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Article

The Neuro-Hepatic-Affective Model (NHAM): A Systems Framework for Liver–Brain Modulation of Emotion in Precision Psychiatry

Afaf El Fettahi ^{1,*} and Jaba Tkemaladze ²

¹ Independent Researcher, France

² Free University of Tbilisi, 240 David Aghmashenebeli Alley, 0159, Tbilisi, Georgia

* Correspondence: afaf.elfettahi@gmail.com

Abstract

Background — Emotional regulation has traditionally been modelled within cortico-limbic circuits, yet converging evidence shows that the liver–brain axis continuously modulates affective dynamics through metabolic–endocrine, inflammatory–immune, microbiota–vagal, and autonomic pathways. The absence of a unified quantitative framework linking hepatic biology to parameterized affective oscillations limits early detection, mechanistic diagnosis, and personalized interventions in psychiatry. **Methods** — We introduce the Neuro-Hepatic-Affective Model (NHAM), which formalizes mood as a latent affective oscillator: $\mathbf{E}(t) = B_0 + A \cdot e^{-t/\tau} \cdot \sin(\omega t)$ where A = reactivity, B_0 = tonic baseline, ω = recovery tempo, and τ = persistence. Multi-omic and psychophysiological biomarkers are mapped to pathway-specific parameter shifts: bile acids & FGF19 → metabolic–endocrine; CRP, IL-6, kynurenine/tryptophan ratio → inflammatory–immune; microbial diversity & short-chain fatty acids → microbiota–vagal; heart rate variability (HRV) → autonomic regulation. Biomarker–parameter mappings were derived from meta-analyses, randomized controlled trials, and longitudinal studies. **Results** — Distinct biomarker profiles yield reproducible parameter shifts. Elevated IL-6 predicts $\uparrow B_0$ and $\downarrow \omega$; high bile acids (FXR–TGR5/FGF19) predict $\downarrow A$, $\uparrow \omega$, $\downarrow \tau$; higher microbial diversity / HF-HRV predict $\downarrow A$, $\downarrow B_0$, $\uparrow \omega$, $\downarrow \tau$. This mapping enables pathway-specific diagnostics and quantitative tracking of affective dynamics. **Conclusions** — NHAM is the first systems biology framework to integrate liver–brain pathways into a parameterized model of emotion. By linking multi-omic biomarkers to latent affective dynamics, NHAM offers a foundation for precision psychiatry — enabling real-time monitoring, mechanistic diagnosis, and targeted interventions. Future work should combine wearable biosensors, laboratory assays, and ecological momentary assessment to validate NHAM in clinical populations and develop closed-loop therapeutic systems.

Keywords: neuro-hepatic axis; affective regulation; psychoneuroimmunology; inflammation; cytokines (IL-6; CRP); kynurenine pathway; liver-brain communication; vagal pathways; circadian rhythms; systems biology

1. Introduction

For decades, affective science has been dominated by a brain-centered paradigm, which posits that emotional states are generated and regulated primarily within cortico-limbic circuits of the central nervous system (LeDoux, 2012). This framework has been instrumental in mapping key neural structures such as the amygdala, prefrontal cortex, and insula (Pessoa, 2017), yet it remains incomplete.

Increasing evidence reveals that emotions are emergent properties of distributed, multi-organ systems, in which peripheral organs—including the gut, liver, and immune system—play active roles in shaping affective dynamics (Mayer et al., 2014; Osadchiy et al., 2019).

Recent advances in psychoneuroimmunology and systems biology have challenged the neurocentric model, highlighting bidirectional communication between the brain and peripheral physiology (D’Mello & Swain, 2021; Fung et al., 2017). The gut–brain axis has received particular attention for its influence on mood and behavior through microbial metabolites, vagal afferents, and endocrine

detoxification, and immunological surveillance—remains largely overlooked in emotion research despite dense neuroanatomical, endocrine, and immune connections with both the gut and the brain (Boeckxstaens et al., 2014; Hsueh et al., 2012).

Hepatology research now demonstrates that patients with chronic liver disease frequently exhibit depression, anxiety, fatigue, and social withdrawal, independent of hepatic encephalopathy (Albillos et al., 2020). These symptoms are increasingly linked to specific biological mechanisms, including elevated systemic cytokines (IL-6, TNF- α , IL-1 β), altered bile acid signaling, microbiota dysbiosis, endotoxemia, and vagal modulation (D’Mello et al., 2015; Jiang et al., 2021). Experimental studies further show that manipulating these pathways—such as reducing inflammatory cytokines or modifying microbiota composition—can alter affective behavior in both animals and humans (Frost et al., 2014; Yoo & Mazmanian, 2017).

In parallel, affective neuroscience has reframed emotion as a temporally extended, dynamic process, characterized by rise, persistence, and decay phases, measurable via psychophysiological and neural oscillations (McGinley & Spangler, 2025). Oscillatory brain mapping reveals distinct signatures for affective processing across multiple frequency bands—theta, gamma, and beta—each linked to distributed cortical and subcortical networks (Tsurugizawa et al., 2025). Editorial perspectives now call for models that quantify emotional variability over time and directly connect these dynamics to clinical outcomes (McGinley & Spangler, 2025).

Despite these advances, no unified quantitative model currently integrates hepatic biology with the temporal architecture of emotional dynamics. To address this gap, we developed the

Neuro-Hepatic-Affective Model (NHAM)—a systems-level formalism in which mood is represented as a damped affective oscillator whose parameters are modulated by three primary hepatic pathways:

1. **Metabolic–endocrine** (bile acids / FXR–TGR5 / FGF19),
2. **Inflammatory–immune** (cytokines / tryptophan–kynurenine metabolism),
3. **Microbiota–vagal** (short-chain fatty acid production, vagal afferents).

These pathways are hypothesized to produce characteristic shifts in the oscillator’s core parameters—reactivity (A), tonic baseline (B_0), recovery tempo (ω), and persistence (τ)—which in turn influence clinical presentation and treatment response. Parameter shifts are measured via targeted biomarkers (e.g., bile acids, FGF19, IL-6, kynurenine/tryptophan ratio, microbiota diversity, SCFA levels) and psychophysiological readouts such as high-frequency heart rate variability (HF-HRV), electrodermal activity, and ecological momentary assessment.

By situating NHAM at the intersection of hepatology, psychoneuroimmunology, affective neuroscience, and systems biology, this framework provides a falsifiable, mechanistic link between peripheral biology and the dynamics of emotion. It reframes mood disorders as systemic, liver–brain phenotypes and offers a pathway toward biomarker-based mood stratification and liver-targeted psychiatric interventions (Albillos et al., 2020; Yoo & Mazmanian, 2017).

1.1. Classical Neural Basis of Emotion

The traditional understanding of emotion has been rooted in the central nervous system (CNS), with particular emphasis on the limbic system, prefrontal cortex (PFC), and key neurotransmitter systems (Pessoa & Adolphs, 2010). This framework has dominated affective neuroscience for decades, shaping both theoretical models and clinical approaches to mood disorders (LeDoux, 2012). Below, we review the classical neural substrates of emotion, their functional roles, and their limitations in explaining the full spectrum of affective phenomena.

The amygdala has long been considered the fear center of the brain, playing a crucial role in threat detection, emotional memory, and physiological arousal (Janak & Tye, 2015). Functional neuroimaging studies consistently show amygdala activation in response to aversive stimuli, and lesions in this region lead to blunted fear responses (Davis & Whalen, 2001). However, recent evidence suggests that the amygdala is not solely a fear module but a salience detector, integrating sensory and interoceptive signals to guide adaptive behavior (Seymour & Dolan, 2008).

The hippocampus, traditionally associated with memory formation, also modulates emotional responses by contextualizing affective experiences (Fanselow & Dong, 2010). Stress-induced hippocampal dysfunction, for example, is linked to impaired fear extinction and heightened anxiety (Kim & Diamond,

2002). Moreover, the hippocampus interacts with the amygdala to regulate emotional memory consolidation, a process disrupted in post-traumatic stress disorder (PTSD) (Shin & Liberzon, 2010).

The hypothalamus serves as a neuroendocrine hub, connecting emotional stimuli with autonomic and hormonal responses (Ulrich-Lai & Herman, 2009). Through its control of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamus modulates stress responses by releasing corticotropin-releasing hormone (CRH), which in turn stimulates cortisol secretion (Smith & Vale, 2006). Dysregulation of this axis is implicated in depression and anxiety disorders (Pariante & Lightman, 2008).

While the limbic system generates rapid emotional reactions, the prefrontal cortex (PFC) exerts top-down regulation, enabling emotional control and decision-making (Ochsner & Gross, 2005). The ventromedial PFC (vmPFC) is critical for fear extinction and reward valuation, whereas the dorsolateral PFC (dlPFC) supports cognitive reappraisal of emotional stimuli (Etkin et al., 2011). Patients with vmPFC lesions exhibit impulsivity and poor emotional regulation, highlighting its role in affective control (Bechara et al., 2000).

The anterior cingulate cortex (ACC), a key node in the salience network, monitors conflict and modulates emotional responses through its connections with the amygdala and PFC (Bush et al., 2000). Abnormal ACC activity is observed in major depressive disorder (MDD) and generalized anxiety disorder (GAD), suggesting its involvement in mood dysregulation (Disner et al., 2011).

The serotonergic system, originating in the raphe nuclei, is a major modulator of mood, anxiety, and aggression (Berger et al., 2009). Selective serotonin reuptake inhibitors (SSRIs), which enhance 5-HT signaling, are first-line treatments for depression and anxiety (Cipriani et al., 2018). However, serotonin's role is complex—while it promotes emotional stability in the PFC, it also enhances amygdala reactivity under stress (Hariri & Holmes, 2015).

Dopamine, primarily synthesized in the ventral tegmental area (VTA) and substantia nigra, drives reward processing and motivation (Schultz, 2016). Dysregulation of the mesolimbic dopamine pathway is implicated in anhedonia (reduced pleasure), a core symptom of depression (Nestler & Carlezon, 2006). Conversely, excessive dopaminergic signaling is linked to mania and psychosis (Howes & Kapur, 2009).

As the brain's primary inhibitory neurotransmitter, GABA counterbalances excitatory glutamatergic signaling, preventing neural overactivation (Luscher et al., 2011). Reduced GABAergic tone in the PFC and amygdala is associated with anxiety and panic disorders (Nemeroff, 2003). Benzodiazepines, which enhance GABA-A receptor activity, are commonly prescribed for acute anxiety (Griffin et al., 2013).

Despite its explanatory power, the brain-centric model of emotion has several limitations:

1. Neglect of Peripheral Contributions – The CNS does not operate in isolation; gut-derived metabolites, liver-synthesized proteins, and immune signals modulate neural activity (Mayer et al., 2014).
2. Overemphasis on Localized Brain Regions – Emotions arise from distributed networks, not isolated structures (Lindquist et al., 2012).
3. Inadequate Explanation of Psychosomatic Links – Many mood disorders co-occur with metabolic and inflammatory conditions, suggesting systemic involvement (Felger & Lotrich, 2013).

While the limbic system, PFC, and neurotransmitter networks remain foundational to emotion research, emerging evidence calls for a more integrative approach that incorporates gut-liver-brain interactions (D'Mello & Swain, 2021). The next section explores how hepatic signaling influences these classical neural pathways, offering a more holistic understanding of emotional regulation.

1.2. Hepatic Modulation of Affective Oscillations: Neural, Circadian, and Inflammatory Pathways

The liver is not only a metabolic hub but also a dynamic interface capable of modulating emotional state trajectories via multi-level coupling with the brain. Anatomically, the liver communicates with central affective networks through vagal afferents, spinal splanchnic nerves, and humoral mediators transported via the portal and systemic circulation (Bonaz et al., 2018; Woodie et al., 2024). These afferent signals converge onto the nucleus tractus solitarius (NTS), which projects to the parabrachial nucleus, hypothalamus, amygdala, and prefrontal cortex—structures critical for shaping affective oscillations.

Physiologically, hepatic influence on emotion is embedded within circadian and ultradian rhythms that synchronize metabolic, immune, and neural oscillations (Mukherji et al., 2015; Xu et al., 2023). The liver's intrinsic circadian clock regulates bile acid synthesis, glucose homeostasis, and cytokine release, each following rhythmic patterns that can entrain or disrupt emotional recovery cycles. Experimental disruption of hepatic clocks alters feeding patterns, autonomic tone, and hypothalamic activity, with downstream effects on mood-related behavior (Woodie et al., 2024).

From a neuroimmune perspective, hepatic inflammation propagates via cytokines (e.g., IL-6, TNF- α) and metabolites of the tryptophan–kynurenine pathway, which can cross the blood–brain barrier and influence cortical excitability (D'Mello et al., 2015; Zhou et al., 2022). These molecular mediators can shift the parameters of the affective oscillator—raising tonic negativity (B_0), slowing recovery tempo (ω), and prolonging persistence (τ).

Oscillatory brain mapping further supports the concept that peripheral inputs from the liver can modulate central affective dynamics. Alterations in systemic metabolic and immune tone have been shown to impact neural oscillations across theta, beta, and gamma bands, which are differentially involved in emotion generation, maintenance, and resolution (Flandin & Friston, 2024). Such coupling suggests that the liver operates as a peripheral emotional oscillator—entraining or perturbing central affective rhythms via its metabolic–neuroimmune outputs.

Within the NHAM framework, this evidence positions the liver not merely as a background regulator but as an active modulator of affective oscillations, capable of shifting the amplitude (A), baseline (B_0), tempo (ω), and persistence (τ) of emotional trajectories in health and disease.

1.3 The Liver's Emerging Role in Affective Modulation

While the brain remains the central orchestrator of emotional processing, emerging research highlights the liver as a critical modulator of affective states through its metabolic, inflammatory, and microbiota-mediated functions (D'Mello & Swain, 2021). The liver is not merely a passive filter but an active participant in the gut–liver–brain axis, influencing mood via tryptophan metabolism, cytokine signaling, and bile acid regulation (Jiang et al., 2021).

Within the Neuro-Hepatic-Affective Model (NHAM), these influences are formalized as three hepatic pathways, each exerting pathway-specific effects on the four oscillator parameters $\{A, B_0, \omega, \tau\}$ (with higher B_0 = more negative baseline; higher ω = faster recovery; higher τ = longer persistence).

Pathway I — Metabolic–endocrine (bile acids / FGF19 axis)

The liver regulates bile acid signaling through farnesoid X receptors (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), both of which influence hypothalamic and limbic circuits (Hsuchou et al., 2012). Elevated FXR–TGR5 tone, reflected in increased circulating FGF19, is predicted by NHAM to reduce A (emotional reactivity), lower B_0 (improved baseline), and decrease τ (faster recovery). Conversely, hepatic ammonia accumulation, common in cirrhosis, slows updates ($\downarrow\omega$) and prolongs after-effects ($\uparrow\tau$), often manifesting as cognitive fatigue and affective inertia (Butterworth, 2015).

Pathway II — Inflammatory–immune (cytokines, kynurenine metabolism)

The liver is a major source of pro-inflammatory cytokines, including IL-6, TNF- α , and IL-1 β , which communicate with the brain via humoral and neural routes (D'Mello et al., 2015). Under chronic inflammation, activation of indoleamine 2,3-dioxygenase (IDO) diverts tryptophan metabolism toward kynurenine and quinolinic acid, reducing serotonin synthesis and increasing neurotoxic load (Dantzer et al., 2008). In NHAM terms, this state often increases A (threat reactivity), raises B_0 (more negative baseline), decreases ω (slower update), and increases τ (prolonged recovery). Clinically, these shifts align with sustained hypervigilance and difficulty returning to baseline after stress.

Pathway III — Microbiota–vagal (SCFAs, α -diversity, HF-HRV)

The liver receives portal blood enriched with gut-derived metabolites, including short-chain fatty acids (SCFAs) and bile acids, which can activate vagal afferents and modulate limbic activity via the nucleus tractus solitarius (Bonaz et al., 2018). Higher microbial α -diversity and SCFA production are associated with elevated HF-HRV, which in NHAM predicts reduced A (lower reactivity), increased ω (faster update), and decreased τ (improved recovery). These effects are consistent with a resilience-promoting vagal tone.

1.4. Theory — NHAM formalism

NHAM – Mathematical Formalism

We formalize mood as a damped stochastic oscillator with four latent parameters — reactivity (A), tonic baseline (B_0), recovery tempo (ω), and persistence (τ). These parameters are modulated by three hepatic pathways: metabolic–endocrine, inflammatory–immune, and microbiota–vagal. Each pathway shifts parameters in a reproducible, biologically interpretable way, measurable via targeted biomarkers and psychophysiological readouts.

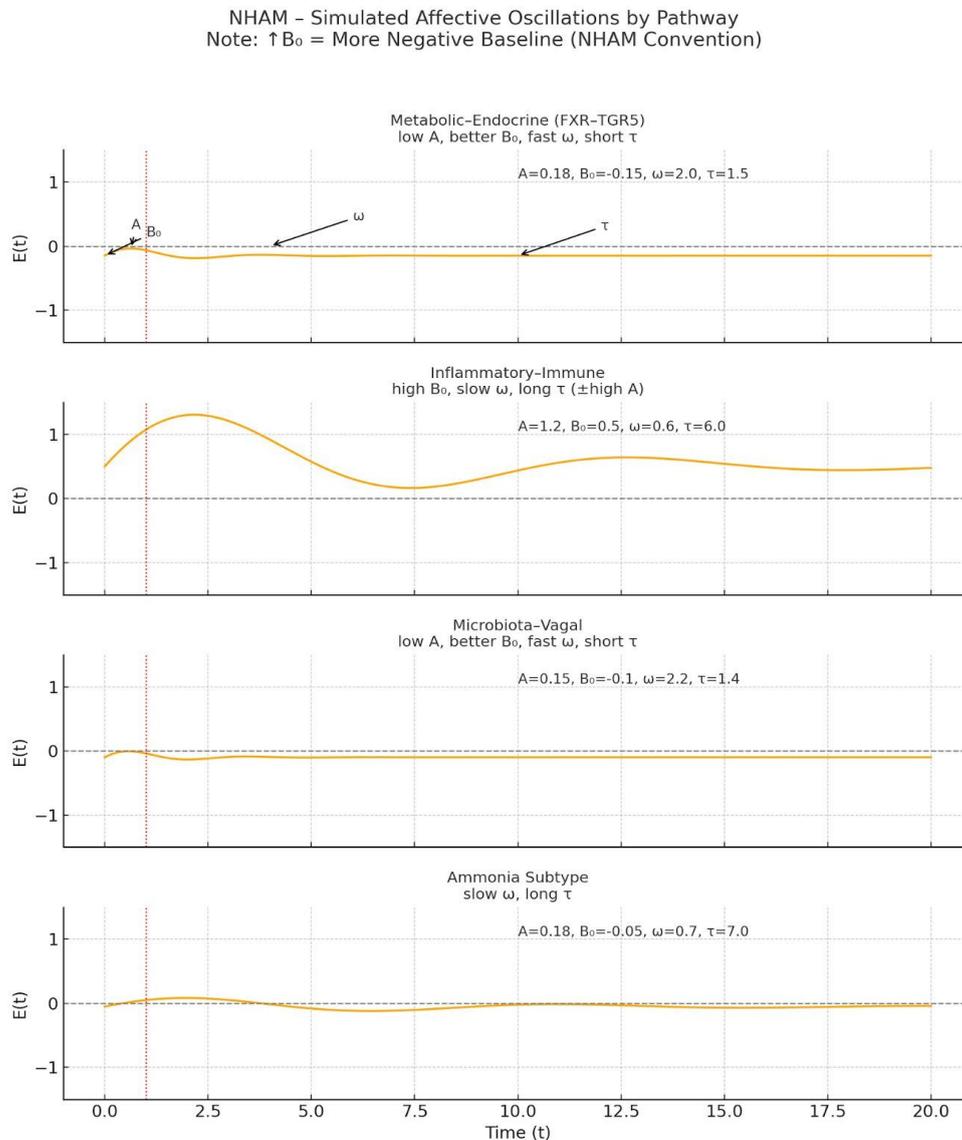


Figure 1. Pathway-Specific Affective Oscillation Simulations in the NHAM Framework. Each panel shows simulated emotional dynamics $E(t)$ following a perturbation (red dashed line, t_0) for four pathway-specific profiles in the Neuro-Hepatic-Affective Model (NHAM): (a) *Metabolic-Endocrine (FXR-TGR5)* — low amplitude (A), improved baseline mood (lower B_0), faster oscillatory frequency (ω), and shorter persistence (τ); (b) *Inflammatory-Immune* — high baseline negativity (higher B_0), slower ω , prolonged τ , and often elevated A ; (c) *Microbiota-Vagal* — low A , improved B_0 , fast ω , short τ ; (d) *Ammonia subtype* — slow ω and long τ , with baseline close to neutral. Horizontal dashed lines represent affective neutrality ($E = 0$). The vertical dashed red line (t_0) indicates the onset of perturbation. Parameter values (A, B_0, ω, τ) for each simulation are shown within panels. According to NHAM convention, $\uparrow B_0$ indicates a more negative affective baseline.

Integrative Mechanistic Diagram

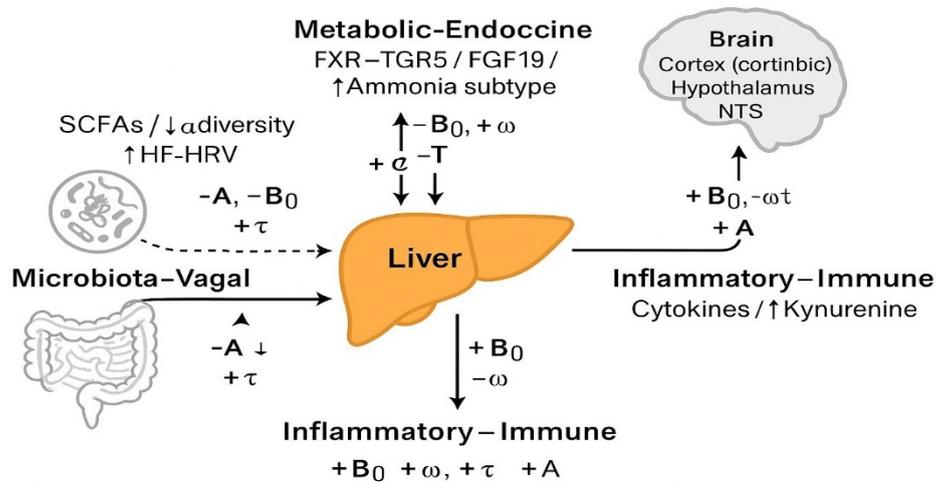


Figure 2. Integrative Mechanistic Diagram. The gut–liver–brain axis mediates the effects of three major physiological pathways—Microbiota–Vagal, Metabolic–Endocrine, and Inflammatory–Immune—on the parameters of emotional oscillation: amplitude (A), baseline affect (B_0), frequency (ω), and persistence (τ).

Each pathway modulates a distinct profile:

- **Microbiota–Vagal** (SCFAs, α -diversity, HRV) leads to $\downarrow A$, $\downarrow B_0$, $\uparrow \omega$, $\downarrow \tau$ — a resilient affective signature.
- **Metabolic–Endocrine** (bile acids, FGF19, insulin) produces a similar beneficial pattern: $\downarrow A$, $\downarrow B_0$, $\uparrow \omega$, $\downarrow \tau$.
- **Inflammatory–Immune** (IL-6, CRP, Kyn/Trp) drives $\uparrow B_0$, $\uparrow A$, $\downarrow \omega$, $\uparrow \tau$ — a high-persistence, high-reactivity affective state.

Dashed arrows indicate pathway inputs; solid arrows denote physiological transmission via the liver and brain. According to NHAM convention, $\uparrow B_0$ indicates a more negative affective baseline.

NHAM Pathway	Affective Signature (A, B_0, ω, τ)	Typical Symptoms	Illustrative Clinical Profiles
Microbiota-Vagal	$\downarrow A, \downarrow B_0, \uparrow \omega, \downarrow \tau$	Resilience, rapid affective recovery, euthymia, good vagal tone	Adaptive or subclinical wellbeing
Metabolic-Endocrine	$\downarrow A, \downarrow B_0, \uparrow \omega, \downarrow \tau$	Improved baseline mood, embodied arousal, stable affect	Euthymic or mild mood stability
Inflammatory-Immune	$\uparrow B_0, \downarrow \omega, \uparrow \tau$	Fatigue, prolonged negative mood, high inertia, rumination	Inflammatory mood subtype, atypical depression traits
Ammonia Subtype	$-(\downarrow \omega, \uparrow \tau)$	Slow return to baseline, cognitive fog, sub-beneficial affect	Metabolic-inertial subtype, low-fluctuation dysthymia

Figure 3. Clinical Expression of NHAM Pathways. Clinical profiles in the Neuro-Hepatic-Affective Model (NHAM). Each pathway produces a distinct affective signature, defined by its effect on amplitude (A), baseline mood (B_0), frequency (ω), and persistence (τ). These patterns yield characteristic psychological features and correspond to plausible clinical subtypes. The microbiota–vagal and metabolic–endocrine pathways support affective resilience ($\downarrow A$, $\downarrow B_0$, $\uparrow \omega$, $\downarrow \tau$), while inflammatory and ammonia-linked profiles drive higher affective inertia ($\uparrow B_0$, $\uparrow \tau$, $\downarrow \omega$). NHAM suggests that peripheral physiology may shape distinct emotional trajectories.

Core dynamics

Let $E(t)$ denote the latent affective state centered around a tonic baseline B_0 . External events $u(t)$ (stimuli, stressors, social cues) drive rapid reactivity, while hepatic pathways modulate parameters over slower timescales:

$$d^2E/dt^2 + \gamma dE/dt + \omega^2(E - B_0) = A u(t) + \varepsilon(t),$$

with $\gamma = 2/\tau$, where $\varepsilon(t)$ is zero-mean noise capturing unmodeled fluctuations.

This second-order formulation captures rise, persistence, and decay phases of emotion, linking peripheral biology to affective dynamics.

State–space formulation

For Bayesian inference and joint biomarker–psychophysiology fitting, we rewrite NHAM in continuous state–space form:

$$\dot{z} = F(\theta) x + G u(t) + \eta(t),$$

where $x = [E, \dot{E}]^T$, $\theta = \{A, B_0, \omega, \tau\}$, and $\eta(t)$ is Gaussian process noise. Parameter priors are informed by known gut–liver–brain mechanisms (D’Mello & Swain, 2021; Jiang et al., 2021).

Biomarker → parameter mapping

Pathway	Primary biomarkers	Predicted parameter shifts	Functional impact
Metabolic–endocrine	Total bile acids, FGF19, HOMA-IR, ammonia	$\downarrow A, \downarrow B_0, \uparrow \omega, \downarrow \tau$; ammonia → $\downarrow \omega, \uparrow \tau$	Reduced reactivity, lower tonic negativity, faster updates ($\uparrow \omega$) & shorter persistence ($\downarrow \tau$); ammonia subtype: slower updates & longer persistence
Inflammatory–immune	IL-6, TNF- α , CRP, Kyn/Trp ratio, LPS/LBP	$\uparrow B_0, \downarrow \omega, \uparrow \tau$	Elevated baseline negativity, slower updates ($\downarrow \omega$) & prolonged recovery ($\uparrow \tau$)
Microbiota–vagal	SCFA levels, vagal tone (HF-HRV), diversity index	$\downarrow A, \downarrow B_0, \uparrow \omega, \downarrow \tau$	Lower reactivity, lower tonic negativity, faster recovery ($\uparrow \omega$) & shorter persistence ($\downarrow \tau$) – i.e., greater flexibility

2. Definitions and Hypotheses (H1–H3)

In the NHAM framework, emotional dynamics are modeled through four key parameters:

- **Amplitude (A)** – intensity of transient affective responses.
- **Baseline mood (B₀)** – tonic affective set-point.
- **Frequency (ω)** – rate of oscillatory cycles (emotional adaptability).
- **Persistence (τ)** – temporal inertia of affective states.

H1 – Metabolic–Endocrine Pathway:

Elevated metabolic–endocrine markers (\uparrow total bile acids, \uparrow FGF19, \uparrow HOMA-IR, \uparrow plasma ammonia) will be associated with reduced reactivity ($\downarrow A$), higher tonic negativity ($\uparrow B_0$), and slower recovery ($\downarrow \omega, \uparrow \tau$).

H2 – Inflammatory–Immune Pathway:

Increased inflammatory activity (\uparrow IL-6, \uparrow TNF- α , \uparrow CRP, \uparrow Kyn/Trp ratio, \uparrow LPS/LBP) will predict elevated tonic negativity ($\uparrow B_0$), slower recovery ($\downarrow \omega$), and greater persistence ($\uparrow \tau$).

H3 – Microbiota–Vagal Pathway:

Higher vagal tone (\uparrow HF-HRV), greater SCFA levels, and higher microbial diversity will be linked to greater affective resilience ($\downarrow A, \downarrow B_0, \uparrow \omega, \downarrow \tau$).

3. Expected Results and Feasibility

NHAM predicts that pathway-specific parameter shifts can be empirically quantified via:

Peripheral biomarkers (bile acids, inflammatory cytokines, SCFAs, ammonia).

- **Autonomic indices** (high-frequency HRV for vagal tone).
- **Affective signal analysis** from EDA and facial EMG.
- **Ecological Momentary Assessment (EMA)** for real-time emotional variability.

Feasibility is supported by prior literature showing reliable links between these markers and affective regulation, enabling targeted modeling and simulation of clinical phenotypes.

4. Clinical Implications and DSM/ICD Mapping

The parameter-based language of NHAM enables cross-diagnostic classification, identifying shared oscillatory signatures across distinct DSM/ICD categories.

DSM/ICD Diagnosis	NHAM Signature	Candidate Pathway	Suggested Intervention
Major Depressive Disorder	$\uparrow B_0, \uparrow \tau, \downarrow \omega$	Inflammatory–Immune	Anti-inflammatory modulation
Generalized Anxiety Disorder	$\uparrow A, \uparrow B_0, \uparrow \tau$	Metabolic–Endocrine	Bile acid regulation
Irritable Bowel Syndrome	$\uparrow A, \uparrow B_0, \downarrow \omega$	Microbiota–Vagal	SCFA and vagal tone enhancement
Chronic Fatigue Syndrome	$\uparrow B_0, \uparrow \tau, \downarrow \omega$	Ammonia-linked Metabolic	Ammonia clearance strategies

5. Targeted Intervention Strategies

NHAM shifts the focus from categorical nosology to **parameter-targeted modulation**:

- **Metabolic–Endocrine:** FXR–TGR5 modulation, bile acid sequestration, insulin sensitivity improvement.
- **Inflammatory–Immune:** Cytokine-targeted therapy, gut permeability reduction, kynurenine pathway modulation.
- **Microbiota–Vagal:** SCFA supplementation, vagal nerve stimulation, microbiome diversity enhancement.

Interventions are tailored to reverse specific parameter deviations (e.g., reduce $\uparrow B_0$, restore $\uparrow \omega$), enabling personalized affective modulation.

6. Research Priorities and Limitations

Validating and operationalizing the Neuro-Hepatic-Affective Model (NHAM) requires coordinated research across multiple domains. We outline five priorities:

1. Longitudinal multi-omics cohorts

Prospective studies combining plasma bile acids, inflammatory markers, and microbiota metrics with psychophysiological parameters $\{A, B_0, \omega, \tau\}$ are essential to assess parameter stability and transitions over time (Albillos et al., 2020; Nikkheslat et al., 2025). Such designs would clarify whether shifts in metabolic–endocrine, inflammatory–immune, or microbiota–vagal profiles precede affective changes.

2. Randomized controlled trials with oscillatory endpoints

Interventional studies should test pathway-specific modulation—e.g., FXR/TGR5 agonists, probiotics, or anti-inflammatory agents—using $\{A, B_0, \omega, \tau\}$ as mechanistic primary outcomes (Schaub et al., 2022; Dacaya et al., 2025). This approach aligns with the precision-medicine framework proposed in recent gastro-neuropsychiatric trials.

3. Computational modeling of network-wide affective shifts

Bayesian state–space and oscillatory network models can simulate how pathway-specific perturbations propagate through affective dynamics (Tozzi & Peters, 2023). Integrating circadian gating and mood inertia (τ) into such simulations could identify optimal intervention timing.

4. Sex-specific analyses

Given documented sex differences in kynurenine metabolism and microbiota–vagal interactions (Nikkheslat et al., 2025), trials should be powered for sex-stratified analyses, with pre-specified interaction terms to detect differential pathway dynamics.

5. Closed-loop adaptive systems

Wearable-enabled biofeedback integrating HRV, EDA, and biomarker readouts could trigger real-time intervention when parameter thresholds are breached (Wu et al., 2023; Wang et al., 2025). Such systems could be embedded within AI-driven digital twins for personalized simulation before clinical application.

Limitations and Challenges

- **Heterogeneity of affective phenotypes:** Mixed presentations may not align with a single pathway, requiring weighted or composite signatures (Koenig et al., 2020).
- **Evidence gaps:** Pathway-to-parameter mapping remains largely cross-sectional; longitudinal causality is not yet established.
- **Operational constraints:** Multi-omics collection and continuous psychophysiological monitoring remain costly and logistically demanding outside specialized centers.
- **Regulatory considerations:** Closed-loop interventions will require robust safety validation and cross-disciplinary ethical oversight.

7. Discussion

The Neuro-Hepatic-Affective Model (NHAM) reframes affective regulation as an emergent property of coupled brain–liver–gut oscillatory systems, integrating metabolic–endocrine, inflammatory–immune, microbiota–vagal, and autonomic pathways into a unified mathematical and physiological formalism. This perspective addresses a critical gap in affective neuroscience: despite decades of cortico-centric research, the contributions of peripheral metabolic and immunological systems to mood regulation remain under-integrated in predictive, quantitative parameterizations. By positioning the liver as a dynamic central hub whose circadian, immuno-metabolic, and neurochemical outputs continuously reshape central affective networks, NHAM opens a systems-level paradigm for psychiatry.

7.1. Positioning within Existing Literature

Prior work has typically examined segments of the liver–brain axis in isolation. Elevated inflammatory cytokines (e.g., IL-6, CRP) are prospectively associated with incident depression (Valkanova et al., 2013; Osimo et al., 2020), and altered kynurenine metabolism is implicated in MDD and bipolar disorder (Almulla et al., 2022; Nikkheslat et al., 2025). Gut-microbiota studies reveal compositional shifts in MDD, with *Lactobacillus*/*Bifidobacterium* linked to symptom improvement in some probiotic RCTs (Schaub et al., 2022; Dacaya et al., 2025). Bile-acid signaling via FXR/TGR5 influences neuroinflammation and neurotransmission (Romero-Ramírez & Mey, 2024; McMillin & DeMorrow, 2016). In parallel, meta-analytic evidence links reduced high-frequency HRV to slower emotional recovery (Kemp et al., 2010; Koenig et al., 2020; Wang et al., 2025). NHAM unifies these fragmentary insights into a coherent parameter-based mapping, enabling cross-domain integration.

7.2. Innovations and Conceptual Advances

(i) Parameter-based interpretation. NHAM translates heterogeneous multi-omic and psychophysiological data into four interpretable parameters: **amplitude (A)**, **tonic baseline (B₀)**, **update/recovery speed (ω)**, and **persistence (τ)**.

(ii) Phenotype-specific mapping. Patients are stratified into metabolic–endocrine, inflammatory–immune, microbiota–vagal, and autonomic phenotypes with defined biomarker profiles and directional parameter shifts (e.g., metabolic–endocrine → ↓A, ↓B₀, ↑ω, ↓τ; inflammatory–immune → ↑B₀, ↓ω, ↑τ; microbiota–vagal → ↓A, ↓B₀, ↑ω, ↓τ; low-HRV autonomic → ↓ω, ↑τ; ammonia subtype → ↓ω,

↑ τ).

(iii) Closed-loop potential. Combining wearable HRV, EMA, and lab panels enables continuous monitoring and adaptive interventions with parameter-level endpoints—analogue to feedback-controlled models in cardiology/endocrinology. (Operational thresholds—for example a drop in $\omega \geq 20\%$ —are heuristics pending prospective validation.) These thresholds are operational heuristics pending prospective validation.

Pathway	Biomarkers	A	B_0	ω	τ
Metabolic-Endocrine (FXR)	FGF19, Bile Acids, Insulin	↓	↓	↑	↓
Ammonia Subtype	↑ Ammonia	-	-	↓	↑
Inflammatory-Immune	IL-6, CRP, Kynurenine	↑ (±)	↑	↓	↑
Microbiota-Vagal	SCFAs, HRV, α -diversity	↓	↓	↑	↓

Figure 4. Biomarker–Parameter Mapping in NHAM. Each NHAM pathway modulates the core parameters of the affective oscillator — amplitude (A), tonic baseline (B_0), frequency (ω), and persistence (τ) — through specific biomarkers. The metabolic–endocrine axis (e.g., FGF19, bile acids, insulin) reduces reactivity (↓A), improves baseline mood (↓ B_0), and accelerates recovery (↑ ω , ↓ τ). Inflammatory markers (e.g., IL-6, CRP, kynurenine) predict elevated tonic negativity and affective inertia (↑ B_0 , ↑ τ , ↓ ω). Ammonia elevation leads to slowed recovery and prolonged persistence (↓ ω , ↑ τ), without direct impact on reactivity or baseline. Microbiota–vagal indicators (e.g., SCFAs, HRV) support resilient affective dynamics (↓A, ↓ B_0 , ↑ ω , ↓ τ).

Topological and dynamical framing

Building on the topological framework proposed by Tozzi and Peters (2023), multi-scale correspondences can be conceptualized between hepatic-driven oscillatory states and brain functional manifolds. From a Borsuk–Ulam perspective, distinct affective configurations—despite arising from different physiological perturbations (e.g., cytokine surges, ammonia accumulation)—may share common topological signatures across brain regions. This theoretical bridge supports the NHAM proposition that parameter-based characterization of oscillatory dynamics offers a more mechanistically informative approach than purely categorical nosologies.

Clinical implications

NHAM can be implemented across resource settings. In low-resource contexts, HRV monitoring (Kemp et al., 2010; Wu et al., 2023), basic inflammatory panels, and smartphone EMA can yield actionable estimates of {A, B_0 , ω , τ }. In advanced settings, multi-omic profiling (bile acids, cytokines, kynurenines, microbiome sequencing) refines phenotype assignment and targeting. The strongest evidence base currently lies in MDD and anxiety disorders (Schaub et al., 2022; Nikkheslat et al., 2025), but NHAM’s logic extends to bipolar depression, somatic symptom disorder, hepatic encephalopathy, and neurodegeneration.

Challenges and caveats

Validation of parameter identifiability and stability requires prospective, phenotype-stratified cohorts. Phenotypic overlap (e.g., simultaneous inflammatory and autonomic signals) complicates prioritization without weighted or multi-objective algorithms. Probiotic effects are strain-specific (Schaub et al., 2022), and CNS efficacy of bile-acid modulation still needs robust RCTs (Romero-Ramírez & Mey, 2024). Adaptation for low-resource settings demands validated biomarkers/proxies and attention to measurement noise and circadian sampling.

8. Conclusions and Future Perspective

By formalizing affective dynamics as a liver–brain oscillator modulated by measurable biological inputs, NHAM aligns with embodied and network-based emotion models (Barrett, 2017; Craig, 2009)

while adding a predictive, quantifiable dimension. The framework bridges molecular biology and lived affective experience, laying a basis for parameter-focused precision psychiatry. Priorities include high-yield phenotypes (e.g., inflammatory-immune in females with MDD; Nikkheslat et al., 2025), parameter-level endpoints in RCTs, refined decision thresholds, and closed-loop prototypes that are adaptable across biological and socio-cultural contexts.

Ethics approval and consent to participate. This research does not contain any studies with human participants or animals performed by the Author.

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