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

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Overview

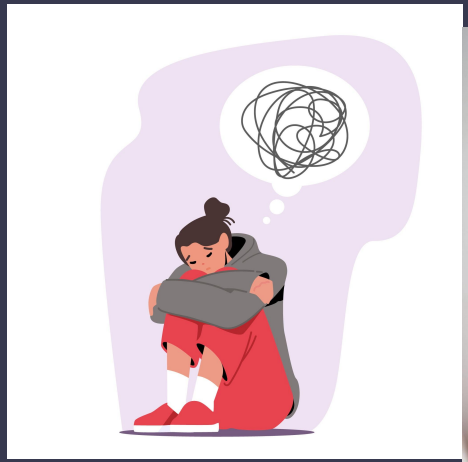
- Obsessive-Compulsive Disorder (OCD) = common and debilitating mental illness
- Current treatments not fully effective
- NMDA-receptor antagonists = a potential new treatment
- **Dynamical systems can be used to make predictions about how treatments may affect symptoms**

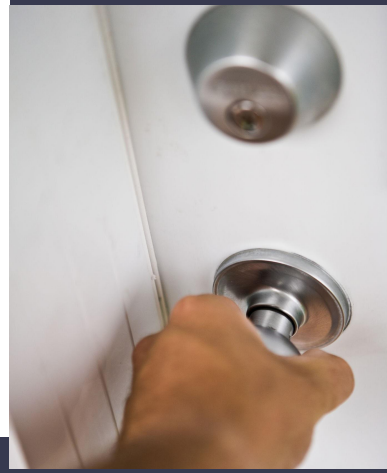
Obsessive-Compulsive Disorder (OCD)

Obsessions – recurrent unwanted thoughts that provoke anxiety

Compulsions – repetitive actions performed to alleviate the anxiety

→ self-reinforcing loop





Neurobiological Underpinnings and Current Treatments

- **Cortico-Striato-Thalamo-Cortical Pathway (CSTC)** → motivation and behavior
- Limbic Areas like **Amygdala** → fear and anxiety

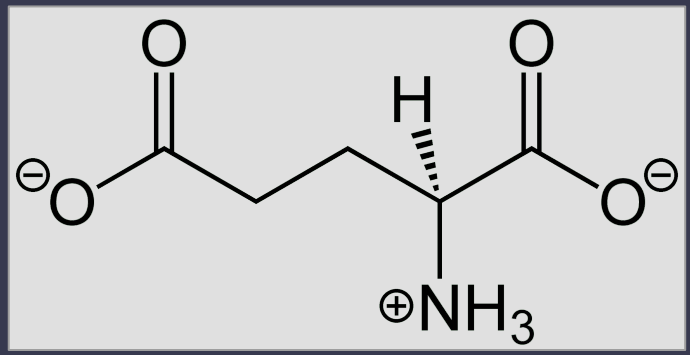
- Current treatments: Cognitive Behavioral Therapy (CBT), Exposure and Response Prevention (ERP) therapy and/or SSRIs
  - Not always effective in alleviating all symptoms

Glutamate: Neurotransmitters

Glutamate: most common neurotransmitter in the brain

- Binding to **NMDA receptors** causes neurons to fire

Glutamatergic overexcitation in the CSTC is linked to OCD symptoms



NMDA Receptor Antagonists

- Drugs that bind to NMDA receptors, blocking their activation
  - E.g. Ketamine, Memantine
- Associated with decrease in glutamate activation

→ effective for OCD?

Prior Work – Radulescu and Marra

- Paper: “A Dynamical Systems Model of Reward and Executive Circuitry in Obsessive-Compulsive Disorder” (2016)
- Dynamical systems model described interactions between 6 brain regions thought to be involved in OCD
- Visualized obsessive-compulsive loop as oscillations between high amygdala activation and high anterior cingulate cortex activation

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

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

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

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

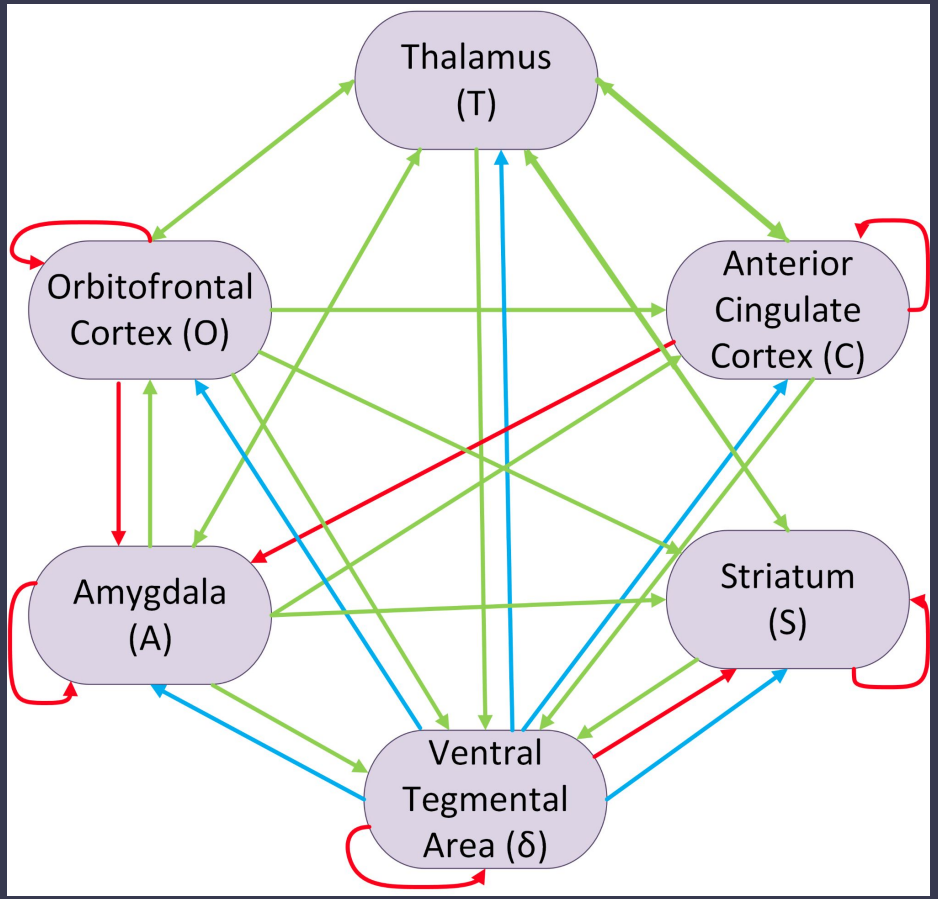
$$\frac{dS}{dt} = b_1 O + b_2 O + mT - nS - m\delta + f_\lambda(O, \delta)$$

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

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

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

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



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

$$\frac{dC}{dt} = mO - nC + mT + f_\mu(C, \delta)$$

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

$$\frac{dT}{dt} = mO + mC + mA - nT + mS + f_\mu(T, \delta) + 1$$

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

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

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

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

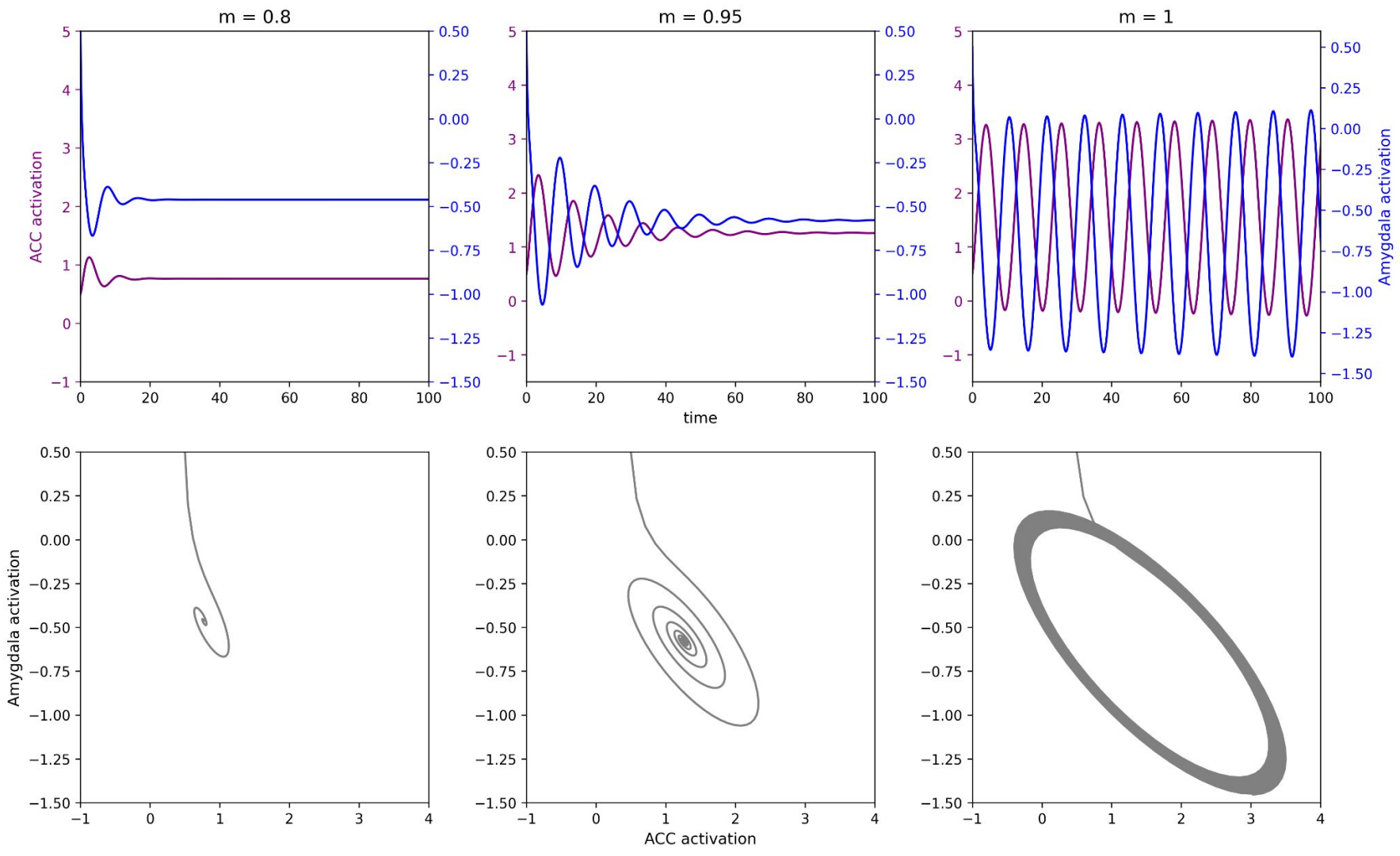
Their Results

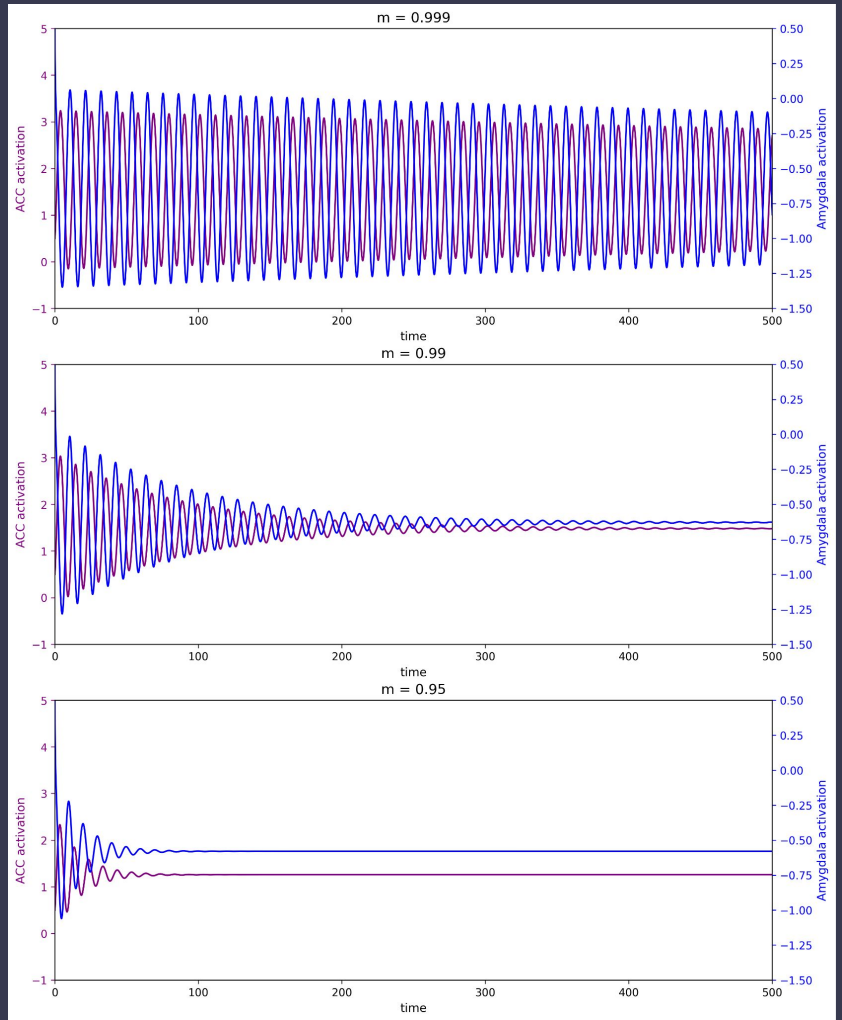
From analyzing different parameter combinations, they observed three main system states:

1) **Obsessive-compulsive cycle** (oscillations between high amygdala and high ACC)
2) **Compulsive release** (convergence to steady state with low amygdala, high ACC)
3) **Control** (convergence to steady state with low amygdala and low ACC)

My Extension: Simulating NMDA receptor antagonist

- m = global glutamate excitatory control in their model
- Observe impact of decreased m value to approximate effect of NMDA receptor antagonist


m = 0.8
m = 0.95
m = 1
ACC activation
Amygdala activation
time
Amygdala activation
ACC activation



Very slight changes in *m* lead to large differences in convergence time

Decreasing m → Decreasing oscillatory behavior

- Theoretical model = consistent with conjectures that glutamate overexcitation can contribute to OCD
  - Indicates that NMDA receptor antagonists are a path worth pursuing clinically
  - (in fact – some clinical studies have shown promising results!)

Future Work

- Hopf bifurcation analysis on this parameter change
- Adjustments to model to make it more biologically informed
  - Non-linear connections
  - Comparisons to fMRI
- More intricate/smaller scope models

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