Targeting Stress-Induced Depression with a Hippocampal-HPA Axis Model and Therapeutical Interventions

Laasya Munjeti

Abstract

Chronic stress is a well-known cause of depression, largely mediated through dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. In this study, we present a modified minimal model of the HPA axis that integrates two key inhibitory pathways: one representing stress-induced hippocampal neuronal loss, and another capturing the impaired inhibitory feedback from the hippocampus to the hypothalamus. Through simulations, we identify specific model parameters that distinguish between resilient and susceptible individuals, demonstrating how prolonged high stress can lead to significant hippocampal dysfunction, diminished HPA regulation, and sustained elevations in stress hormones. Furthermore, we analyzed EEG biomarkers from patients undergoing TMS therapy for depression. By correlating EEG-derived features with model parameters, we identified neurophysiological signatures associated with depression. This integration of patient data with computational modeling provides a mechanistic framework for understanding individual variability in treatment response and offers potential biomarkers for predicting TMS efficacy.

Introduction

Depression is a prevalent and debilitating mental health disorder, affecting hundreds of millions of people worldwide[1, 6]. It is characterized by persistent low mood, loss of interest or pleasure, and cognitive and physiological disturbances[3, 5]. While its causes are multifactorial, accumulating evidence points to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis as a central mechanism underlying the disorder [4, 2]. The HPA axis governs the body's stress response by regulating cortisol release through a cascade involving the hypothalamus, pituitary gland, and adrenal cortex. In healthy individuals, negative feedback from brain regions such as the hippocampus keeps cortisol levels within a balanced range. In depression, this feedback can be impaired, leading to sustained cortisol overproduction, structural brain changes, and further disruption of mood regulation.

In this work, we study depression in the context of HPA axis dysfunction using a minimal mathematical model that incorporates an inhibitory connection from the hippocampus to the hypothalamus[8]. The model captures the interactions between CRH, ACTH, cortisol, and structural adaptations in pituitary and adrenal tissues, along with stress-induced changes in hippocampal inhibitory activity[5].

We use the model to analyze system dynamics under different conditions, including the effects of antidepressant treatment and varying susceptibility to persistent depressive states. Phase portrait analysis is employed to illustrate how a key resilience parameter D determines whether the system remains in a healthy (euthymic) state or can shift into a pathological (depressed) equilibrium. We also compare short- and long-term antidepressant interventions and relate model predictions to neurophysiological measures such as alpha wave power observed in EEG and transcranial magnetic stimulation (TMS) studies[7]. This integrated approach links mathematical modeling with experimental findings to better understand how restoring HPA axis stability can alleviate depression.

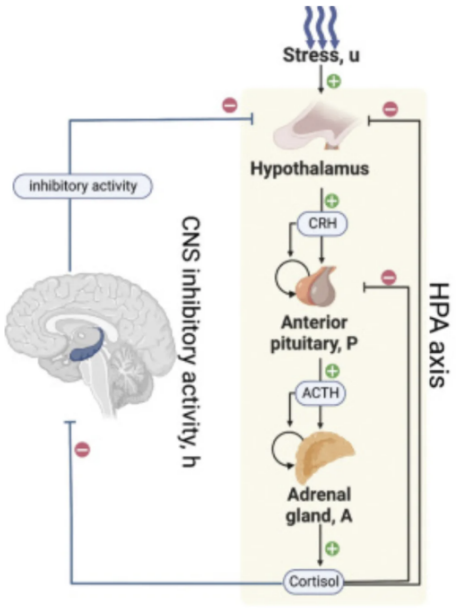

Figure 1: Schematic of the hypothalamic–pituitary–adrenal (HPA) axis with hippocampal inhibitory feedback. Stress input (u) stimulates the hypothalamus to release corticotropin-releasing hormone (CRH), which triggers the anterior pituitary (P) to secrete adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal gland (A) to produce cortisol, which exerts negative feedback on both the hypothalamus and pituitary. The hippocampus provides additional inhibitory control over the hypothalamus, a pathway that can be weakened under chronic stress (taken from [5]).

Methods

Minimal HPA Axis Model

We employed a minimal mathematical model of the hypothalamic–pituitary–adrenal (HPA) axis that explicitly incorporates hippocampal inhibitory activity. The model tracks the concentrations of corticotropin-releasing hormone (CRH, x_1), adrenocorticotropic hormone (ACTH, x_2), and cortisol (x_3), along with structural variables representing pituitary cell activity (P) and adrenal cell activity (A). The hippocampal inhibitory signal is denoted by h and represents central nervous system (CNS) activity that suppresses hypothalamic output (see figure 1). Chronic stress and elevated cortisol can reduce h, weakening negative feedback and predisposing the system to pathological states.

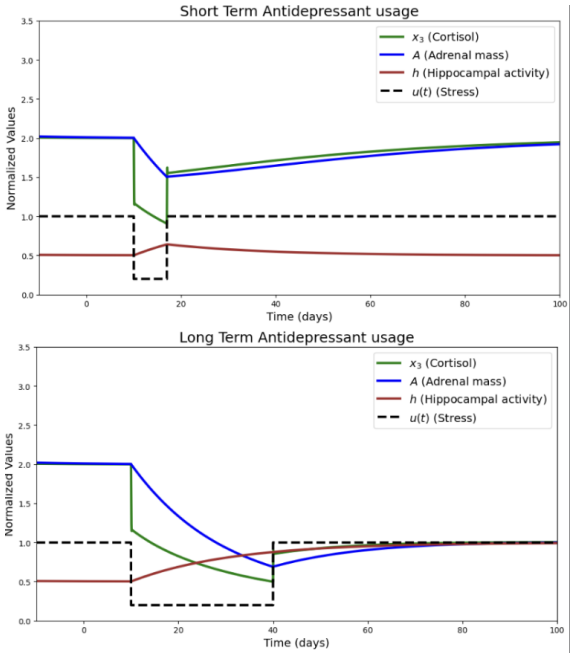

Figure 2: Response to antidepressants

The model is described by the following system of ordinary differential equations:

$$\frac{dx_1}{dt} = q_1 \frac{Hu}{hx_3} - \alpha_1 x_1, \tag{1}$$

$$\frac{dx_2}{dt} = q_2 \frac{Px_1}{x_3} - \alpha_2 x_2, \tag{2}$$

$$\frac{dx_3}{dt} = q_3 A x_2 - \alpha_3 x_3, \tag{3}$$

$$\frac{dP}{dt} = P(b_p x_1 - a_p), \tag{4}$$

$$\frac{dA}{dt} = A(b_A x_2 - a_A), \tag{5}$$

$$\frac{dh}{dt} = a_h \frac{D}{a + b\Theta(x_3 > T)} - b_h h. \tag{6}$$

Equations (1)–(3) describe hormone dynamics, balancing production rates (scaled by q_i) and clearance rates (α_i). CRH secretion is driven by stress input u and modulated by hippocampal inhibition h and cortisol feedback via x_3. ACTH production depends on CRH and pituitary cell activity P, while cortisol production depends on ACTH and adrenal mass A.

Equations (4) and (5) describe slow-timescale changes in pituitary and adrenal mass, capturing structural adaptation to chronic hormone exposure. Growth rates b_p and b_A are opposed by natural decay rates a_p and a_A.

Equation (6) introduces the novel hippocampal inhibitory dynamics. Here, D is a resilience parameter controlling the rate of recovery of h, while $\Theta(x_3 > T)$ is a threshold function that reduces h when cortisol exceeds a damage threshold T. This formulation allows simulation of both acute stress resilience and long-term hippocampal degradation under chronic stress.

This model illustrates the complex interactions within the Hypothalamic-Pituitary-Adrenal (HPA) axis, which serves as the body's primary stress response system. The HPA axis operates through a carefully orchestrated cascade where the hypothalamus releases Corticotropin-Releasing Hormone (CRH) in response to stress signals, which then stimulates the pituitary gland to produce Adrenocorticotropic Hormone (ACTH). Subsequently, ACTH triggers the adrenal gland to

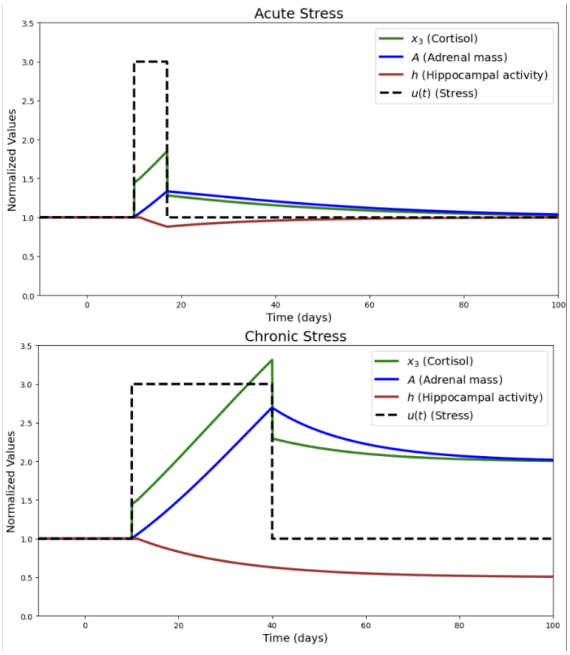

Figure 3: Response to Acute/Chronic Stress

release cortisol, the primary stress hormone that helps the body respond to challenging situations. A critical component of this system is the regulatory feedback mechanism provided by the hippocampus, which normally inhibits the hypothalamus to prevent excessive cortisol production. However, chronic stress exposure creates a pathological cycle where prolonged elevation of stress hormones leads to hippocampal damage and reduced inhibitory capacity. This weakening of the feedback loop results in dysregulated cortisol levels, as the hippocampus becomes less effective at signaling the hypothalamus to reduce CRH release, ultimately contributing to the pathophysiology of stress-related disorders such as depression. The mathematical framework underlying this model consists of six differential equations that capture the dynamic relationships between these key components. Equations (1)-(3) govern the production and clearance dynamics of CRH, ACTH, and cortisol respectively, tracking their concentrations over time as they respond to stress inputs and regulatory signals. Equations (4)-(5), developed by previous researchers, model the changes in pituitary cell activity (P) and adrenal cell activity (A) over time. The novel contribution is equation (6), which I derived to specifically model hippocampal activity (h) and its decline under chronic stress conditions. This new equation incorporates a threshold mechanism where hippocampal inhibitory function decreases when cortisol levels exceed a critical value T, providing a mathematical representation of how prolonged stress weakens the crucial feedback mechanism that normally maintains HPA axis homeostasis.

Results

The model simulation results (see figure 3 top) demonstrate distinct responses of the HPA axis to acute versus chronic stress conditions. Under acute stress, the model shows that cortisol levels (x_3) rise rapidly but return to baseline within approximately 20 days, while adrenal mass (A) and hippocampal activity (h) remain relatively stable throughout the stress period. This pattern reflects a healthy, well-regulated stress response where negative feedback mechanisms effectively prevent excessive cortisol secretion, supporting the system's natural resilience to short-term stressors. In contrast, chronic stress exposure leads to sustained HPA axis activation with prolonged cortisol overproduction and significant adrenal gland enlargement that persists even after the stressor

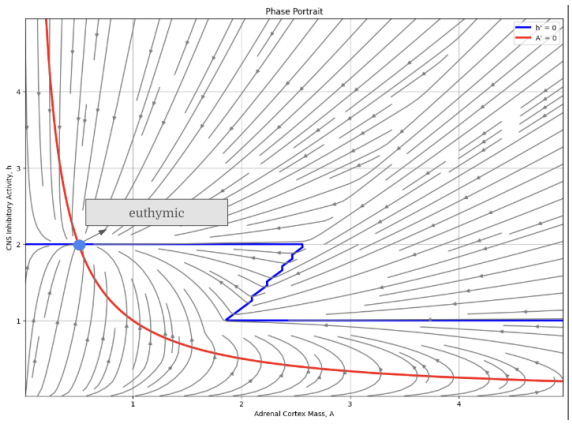

Figure 4: Non Susceptible (D = 2)

is removed. The model reveals that hippocampal activity progressively declines during chronic stress, indicating weakened inhibitory feedback capacity. This dysregulation disrupts normal CNS function and creates a pathological state where the system cannot effectively return to baseline, thereby increasing depression risk and worsening overall stress regulation capabilities.

The antidepressant treatment simulations reveal important differences between short-term and long-term therapeutic approaches (see figure 3 bottom). Short-term antidepressant use initially helps stabilize CNS activity and temporarily reduces stress levels, as evidenced by the brief normalization of cortisol and improved hippocampal function. However, the model shows that once treatment is discontinued, cortisol levels begin fluctuating again and the HPA axis becomes unbalanced, leading to reduced long-term stress regulation and potential relapse of symptoms. Long-term antidepressant treatment demonstrates superior therapeutic outcomes by helping restore sustained HPA axis balance and preventing cortisol overproduction throughout the extended treatment period. The simulation shows that prolonged medication use supports gradual recovery of hippocampal activity and maintains stable cortisol levels, which translates to improved long-term CNS stability. This sustained therapeutic effect significantly reduces the risk of mood disorders like depression by maintaining the crucial feedback mechanisms necessary for proper stress regulation.

The phase portrait analysis reveals fundamental differences in depression vulnerability between susceptible and non-susceptible populations. In non-susceptible individuals (D = 2), the model identifies a single stable fixed point representing a mentally healthy, well-regulated stress response system (see figure 4). The trajectory flows demonstrate that regardless of life stressors or initial perturbations, these individuals' HPA axis effectively self-corrects and returns to this euthymic (healthy) state, indicating robust psychological resilience that protects against depression development even under chronic stress exposure. The susceptible population (D = 1) exhibits a dramatically different dynamic landscape characterized by bistable behavior with two distinct stable fixed points that explains why some individuals are prone to depression (see figure 5). One fixed point corresponds to the healthy euthymic state, while the second represents a dysregulated depressed state with chronically elevated cortisol and compromised hippocampal function characteristic of major depressive disorder. This bistability means that vulnerable individuals can be pushed from mental wellness into a pathological depressive state by relatively small stressors or life events, where they become trapped in a cycle of sustained HPA axis dysfunction that maintains depressive symptoms and makes recovery difficult without therapeutic intervention. The EEG recording from electrode Fp1 shows robust alpha wave activity (8-12 Hz) during the initial 2 seconds, with amplitudes reaching approximately 40 µV (see figure 6). However, a marked attenuation of alpha power occurs from 3 seconds onward, where the signal remains substantially suppressed for the remainder of the recording period. This sustained reduction in alpha wave power is clinically significant, as diminished alpha activity has been associated with depressive states and disrupted

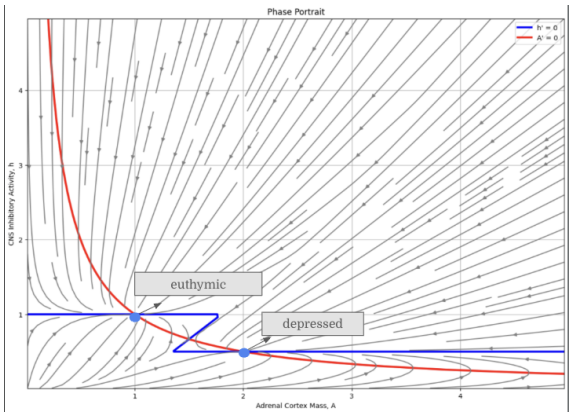

Figure 5: Susceptible (D = 1)

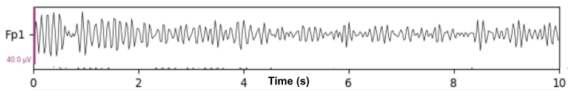

Figure 6: Alpha Wave Signal of a Patient Over Time (FP1)

neural regulation. The persistent alpha suppression may indicate compromised neural network functioning and could serve as a neurophysiological marker for monitoring treatment response.

The EEG topographic maps demonstrate a progressive enhancement of alpha wave power across the scalp throughout the TMS treatment course (see figure 7). At baseline (Week 1), alpha power was uniformly low across all electrode sites, consistent with the suppressed neural activity typically observed in depression. Beginning at Week 2, there was a gradual increase in alpha power, with the most pronounced improvements occurring in posterior regions by Weeks 3-4. Peak alpha power was achieved at Week 5, showing widespread activation across the entire scalp with maximum power concentrated in occipital and parietal areas. By Week 10, alpha power remained elevated compared to baseline but showed a slight decline from peak levels, suggesting stabilization at a therapeutically beneficial level that indicates sustained improvement in neural network functioning. The EEG topographic maps demonstrate a progressive enhancement of alpha wave power across the scalp throughout the TMS treatment course (see figure 8). At baseline (Week 1), alpha power was uniformly low across all electrode sites, consistent with the suppressed neural activity typically observed in depression. Beginning at Week 2, there was a gradual increase in alpha power, with the most pronounced improvements occurring in posterior regions by Weeks 3-4. Peak alpha power was achieved at Week 5, showing widespread activation across the entire scalp with maximum power concentrated in occipital and parietal areas. By Week 10, alpha power remained elevated compared to baseline but showed a slight decline from peak levels, suggesting stabilization at a therapeutically beneficial level that indicates sustained improvement in neural network functioning.

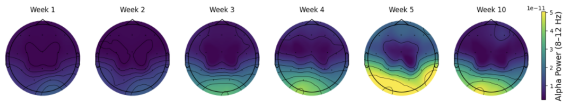

Figure 7: EEG alpha wave power over multiple weeks of TMS treatment

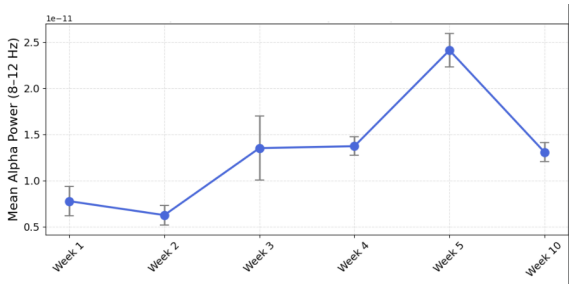

Figure 8: Mean Alpha Power with Susceptible Population (n=10)

Conclusion

This study demonstrates that TMS effectively modulates alpha wave activity as a neurophysiological marker of treatment response in depression. Our findings reveal progressive alpha power enhancement from suppressed baseline activity to sustained elevation, indicating improved neural network functioning. The modified HPA axis model successfully links stress-induced hippocampal neuronal loss to sustained cortisol elevation. Specific model parameters (D and T) may serve as predictive indicators of individual susceptibility to stress-induced depression. The integration of EEG biomarkers with theoretical modeling provides valuable mechanistic insights into depression pathophysiology and therapeutic response. These findings have significant clinical implications for developing targeted interventions and enabling earlier treatment. Current limitations include the model's qualitative approach, necessitating future refinement with neurobiologically accurate parameters. The demonstrated link between alpha wave power and model parameters suggests promising avenues for personalized treatment strategies. Future research should focus on validating the theoretical model with clinical data and identifying additional biomarkers. Machine learning integration may further enhance prediction accuracy and enable individualized intervention approaches that could transform depression treatment.

References

[1] Constance Hammen. "Stress and depression". In: *Annu. Rev. Clin. Psychol.* 1.1 (2005), pp. 293–319.

[2] Andreas Menke. "The HPA axis as target for depression". In: *Current Neuropharmacology* 22.5 (2024), pp. 904–915.

[3] Scott M Monroe and Kate L Harkness. "Major depression and its recurrences: life course matters". In: *Annual review of clinical psychology* 18.1 (2022), pp. 329–357.

[4] Carmine M Pariante and Stafford L Lightman. "The HPA axis in major depression: classical theories and new developments". In: *Trends in neurosciences* 31.9 (2008), pp. 464–468.

[5] Ben Ron Mizrachi et al. "Major depressive disorder and bistability in an HPA-CNS toggle switch". In: *PLoS Computational Biology* 19.12 (2023), e1011645.

[6] Robert M. Sapolsky. *Why Zebras Don't Get Ulcers: The Acclaimed Guide to Stress, Stress-Related Diseases, and Coping*. New York: Holt Paperbacks, 2004.

[7] Yasuo Terao and Yoshikazu Ugawa. "Basic mechanisms of TMS". In: *Journal of clinical neurophysiology* 19.4 (2002), pp. 322–343.

[8] Frank Vinther, Morten Andersen, and Johnny T Ottesen. "The minimal model of the hypothalamic–pituitary–adrenal axis". In: *Journal of mathematical biology* 63.4 (2011), pp. 663–690.