Simulating the Impact of NMDA-Receptor Antagonists on Reward and Executive Circuitry in Obsessive-Compulsive Disorder

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Abstract

Obsessive-compulsive disorder (OCD) is a common and disabling psychiatric disorder that affects 1-3% of people. The defining symptoms are obsessions— intrusive thoughts and fears that cause intense anxiety— and compulsions— repetitive actions performed to alleviate this anxiety.[2] These two symptoms usually feed off of each other: obsessions trigger compulsions that temporarily relieve the anxiety, only for another intrusive thought to restart the cycle. This leads sufferers to become trapped in "loops" of alternating intense anxiety and repetitive behaviors performed for relief.

While current treatments for OCD include Cognitive Behavioral Therapy (CBT), Exposure and Response Prevention (ERP) therapy, and prescription of selective serotonin reuptake inhibitors (SSRIs), these treatments do not always alleviate symptoms.[9] Research into more effective treatment is ongoing, and one area of interest is the impact of glutamate modulation, specifically NMDA receptor antagonists, which decrease glutamate-associated activation.

In this project, an existing dynamical systems model of OCD was extended to simulate the impact of NMDA receptor antagonists by decreasing the global glutamate activation parameter. The results showed a decrease in obsessive-compulsive patterns when glutamatergic excitation was decreased, indicating that this drug class may show promise in alleviating symptoms. Further work is needed to refine the model and to evaluate potential treatments in a clinical setting.

Introduction

OCD is a heterogeneous disorder, meaning that it presents differently in different people and can have a variety of causes and aggravating factors. As such, the underlying dynamics are not fully understood. However, through fMRI studies and other clinical data, researchers have associated a few key regions of the brain with OCD.[3]

OCD has been linked to brain hyperactivity of cortical regions, specifically the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), with obsessive-compulsive symptoms.[3] The orbitofrontal cortex is related to emotion and reward signaling, while the anterior cingulate cortex is linked to motivation and action.[8] The ACC and OFC communicate often with the striatum, and this general neural pathway involving feedback between these areas is sometimes referred to as the cortico-basal ganglia-thalamo-corticol loop (CBGTC) or the cortico-striatal-thalamo-cortical pathway (CSTC)[3]. The CSTC is associated with OCD as well as several other mental health disorders, including major depression, eating disorders, and substance use disorders.[4] The limbic areas, including the hippocampus and the amygdala, which drives anxiety, have been linked to OCD as well, and the ventral tegmental area (VTA) is also included in some models of the disorder.[8]

Because the CSTC pathway is highly associated with OCD and is activated via glutamatergic excitation[2], the neurotransmitter glutamate has emerged as a molecule of interest in treatment for the disorder. Glutamate is an excitatory neurotransmitter that plays a role in almost every neural system. It binds N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and increases the probability for neurons to fire, leading to its classification as excitatory.[5] The CSTC pathway's activity is impacted by NMDA receptors, so if overactivation of the CSTC pathway is associated with persistent OCD symptoms, glutamatergic agents that can reduce this activation are a promising avenue for treatment. The primary drugs with this ability are NMDA receptor antagonists, including compounds like ketamine, memantine, and amantadine.[5] These molecules block NMDA receptors, which prevents glutamate-triggered activation.

However, using NMDA receptor antagonists as an OCD treatment is not only a theoretical idea: while research on the impact of NMDA receptor antagonists on OCD is not extensive, many studies have shown promising results. A 2022 systematic review of NMDA receptor antagonist treatment for OCD found that 80% of the reviewed ketamine studies lead to significant improvement in symptoms, and success was seen with several memantine and amantadine treatment studies as well. Doubts remain about whether these drugs can fully alleviate symptoms, but reduction of symptoms was observed. The reviewers noted that ketamine was effective specifically in non-refractory cases—cases that were not treatment-resistant, leaving questions about whether refractory cases would see the same benefits.[1]

A growing subfield of psychiatry is computational psychiatry, which uses simulations and models to characterize mental disorders and compare these dynamics to clinical observations. Dynamical systems modeling has allowed researchers to draw connections between activity in different brain regions involved in OCD, revealing links that may not have previously been considered. In addition, modeling like this allows theoretical frameworks to be used to make predictions about treatments that haven't yet been tested clinically.[10]

The dynamics of an "OCD brain" can be visualized in this way with models that consider different connectivity levels and relationships between involved brain regions. In "A mathematical model of reward and executive circuitry in obsessive compulsive disorder", published in the *Journal of Theoretical Biology* in 2016, researchers Rădulescu and Marra propose a model to describe the dynamics of several brain regions thought to be involved in OCD symptoms, including the CSTC/CBGTC pathway.[8] Their model also takes into account the amygdala and hippocampus (limbic areas) and other related dopamine pathways. The connections between nodes in the model are modulated by variables representing excitation, inhibition, and strength of dopaminergic connections. (Table 1)

Rădulescu and Marra tested several hypotheses in their work, each hypothesis focused on the impact of a different parameter on the overall system dynamics. Through simulation of different parameters, they identified three main possible behaviors of the system, categorized by activity levels in the amygdala and in the anterior cingulate cortex (ACC). These activity levels are related to the symptoms of OCD: high excitation in the amygdala represents a state of high anxiety caused by an obsession, and high excitation in the anterior cingulate cortex represents compulsive activity performed to alleviate anxiety.

The first possible system behavior was the obsessive-compulsive cycle. The system could be described as existing in obsessive-compulsive cycle, corresponding to pathological OCD symptoms, when it fell into persistent oscillations between high amygdala activity (obsessions) and high ACC activity (compulsions). The second possible system behavior was defined as "compulsive release." In this paradigm, the system did not oscillate, but instead came to a stable point where ACC activity remained high. This translated to sustained repetitive behavior that relieves anxiety but is still impairing to daily function— a state that many OCD sufferers find themselves in. The third behavior, where the system converged to a stable state with low amygdala and ACC activity, corresponded to a decrease in OCD symptoms and was labeled the control baseline by the researchers.

Changes in parameter values in the model led to transitions between these three behaviors. For example, an increase in the value of the parameter that represented the connectivity between the amygdala and the striatum caused the system to cross a Hopf bifurcation and go from the "control" behavior to the obsessive-compulsive cycle. This insight allowed them to hypothesize that increased connectivity between the amygdala and striatum corresponded with worsening OCD symptoms.

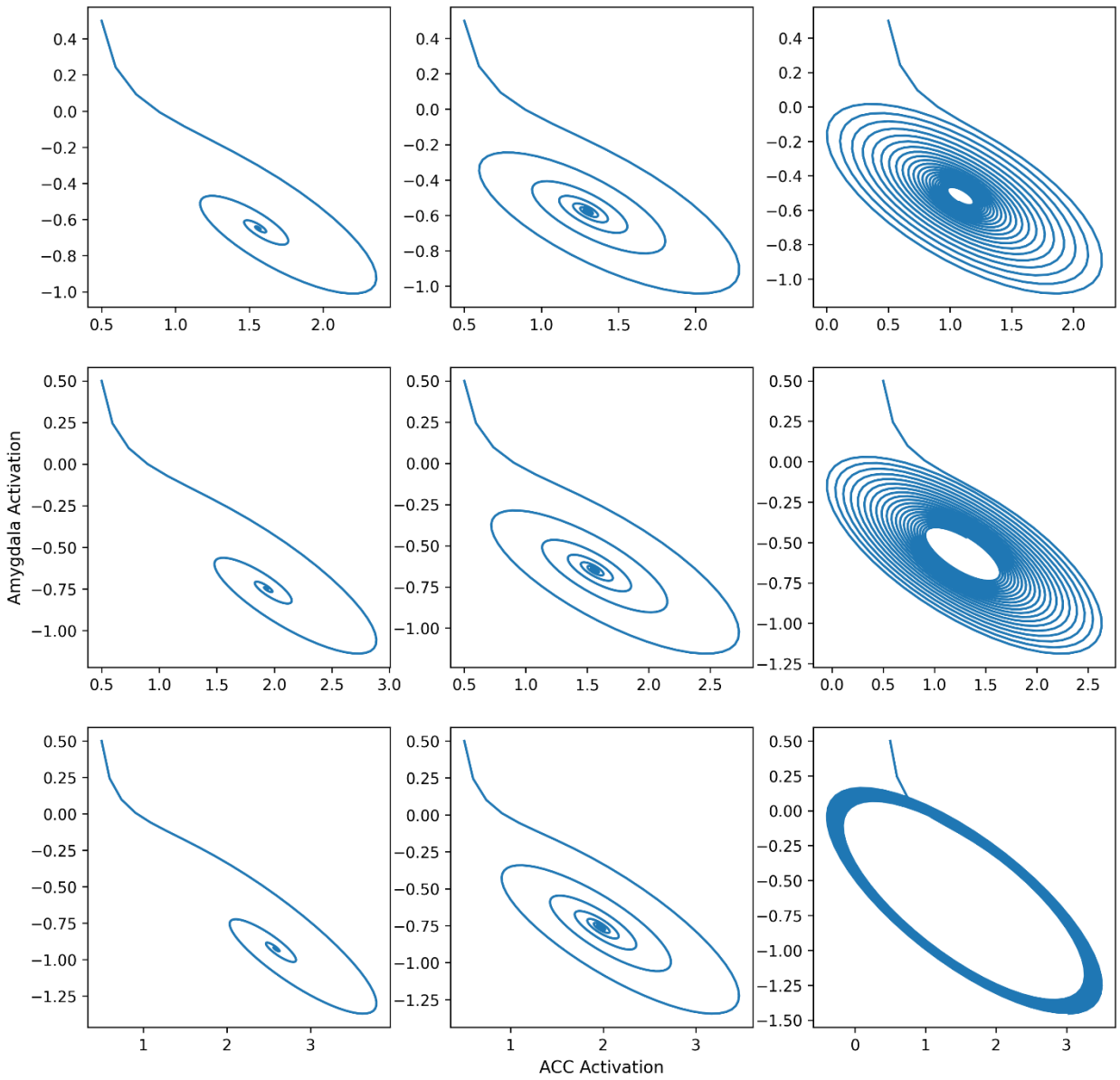

Figure 1. *a reproduction of figure 2 from Radulescu and Marra's paper, displaying phase plots between activity in the amygdala and activity in the ACC for different levels of connectivity between the orbitofrontal cortex and the striatum and between the angular cingulate cortex and the striatum. The rightmost column demonstrates obsessive-compulsive oscillation behavior. The left two graphs in the bottom row demonstrate the "compulsive release" behavior, while the left two graphs in the top row demonstrate the convergence to the control baseline.*

Although they explore the impact of several parameter modulations, the paper does not investigate the impact of changing the global glutamatergic excitation parameter, *m*. Because *m* is used in their model to simulate glutamate excitation throughout the entire system, it follows that a decrease in this parameter value would be a reasonable proxy to investigate the potential impact of an NMDA-receptor antagonist.

Methods:

Rădulescu and Marra's full model consists of six ordinary differential equations and two supplementary sigmoidal functions.

The system of equations represents the level of activation in six brain regions: the thalamus (T), the orbitofrontal cortex (O), the anterior cingulate cortex (C), the amygdala (A), the striatum (S), and the ventral tegmental area (δ). The influence of each node on others is modulated by coefficients. The coefficient *m* represents global glutamatergic excitation, while the *n* represents global GABA inhibition and is negative to indicate downregulation. δ also represents dopaminergic modulation, as the ventral tegmental area (VTA) releases dopamine. δ is the only nonlinear regulator in the model. *nA, b1, b2,* and *a* are more specific parameters that represent the interactions between nodes of interest (Table 1)

$$\frac{dO}{dt} = -nO + mA + mT + f_\mu(O, \delta)$$

$$\frac{d\mathrm{C}}{dt} = \mathrm{m}O - nC + mT + f_\mu(\mathrm{C}, \delta)$$

$$\frac{d\mathrm{A}}{dt} = -aO - aC + n_A A + mT + f_\mu(\mathrm{A}, \delta)$$

$$\frac{d\mathrm{T}}{dt} = \mathrm{m}O + m\mathrm{C} + m\mathrm{A} - nT + mS + f_\mu(\mathrm{T}, \delta) + 1$$

$$\frac{dS}{dt} = b_1 O + b_2 O + mT - nS - m\delta + f_\lambda(O, \delta)$$

$$\frac{d\delta}{dt} = m(O + C + A + T + S) - n\delta$$

$$f_\mu(X, \delta) = \frac{1}{e^{-\mu(X-\delta)} + 1} - \frac{1}{2}$$

$$f_\lambda(X, \delta) = \frac{1}{e^{-\lambda(X-\delta)} + 1} - \frac{1}{2}$$

O	orbitofrontal cortex
C	anterior cingulate cortex
A	amygdala
T	thalamus
S	ventral striatum / nucleus accumbens
δ	dopamine / ventral tegmental area
n	network-wide inhibition level
m	network-wide excitation level
μ	dopamine sensitivity level
λ	nucleus accumbens dopamine sensitivity
n_A	amygdala self-inhibition
a	amygdala inhibition by cortex
b_1	striatum excitation by orbitofrontal cortex
b_2	striatum excitation by amygdala

***Table 1**. parameter definitions*

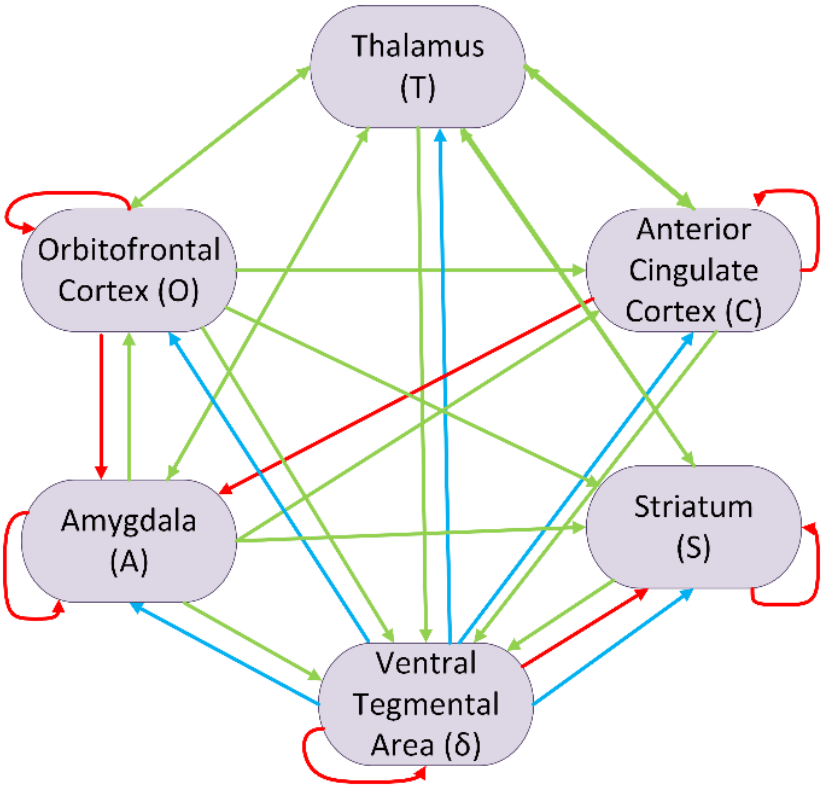

***Figure 2.** Representation of brain circuit model, adapted from Rădulescu and Marra's paper. Nodes represent the brain regions included in the model, and connecting arrows represent the effects of each region on the activity of other regions, including dopaminergic (blue), glutamatergic (green) and GABA (red) modulation*

For the sake of simplicity, this model was constructed under a few limiting assumptions: first, only six brain regions were included in the model. Second, the relationships between nodes were almost always approximated linearly. This meant that in the model, an increase in one node's activity would linearly increase the activity in a connected node. However, this is an oversimplification of how biological systems work. The only nonlinear terms in the model were dopaminergic connections, which were modulated by the sigmoidal functions, f_λ and f_μ. Another assumption was the specific parameter values used and the initial conditions of the model. Because of the theoretical nature of the work, however, these two assumptions were less consequential. The main source of information was the overall behavior of the system, not the precise values of parameters.

To analyze the impact of changing the parameter *m* on the system dynamics, the system of equations was represented computationally using Python.

```python
# sigmoidal function that represents dopamine modulation on all areas of network
def f_mu(X, delta, pars):
    return (1/(np.exp(-pars['mu']*(X-delta))+1)) - 0.5

# sigmoidal function that represents dopamine modulation specifically on nucleus accumbens
def f_lambda(X, delta, pars):
    return (1/(np.exp(-pars['lambda']*(X-delta))+1)) - 0.5

def network(x, t, pars):
    O, C, A, T, S, delta = x
    # dO/dt = -nO + mA + mT + f_mu(O, delta)
    dO_dt = -pars['n']*O + pars['m']*A + pars['m']*T + f_mu(O,delta,pars)
    # dC/dt = mO - nC + mT + f_mu(C, delta)
    dC_dt = pars['m']*O - pars['n']*C + pars['m']*T + f_mu(C,delta,pars)
    # dA/dt = -aO - aC - n_A*A + mT + m*delta + f_mu(A, delta)
    dA_dt = -pars['a']*O - pars['a']*C - pars['nA']*A + pars['m']*T + pars['m']*delta + f_mu(A,delta,pars)
    # dT/dt = mO + mC + mA - nT + mS + f_mu(T, delta) + 1
    dT_dt = pars['m']*O + pars['m']*C + pars['m']*A - pars['n']*T + pars['m']*S + f_mu(T,delta,pars) + 1
    # dS/dt = b1*O + b2*A + mT - nS - m*delta + f_lambda(S, delta)
    dS_dt = pars['b1']*O + pars['b2']*A + pars['m']*T - pars['n']*S - pars['m']*delta + f_lambda(S,delta,pars)
    # ddelta/dt = m(O + C + A + T + S) - n*delta
    ddelta_dt = pars['m']*(O + C + A + T + S) - pars['n']*delta
    return (dO_dt, dC_dt, dA_dt, dT_dt, dS_dt, ddelta_dt)
```

Figure 3. *Programmatic representation of the system of differential equations*

The following base connectivity parameter values and initial conditions were used:

μ	0.1
λ	0.1
n_A	1.4
n	2
b_1	1
b_2	1.2
a	1.2
m	1

O	0.5
C	0.5
A	0.5
T	0.5
S	0.5
δ	0.5

Table 2a. *(left), connectivity parameter values*
Table 2b. *(right) node parameter values*

These parameter values were chosen from the prior work of Rădulescu and Marra as a combination of parameters that was known to lead to obsessive-compulsive cycle behavior (the bottom left panel of Figure 1). This parameter selection was made to mimic a clinical patient who would take NMDA receptor antagonists.

Results:

Using the aforementioned parameter values from Tables 2a and 2b, the system of equations was integrated over 200 timesteps using the SciPy `integrate` function, first with $m = 1$ to recreate the obsessive-compulsive dynamics, and then with $m = 0.95$ and $m = 0.8$ to mimic the effect of decreased glutamatergic excitation caused by the administration of an NMDA-receptor antagonist.

The results were visualized by plotting both ACC and amygdala activation as a function of time over 100 timesteps, and by constructing phase plots of ACC vs. amygdala activation over all 200 timesteps. This provided a clear visualization of the oscillatory vs. stabilizing dynamics for different values of m.

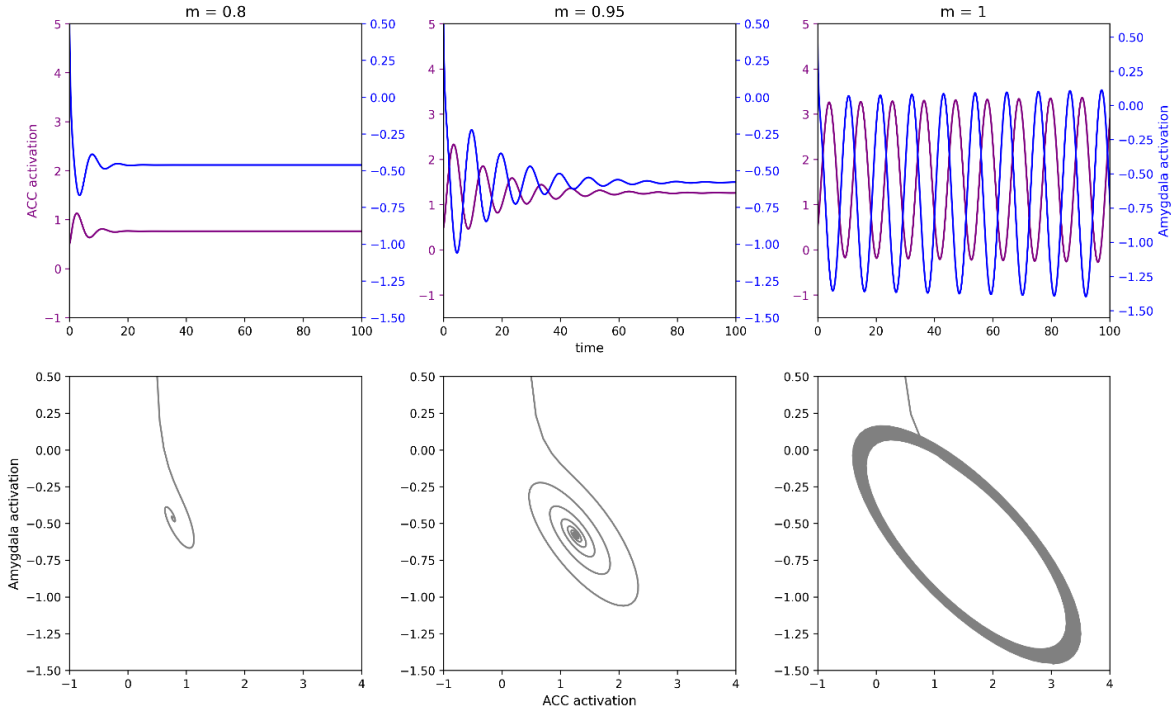

Figure 4. *Effect of changing* m *parameter on system dynamics, visualized both as a function of time over 100 timesteps (row 1) and in amygdala/ACC phase space over 200 timesteps (row 2)*

While the original (control) m value of 1 led to obsessive-compulsive oscillations that did not decrease in amplitude over the time period of the simulation, m values of 0.95 and 0.8 led to significantly different dynamics. Both $m = 0.8$ and $m = 0.95$ yielded eventual stabilization of the system, with stabilization occurring more rapidly with the lower value of m. Intriguingly, the stable state when $m = 0.8$ had slightly higher activation in the amygdala than the stable state when $m = 0.95$, while the final ACC activation was lower when $m = 0.8$ than when $m = 0.95$. More analysis should be done to determine if this aligns with clinical observations of patients.

However, the primary takeaway from this analysis was that in this model, small decreases in the value of m quickly changed the dynamics from oscillatory to convergent.

To better evaluate the sensitivity of this parameter, further analysis was done, keeping all other parameters the same but increasing the simulation time to 500 and observing the dynamics for even more slight changes in the value of *m*. Once again, ACC and amygdala were plotted as a function of time for a clear visualization.

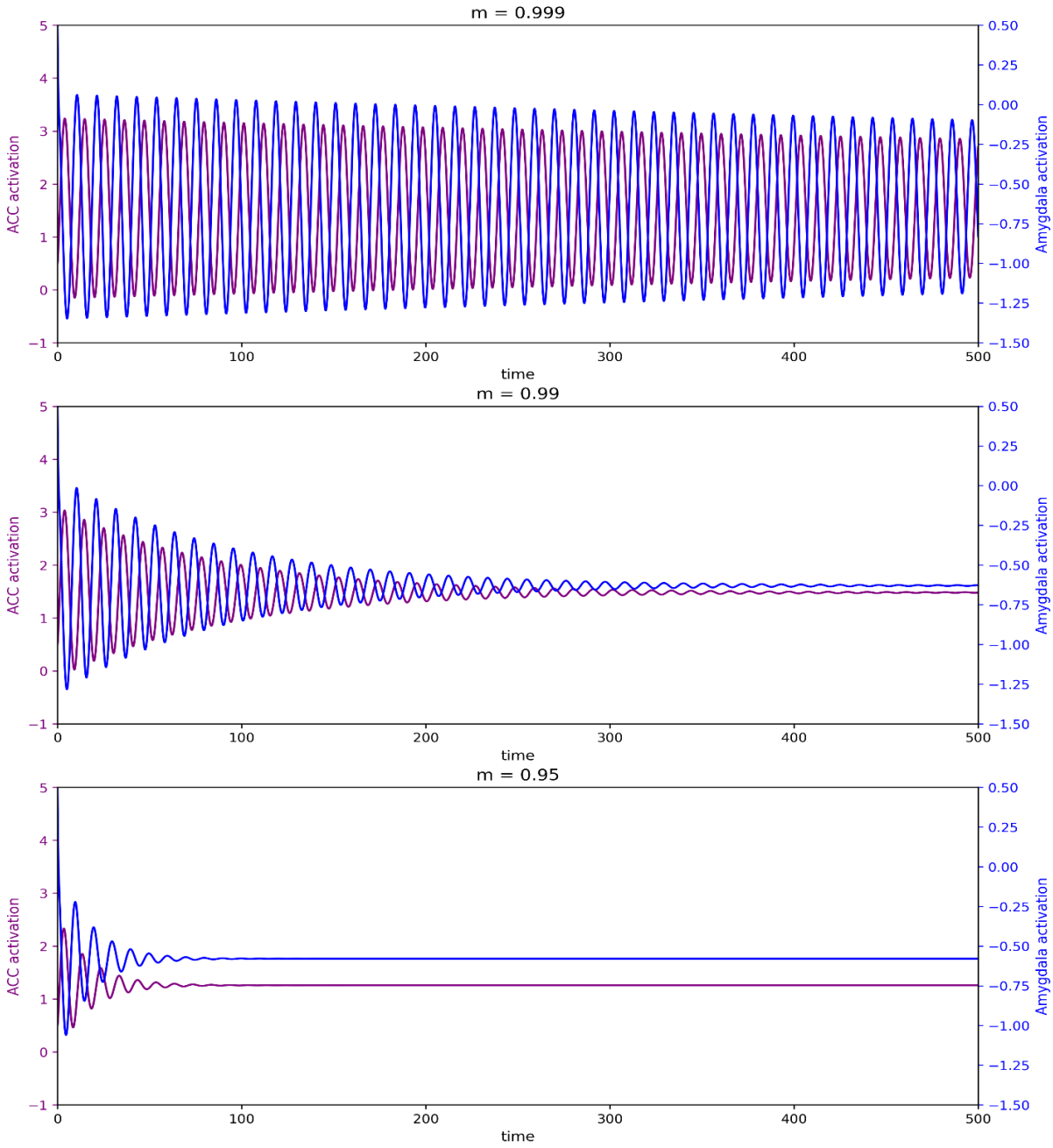

Figure 4. *ACC and Amygdala activity as a function of time for a simulation length of 500 and 3 different values of m: m = 0.999, m = 0.99, and m = 0.95*

Discussion:

The results of this analysis indicate that according to this model, a decrease in global glutamatergic excitation leads to cessation of obsessive-compulsive dynamics symptoms corresponding with pathology. This validates theoretical predictions about the role of glutamate overexcitation in OCD, suggests that medications that reduce glutamate activation, like NMDA receptor antagonists, are a potential treatment for this mental illness, and aligns with early clinical studies that showed reduction in symptoms after treatment with NMDA receptor antagonists.

However, it should be more thoroughly studied before definitive conclusions can be made. More detailed analysis on this extended model, such as Hopf bifurcation analysis and sensitivity analysis given different initial conditions and other parameter values, should be performed. More nonlinearity should be incorporated into the representations of neural connectivity, as linear connections were a large assumption made in this model.

Future work entails constructing generally more detailed models that consider intricate brain dynamics, and extending other existing models to determine whether they agree with the results found here. fMRI data should be used to inform the development of additional models, and tractability can be maintained by increasing the detail of models but decreasing their scope. Additionally, results from modeling should be integrated into a broader context of clinical trials and results. While these results are positive, their theoretical nature makes it difficult to make definitive conclusions about clinical treatments. Nonetheless, they provide insight into an avenue of OCD treatment research that deserves attention.

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