

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

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Introduction

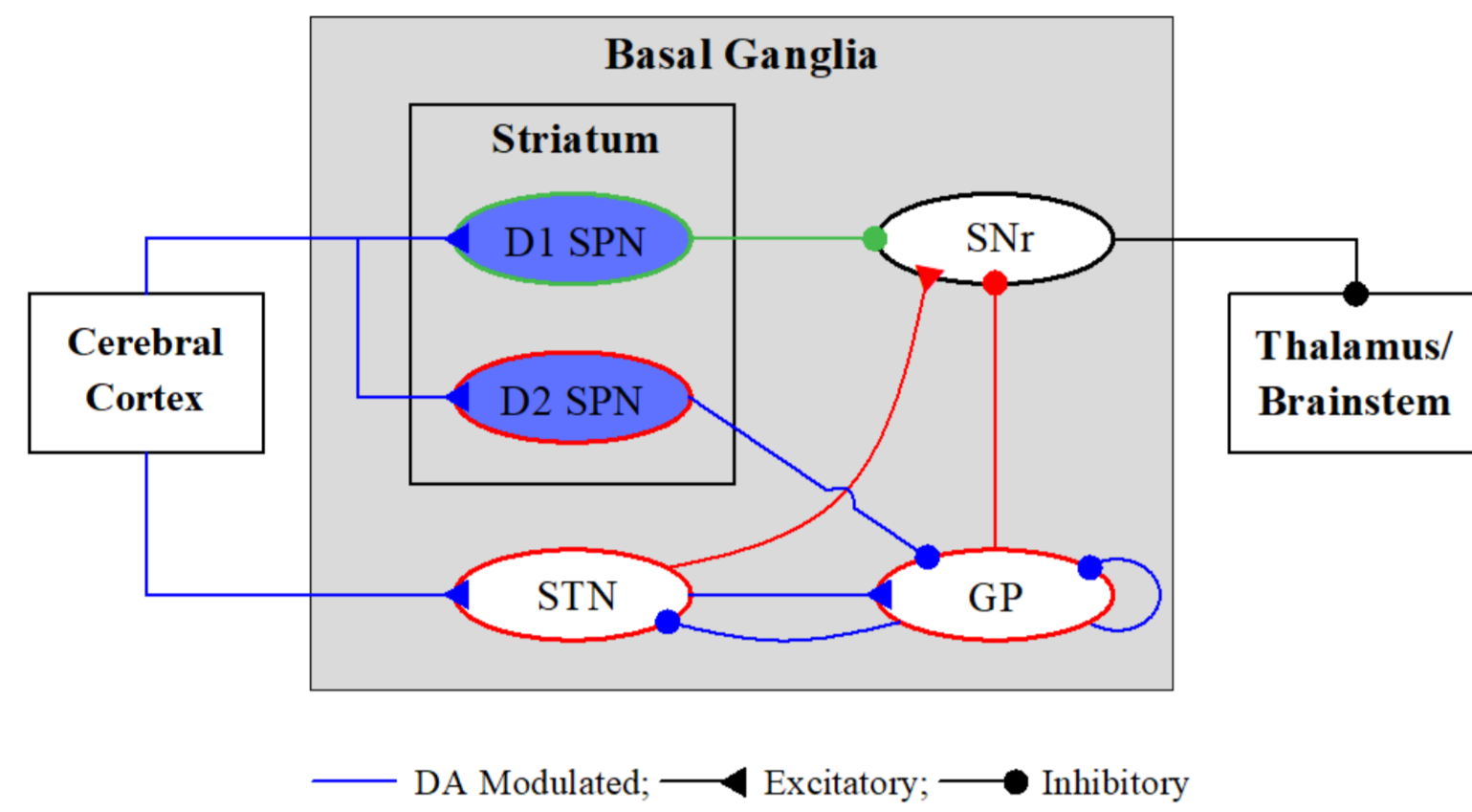
- Basal Ganglia (BG)**
A group of subcortical deep-lying nuclei ("dark basement" of the brain)
- A variety of functions for motor and cognition
- Control of voluntary movement and important roles in cognitive processes (e.g., action selection, motor planning)

- 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 modulated: green color]



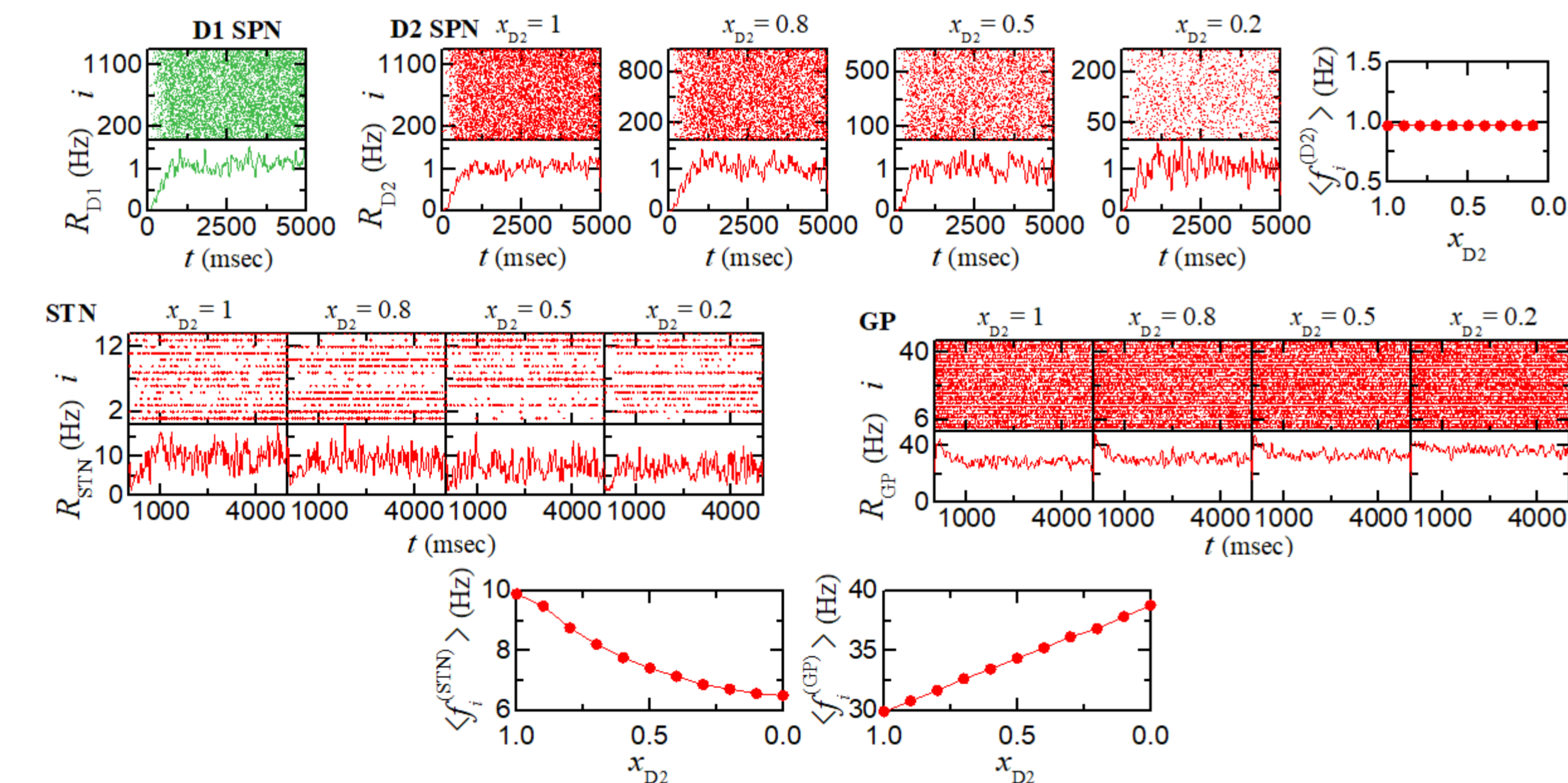
- Input Nuclei**
- Striatum (principal input to the BG) spiny projection neurons (SPNs) with D1/D2 receptors for the DA
- STN (subthalamic nucleus) only excitatory nucleus in the BG
- Output Nuclei**
- SNr (substantia nigra pars reticulata)
- Intermediate Control Nucleus**
- GP (globus pallidus external 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} ($1 > x_{D2} \geq 0$),
Decrease in increase in activity of GP and decrease in activity of STN → **Under-active IP**

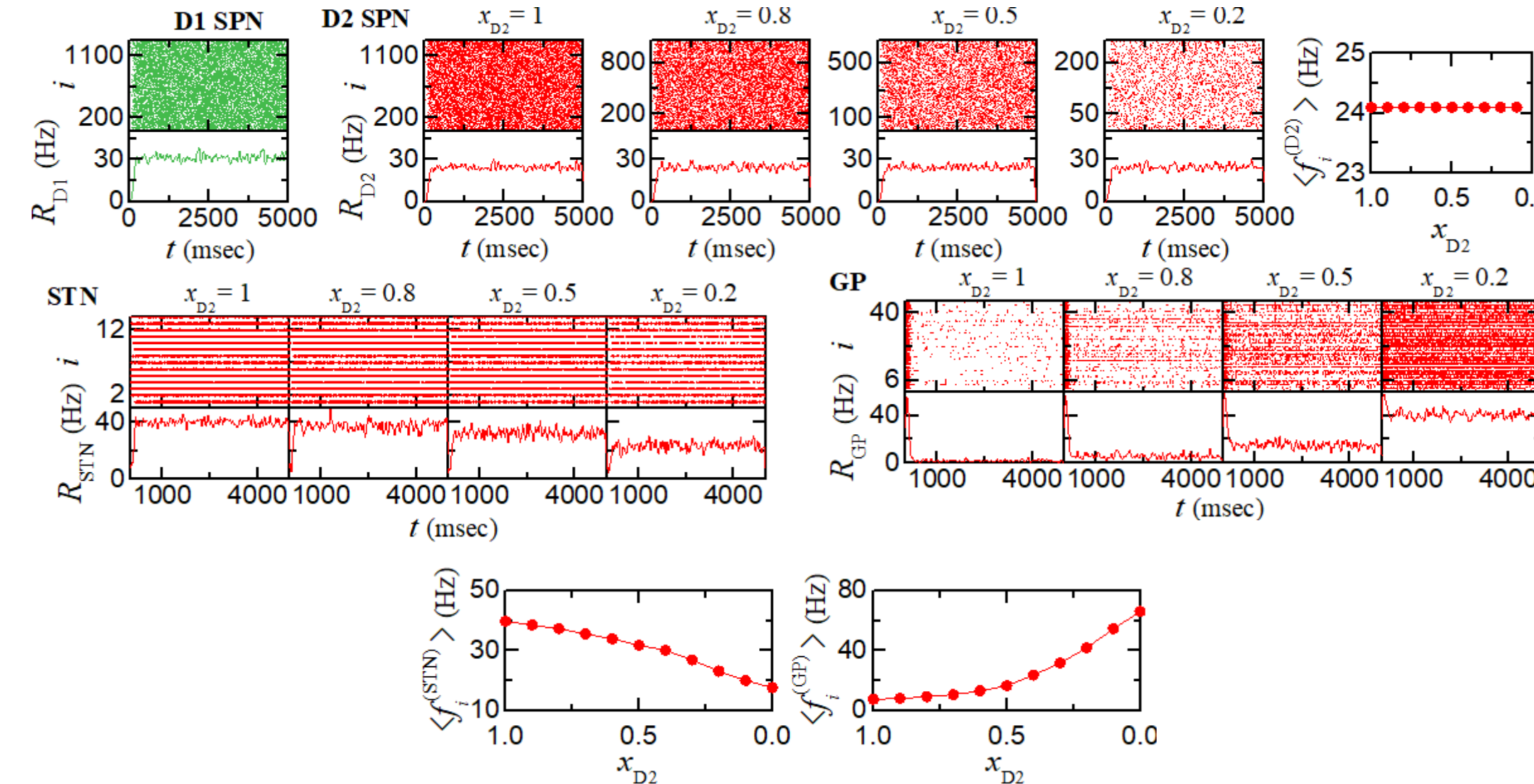


Strengths of DP & IP Currents and Competition Degree

- With decreasing fraction of number of D2 SPNs, Decrease in s_{IP} → Increase in 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 D2SPNs
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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} ($1 > x_{D2} \geq 0$),
Decrease in increase in activity of GP and decrease in activity of STN → **Under-active IP**

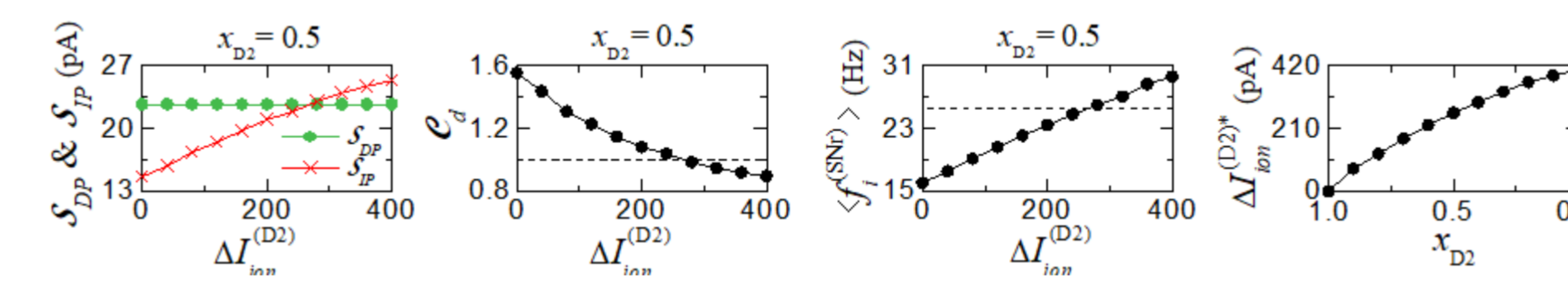


Strengths of DP & IP Currents and Competition Degree

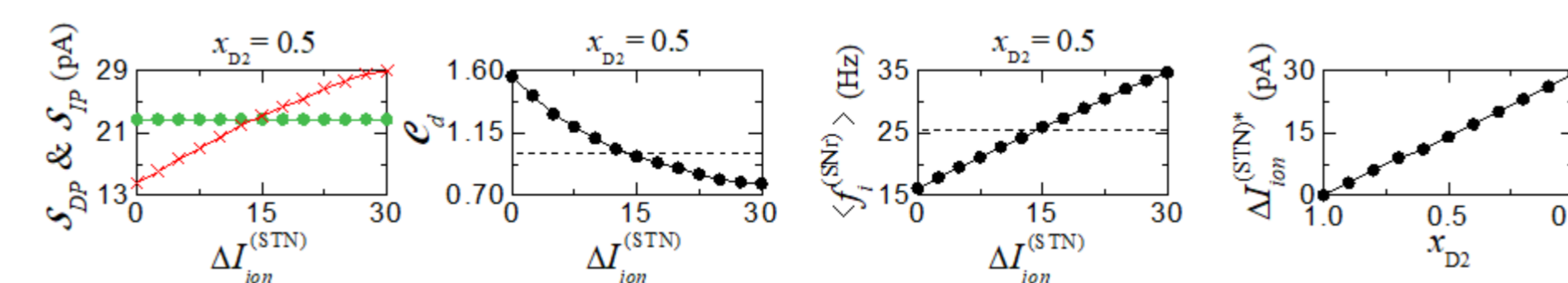
- With decreasing fraction of number of D2 SPNs, Decrease in s_{IP} → Increase in C_d
 - Decrease in activity of SNr
 - Appearance of pathological states (where harmony between DP and IP is broken up) due to degenerative loss of D2SPNs
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Treatment of Tonic Pathological State by Strengthening IP

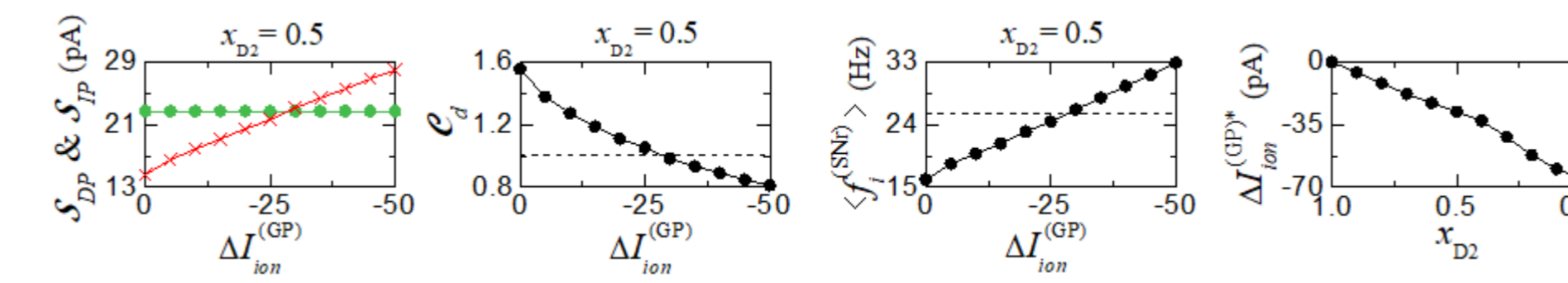
- Strengthening IP via Activation of D2 SPN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in C_d
 $\Delta I_{ion}^{(D2)*} = 262$ pA → $C_d = C_d^*$ ($=1$ for tonic healthy state) → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(D2)*}$
→ More $\Delta I_{ion}^{(D2)*}$ is necessary for recovery of harmony between DP & IP



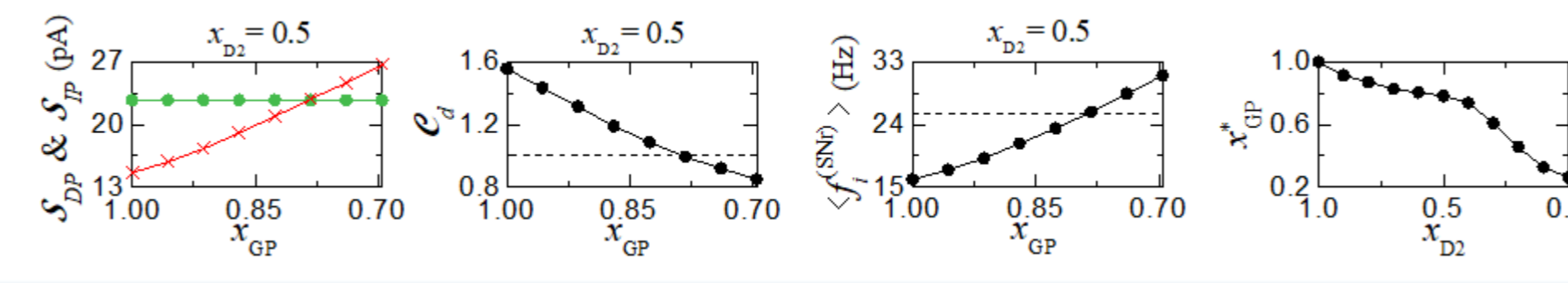
- Strengthening IP via Activation of STN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in C_d
 $\Delta I_{ion}^{(STN)*} = 14$ pA → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(STN)*}$
→ More $\Delta I_{ion}^{(STN)*}$ is 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 C_d
 $\Delta I_{ion}^{(GP)*} = -28$ pA → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $\Delta I_{ion}^{(GP)*}$
→ More negative $\Delta I_{ion}^{(GP)*}$ is necessary for recovery of harmony between DP & IP



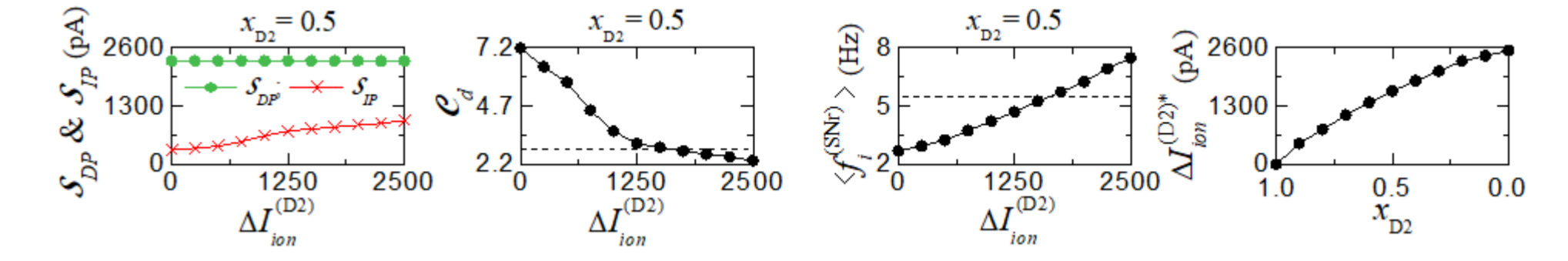
- Strengthening IP via Ablation of GP**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in C_d
 $x_{GP} \approx 0.78$ → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in x_{GP}
→ More ablation (smaller x_{GP}) is necessary for recovery of harmony between DP & IP



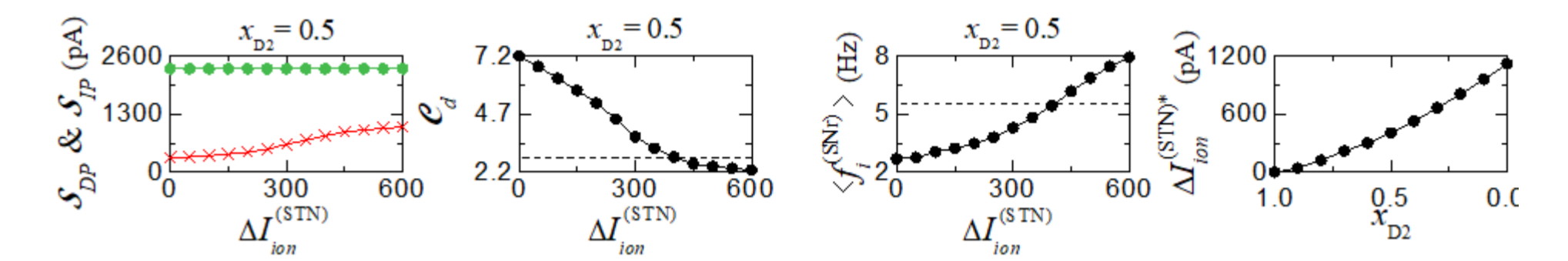
Treatment of Phasic Pathological State by Strengthening IP

- Strengthening IP via Activation of D2 SPN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in C_d
 $\Delta I_{ion}^{(D2)*} = 1,636$ pA → $C_d = C_d^*$ ($=2.82$ for phasic healthy state)
→ Harmony between DP & IP is recovered

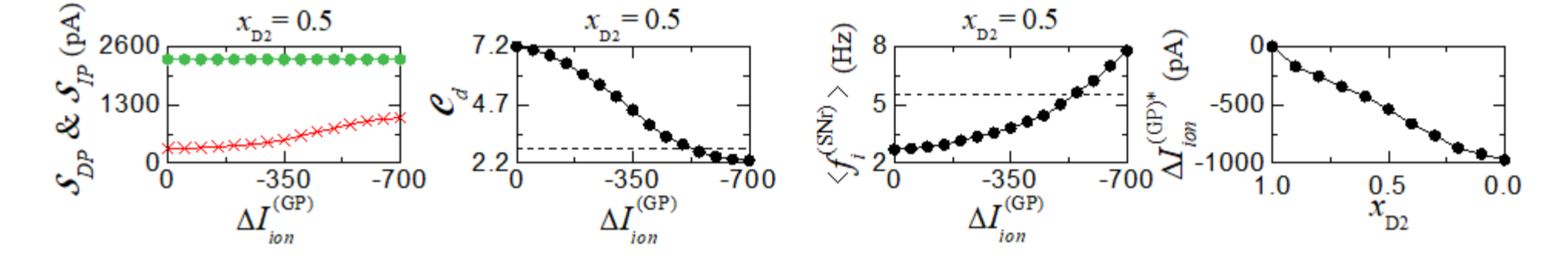
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(D2)*}$
→ More $\Delta I_{ion}^{(D2)*}$ is necessary for recovery of harmony between DP & IP



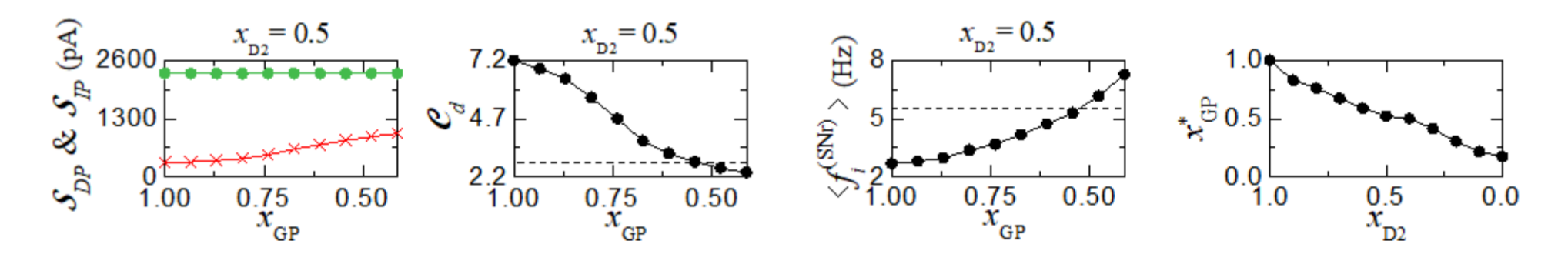
- Strengthening IP via Activation of STN via Optogenetics**
For $x_{D2} = 0.5$, Strengthened IP → Decrease in C_d
 $\Delta I_{ion}^{(STN)*} = 405$ pA → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, increase in $\Delta I_{ion}^{(STN)*}$
→ More $\Delta I_{ion}^{(STN)*}$ is 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 C_d
 $\Delta I_{ion}^{(GP)*} = -540$ pA → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in $\Delta I_{ion}^{(GP)*}$
→ 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 C_d
 $x_{GP} \approx 0.52$ → $C_d = C_d^*$ → Harmony between DP & IP is recovered
As x_{D2} is decreased, decrease in x_{GP}
→ 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 $C_d (= s_{DP}/s_{IP})$: Ratio of strength of DP (s_{DP}) to strength of IP (s_{IP})
- Tonic healthy BG state: $C_d \approx 1$ → DP and IP are nearly balanced
→ Locked state of BG gate to the thalamus → No voluntary movement
- Phasically-active healthy state: $C_d = 2.82$ → 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 C_d → Harmony between DP & IP is recovered