Modeling the Effects of Dopamine Neurotransmitter and Receptor Prevalence on Basal Ganglia Cell Responses

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Introduction

- **Nucleus Accumbens**
  - Reward center of the brain within the basal ganglia. Contains dopaminergic receptors.

- **Schizophrenia & OCD - High Dopamine**
  - Increased dopamine receptors and neurotransmitters have been recorded in the nucleus accumbens and caudate nucleus of schizophrenic patients (1), and addition of a dopamine antagonist (blocking dopamine receptors) improves symptoms in OCD patients who do not respond to the typical serotonin-reuptake inhibitors (2).
  - Excess dopamine causes elevated levels of focus in OCD patients (2) and misdirected motivation in schizophrenic patients (1).

- **ADHD & Depression - Low Dopamine**
  - ADHD patients possess an allele called DRD2 A1, which prevents the appropriate expression of dopamine receptors (3), and levels of dopamine metabolite homovanillic acid in depressed patients point to decreased dopamine activity (4).
  - Lowering dopamine levels causes a lack of focus in ADHD patients (3) and low motivation in depressed patients (4).

- **Cell Types**
  - **D1 and D2**
    - Dopaminergic receptors in superfamily of G-protein coupled receptors. Reward regulation occurs when both are activated in a process called “requisite” D1/D2 synergism (5).
  - **Subthalamic Nucleus (STN) Neurons**
    - Involved in action selection and impulse control. When the STN region is disinhibited (not stopped from firing by the thalamus), involuntary motor movements occur (6).
  - **Fast spiking (FS) Neurons**
    - Inhibitory interneurons that are excited by dopamine (7). Deficit can cause involuntary muscle movements (8).
  - **External and Internal Globus Pallidus (GPe and GPI)**
    - Regions that inhibit movement. Loss of dopamine contributes to some Parkinsonian symptoms, likely slowness and rigidity (9).

- Aimed to model the differences in basal ganglia cell activity in response to altered dopamine neurotransmitter and receptor levels that we might see in actual brains with one of these four conditions.

Method

- Utilized contracting basal ganglia model.
  - “daWeight” parameter represented levels of dopamine receptors and neurotransmitters.
  - Assuming severity of dopamine abundance or deficit, “daWeight” was set to 0.25, 0.5, 1.2, and 4, corresponding to depression, ADHDF, baseline activity, OCD, and schizophrenia respectively.
  - Graphs were generated, documented FS (fast spiking), D1, D2, STN (subthalamic nucleus), GPe (external globus pallidus), and GPI (internal globus pallidus) cell responses over time.
  - Graphs showcased the activity of six channels, each corresponding to an action primitive (basic, possible movements).

Results

- **Figure 1. D1 cell response at various daWeights**
  - Channel 1 activity decreases as daWeight decreases.
  - Channel 2 activity decreases at timestep 6000-8000 as daWeight decreases.
  - Channels 1 and 2 reach a maximum cell response as daWeight increases.
  - Same trends as D1, but no channel activity at .25 daWeight.

- **Figure 2. GPe cell response at various daWeights**
  - Channel 6 increases slightly with increasing daWeight and vice versa.
  - Channel 1 increases on timestep 2000-4000 and 4000-6000 at .5 daWeight.
  - Overall, cell response decreases as daWeight increases.
  - Same trends as GPe, but no lower cell response.

- **Figure 3. STN cell response at various daWeights**
  - Channel 6 does not change.
  - Channel 1 cell response decreases slightly as daWeight decreases.
  - Channel 2 cell response decreases slightly at timestep 6000-8000 as daWeight decreases.
  - Channels 1 increases as daWeight increases.
  - Channel 2 increases overall as daWeight increases.

Discussion

- Generally, our results were consistent with the fact that dopamine elevation can cause schizophrenia and OCD symptoms while dopamine depletion can cause ADHD and depression symptoms.
  - However, there were some deviations from current studies:
    - The D1 and D2 cell response reached a maximum more easily than it reached a minimum, suggesting that illnesses caused by dopamine abundance may require similar treatments while those caused by dopamine deficiency may have more variability in potential medication.
    - Additionally, a deficit in FS interneurons has been discovered in Tourette patients, implying that the decreased inhibition causes their tics (8).

- Also, the increase of GPe and GPI cell activity in response to diminished dopamine levels is not consistent with observed ADHD symptoms like excitability and fidgeting. However, Channel 6 increases with increasing daWeight and vice versa, which is consistent with these observations. The globus pallidus is also connected to the STN, so increased cell activity in these regions may also inhibit action selection and cause the inability to focus (9).
  - Channel activity for GPe and GPI diminishes at 0.25 daWeight (and in GPI Channel 4 at 0.5 daWeight) even though it was projected to increase. A possible cause is that there are too few dopamine receptors at this daWeight for the system to evoke any response. As these daWeights correspond to depression and ADHD, this could suggest an error in assuming 0.25 and 0.5 daWeight levels of dopamine deficiency.

- Overall, the model has applications in discovering the causes of the four mental illnesses schizophrenia, OCD, ADHD, and depression and personalizing medication more effectively treat them.

References

3. Berke, J. D.; Gurney, K.; Prescott, T. J.; Redgrave, P.; and 4, corresponding to depression, ADHDF, baseline activity, OCD, and schizophrenia respectively.

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