Review Article

# The Scarred Circuitry of Fear: A Computational–Clinical Synthesis of PTSD Neurobiology

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**Post-traumatic stress disorder (PTSD) can be understood as a disorder of threat inference: after trauma, the brain assigns excessive probability and excessive cost to danger, while failing to consolidate safety when objective contingencies change. This article synthesizes convergent findings across fear-circuit neurobiology—amygdala reactivity, ventromedial prefrontal and anterior cingulate regulatory control, and hippocampal context processing—together with stress-system and neuromodulatory mechanisms (noradrenergic gain control and heterogeneous hypothalamic–pituitary–adrenal axis alterations). The aim is not to restate the circuit model, but to formalize how these components jointly generate hallmark clinical phenomena: cue-triggered intrusions, hyperarousal, avoidance, and fear generalization with context-dependent relapse. To that end, the paper proposes a minimal multi-scale computational framework that links (i) a gain-modulated threat–control dynamical system (capturing defensive attractor dynamics and state-dependent control collapse) with (ii) latent-context learning models of extinction and renewal. Key parameters are mapped to measurable proxies and intervention targets, yielding falsifiable predictions about individual differences in extinction retention, renewal, stress recovery time, and treatment response. Throughout, claims are framed at the level supported by current evidence, emphasizing heterogeneity, moderators, and the limits of biomarker determinism.**

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## 1. Introduction: From psychological shock to biological inference

PTSD is a trauma- and stressor-related syndrome characterized by intrusive re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal. A durable challenge for theory is to explain the coexistence of preserved explicit knowledge (for example, the individual may recognize that the present situation is safe) with persistent defensive action tendencies and maladaptive learning (for example, recurrent physiological alarm, intrusive memories, and context-independent fear). The dominant neurobiological account has converged on an interacting network involving the amygdala, medial prefrontal regulatory regions (vmPFC/ACC), and the hippocampus[1] (Shin & Liberzon, 2010). Yet circuit descriptions often remain mechanistically underspecified: they identify where alterations occur but less clearly how they combine to produce symptom dynamics, relapse, and heterogeneity.

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This article advances a computational–clinical synthesis with two goals. First, it consolidates current evidence on core circuit nodes and on modulatory systems that shape circuit gain, plasticity, and recovery. Second, it presents a minimal formal framework that makes explicit predictions, clarifies subtypes as regions of parameter space, and provides a disciplined bridge from biology to measurable behavior and to treatment response. The paper is theory-driven; it therefore treats formalization as a constraint on interpretation, not as a substitute for empirical adjudication.

## 2. Core neurocircuitry of dysregulated fear

A widely supported model emphasizes an imbalance between exaggerated threat signaling and insufficient regulation and contextualization. Across imaging, psychophysiology, and experimental learning paradigms, PTSD is associated with heightened reactivity to trauma-relevant or threat-related cues, diminished recruitment of prefrontal regulatory regions during safety learning and extinction recall, and compromised contextual discrimination that promotes overgeneralization and renewal[2] (Shin & Liberzon, 2010). These components are better treated as interacting control and inference processes than as isolated lesions.

### *2.1. Amygdala-centered threat encoding*

The amygdala is critical for associating cues with aversive outcomes and for orchestrating defensive responding. In PTSD, many studies report heightened amygdala responsivity to trauma-related cues and threat anticipation, although null findings occur and are plausibly moderated by task demands, chronicity, and symptom profile[3] (Shin & Liberzon, 2010). Across recent syntheses, alterations in amygdala functional connectivity—particularly within basolateral and centromedial subnuclei networks—may be more consistently observed than mean task-evoked reactivity, emphasizing network-level dysregulation rather than a simple ‘hyperreactive node’ [4][3]. Mechanistically, elevated amygdala drive can be interpreted as increased outcome sensitivity (threat cost), increased precision of threat-related prediction errors, or lowered thresholds for salience assignment under high arousal. These interpretations make distinct predictions when coupled to prefrontal and hippocampal dynamics, as developed below.

### *2.2. Prefrontal regulation and extinction recall*

Extinction is not erasure of fear learning but new inhibitory learning that is context-dependent and susceptible to relapse. vmPFC and anterior cingulate subdivisions contribute to safety learning, extinction consolidation/recall, and the regulation of amygdala-driven responding [2][5]. Prefrontal roles are not unitary: vmPFC activity is most consistently linked to extinction recall and safety signaling, whereas dorsal ACC/dmPFC engagement is more often linked to threat expression and sustained defensive responding, with downstream interactions that can recruit brainstem defensive circuits (e.g., periaqueductal gray)[5]. In PTSD, reduced prefrontal recruitment and altered connectivity can be conceptualized as weakened top-down inhibition and as state-dependent control collapse under high arousal. The latter

matters clinically: a patient may show apparent learning within a session yet fail to retrieve safety under stress, consistent with relapse and context-dependent symptom return.

### *2.3. Hippocampal context inference and overgeneralization*

The hippocampus supports episodic memory, pattern separation, and context discrimination—functions central to distinguishing "then" from "now." Meta-analytic work has reported smaller hippocampal volume in PTSD, with moderation by severity, comorbidity, and methodological factors[6][7]. Functionally, impaired context inference can yield two clinically salient phenomena: fear generalization (defensive responding in safe contexts) and renewal (the return of fear when context shifts). In computational terms, this is a failure to assign sufficient precision to contextual evidence that the present differs from the trauma context. The model below represents this as a hippocampal–cortical context-gating signal that can be biased upward in ambiguous situations, especially under high arousal.

## 3. Stress physiology and neuromodulatory gain control

Fear circuitry operates under neuromodulatory and endocrine constraints that shape salience, plasticity, and recovery. Two systems are particularly relevant: (i) the locus coeruleus–noradrenergic system, which regulates gain and arousal, and (ii) the hypothalamic–pituitary–adrenal (HPA) axis, which modulates stress responses and feedback control. Importantly, the empirical record supports heterogeneity and moderation rather than a single endocrine phenotype.

### *3.1. HPA axis alterations: heterogeneity, feedback sensitivity, and moderators*

Many studies report lower basal cortisol in PTSD cohorts, but findings vary by sampling method, trauma type, timing, comorbidity, medication, and chronicity. Meta-analytic and review work has highlighted that PTSD can co-occur with enhanced glucocorticoid negative feedback (for example, greater cortisol suppression after dexamethasone), consistent with altered receptor sensitivity rather than a simple failure to terminate the stress response[8][9][10]. Accordingly, endocrine language should be phrased in terms of effective feedback gain and subgroup structure. Clinically, this implies that HPA-related biomarkers are better treated as stratification candidates than as diagnostic markers, and that mechanistic interpretations must control for sleep disruption, major depression, and ongoing stress exposure.

### *3.2. Noradrenergic hyperarousal and symptom amplification*

The locus coeruleus–noradrenergic system increases the gain of sensory and associative processing, enhancing vigilance and the impact of salient cues. In PTSD, noradrenergic hyperreactivity has been linked to hyperarousal, sleep disturbance, and heightened startle, and it plausibly amplifies threat prediction errors. Symptom-targeted pharmacology illustrates why evidence must be treated with nuance. Prazosin, an α1-adrenergic antagonist, showed benefits for trauma-related nightmares and sleep in several smaller randomized trials, including active-duty soldiers[11], but a larger multi-site trial in veterans found no significant benefit over placebo on nightmares or sleep quality[12]. Contemporary guidelines therefore tend to frame prazosin as a symptom-targeted option for nightmares rather than a

core PTSD treatment, and they suggest against its use as monotherapy for overall PTSD symptoms[13][14]. This pattern is consistent with a model in which noradrenergic gain modulates arousal and sleep-related symptom expression, while core threat learning and context inference may require additional mechanisms.

## 4. Molecular mediators of plasticity and learning

At the synaptic and molecular levels, PTSD-relevant learning depends on glutamatergic plasticity and on stress-buffering peptide systems. These mechanisms are not direct evidence of memory rewriting, but they delineate plausible levers for modifying learning, consolidation, and reconsolidation when paired with behavioral interventions.

### *4.1. Glutamatergic plasticity, NMDA signaling, and rapid-acting interventions*

Fear acquisition and extinction depend on NMDA receptor–mediated plasticity within amygdala–prefrontal–hippocampal circuits. Pharmacologic manipulation of glutamatergic systems can therefore influence learning windows. Ketamine has been examined as a rapid-acting intervention in PTSD: an early randomized crossover trial found rapid symptom reduction after a single infusion compared with a psychoactive placebo[15], and a subsequent randomized trial of repeated infusions reported greater improvement in PTSD symptoms over two weeks relative to midazolam in a chronic PTSD sample[16]. Reviews emphasize, however, that results vary across populations and dosing schedules, including less consistent effects in veteran/military samples[17]. Mechanistic claims should therefore be limited to what is measurable: ketamine may transiently alter network connectivity and synaptic plasticity in ways that could facilitate extinction learning or cognitive reappraisal when paired with structured psychotherapy, but it should not be described as directly rewriting traumatic memories without specifying operational criteria.

### *4.2. Neuropeptide Y and endogenous stress buffering*

Neuropeptide Y (NPY) is implicated in stress resilience and autonomic regulation. Human and translational studies suggest that higher NPY may index more effective coping, and that NPY alterations are associated with trauma exposure and PTSD symptomatology[18][19]. A systematic review and meta-analysis reported lower NPY levels in plasma and cerebrospinal fluid in PTSD patients versus controls, while also emphasizing confounding by sex and psychotropic medication status[20]. This supports cautious framing: NPY may be a resilience-linked modulator rather than a disorder-specific marker, and observed differences should be interpreted within well-controlled designs.

## 5. Risk, resilience, and developmental programming

PTSD is not an inevitable consequence of trauma. Vulnerability reflects interactions among genetic predisposition, prior learning history, developmental timing, and the characteristics of the traumatic exposure itself. A mechanistic synthesis should therefore treat risk as parameter priors and developmental constraints on learning, not as fixed determinants.

### *5.1. Genetic and epigenetic susceptibility*

Genetic findings implicate stress-system and plasticity-related pathways, often with small effects and substantial heterogeneity. For example, FKBP5 variation has been associated with PTSD symptom severity in some cohorts[21], consistent with broader evidence that glucocorticoid signaling and stress response calibration matter. At present, the most defensible interpretation is that polygenic and gene–environment interactions bias the learning and arousal parameters that shape post-trauma trajectories, rather than specifying a single causal pathway.

### *5.2. Developmental timing and early-life adversity*

Early-life adversity can calibrate stress reactivity and shape frontolimbic development, increasing vulnerability to later trauma. Neurodevelopmental work has linked childhood maltreatment to enduring alterations in brain structure and connectivity relevant to threat processing and regulation[22][23]. In a computational framing, early adversity may set higher priors on threat context, increase gain, and reduce the stability of regulatory control under stress, thereby lowering the threshold for transition into a defensive attractor after trauma.

### *5.3. Sex differences: prevalence, mechanisms, and cautions*

Epidemiologic data consistently indicate higher PTSD prevalence in women than men, with effect sizes that vary across samples and are shaped by both differential trauma exposure patterns and conditional risk given exposure[24][25]. Mechanistic explanations are multifactorial, involving trauma type distribution, hormonal modulation, social context, and interacting genetic and neuropeptidergic pathways. The PACAP/PAC1 receptor system has been proposed as one sex-linked pathway: a seminal report identified female-specific associations between PTSD and PACAP/PAC1 receptor variation, with estrogen-related regulatory features[26], and subsequent reviews discuss plausibility and boundary conditions[27]. Such findings should be presented as candidate mechanisms rather than as definitive bases of sex differences, and claims should remain sensitive to replication, cohort composition, and moderator effects.

## 6. A minimal multi-scale computational framework

The purpose of formalization here is operational: to specify mechanisms clearly enough to generate falsifiable predictions and to map heterogeneity onto measurable parameters. The framework is intentionally minimal and is not proposed as the only plausible formalization. It comprises three linked layers: (1) gain-modulated threat–control dynamics with context gating; (2) latent-context learning models of extinction, renewal, and generalization; and (3) clinical subtypes as regions of parameter space.

### *6.1. Operationalization and parameter mapping*

Table 1 maps each construct to biological interpretation, predicted signatures, measurement proxies, and candidate clinical levers. The purpose is to make clear what would count as evidence for or against each mechanistic component and to minimize interpretive drift.

| Parameter / construct | Biological scope | Mechanistic interpretation | Predicted signature | Measurement proxy (examples) | Clinical lever (examples) | Key references (examples) |
|---|---|---|---|---|---|---|
| w_PA (P→A inhibition) | Human + translational | Effective top-down regulatory control from vmPFC/ACC over amygdala-driven threat responding. | Weaker extinction retention; greater cue-triggered reactivity; reduced safety signaling. | Extinction recall paradigms; vmPFC–amygdala effective connectivity; skin conductance during safety cues. | Optimize exposure structure; cognitive control training; neuromodulation where evidence supports. | [2][5] |
| w_AP (A→P suppression) | Human + translational | Bottom-up interference of high threat/arousal with prefrontal control (stress-related control collapse). | State-dependent loss of inhibition under high arousal; defensive responding despite explicit safety knowledge. | Control tasks under threat; arousal–performance coupling; connectivity during stress induction. | Stabilize arousal before/during exposure; titrate intensity; adjuncts targeting arousal–control coupling. | [5] |
| w_HA (H→A coupling) | Translational + human | Strength of context 'trauma-like' gating into amygdala threat drive (context-driven threat amplification). | Strong renewal when context changes; context-triggered surges in reactivity even with stable cue contingencies. | Renewal / context-shift paradigms; context-modulated startle/SCR; hippocampal–amygdala connectivity indices. | Contextualized exposure; discrimination training; reduce ambiguity; relapse-prevention strategies. | Shin & Liberzon, 2010; [6][7] |
| u_P (baseline control drive) | Human | Trait/state baseline of regulatory capacity independent of immediate threat input. | Individual differences in cognitive control and extinction recall at low arousal. | Executive control tasks; baseline PFC recruitment/connectivity; working memory performance. | Skills training; sleep stabilization; comorbidity treatment that improves executive function. | [5] |
| H (context threat-gating | Human + translational | Hippocampal–cortical context | Fear overgeneralization; | Context discrimination/renewal; | Contextualized exposure; | [6][7] |

| Parameter / construct | Biological scope | Mechanistic interpretation | Predicted signature | Measurement proxy (examples) | Clinical lever (examples) | Key references (examples) |
|---|---|---|---|---|---|---|
| state) | | inference signal encoding perceived similarity of the current context to the trauma context (higher H = more 'trauma-like'). | strong renewal in objectively safe contexts; context-dependent relapse. | hippocampal volume/activation; pattern separation tasks. | address sleep/stress that degrade hippocampal function. | |
| π_H (context precision) | Computational construct anchored in human tasks | Precision/weight of contextual evidence in latent-context inference (higher π_H = better discrimination). | Steeper generalization gradients and stronger renewal when π_H is low; impaired 'then vs now' discrimination. | Behavioral context discrimination; computational fits to renewal/generalization; hippocampal pattern separation tasks. | Increase context salience; training on discrimination; consolidate learning (sleep). | [2] |
| κ (A→H suppression) | Translational + human | Stress-related suppression of context processing by high threat/arousal (threat 'hijacks' contextualization). | Under stress, reduced context discrimination and increased relapse despite prior learning. | Stress induction × context discrimination; hippocampal engagement under stress; volatility in renewal measures. | Arousal regulation prior to context work; pacing exposure; reduce concurrent stress load. | [5] |
| δ (H decay) | Model parameter | Passive decay rate of the context-gating state back toward baseline. | Persistence of context-triggered symptoms after safe re-exposure; prolonged 'carryover' of trauma-context similarity. | Time-to-baseline in context-related physiology; EMA decay of triggers. | Relapse prevention; sleep and stress recovery optimization. | — |
| g_LC (noradrenergic | Human + translational | LC–noradrenergic gain control | Hyperarousal; exaggerated | Startle potentiation; pupillometry; HRV; sleep | Nightmare/sleep-targeted options | [11][12][14] |

| Parameter / construct | Biological scope | Mechanistic interpretation | Predicted signature | Measurement proxy (examples) | Clinical lever (examples) | Key references (examples) |
|---|---|---|---|---|---|---|
| gain) | | amplifying salience, vigilance, and defensive responding. | startle; sleep fragmentation; reduced benefit from extinction when gain remains high. | metrics. | when indicated; autonomic regulation; pacing exposure intensity. | |
| ρ (LC recovery) | Model parameter | Recovery/decay rate of noradrenergic gain toward baseline after stress. | Prolonged hyperarousal and insomnia after stressors; delayed recovery trajectories. | Time constants from physiology (HRV, startle) after stress; sleep recovery profiles. | Target sleep and autonomic recovery; reduce sustained stress exposure. | — |
| γ_E (effective glucocorticoid feedback gain) | Human | Net endocrine feedback influencing arousal circuits (captures cortisol output and receptor sensitivity as an 'effective' feedback parameter; directionality may vary by subgroup). | Subgroup-specific cortisol profiles; differential recovery times after stress; relapse vulnerability under re-exposure. | Diurnal cortisol; dexamethasone suppression (research); downstream inflammatory markers. | Stratify rather than assume a single HPA phenotype; address comorbidity, sleep, chronic stress load. | [8][9][10] |
| λ (endocrine recovery) | Model parameter | Recovery/decay rate of endocrine stress state toward baseline after perturbation. | Prolonged stress recovery time; sustained arousal after triggers. | Cortisol recovery after stress tasks; recovery of autonomic indices. | Stress recovery interventions; sleep optimization; reduce ongoing stress exposure. | [8][9] |
| α_threat (threat learning rate) | Computational construct anchored in | Rate of acquisition of threat value/policies from aversive | Faster conditioning; stronger cue reactivity; rapid | Conditioning tasks; computational RL fits (learning rate, outcome sensitivity). | Dose and pacing of exposure; learning-window optimization. | [2] |

| Parameter / construct | Biological scope | Mechanistic interpretation | Predicted signature | Measurement proxy (examples) | Clinical lever (examples) | Key references (examples) |
|---|---|---|---|---|---|---|
| | human conditioning | outcomes and prediction errors. | consolidation of threat priors after trauma. | | | |
| α_ext (extinction / safety learning rate) | Computational construct anchored in human extinction | Rate of updating toward safety under exposure; reflects vmPFC-mediated inhibitory learning and context dependence. | Slower extinction; poorer extinction retention; higher renewal. | Extinction learning and recall tasks; within-session vs between-session change patterns. | Enhance learning context, consolidation, and adherence; empirically supported augmentation strategies. | [2] |
| η (stochastic stress input / noise) | Clinical heterogeneity placeholder | Unmodeled stressors, volatility, and state fluctuations that perturb the system toward defensive attractors. | Symptom volatility; stress-triggered relapse; within-person variability. | EMA symptom tracking; variability metrics; stress reactivity measures. | Relapse-prevention planning; monitoring; stress inoculation/skills training. | — |

**Table 1.** Parameter-to-measurement mapping (with biological scope and exemplar references) for the multi-scale PTSD model.

### *6.2. Layer 1: Threat–control dynamics with gain and context gating*

Let A(t) denote amygdala-centered threat drive, P(t) denote effective prefrontal regulatory control, H(t) denote a hippocampal–cortical context-gating signal reflecting perceived trauma-context similarity, L(t) denote noradrenergic gain, and E(t) denote an effective endocrine state influencing arousal circuitry. A minimal stochastic dynamical system can be written as:

$dA/dt = \sigma_A(A) - w_{PA} \cdot P + w_{HA} \cdot H + g_{LC} \cdot L + \eta_A(t)$

$dP/dt = \sigma_P(P) - w_{AP} \cdot A + u_P + \eta_P(t)$

$dH/dt = \sigma_H(\text{context cues}; \pi_H) - \kappa \cdot A - \delta \cdot H + \eta_H(t)$


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$dL/dt = \sigma_L(\text{stress cues}) - \gamma_E \cdot E - \rho \cdot L + \eta_L(t)$

$dE/dt = \sigma_E(\text{stress cues}, L) - \lambda \cdot E + \eta_E(t)$

Here $\sigma(\cdot)$ are bounded nonlinearities (for example, tanh or logistic functions) that allow multiple stable regimes; $\eta(t)$ are stochastic perturbations; $u_P$ is a baseline control drive (trait-like or state-dependent); $w_{HA}$ is the coupling from context threat-gating to amygdala threat drive; $\pi_H$ captures the precision of context inference from environmental cues (higher $\pi_H$ yields better discrimination); $\kappa$ captures stress-related suppression of context processing by high threat drive; $\delta$ is passive decay of the context-gating state; $\rho$ is recovery (decay) of noradrenergic gain; and $\gamma_E$ and $\lambda$ encode net endocrine feedback and recovery. PTSD-relevant dynamics correspond to parameter regimes in which (i) the defensive attractor is deep, so that high A is stable; (ii) control collapses under arousal (high $w_{AP}$ and/or low $w_{PA}$); and (iii) context gating remains elevated in safe contexts (biased H), producing persistent hyperarousal and context-independent fear.

### *6.3. Layer 2: Extinction and renewal as latent-context inference*

To model extinction failure, renewal, and fear generalization, let $C_t$ denote a latent context variable (for example, safe versus threat context), inferred from observations $o_t$. Context inference can be formalized as:

$P(C_t \mid o_{1:t}) \propto P(o_t \mid C_t; \pi_H) \cdot P(C_t \mid C_{t-1})$

$V_{t+1} = V_t + \alpha(C_t) \cdot (r_t - V_t)$

$\text{Fear}_t = \varphi(V_t, A_t, L_t)$

$V_t$ is an expected threat value updated via prediction errors ($r_t - V_t$), with learning rate $\alpha$ that can depend on inferred context. PTSD-like phenotypes arise when context precision $\pi_H$ is reduced or biased and when extinction learning rates are reduced, yielding shallower safety updating and greater renewal. The coupling term $\varphi$ makes explicit that the same learned value can express differently depending on current arousal gain $L_t$ and on the threat-control state ($A_t$, $P_t$).

### *6.4. Layer 3: Clinical subtypes as regions of parameter space*

This framework encodes heterogeneity without reifying categories. A control-deficit subtype is characterized by low $w_{PA}$ and/or high $w_{AP}$, with relatively intact context inference. A context-deficit subtype is characterized by biased or low-precision context inference (low $\pi_H$ and/or biased H), even with moderate control capacity. A gain-dominant subtype is characterized by elevated $g_{LC}$ and slow recovery (low $\lambda$), producing high arousal and volatility. These are testable regions of parameter space that can be estimated and compared, rather than diagnostic categories.

## 7. Empirical evaluation and secondary-data calibration

### *7.1. What can be tested with existing evidence*

This framework is designed to be testable even when individual-level multimodal datasets are scarce. Two complementary strategies are feasible: (i) secondary-data calibration using published group-level effects and task outcomes (effect sizes, means/variances, connectivity contrasts), and (ii) re-analysis of structured trial and task repositories that already aggregate standardized outcomes. The aim is not to 'prove' the model, but to quantify which parameter regimes are compatible with current evidence and to identify discriminative tests that would falsify key components.

### *7.2. Candidate data sources (human-first)*

Three practical sources support immediate testing without new data collection. First, the PTSD-Repository aggregates randomized controlled trial data with standardized outcomes and can be used to evaluate treatment-response predictions at the symptom-domain level[28]. Second, FearBase is a living database of human fear-conditioning and extinction datasets, including acquisition/extinction/reinstatement/renewal variants with common outcomes such as skin conductance and expectancy ratings[29]. Third, individual published studies with openly accessible task and neuroimaging data can be used as anchors for mechanistic mapping; for example, virtual-reality fear learning datasets that quantify threat imminence effects and amygdala–cortical connectivity changes[30].

### *7.3. Linking observables to parameters (minimal observation model)*

To minimize over-interpretation, parameter estimation should proceed through an explicit observation model. For example: SCR/startle and autonomic arousal index the combined expression of threat drive A(t) under gain modulation L(t); extinction-retention slopes and renewal magnitudes constrain (w_PA, w_AP, $\alpha$_ext, $\pi$_H, w_HA); stress-recovery time constants constrain ($\rho$, $\lambda$, $\gamma$_E); and within-person volatility (EMA) constrains $\eta$. Where neuroimaging is available, effective connectivity contrasts (vmPFC→amygdala; amygdala subnuclei networks) provide additional constraints on w_PA and network-level threat coupling[4].

### *7.4. Calibration protocol using published effect sizes*

A conservative protocol is: (1) choose a small set of benchmark paradigms (extinction recall, renewal/context shift, startle potentiation, stress recovery); (2) extract published effects with clear operational definitions; (3) define priors that respect biological scope (human vs translational) and measurement error; (4) fit the model using hierarchical Bayesian inference or approximate Bayesian computation, treating effect sizes as noisy observations; and (5) perform posterior predictive checks against held-out studies. This yields parameter regions compatible with existing evidence and clarifies which new measurements are most informative.

### *7.5. Falsification criteria (examples)*

The model should be considered incorrect (or in need of structural revision) if any of the following patterns persist across well-powered studies: (i) extinction retention and renewal are unrelated to vmPFC–amygdala directed coupling measures under arousal manipulation; (ii) arousal-gain indices fail to moderate the gap between within-session fear reduction and between-session safety retrieval; (iii) context-discrimination measures do not explain renewal/generalization beyond non-specific anxiety; or (iv) endocrine recovery phenotypes do not relate to stress-recovery time constants when confounds are controlled. These are discriminative failures rather than mere ‘nulls’, and they are explicitly testable within the proposed mapping.

### *7.6. Prediction-to-observable validation matrix (plug-and-play)*

To reduce ambiguity and reviewer latitude, Table 2 maps each core mechanism to a falsifiable prediction, observable readouts, a minimal design, and a discriminative failure mode.

| Mechanism / parameter(s) | Prediction | Observable(s) | Minimal design | Discriminative failure |
|---|---|---|---|---|
| Control collapse (w_AP, w_PA) | Extinction recall breaks under high arousal despite within-session extinction. | Recall SCR/EDA; vmPFC→amygdala connectivity; pupil/HRV. | Extinction training; recall under stress vs neutral blocks (within-subject). | No arousal×recall interaction; α-only models fit equally well. |
| Context deficit (π_H, H bias) | Strong renewal/generalization after context change; poor "then vs now" discrimination. | ABA renewal; generalization gradient; hippocampal pattern separation/volume. | Acquire A, extinguish B, test A; graded generalization stimuli. | Context-precision term adds no incremental value. |
| Gain modulation (g_LC) | Physiological expression inflated at matched learned value; startle/sleep track gain. | Startle EMG/SCR; pupil; HRV; sleep indices. | Arousal manipulation or high-arousal blocks; compare expression conditional on V. | Expression differences explained by learning/baseline only. |
| Recovery + endocrine (ρ, λ, γ_E) | Recovery time constants predict volatility/relapse; endocrine phenotype moderates direction. | EDA/HRV recovery; cortisol (diurnal/dex); EMA volatility; relapse indices. | Stress pulse→recovery fit→later renewal/reinstatement; stratify by endocrine phenotype. | Recovery constants unstable/non-predictive; no moderation after confounds. |
| Learning rates (α_threat, α_ext) | Fast acquisition vs slow safety updating dissociate; between-session retention depends on α_ext. | Acquisition slope; day-2 recall; between-session SCR change. | Conditioning + multi-session extinction with delayed recall. | Parameters not identifiable; no prediction of held-out retention. |
| Resilience modifier ($\mathscr{R}$) | Higher $\mathscr{R}$ buffers gain and improves recovery/precision → less renewal at matched learning/arousal. | Resilience scales; NPY (exploratory); recovery indices; renewal magnitude. | Moderation: $\mathscr{R}$ ×(gain/context) predicting recovery and renewal. | No moderation; $\mathscr{R}$ adds nothing beyond severity/baseline physiology. |

## 8. Simulation protocol and representative outcomes

Simulations are offered as a disciplined way to check internal consistency and to generate quantitative predictions; they are not presented as evidence. The following protocols can be used to demonstrate qualitative correspondences with clinical phenomena, and each has a direct measurement analogue.

### *8.1. Attractor depth, recovery time, and arousal gain*

Apply a transient stress perturbation (increase in σ_E and σ_L) and measure the time for A(t) and L(t) to return to baseline. In deeper-attractor regimes, recovery is slow and small perturbations can trigger persistent high-A states,


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providing a mechanistic interpretation of sustained hypervigilance and exaggerated startle. Recovery time is predicted to depend on λ (endocrine recovery) and on γ_E (feedback gain), with subgroup-specific patterns rather than a single endocrine signature.

### *8.2. Extinction, renewal, and generalization gradients*

Simulate acquisition and extinction across contexts and then evaluate renewal (fear return when context changes). Lower π_H or biased H predicts steeper generalization gradients and stronger renewal in nominally safe contexts. Control-deficit regimes predict within-session gains with poor between-session retrieval under stress, whereas gain-dominant regimes predict variable performance sensitive to arousal manipulation.

## 9. High-value predictions and falsifiable hypotheses

The model yields a compact set of hypotheses that can be tested with behavioral tasks, physiology, and network measures. Each hypothesis is intended to be falsifiable by design and to discriminate among competing mechanisms.

1. Directed effective connectivity from vmPFC/ACC to amygdala during extinction recall will be reduced in individuals with prominent control-deficit parameters (low w_PA/high w_AP), with the strongest effects under induced arousal.
2. Measures indexing arousal gain (pupillometry, startle potentiation, heart-rate variability) will predict poorer extinction retention when noradrenergic gain is high, even when within-session learning appears intact.
3. Context discrimination performance and renewal magnitude will correlate with hippocampal–cortical context precision (π_H) and with bias of the context-gating signal H in ambiguous contexts, beyond effects of generalized anxiety.
4. Endocrine feedback phenotypes (for example, dexamethasone suppression profiles) will moderate stress recovery time and relapse probability, but directionality will depend on subgroup structure and confounds; a single PTSD cortisol signature is not expected.
5. Rapid-acting plasticity interventions (for example, ketamine protocols) will show the most durable benefits when paired with structured learning windows (exposure or reappraisal), consistent with a facilitation-of-learning account rather than an isolated pharmacologic memory-rewrite effect.

## 10. Clinical relevance and translational implications

Clinically, the framework's value depends on whether parameter estimates improve prediction of course and treatment response beyond symptom counts. The clearest translational claim is modest: patients differ in the relative contribution of control capacity, context inference, and arousal gain, and these differences should influence how exposure-based treatments are paced and supported. When gain is persistently high, preparatory sleep stabilization and autonomic regulation may be prerequisites for reliable retrieval of safety learning. When context inference is weak, contextualized

exposure and discrimination training may be prioritized. At the same time, the paper rejects biomarker determinism: circuit or endocrine markers should inform hypotheses, not substitute for clinical formulation.

## 11. Limitations and future work

This model compresses multi-system heterogeneity into a small set of variables and parameters. As such, it omits important mechanisms (for example, inflammation, dissociation-related network shifts, social threat processing, and bidirectional sleep–memory interactions) and should be extended only where added complexity improves identifiability and prediction. Empirically, progress depends on joint modeling of behavior, physiology, and neural measures with careful control of confounds and on longitudinal designs that can distinguish risk markers from consequences. Future work should test whether parameter-based subtyping predicts relapse under context change and supports individualized selection of augmentation strategies.

## 12. Conclusion

PTSD can be framed as maladaptive threat inference implemented in a distributed circuit constrained by gain control, endocrine feedback, and context learning. A computational–clinical synthesis clarifies how these components combine to produce intrusive re-experiencing, hyperarousal, avoidance, and fear generalization with relapse. The proposed minimal framework is intended to be wrong in informative ways: it generates discriminative predictions, makes heterogeneity explicit, and provides a disciplined bridge between neurobiology, experimental tasks, and clinical trajectories.

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