A Coupled HPA–Mirror Neuron Model of Chronic Maternal Stress and Autism Susceptibility

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Abstract

Stress experienced by a mother during pregnancy can profoundly influence the neurodevelopment of the fetus, potentially increasing susceptibility to autism spectrum disorders. We investigate these effects by extending a minimal mathematical model of the hypothalamic–pituitary–adrenal (HPA) axis to include mirror neuron activity in the premotor cortex. Our coupled system of differential equations captures the short-term (acute) versus long-term (chronic) impacts of maternal stress on embryonic development. We show that acute stress causes transient elevations in cortisol and mild alterations in mirror neuron activity, whereas chronic stress yields persistent physiological changes—elevated adrenal gland mass, higher baseline cortisol levels, and diminished mirror neuron activity that can remain even after the stressor is removed. Through phase-portrait and fixed-point analysis, we identify a key parameter, D, which governs the dynamics of mirror neuron activity. When D is small, three fixed points arise, including two stable equilibria—one corresponding to a "healthy" (euthymic) state and the other associated with reduced mirror neuron activity (an "autistic" state). Under large D, the system supports only the euthymic fixed point, indicative of a non-susceptible population. Finally, we demonstrate that while acute reductions in stress have negligible impact on the long-term dynamics, chronic reduction of stress can restore cortisol levels and mirror neuron activity to the euthymic range. These findings suggest that chronic maternal stress can be a critical determinant in the onset of autism-like neurodevelopmental trajectories for susceptible individuals and underscore the importance of sustained stress management interventions during pregnancy.

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition whose etiology is influenced by a combination of genetic predisposition and environmental factors. Among the environmental stressors, maternal stress during pregnancy has garnered particular attention for its potential to alter fetal neurodevelopment [1, 8]. In this context, the hypothalamic–pituitary–adrenal (HPA) axis—one of the body's primary stress-response systems—plays a crucial role. Chronic activation of the HPA axis leads to prolonged elevations in glucocorticoids (e.g., cortisol), which, in turn, can induce structural and functional changes in the developing fetal brain ([9]). Mirror neurons, located primarily in the premotor cortex and implicated in social cognition and imitation, have been proposed as key players in typical social development ([7]). Dysfunctions in mirror neuron systems have been hypothesized to underlie aspects of ASD, such as deficits in social interaction and communication ([6]).

Despite growing evidence linking prenatal stress and atypical neurodevelopmental outcomes, our understanding of the mechanisms and possible tipping points that lead to a heightened ASD risk remains incomplete. In this work, we propose a minimal mathematical framework that couples a simplified HPA axis model to a mirror neuron system. Our goal is to identify how transient

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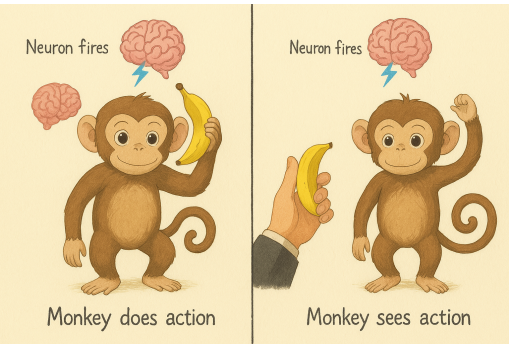

Figure 1: Mirror neuron network under normal conditions

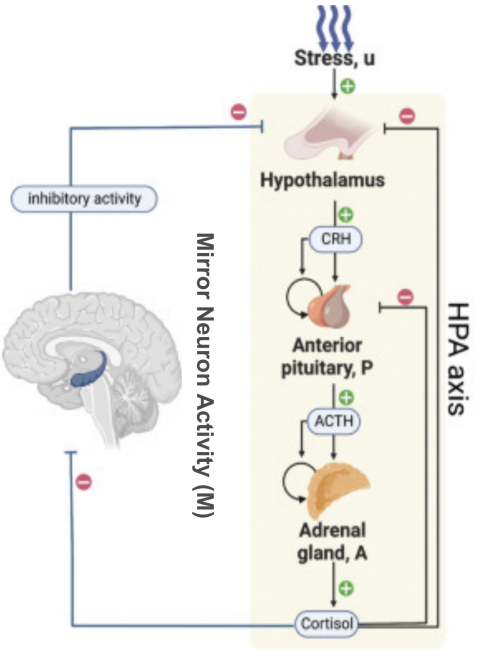

Figure 2: How prolonged stress levels impact mirror neurons

(acute) versus prolonged (chronic) maternal stress can drive divergent neurodevelopmental trajectories, potentially culminating in an autism-like condition for some susceptible populations. The model incorporates a stress-related parameter D, which modifies the mirror neuron dynamics. We show that for sufficiently small D, the model supports two stable fixed points, one corresponding to a normative or "euthymic" state and another reflecting reduced mirror neuron activity, which we link to an "autistic" state. Larger values of D consolidate the model into a single euthymic attractor, suggesting a non-susceptible population. These findings underscore the significance of chronic stress in gestation and highlight the interplay between the HPA axis and mirror neuron systems in influencing an individual's developmental trajectory.

Methods

Overview of the Model

We developed a coupled system of ordinary differential equations (ODEs) that combines a minimal hypothalamic–pituitary–adrenal (HPA) axis model with a simplified representation of mirror neuron activity in the premotor cortex[11]. The model tracks the dynamics of key hormones (corticotropin-releasing hormone, CRH; adrenocorticotropic hormone, ACTH; and cortisol) alongside the activity level M of mirror neurons.

Minimal HPA model

Equations (1)–(3) describe the rate of change in concentration of three key hormones: corticotropin-releasing hormone (CRH, denoted as x_1), adrenocorticotropic hormone (ACTH, x_2), and cortisol (x_3). The dynamics of CRH are modeled in Equation (1), where its production rate is modulated by stress input H, scaled by pituitary size u and cortisol concentration x_3, and its removal is proportional to $\alpha_1 x_1$. Equation (2) models the synthesis of ACTH, which is produced in response to CRH (x_1) and inhibited by cortisol levels (x_3), while undergoing natural degradation at rate $\alpha_2 x_2$.

Similarly, cortisol production, as shown in Equation (3), is driven by ACTH (x_2) and removed at a rate proportional to its concentration ($\alpha_3 x_3$). The constants q_1, q_2, and q_3 represent production rate coefficients for CRH, ACTH, and cortisol respectively, while α_1, α_2, and α_3 account for their respective degradation rates. These parameters allow the system to capture the interplay of production and removal that characterizes endocrine feedback loops.

$$\frac{dx_1}{dt} = q_1 \frac{Hu}{Mx_3} - \alpha_1 x_1 \tag{1}$$

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

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

For finding steady state set,

$$\frac{dx_1}{dt} = 0, \quad \frac{dx_2}{dt} = 0, \quad \frac{dx_3}{dt} = 0$$

After algebraic manipulations, we get for steady state,

$$x_1^{st} \sim P^{-1/3} A^{-1/3} u^{2/3}$$
$$x_2^{st} \sim P^{1/3} A^{-2/3} u^{1/3}$$
$$x_3^{st} \sim P^{1/3} A^{1/3} u^{1/3}$$

Incorporating pituitary and adrenal gland dynamics

Equations (4) and (5) extend the model to include the growth dynamics of the pituitary gland (P) and adrenal gland (A) [2, 3, 4]. Equation (4) describes pituitary expansion as a function of CRH stimulation, governed by a production term $P(b_p x_1 - a_p)$, where b_p is a sensitivity coefficient and a_p represents a baseline level required for pituitary maintenance. Equation (5) follows a similar formulation for adrenal growth, which is modulated by ACTH levels, expressed as $A(b_A x_2 - a_A)$, where b_A and a_A play analogous roles.

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

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

To analyze steady-state behavior and understand long-term hormone regulation, the equations are often studied by setting the time derivatives to zero. This allows the derivation of baseline hormone levels under non-stress conditions, revealing how hormone concentrations stabilize over time. The steady state values are given by:

$$x_1^{st} = \frac{a_P}{b_P}$$
$$x_2^{st} = \frac{a_A}{b_A}$$
$$x_3^{st} = \frac{q_1 H}{\alpha_1 x_1^{st}} u = \frac{q_1 b_P H}{\alpha_1 a_P} u$$
$$P^{st} = \frac{\alpha_2 x_2^{st} x_3^{st}}{q_2 x_1^{st}} = \frac{\alpha_2 a_A q_1 b_p^2 H}{q_2 b_A \alpha_1 a_P} u$$
$$A^{st} = \frac{\alpha_3 x_3^{st}}{q_3 x_2^{st}} = \frac{\alpha_3 b_A q_1 b_P H}{q_3 a_A \alpha_1 a_P} u$$

Through this modeling framework, one can explore how the hypothalamus, pituitary, and adrenal glands dynamically respond to stress inputs and regulate each other to maintain homeostasis.

Parameter	Value	Unit
q_1	244.8	-
q_2	50.4	-
q_3	12.384	-
α_1	244.8	min
α_2	50.4	min
α_3	12.384	min
a_p	0.05	days
b_p	0.05	days
a_m	0.047	-
b_m	0.047	-
a_a	0.1	days
b_a	0.1	days
a	1.0	-
b	1.0	-
T	1.5	-
D	1.0	-

Table 1: Parameter values used in simulation

Mirror Neuron Dynamics

To represent mirror neuron activity, we introduce a variable $M(t)$, which denotes the activity level of the mirror neuron population over time. Equation (6) models the rate of change in M as a function of external drive and cortisol-dependent modulation.

The first term on the right-hand side,

$$a_m \frac{D}{a + b\,\Theta(x_3 > T)},$$

represents the activation of mirror neurons in response to a driving signal D, scaled by the factor a_m. The denominator modulates this activation based on the level of cortisol (x_3). Specifically, $\Theta(x_3 > T)$ is a Heaviside step function that takes the value 1 if $x_3 > T$ (i.e., cortisol exceeds a threshold T), and 0 otherwise. The parameters a and b control the baseline and sensitivity of this suppression effect, respectively. When cortisol levels are high (i.e., $x_3 > T$), the denominator increases, thereby reducing mirror neuron activation—capturing the hypothesized inhibitory effect of elevated cortisol on social or empathic processing.

The second term, $-b_m M$, models the natural decay of mirror neuron activity over time, with b_m representing the rate of decay.

This formulation allows the mirror neuron dynamics to be sensitive to stress-induced cortisol fluctuations, providing a mechanistic link between hormonal state and socially responsive neural activity.

$$\frac{dM}{dt} = a_m \frac{D}{a + b\Theta(x_3 > T)} - b_m M \tag{6}$$

Results

Figure 3 shows the chronic and acute stress effect on cortisol, adrenal mass, and mirror neurons. These are indicated through panels producing time series data for each state variable. The first panel plots the evolution of cortisol, adrenal mass, mirror neuron activity, and the input stress function u(t), highlighting how the system reacts during and after the stressor. The second panel

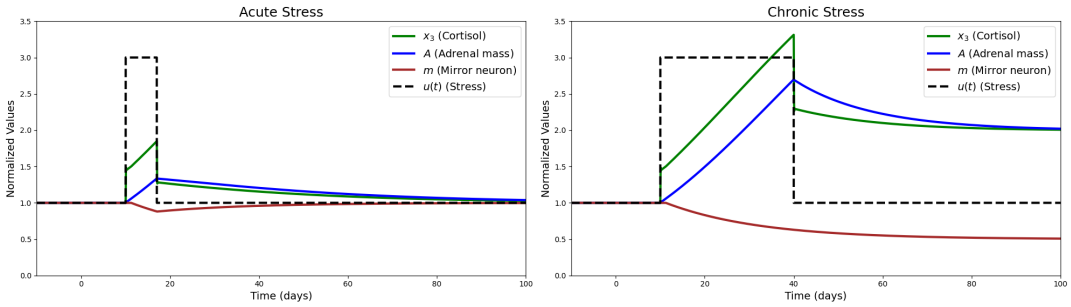

Figure 3: Chronic and acute stress effect on cortisol, adrenal mass, and mirror neurons

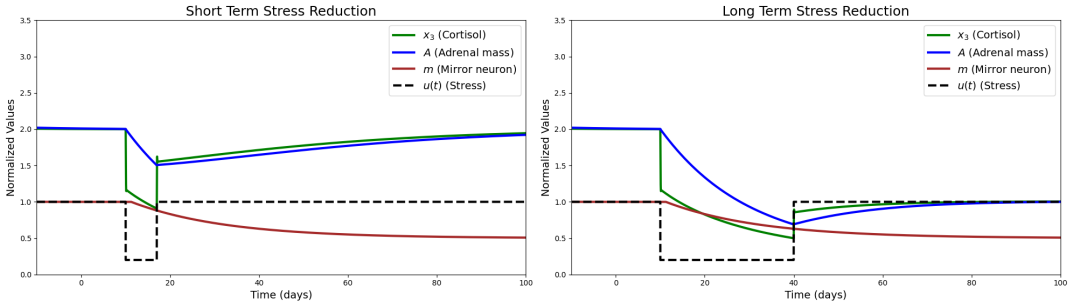

Figure 4: Short term and long term stress reduction on cortisol, adrenal mass, and mirror neurons

describes shows the internal HPA axis variables, allowing examination of pituitary and adrenal signaling dynamics and hormonal feedback mechanisms.

When observing the cortisol dynamics, Figure 4 shows that drug-induced stress reduction on the mass of adrenal gland and mirror neurons present. In both panels, the black, dotted line refers to extrenal stress input, which abruptly decreases, mimicing the effects of a drug. In the left panel, the blue line showcases cortisol levels and the green line describes adrenal mass. Both cortisol levels and adrenal mass show a quick drop following stress reduction, but the mirror neurons indicated by the red line remains low. This reflects the limited neural recovery. In contrast, the long term stress reduction scenario shown in the right panel describes how a prolonged decrease in chronic stress allow adrenal mass and cortisol levels to normalize over time, and mirror neurons steadily increase to healthy levels. This highlights the difference between the effects of a drug on acute and chronic stress, influencing the recovery of mirror neurons.

Figure 5 shows how the coupled dynamics of adrenal cortex mass and mirror neuron activity are affected across different diffusion coefficients. This information is modeled using a phase portrait with A referring to adrenal cortex mass and m referring to mirror neuron activity. Additionally, the pituitary and adrenal responses initially increase under stress due to the strong stimulus (adrenal gland follows after a brief delay), showing the signal transmission through HPA axis. After stress, both variables gradually decline but remain elevated for a short duration. The regulatory factor shows a pattern in which it increases early during the stressful period, reflecting positive feedback. However, as stress continues, it plateaus and slightly declines, due to feedback from elevated cortisol.

In Figure 5 each subplot displays a vector field overlaid with nullclines [10, 5]: the red curve denotes the nullcline for adrenal cortex mass ($A' = 0$), and the blue curve denotes the nullcline for mirror neuron activity ($m' = 0$). Steady states (intersections of the nullclines) are highlighted in yellow.

- **Left panel (D = 0.5):** The system stabilizes at a low mirror neuron activity and high adrenal cortex mass, corresponding to a dominant autistic state. The flow trajectories converge toward this single attractor, indicating limited plasticity under low diffusion.

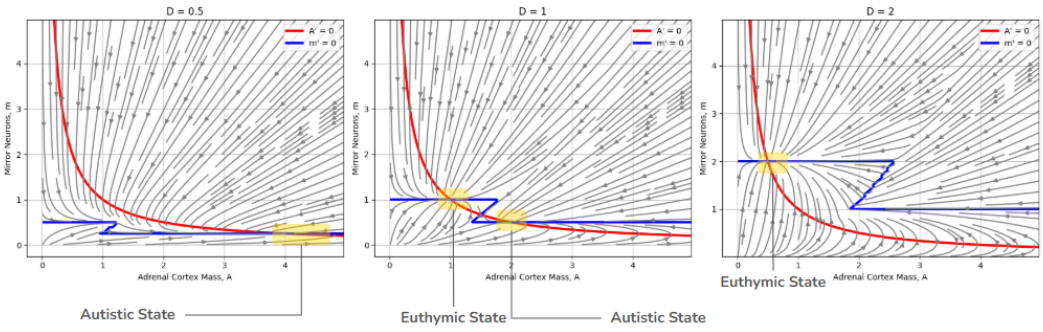

Figure 5: Phase portraits illustrating the coupled dynamics of adrenal cortex mass (A) and mirror neuron activity (m) across different diffusion coefficients (D = 0.5, 1, 2).

- **Middle panel (D = 1):** Multiple steady states emerge—one associated with high mirror neuron levels (interpreted as a euthymic state), and another with low mirror neuron activity (an autistic state). This bistability suggests that intermediate diffusion levels support both healthy and pathological neuroendocrine configurations depending on initial conditions.
- **Right panel (D = 2):** A single attractor appears again, but this time centered around higher mirror neuron activity and lower adrenal cortex mass, corresponding to a stable euthymic state. This shift implies that increased diffusion enhances the system's resilience and promotes social cognitive balance.

Overall, the transition from monostable to bistable and back to monostable dynamics across increasing diffusion levels highlights how neuroendocrine coupling strength influences susceptibility to or recovery from autistic-like states.

Discussion

In the presented simulation, when circulating cortisol exceeds a threshold, the production of mirror neurons is surpressed. This is proven as during the stress phase between day 10-50, cortisol rises significantly and remains above the threshold, but as a result, the mirror neuron activity declines, showcasing functional suppression and neuronal degradation. After the period of chronic stress has passed, cortisol gradually decreases, eventually falling below threshold levels. The mirror neuron activity begins to recover with a lag, suggesting a delayed or incomplete restoration of socio-cognitive function. The "shattering" of mirror neurons and incomplete restoration of socio-cognitive function during periods of sustained stress have parallels with autism spectrum disorder (ASD) research. Core symptoms of ASD include reduced social reciprocity, impaired imitation and empathy, and difficulty understanding others intentions. Chronic dysregulation of the HPA axis may contribute to neurodevelopmental changes and functional deficits within an individual, supporting the hypothesis that early or prolonged stress could result in conditions that mimic ASD-like symptoms, especially in the fetus of pregnant women enduring chronic maternal stress.

Conclusion

This study introduces a minimal mathematical model coupling the HPA axis with mirror neuron activity to explore how maternal stress—particularly when chronic—can influence fetal neurodevelopment and potentially raise autism risk. Our analysis reveals that while acute stress causes only short-lived disruptions, prolonged exposure to stress leads to enduring physiological changes:

elevated adrenal and pituitary gland mass, persistently high cortisol levels, and substantially reduced mirror neuron activity.

A pivotal finding is the role of the model parameter D, which determines how sensitively mirror neurons respond to cortisol dysregulation. When D is below a critical threshold, the system admits a second stable equilibrium associated with diminished mirror neuron activity—an "autistic" state. By contrast, larger values of D preserve a single, euthymic steady state even under chronic stress, suggesting that an individual's susceptibility to autism-like outcomes is shaped by their physiological resilience.

Finally, we show that chronic interventions to reduce stress can restore cortisol and mirror neuron levels to near-euthymic ranges. This highlights the importance of sustained therapeutic strategies and robust stress management during pregnancy, particularly for individuals who exhibit higher vulnerability. Future modeling refinements could incorporate additional hormonal axes and neurodevelopmental processes, aiming to offer deeper insight into prevention or early-intervention protocols for stress-related neurodevelopmental disorders.

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