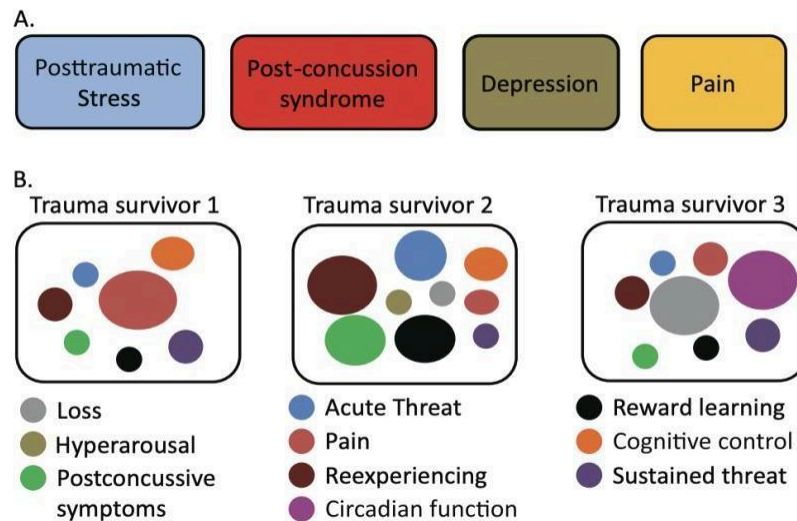


Figure 1. Symptom heterogeneity in PTSD. Individuals with PTSD exhibit distinct patterns of dysfunction across multiple neurobehavioral domains, highlighting limitations of syndrome-based diagnosis. *Adapted from the AURORA Consortium conceptual framework (McLean et al., 2019).*

Growing evidence from structural and functional neuroimaging studies supports the notion that PTSD reflects dysfunction across multiple neural systems. Altered activity within the amygdala–ventromedial prefrontal cortex (vmPFC) circuit has been linked to exaggerated fear responses and impaired emotional regulation. Reductions in hippocampal volume have been associated with deficits in contextual memory processing and trauma-related learning (Logue et al., 2018). Additionally, abnormalities within anterior cingulate and prefrontal cortical networks have been implicated in attentional control and executive functioning deficits commonly observed in PTSD.

Importantly, these neural systems may also contribute to variability in psychotherapy outcomes. Greater hippocampal volume has been associated with improved response to cognitive

behavioral therapy (Rubin et al., 2016), while increased vmPFC activation during emotional regulation tasks predicts stronger symptom reduction following psychotherapy (Fonzo et al., 2017). Such findings suggest that treatment response may be influenced not only by clinical symptom severity but also by underlying neural circuitry.

To better understand this treatment heterogeneity, Keyan et al. (2024) conducted a systematic review and meta-analysis of predictors of response to trauma-focused psychotherapy for PTSD, synthesizing findings from 114 studies comprising 61,970 participants. Their findings demonstrated that treatment outcomes are influenced by a diverse range of demographic, clinical, cognitive, social, and biological factors rather than any single predictor.

While the original review identified numerous predictors of treatment response, the neurobiological mechanisms underlying these relationships remain less clearly understood. To address this limitation, the present study replicates and extends the original meta-analysis by reorganizing identified predictors according to neural systems implicated in PTSD pathophysiology. Specifically, predictors are interpreted within three major domains: fear-regulation circuits, contextual-memory circuits, and cognitive-control circuits. By integrating evidence from neuroimaging studies with established psychotherapy predictors, this extension seeks to provide a more mechanistic framework for understanding treatment heterogeneity and to explore how circuit-based models may contribute to future precision psychiatry approaches.

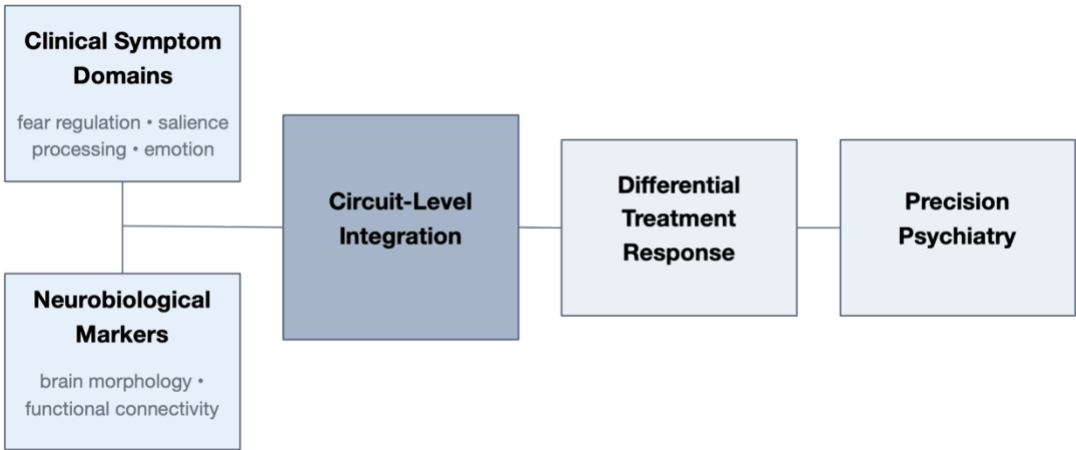


Figure 2. Conceptual framework illustrating the integration of clinical symptom domains and neurobiological markers to model circuit-level mechanisms underlying differential treatment response in PTSD and inform precision psychiatry approaches.

2. Replication Methods

The original study conducted a systematic review and meta-analysis to identify predictors of response to trauma-focused psychotherapy among individuals diagnosed with posttraumatic stress disorder (PTSD). The primary objective was to determine which demographic, clinical, and biological factors were consistently associated with treatment outcomes across the existing PTSD psychotherapy literature.

Studies were identified through comprehensive database searches and screened according to predefined inclusion and exclusion criteria. Eligible studies included participants with a diagnosis of PTSD who received evidence-based trauma-focused psychotherapies, including Prolonged Exposure Therapy (PE), Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprocessing (EMDR), and related interventions. To be included, studies were required to report standardized measures of PTSD symptom severity before and after treatment and provide sufficient statistical information to calculate treatment effects.

The original review identified 114 eligible studies ($N = 61,970$ participants) and organized predictors into 24 meta-analytic categories spanning demographic, clinical, trauma-related, cognitive, social, and biological domains. The authors extracted a broad range of variables, including demographic characteristics such as age and sex, clinical characteristics such as pretreatment PTSD severity and psychiatric comorbidities, and biological variables related to

fear reactivity and stress physiology. These predictors were evaluated to determine their relationship with treatment outcomes following trauma-focused psychotherapy.

To synthesize findings across studies, the authors employed random-effects meta-analytic models. Random-effects approaches were selected because they account for variability between studies, including differences in participant characteristics, treatment modalities, measurement instruments, and study design. Effect sizes were calculated and pooled to estimate the overall relationship between each predictor and psychotherapy response.

In addition to evaluating predictor effects, the authors assessed heterogeneity across studies to determine the consistency of findings. Sensitivity analyses were conducted to evaluate the robustness of results, and publication bias was examined using established meta-analytic procedures. Collectively, these analyses were designed to identify factors that reliably predict differential response to trauma-focused psychotherapy while accounting for variability across the broader PTSD treatment literature.

The findings of this meta-analysis provide a comprehensive overview of variables associated with psychotherapy outcomes and establish the foundation for the present replication and extension analysis.

3. Replication Results

3.1 Demographic and Study Characteristics

Descriptive analyses were conducted to characterize the composition of the PTSD psychotherapy dataset used in the original meta-analysis. The dataset consisted of more than 100 studies examining predictors of response to trauma-focused psychotherapy across

diverse clinical populations. Analyses revealed substantial variation in study design, geographic location, participant demographics, and sample size.

Geographic distribution analyses demonstrated a strong concentration of studies originating from the United States, with substantially fewer studies conducted in Europe, Asia, and other regions. This pattern suggests that a large proportion of the evidence base informing PTSD treatment response is derived from Western populations, potentially limiting the generalizability of findings across cultures and healthcare systems.

Participant age distributions indicated that most studies focused on adult populations, with relatively limited representation of adolescents and older adults. Consequently, predictor effects identified within the literature may not fully capture factors influencing treatment outcomes across the lifespan.

3.2 Study Design Characteristics

Examination of study design revealed that randomized controlled trials (RCTs) and uncontrolled treatment studies represented most included investigations. Comparatively fewer controlled clinical trials were identified. The predominance of RCTs reflect the emphasis on experimental rigor within PTSD treatment research, while the inclusion of uncontrolled studies increases the breadth of available evidence.

Differences in study design may contribute to variability in reported treatment outcomes. Studies employing randomized designs often demonstrate stronger internal validity, whereas uncontrolled investigations may be more susceptible to selection bias and confounding variables. As a result, methodological variation represents an important consideration when interpreting meta-analytic findings.

3.3 Sample Size Characteristics

Analysis of sample size distributions revealed considerable variability across studies. Most investigations included small to moderate sample sizes, while a limited number of large-scale studies contributed disproportionately to the overall literature. The resulting distribution was positively skewed, indicating that a small subset of studies enrolled substantially larger participant cohorts than most investigations.

Variation in sample size has important implications for statistical power and effect size estimation. Smaller studies may be more vulnerable to sampling variability, whereas larger studies often exert greater influence within meta-analytic models.

3.4 Summary of Replicated Findings

Collectively, the replication analyses confirmed key descriptive characteristics of the original dataset. PTSD psychotherapy research remains heavily concentrated within Western populations, relies primarily on randomized and uncontrolled trial designs, and exhibits substantial variability in sample size and participant demographics. These findings provide important context for interpreting identified predictors of treatment response and highlight potential limitations related to representativeness and generalizability.

Although the original meta-analysis successfully identified demographic, clinical, and biological variables associated with treatment outcomes, the mechanisms through which these predictors influence psychotherapy response remain incompletely understood. Consequently, the present study extends the original framework by examining these predictors through a neurobiological lens and organizing them according to neural systems implicated in PTSD pathophysiology.

4. Extension Methods

To extend the original meta-analysis, a circuit-based framework was developed to reorganize identified predictors according to neural systems implicated in PTSD pathophysiology. Rather than interpreting predictors solely as demographic, clinical, or biological variables, predictors were categorized according to their relevance to three major neural domains: fear-regulation circuits, contextual-memory circuits, and cognitive-control circuits.

These domains were selected based on convergent evidence from structural and functional neuroimaging studies identifying the amygdala, ventromedial prefrontal cortex (vmPFC), hippocampus, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (dlPFC) as key regions implicated in PTSD symptom expression and recovery. Published neuroimaging studies examining brain structure, functional activation, and treatment outcomes were reviewed and integrated into the extension framework.

This approach allowed previously identified predictors of psychotherapy response to be interpreted through underlying neurobiological mechanisms. The resulting framework was used to evaluate how circuit-level dysfunction may contribute to treatment heterogeneity and inform future precision psychiatry approaches.

5. Extension Results

5.1 Fear-Regulation Circuit

One of the most consistently implicated neural systems in PTSD is the fear-regulation circuit, which primarily involves interactions between the amygdala and ventromedial prefrontal cortex (vmPFC). Dysfunction within this circuit has been associated with heightened threat sensitivity,

impaired emotional regulation, and persistent fear responses following trauma exposure. Given that trauma-focused psychotherapies rely heavily on emotional processing and extinction learning, abnormalities within this circuit may influence treatment responsiveness.

Evidence supporting this relationship was demonstrated by Fonzo et al. (2017), who examined neural predictors of psychotherapy outcomes in individuals with PTSD. Greater pretreatment vmPFC activation during an emotional conflict regulation task predicted stronger symptom reduction following psychotherapy. Individuals demonstrating greater recruitment of regulatory prefrontal regions prior to treatment experienced more favorable outcomes compared to those exhibiting lower vmPFC activation.

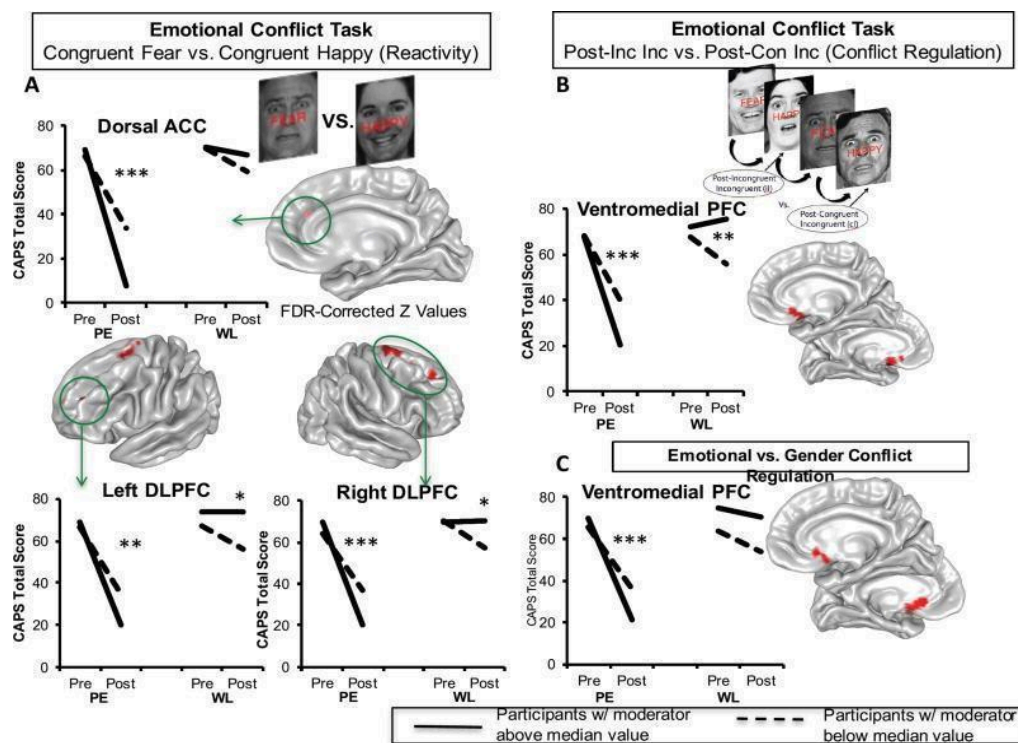


Figure 3. Greater pre-treatment ventromedial prefrontal cortex (vmPFC) activation during emotional conflict regulation predicts stronger symptom reduction following psychotherapy in PTSD (Fonzo et al., 2017).

These findings suggest that successful psychotherapy may partially depend upon the capacity to engage neural systems responsible for emotional regulation. Patients with stronger prefrontal regulatory function may be better able to process traumatic memories, regulate emotional responses, and benefit from therapeutic interventions. Consequently, vmPFC activation may represent a promising functional biomarker for predicting treatment response in PTSD.

5.2 Context-Processing Circuit

A second major neural system implicated in PTSD involves the contextual-memory circuit, centered around the hippocampus. The hippocampus plays a critical role in contextual learning, memory integration, and distinguishing safe environments from threatening ones. Deficits within this system have been hypothesized to contribute to persistent fear generalization and impaired processing of traumatic experiences.

Support for this hypothesis comes from findings reported by the ENIGMA consortium, one of the largest neuroimaging investigations of PTSD to date. Across approximately 1,868 participants, individuals with PTSD demonstrated significantly reduced bilateral hippocampal volume compared to healthy controls, with effect sizes ranging from approximately $d = -0.17$ to

- 0.21 (Logue et al., 2018).

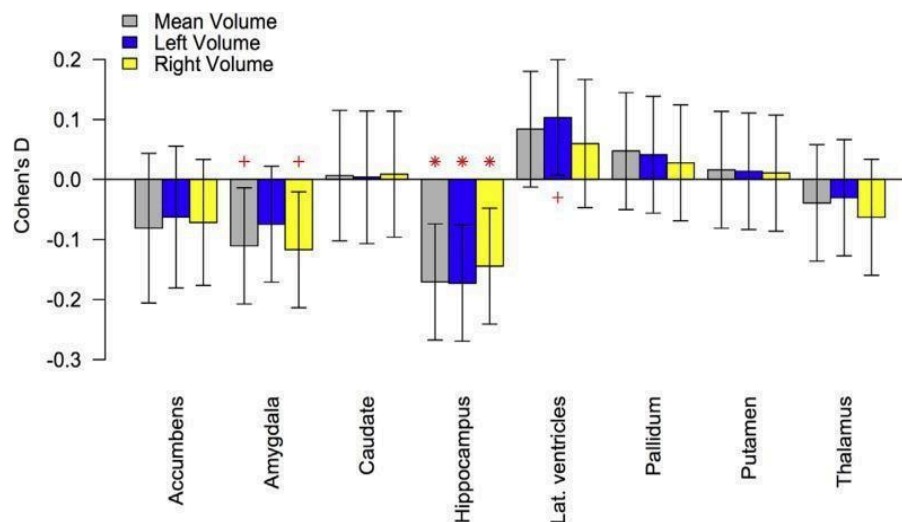


Figure 4. Multisite ENIGMA consortium analysis demonstrating significantly reduced bilateral hippocampal volume in PTSD relative to controls (Cohen's $d \approx -0.17$ to -0.21 ; $N \approx 1,868$) (Logue et al., 2018).

Although these effect sizes were modest, their consistency across multiple sites suggests that hippocampal abnormalities represent a reliable neurobiological feature of PTSD. Structural differences in the hippocampus may influence how traumatic experiences are encoded, consolidated, and integrated into autobiographical memory.

Further evidence linking hippocampal structure to treatment outcomes was reported by Rubin et al. (2016). Greater baseline hippocampal volume significantly predicted stronger symptom reduction following cognitive behavioral therapy, with larger hippocampal volume associated with improved treatment response ($\beta \approx .31$, $p < .01$).

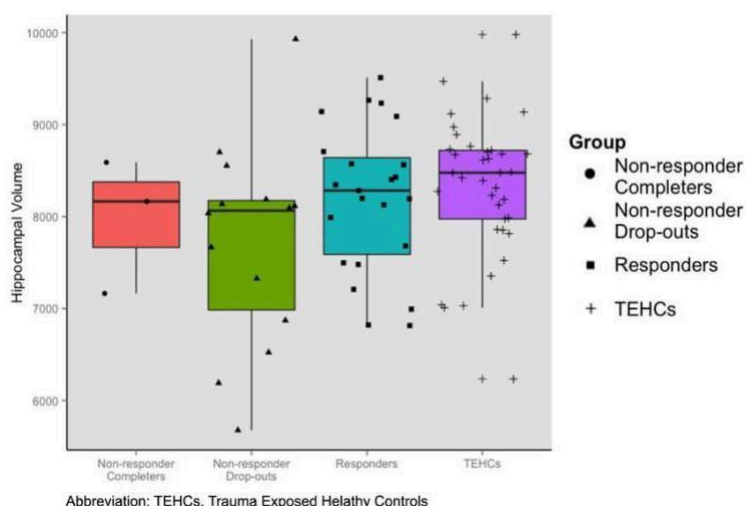


Figure 5. Greater baseline hippocampal volume is associated with significantly greater symptom reduction following cognitive behavioral therapy in PTSD ($\beta \approx .31$, $p < .01$) (Rubin et al., 2016).

Taken together, these findings suggest that hippocampal integrity may contribute both to PTSD symptom expression and to the effectiveness of psychotherapy. Individuals with greater structural preservation of contextual-memory systems may be better positioned to engage with

therapeutic processes that require cognitive restructuring, memory integration, and extinction learning.

5.3 Cognitive-Control Circuit

In addition to fear regulation and contextual memory systems, growing evidence suggests that cognitive-control networks may contribute to variability in PTSD treatment outcomes. These networks primarily involve the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), and related executive control regions responsible for attentional regulation, inhibitory control, and cognitive flexibility.

Although the original meta-analysis identified several predictors related to mood, attention, and psychological functioning, the neurobiological mechanisms underlying these relationships remain less clearly established than those involving the hippocampus or vmPFC. Nevertheless, existing neuroimaging research suggests that deficits in executive control may interfere with an individual's ability to engage in therapeutic exercises, regulate emotional responses, and maintain adaptive cognitive strategies during treatment.

As a result, cognitive-control networks represent an important area for future investigation. Additional longitudinal neuroimaging studies are needed to determine whether structural or functional measures of prefrontal and cingulate regions provide clinically useful predictors of psychotherapy response.

5.4 Integrated Circuit-Based Framework

Collectively, the findings from structural and functional neuroimaging studies support the interpretation that PTSD treatment response is influenced by multiple interacting neural systems

rather than a single clinical characteristic. Fear-regulation circuits involving the amygdala and vmPFC appear to influence emotional processing and regulatory capacity, while contextual-memory circuits centered on the hippocampus contribute to memory integration and learning processes relevant to psychotherapy. Cognitive-control networks may further influence attentional regulation and engagement with treatment.

These findings provide support for a circuit-based framework in which established clinical predictors of treatment response can be interpreted through underlying neurobiological mechanisms. Rather than viewing predictors as isolated demographic or symptom-based variables, this framework suggests that treatment heterogeneity may reflect differences in the structure and function of neural systems implicated in PTSD pathophysiology. Such an approach may ultimately contribute to the development of precision psychiatry models capable of improving treatment selection and therapeutic outcomes.

Circuit	Primary Brain Regions	PTSD Function	Treatment Relevance
Fear Regulation	Amygdala, vmPFC	Emotional regulation and threat processing	Exposure therapy response
Context Processing	Hippocampus	Memory integration and contextual learning	Cognitive behavioral therapy response
Cognitive Control	ACC, dlPFC	Executive functioning and attentional regulation	Treatment engagement and cognitive restructuring

Table 1. Circuit-Based Framework for Understanding PTSD Treatment Response

6. Discussion

The present study replicated and extended a systematic review and meta-analysis examining predictors of response to trauma-focused psychotherapy for posttraumatic stress disorder (PTSD). Consistent with the original investigation, demographic, clinical, and biological factors demonstrated meaningful associations with treatment outcomes. However, the primary contribution of the present extension was the reorganization of these predictors according to neural systems implicated in PTSD pathophysiology. By integrating evidence from structural and functional neuroimaging studies, the findings support a circuit-based framework for understanding treatment heterogeneity and provide a potential foundation for future precision psychiatry approaches.

6.1 Principal Findings

The replication component confirmed that treatment response in PTSD is influenced by a broad range of interacting variables rather than any single predictor. Existing literature has identified pretreatment symptom severity, psychiatric comorbidities, demographic characteristics, and biological factors as important contributors to treatment outcomes. While these predictors have traditionally been interpreted as independent variables, the present extension suggests that many may reflect dysfunction within common neural systems.

Several findings emerged from the neuroimaging literature. First, structural abnormalities within the hippocampus appear to represent a reliable feature of PTSD. Large-scale analyses conducted through the ENIGMA consortium demonstrated significantly reduced hippocampal volume among individuals with PTSD relative to healthy controls (Logue et al., 2018). Second, greater baseline hippocampal volume predicted improved response to cognitive behavioral therapy, suggesting that contextual-memory systems may influence an individual's capacity to benefit

from psychotherapy (Rubin et al., 2016). Finally, greater ventromedial prefrontal cortex activation during emotional regulation tasks predicted stronger treatment outcomes, highlighting the importance of regulatory neural systems in therapeutic recovery (Fonzo et al., 2017).

Collectively, these findings suggest that treatment response may be partially determined by variability in neural circuits responsible for fear regulation, contextual memory processing, and cognitive control.

6.2 Neurobiological Interpretation of Treatment Heterogeneity

One of the central challenges in PTSD research is explaining why individuals sharing the same diagnosis often experience dramatically different treatment outcomes. Traditional symptom-based frameworks assume that patients with similar symptom severity should respond similarly to intervention. However, clinical experience and empirical evidence consistently demonstrate substantial variability in treatment trajectories.

The present framework suggests that this variability may reflect differences in underlying neurobiology. Individuals whose symptoms are driven primarily by disruptions in fear-regulation circuits may require different therapeutic approaches than those whose symptoms are associated with contextual-memory deficits or executive-control dysfunction. Consequently, two patients presenting with comparable symptom severity may possess fundamentally different neural profiles that influence their responsiveness to treatment.

The hippocampus provides a useful example of this principle. Because trauma-focused psychotherapies frequently require memory integration, contextual learning, and cognitive restructuring, individuals with greater hippocampal integrity may possess a neurobiological

advantage that facilitates engagement with therapeutic processes. Similarly, individuals demonstrating stronger vmPFC activation may be better equipped to regulate emotional responses during treatment and derive greater benefit from exposure-based interventions.

6.3 Implications for Precision Psychiatry

The findings of this extension contribute to a growing movement toward precision psychiatry. Current psychiatric treatment models largely rely on symptom-based diagnostic categories when selecting interventions. While these approaches have produced important clinical advances, they often fail to account for substantial neurobiological variability among patients.

A precision psychiatry framework seeks to move beyond symptom presentation alone by incorporating biological markers into treatment decision-making. Within PTSD, structural and functional neuroimaging measures may eventually help identify individuals most likely to benefit from specific therapeutic approaches. For example, markers of hippocampal integrity may provide insight into responsiveness to cognitive-based interventions, whereas measures of prefrontal regulatory function may predict outcomes following exposure-based treatments.

Although neuroimaging is not yet routinely incorporated into clinical practice, advances in large-scale multimodal datasets continue to improve understanding of the biological mechanisms underlying psychiatric disorders. Recent reviews have emphasized that advances in multimodal neuroimaging, computational modeling, and large-scale longitudinal datasets may accelerate the development of clinically useful biomarkers for PTSD treatment prediction (Hinojosa et al., 2024). As evidence accumulates, neurobiologically informed treatment matching may become increasingly feasible.

6.4 Limitations

Several limitations should be considered when interpreting the present findings. First, the extension analysis relied primarily on previously published literature rather than new experimental data. Consequently, conclusions regarding neural mechanisms remain correlational and cannot establish causal relationships between brain structure, brain function, and treatment outcomes.

Second, the proposed circuit-based framework synthesizes findings from studies employing different methodologies, participant populations, and neuroimaging techniques. Variability across studies may influence the consistency and generalizability of observed relationships. Future investigations using standardized imaging protocols and longitudinal designs are needed to evaluate the stability of identified biomarkers.

Third, although evidence supporting hippocampal and vmPFC involvement is relatively robust, evidence concerning cognitive-control networks remains less developed. Additional research is necessary to clarify the role of anterior cingulate and prefrontal systems in treatment responsiveness.

6.5 Future Directions

Future research should evaluate the predictive utility of circuit-based models using prospective longitudinal designs. Large-scale initiatives such as the AURORA study (McLean et al., 2019) provide promising opportunities to integrate neuroimaging, behavioral, genetic, and clinical data within a single framework. Such datasets may facilitate the development of predictive models capable of identifying treatment responders prior to intervention.

Recent studies have demonstrated increasing success in applying machine learning approaches to multimodal neuroimaging data to predict PTSD symptom trajectories and psychotherapy outcomes (Zhutovsky et al., 2019). As large-scale longitudinal initiatives continue to expand, future predictive models may be capable of identifying treatment responders before treatment begins, enabling more personalized and biologically informed intervention strategies.

Additionally, advances in machine learning and multimodal neuroimaging may enable more precise characterization of patient subgroups based on neural profiles rather than symptom presentation alone. Continued integration of clinical psychology, neuroscience, and computational approaches will be essential for advancing personalized treatment strategies in PTSD.

Overall, the present extension highlights the potential value of organizing psychotherapy predictors according to neural systems rather than solely demographic or symptom-based categories. Such approaches may provide a more mechanistic understanding of treatment heterogeneity and contribute to future efforts aimed at optimizing mental health care.

7. Conclusion

Posttraumatic stress disorder remains a highly heterogeneous psychiatric condition characterized by substantial variability in symptom presentation and treatment outcomes. While previous research has identified numerous demographic, clinical, and biological predictors of psychotherapy response, the mechanisms underlying these associations have remained less clearly understood. The present study replicated a systematic review and meta-analysis

examining predictors of response to trauma-focused psychotherapy and extended these findings through a circuit-based neuroimaging framework.

Evidence from structural and functional neuroimaging studies suggests that neural systems involved in fear regulation, contextual memory processing, and cognitive control may contribute to variability in treatment outcomes. Reduced hippocampal volume appears to represent a consistent feature of PTSD, while greater hippocampal integrity and increased ventromedial prefrontal cortex activation are associated with improved psychotherapy response. These findings support the interpretation that treatment heterogeneity may be partially explained by differences in underlying neural circuitry.

By integrating established clinical predictors with neurobiological evidence, this extension provides a more mechanistic framework for understanding PTSD treatment response. Continued development of circuit-based models may contribute to future precision psychiatry approaches capable of improving treatment selection, enhancing therapeutic outcomes, and advancing personalized mental health care.

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