

Break-up and Recovery of Harmony between Direct and Indirect Pathways in A Spiking Neural Network of The Basal Ganglia; Huntington's Disease and Treatment

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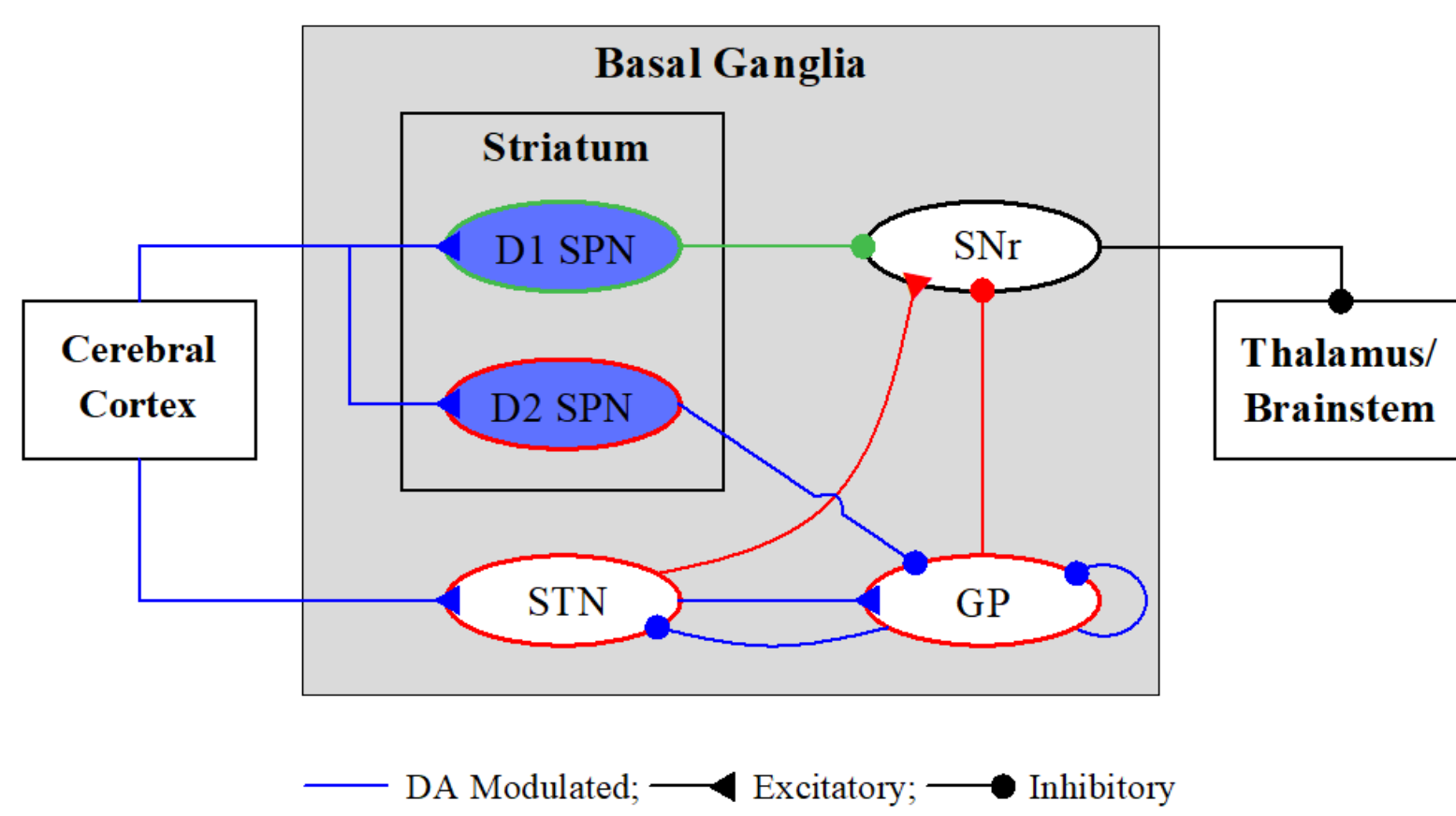
Introduction

- **Basal Ganglia (BG)**
 - A group of subcortical deep-lying nuclei ("dark basement" of the brain)
 - **A variety of functions for motor and cognition**
Control of voluntary movement and important roles in cognitive processes (e.g., action selection, motor planning)
- **Huntington's Disease (HD)**
 - **Dysfunction of BG** (neurodegenerative disease) with severe symptoms for motor, cognition, and emotion
 - Two Types of spine projection neurons (SPNs) with D1 and D2 receptors for the Dopamine (DA)
 - In the early stage of HD, degenerative loss of D2 SPNs occurs due to mutation in the huntingtin (HTT) gene, while DA level in the striatum is nearly normal.
- **Purpose of Our Study**
Quantitative analysis of break-up and recovery of harmony between direct and indirect pathways by using competition degree for the healthy and pathological states

Spiking Neural Network (SNN) of The BG

BG: a collection of subcortical nuclei
[DA (dopamine) modulated: green color]

- **Input Nuclei**
 - **Striatum** (principal input to the BG) spiny projection neurons (SPNs) with D1/D2 receptors for the DA
 - **STN** (subthalamic nucleus) only excitatory nucleus in the BG
- **Output Nuclei**
 - **SNr** (substantia nigra pars reticulata)
- **Intermediate Control Nucleus**
 - **GP** (globus pallidus external segment)

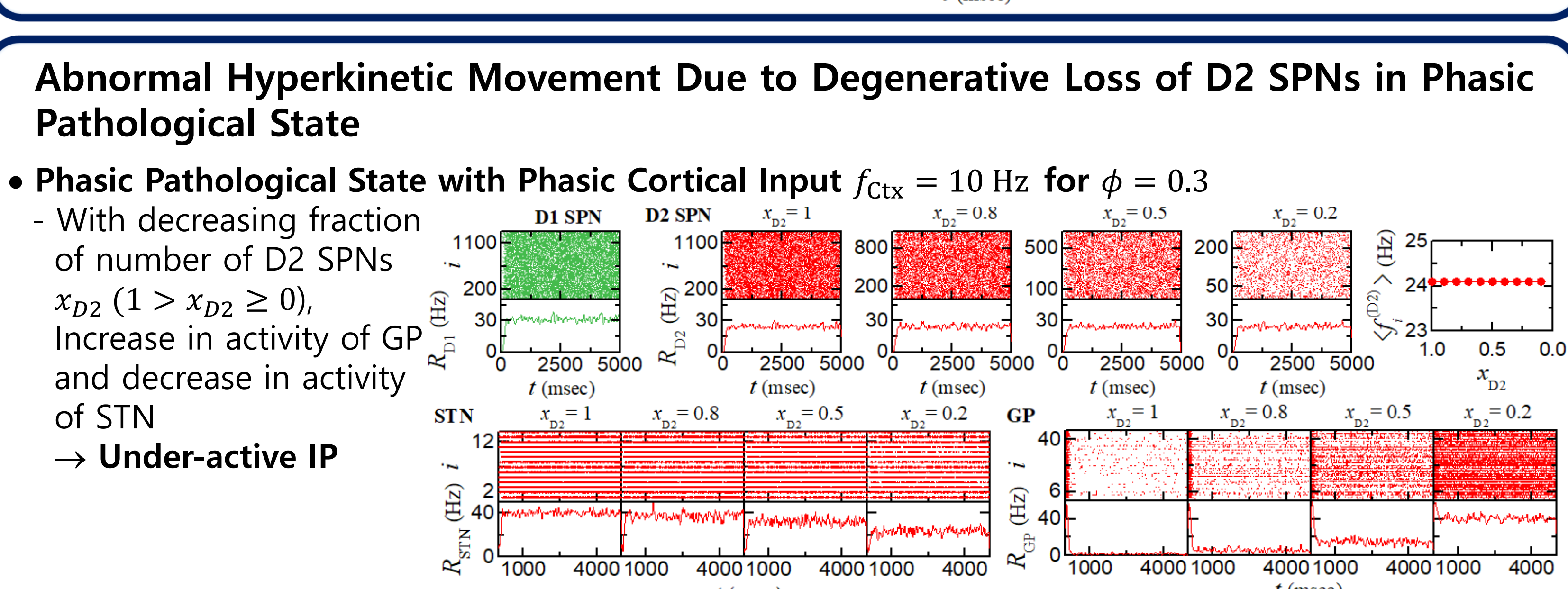


D1 SPNs project inhibition directly to the output nuclei SNr via the **direct ("GO") pathway (DP)**. On the other hand, D2 SPNs are connected to the SNr via the **indirect ("No-GO") pathway (IP)** crossing the GP and the STN.

BG: modulating and gating action selection via balance between the Go and No-Go pathways
→ action selection device (gearbox in an auto)

Involuntary Jerky Movement Due to Degenerative Loss of D2 SPNs in Tonic Pathological State

- **Tonic Pathological State with Tonic Cortical Input $f_{Ctx} = 3$ Hz for $\phi = 0.3$**
 - With decreasing fraction of number of D2 SPNs x_{D2} ($1 > x_{D2} \geq 0$), Increase in activity of GP and decrease in activity of STN
→ **Under-active IP**
- **Strengths of DP & IP Currents and Competition Degree**
 - With decreasing fraction of number of D2 SPNs, Decrease in $\mathcal{S}_{IP} \rightarrow$ Increase in $\mathcal{C}_d (= \mathcal{S}_{DP}/\mathcal{S}_{IP})$
 - Decrease in activity of SNr
 - Appearance of pathological states (where harmony between DP and IP is broken up) due to degenerative loss of D2 SPNs



Abnormal Hyperkinetic Movement Due to Degenerative Loss of D2 SPNs in Phasic Pathological State

- **Phasic Pathological State with Phasic Cortical Input $f_{Ctx} = 10$ Hz for $\phi = 0.3$**
 - With decreasing fraction of number of D2 SPNs x_{D2} ($1 > x_{D2} \geq 0$), Increase in activity of GP and decrease in activity of STN
→ **Under-active IP**
- **Strengths of DP & IP Currents and Competition Degree**
 - With decreasing fraction of number of D2 SPNs, Decrease in $\mathcal{S}_{IP} \rightarrow$ Increase in \mathcal{C}_d
 - Decrease in activity of SNr
 - Appearance of pathological states (where harmony between DP and IP is broken up) due to degenerative loss of D2 SPNs



Reference

- S.-Y. Kim and W. Lim, "Break-up and recovery of harmony between direct and indirect pathways in the basal ganglia; Huntington's disease and treatment," Cognitive Neurodynamics 18, 2909-2924 (2024)

Treatment of Tonic Pathological State by Strengthening IP

- **Strengthening IP via Activation of D2 SPN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(D2)*} = 262$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ ($=1$ for tonic healthy state) → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(D2)*} \rightarrow$ More $\Delta I_{ion}^{(D2)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Activation of STN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(STN)*} = 14$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(STN)*} \rightarrow$ More $\Delta I_{ion}^{(STN)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Deactivation of GP via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(GP)*} = -28$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $\Delta I_{ion}^{(GP)*} \rightarrow$ More negative $\Delta I_{ion}^{(GP)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Ablation of GP**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $x_{GP}^* \approx 0.78 \rightarrow \mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $x_{GP}^* \rightarrow$ More ablation (smaller x_{GP}) is necessary for recovery of harmony between DP & IP

Treatment of Phasic Pathological State by Strengthening IP

- **Strengthening IP via Activation of D2 SPN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(D2)*} = 1,636$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ ($=2.82$ for phasic healthy state) → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(D2)*} \rightarrow$ More $\Delta I_{ion}^{(D2)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Activation of STN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(STN)*} = 405$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(STN)*} \rightarrow$ More $\Delta I_{ion}^{(STN)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Deactivation of GP via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $\Delta I_{ion}^{(GP)*} = -540$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $\Delta I_{ion}^{(GP)*} \rightarrow$ More negative $\Delta I_{ion}^{(GP)*}$ is necessary for recovery of harmony between DP & IP
- **Strengthening IP via Ablation of GP**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in \mathcal{C}_d
 $x_{GP}^* \approx 0.52 \rightarrow \mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $x_{GP}^* \rightarrow$ More ablation (smaller x_{GP}) is necessary for recovery of harmony between DP & IP

Summary

- **Basal Ganglia (BG)**
 - A group of subcortical nuclei exhibiting a diverse of functions for motor and cognition
 - Huntington's disease (HD): motor and cognition deficits
 - In the early stage of HD, degenerative loss of D2 SPNs occurs due to mutation in the huntingtin (HTT) gene, while DA level in the striatum is nearly normal.
- **Quantifying Competitive Harmony between "Go" Direct Pathway (DP) and "No-Go" Indirect Pathway (IP)**
 - Competition degree $\mathcal{C}_d (= \mathcal{S}_{DP}/\mathcal{S}_{IP})$: Ratio of strength of DP (\mathcal{S}_{DP}) to strength of IP (\mathcal{S}_{IP})
 - Default BG state: $\mathcal{C}_d \approx 1 \rightarrow$ DP and IP are nearly balanced
→ Locked state of BG gate to the thalamus → No voluntary movement
 - Phasically-active healthy state: $\mathcal{C}_d = 2.82 \rightarrow$ DP is 2.82 times stronger than IP
→ Opened state of BG gate to the thalamus → Normal movement
- **Pathological State and Treatment**
 - Pathological state: Decrease in number of D2 SPNs
→ Decrease in increase in activity of GP and decrease in activity of STN → **Under-active IP**
 - Treatment of pathological state
Strengthening IP via Activation of D2 SPN & STN, Deactivation of GP, or Ablation of GP
→ Decrease in $\mathcal{C}_d \rightarrow$ Harmony between DP & IP is recovered