Advancing Closed-Loop Epidural Electrical Stimulation for Gait Deficits in Parkinson's Disease

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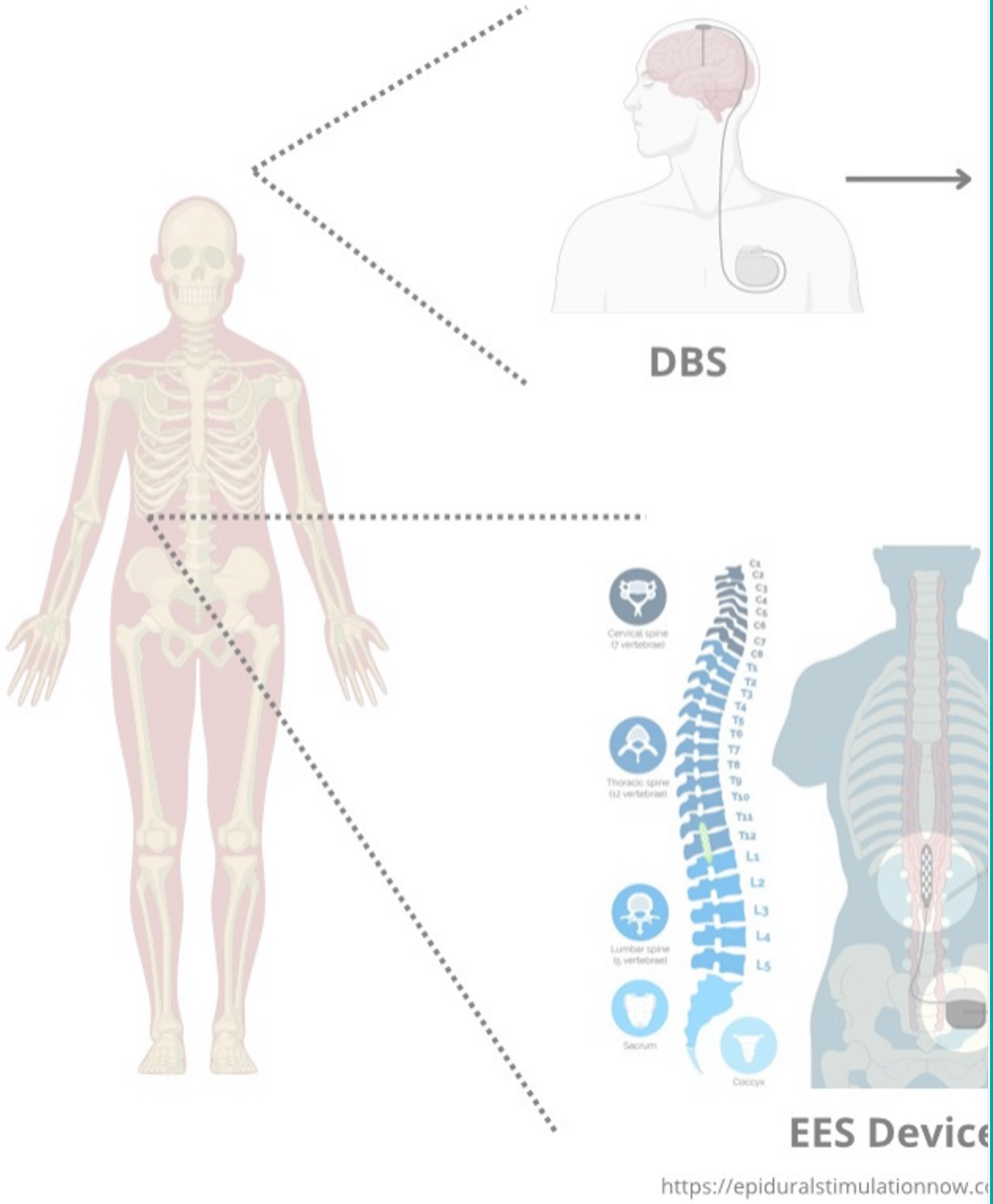
(Mizrahi-Kliger & Ganguly et al., 2023)



Summary

Background

Motivation and Proposed Solution

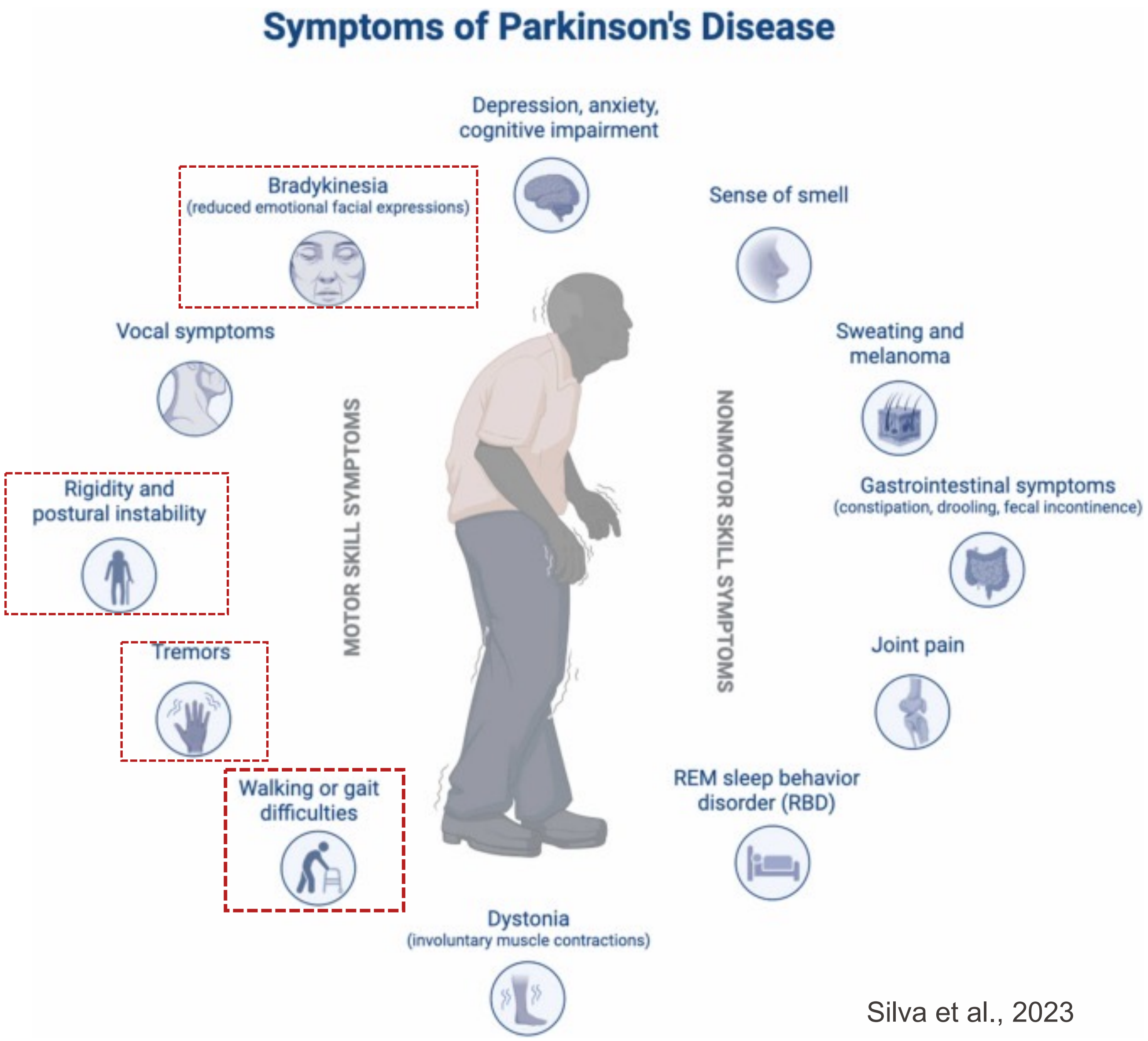
Technical

Clinical Translation

Limitations

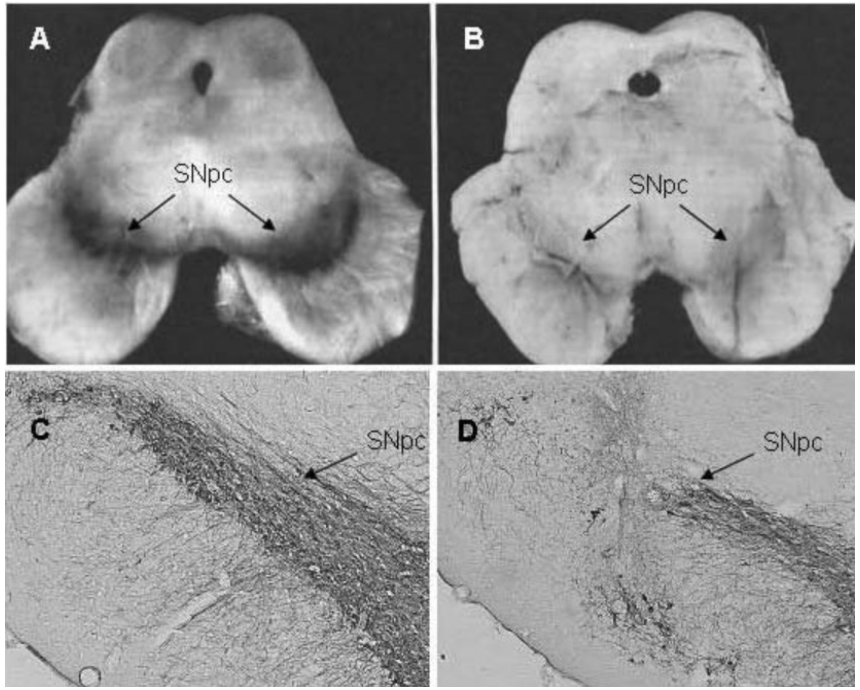
Conclusions

Introduction and Background : Parkinsons Disease



Silva et al., 2023

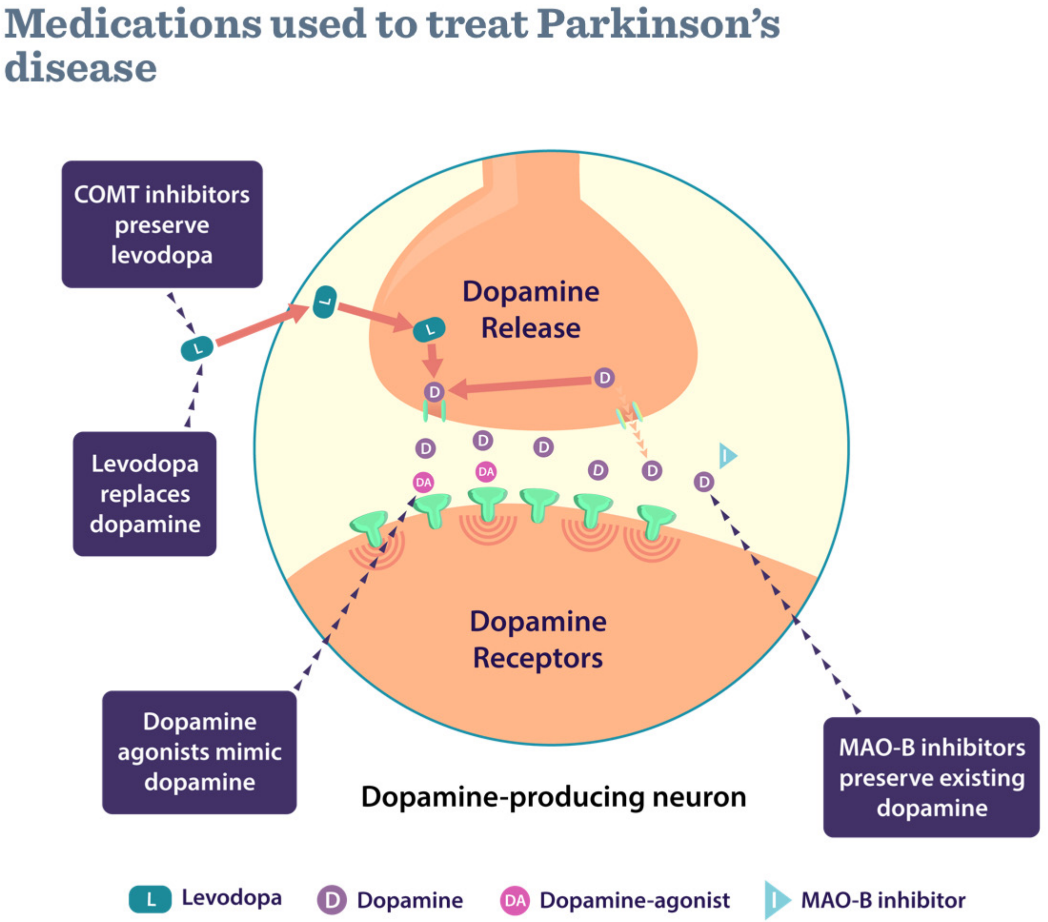
- Over **10 Mio** people living with PD (parkinson.org)
- More than **1/1000** people



Lima et al., 2012

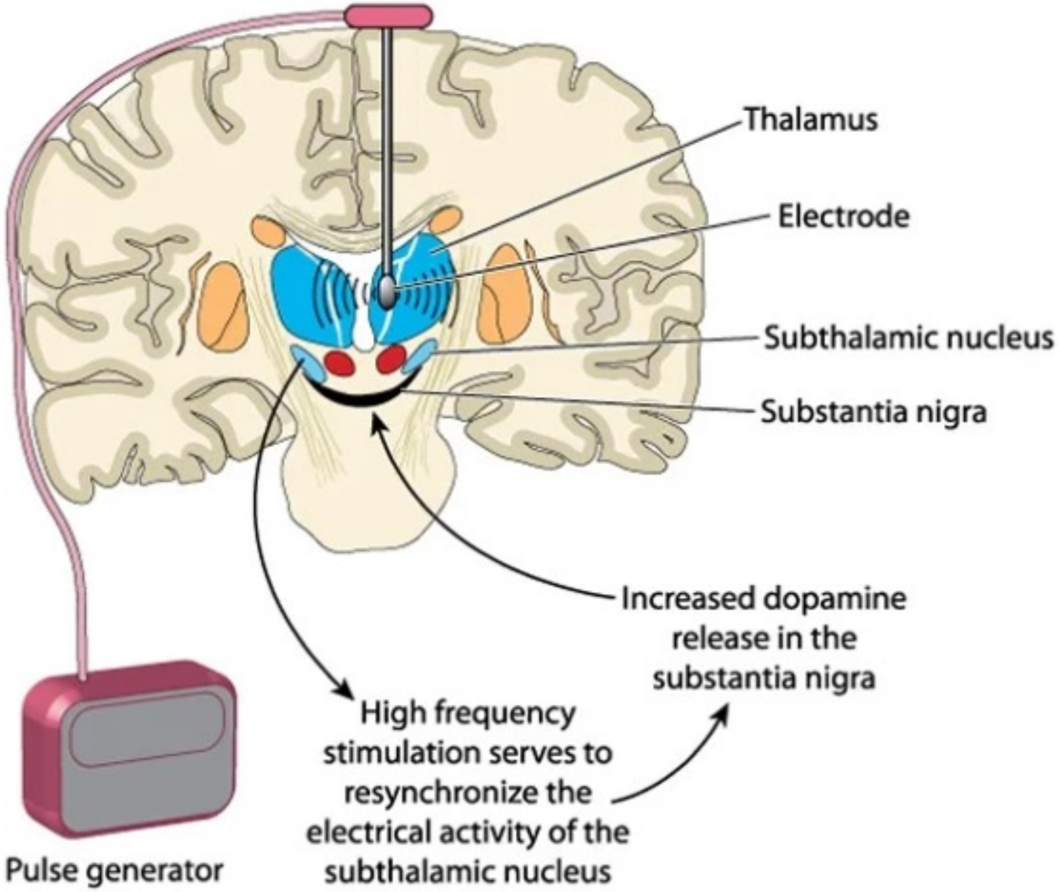
Introduction and Background : Current treatments for PD

1. Dopaminergic therapy



parkinsonsdisease.net

2. DBS



news-medical.net

Current Treatments Limitations :

Dopaminergic therapy :

- Limited long-term efficiency
- Motor complications / fluctuations
- Resistance to Non-Motor Symptoms
- Side Effects

Rascol et al. 2003

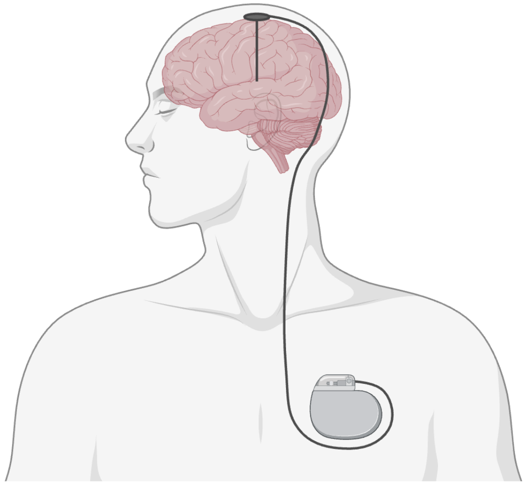
DBS

- **Limited effect on gait and postural instability, especially due to gait fluctuations**

Other limitations (which our model will not focus on)

- Speech and Cognitive Decline
- Neuroinflammatory Response
- Surgical Risks
- Behavioral and Emotional Changes:

Rossi et al. 2018, Lozano et al. 2019, Meng et al. 2023



Proposed Solution: Closed-Loop EES System (1)
Why ?

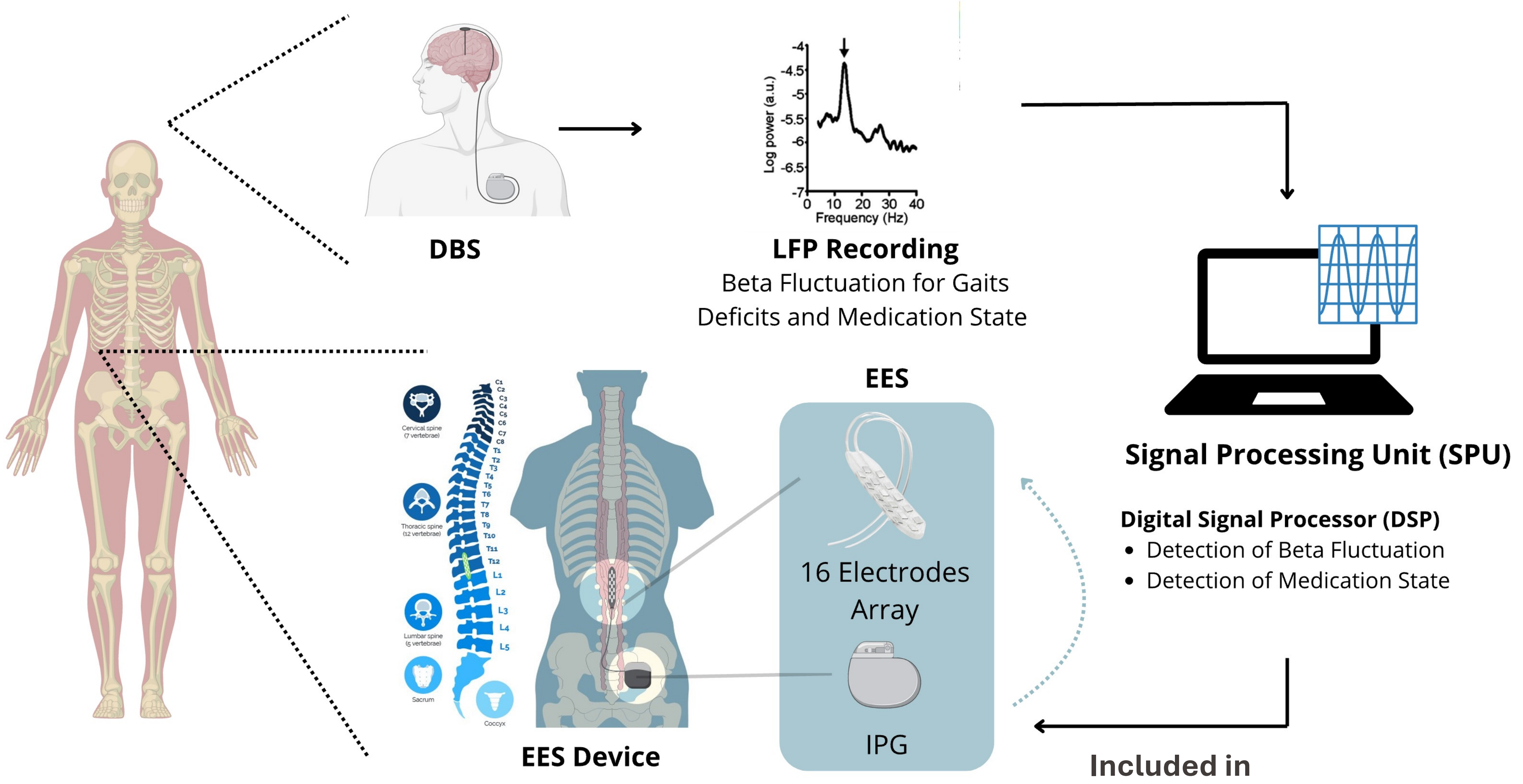
Problems	Solutions
1. Current treatments ineffectiveness for Gait Deficits	→ Add Electrical Epidural Stimulation
2. Motor Fluctuations and Symptom Variability	→ Real-Time Adaptive Closed-Loop EES
3. Overstimulation and Energy Inefficiency	→ Closed-Loop to reduce stimulation

Proposed Solution: Closed-Loop EES System (2)
Why ?

Proposed Solution

Closed-Loop Epidural Electrical Stimulation (EES) coupled with Deep Brain Stimulation (DBS) recording for Gait Deficits in Parkinson's Disease

Proposed Solution: Closed-Loop EES System

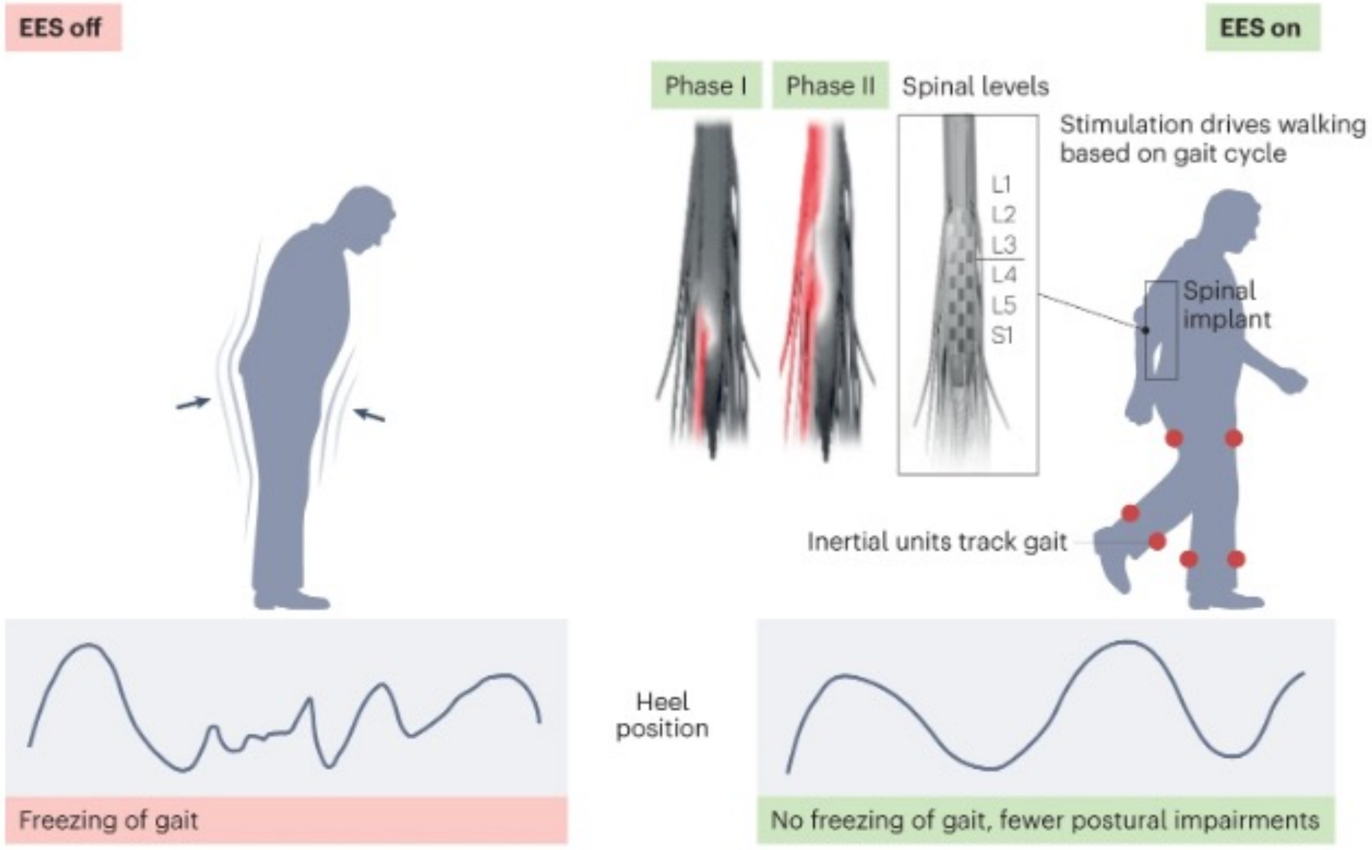


https://epiduralstimulationnow.com/treatment/

Proposed Solution: Closed-Loop EES System

Electric Epidural Stimulation (EES) : Mizrahi-Kliger & Ganguly, 2023

- **Mechanism:**
  - Stimulates sensory afferent fibers in the dorsal roots.
  - Activates spinal central pattern generators (CPGs) to drive rhythmic walking.
- **Effect:** Restores muscle activation, step dynamics, and gait coordination.
- **Outcome:** Bypasses impaired brain-spinal communication to improve gait.



Expected Benefits

1. This Closed-Loop System would avoid **unnecessary electrical epidermal stimulation** when not needed. Beneficial for the battery duration
2. Potentially, if we can **communicate wireless from DBS-IPG** (Implanted Pulse generator) to EES-IPG, not induce a too complicated surgery as not a long wire throughout the body
3. Stimulation would be **adaptive on the medication estate**

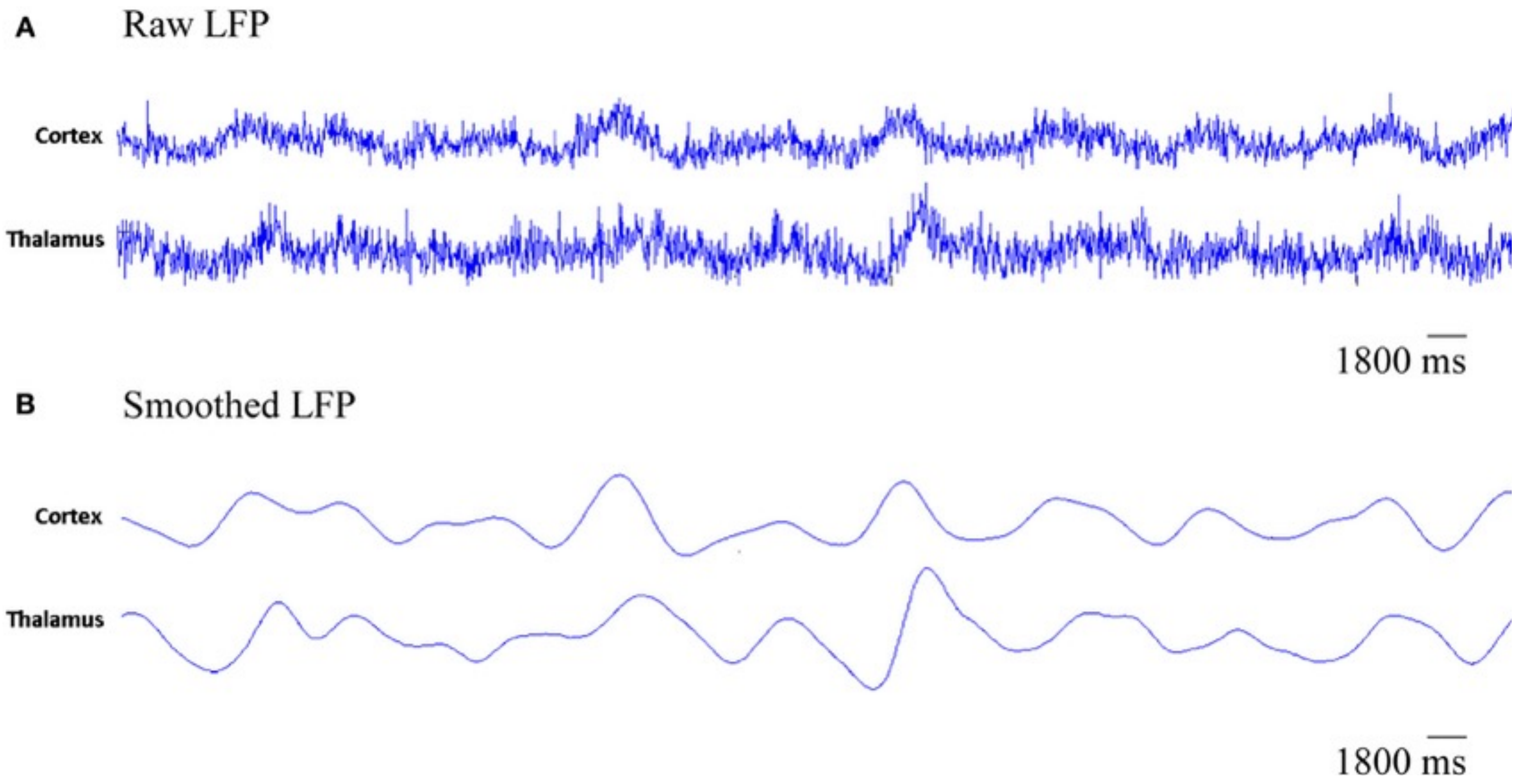
EPFL

Building Blocks of the Device

1. **LFP recordings** of beta fluctuations with **DBS**
2. **Adaptative Treatment** based on **Medication Estate**
3. **Communication to EES** device and individual **optimization**

Local Field Potential (LFP) (1)

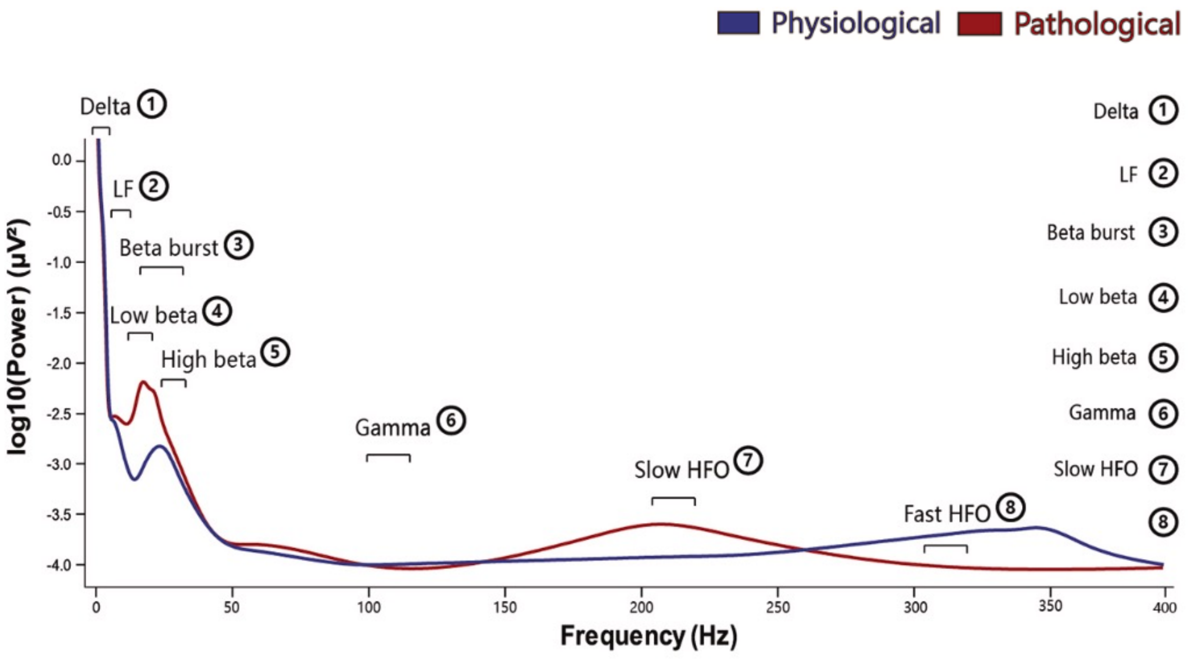
- LFP signal represents the activation of neuronal population. It captures **the local synaptic activity** and can be recorded from DBS and communicated by Bluetooth (Yin et al., 2021)
- Output signal processed by **real-time Fourier Transform** to highlight peaks in beta-frequency



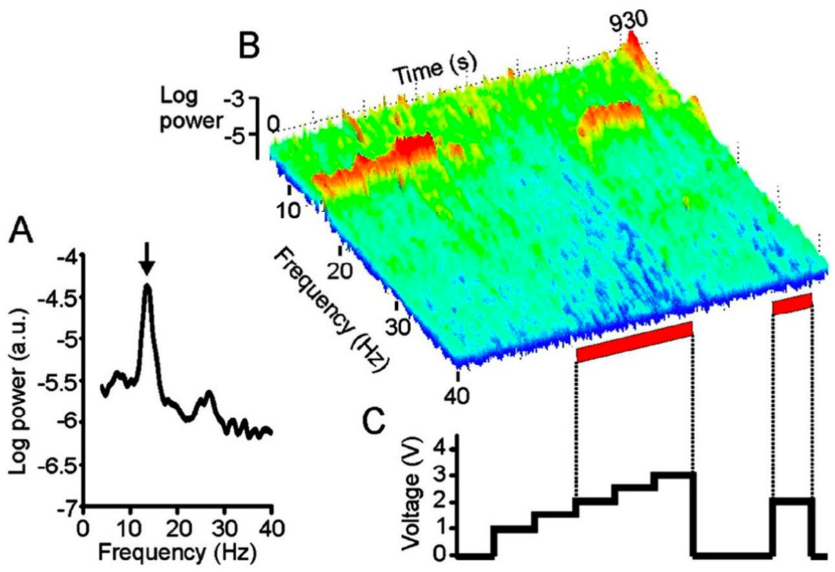
Local Field Potential Processing (Abuhassan et al., 2014)

Local Field Potential (LFP) (2)

- No universal **threshold** of pathological beta fluctuations → must be determined individually
- Larger beta bursts and higher beta power are associated with gait impairments (Yin et al., 2021)



Power Spectrum Analysis of STN LFP in Parkinson's Disease patients (Yin et al., 2021)



LFP recording from DBS in Parkinson's Disease Patients, with (A) large beta peak at 14 Hz without stimulation in comparison to (B) stimulation in red that suppresses Beta peaks (Little et al., 2013)

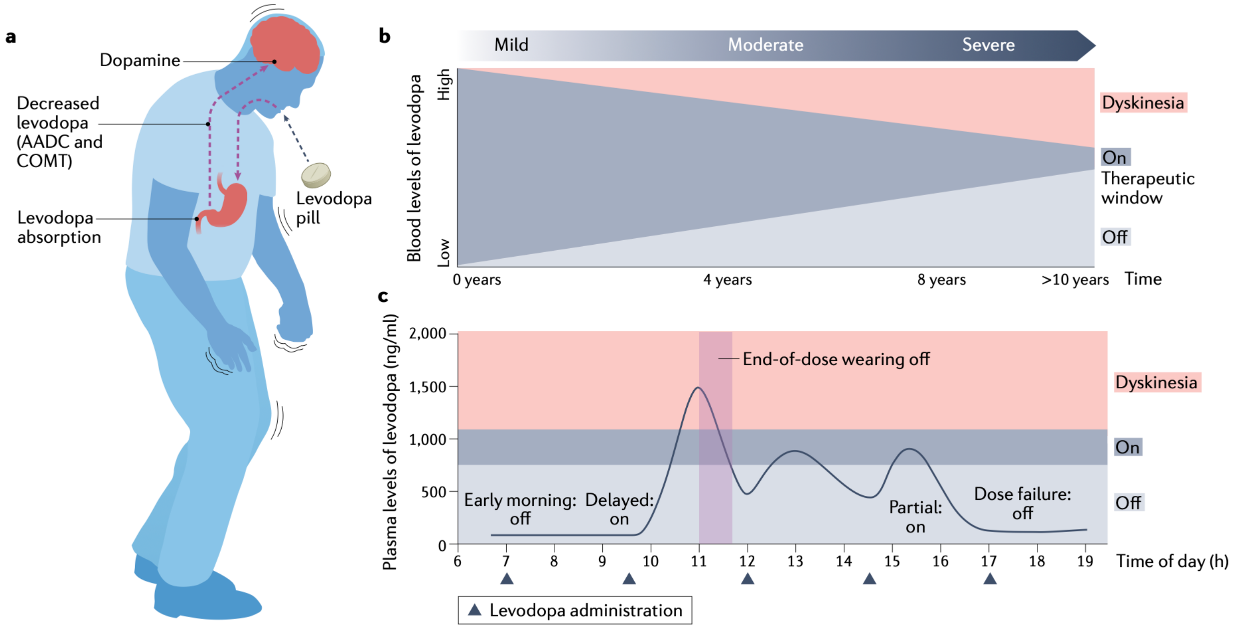
Building Blocks of the Device

2. Adaptative Treatment
based on **Medication Estate**

Stimulation Based on Medication Intake (1)

- **ON Medication:**
  - motor control typically improves
  - freezing and rigidity reduce
  - weaker EES stimulation needed
  - **avoid overstimulation**

- **OFF Medication:**
  - symptoms (bradykinesia, freezing of gait, and rigidity) worsen
  - Require **stronger and more frequent** EES stimulation to compensate

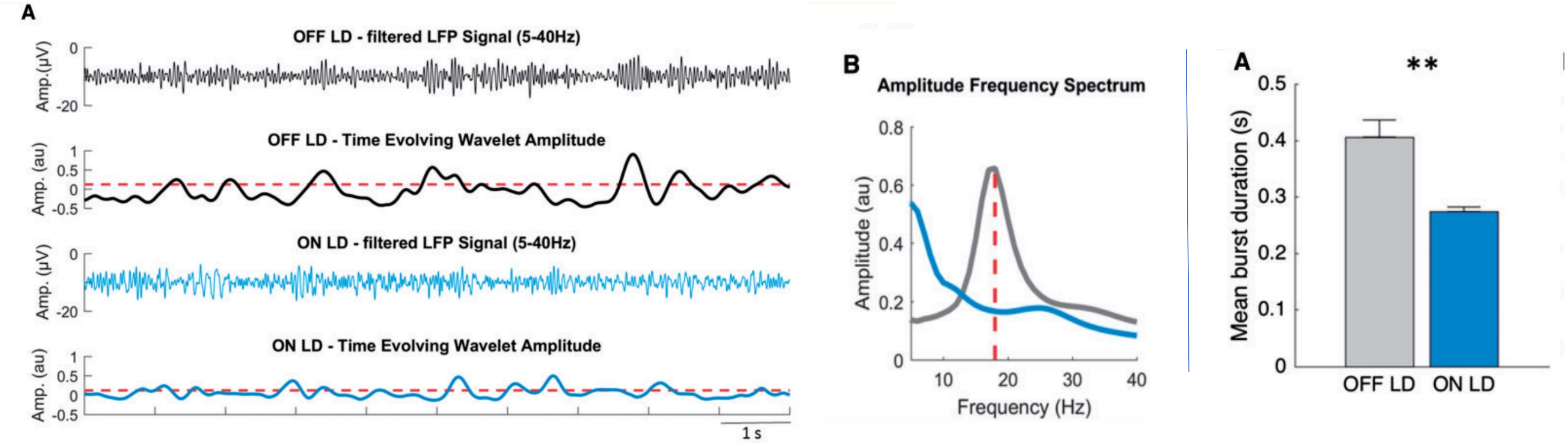


As PD progresses, achieving optimal motor control becomes more challenging due to both levodopa tolerance and disease severity. (Teymourian et al., 2022)

Therefore → Closed-Loop must consider the medication state of the patient

Stimulation Based on Medication Intake (2)

- Difference in range of beta peaks during ON and OFF states ⟶ Need two thresholds to adapt stimulation
- Moreover, pathological beta bursts duration are longer in "OFF" states ⟶ Identify state
- Dual Threshold Algorithm with one threshold for ON medication and one for OFF medication. (Fleming et al., 2020)



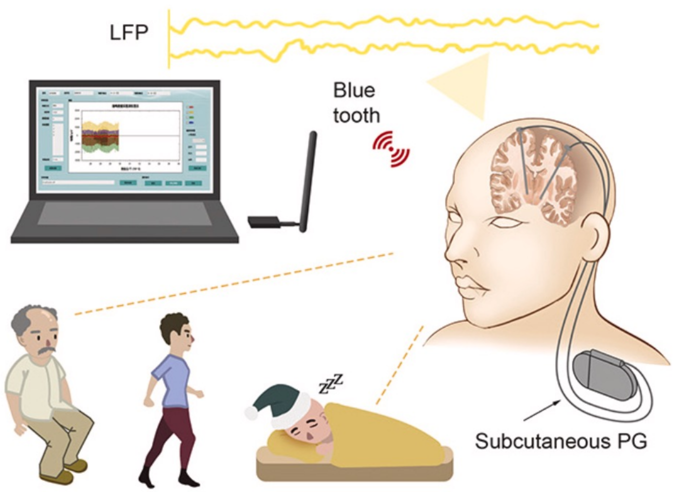
Differences in Peaks between ON and OFF medication (Tinkhauser et al., 2017)

LFP Processor Integration

3. Communication to EES
device and individual
optimization

LFP Processor Integration

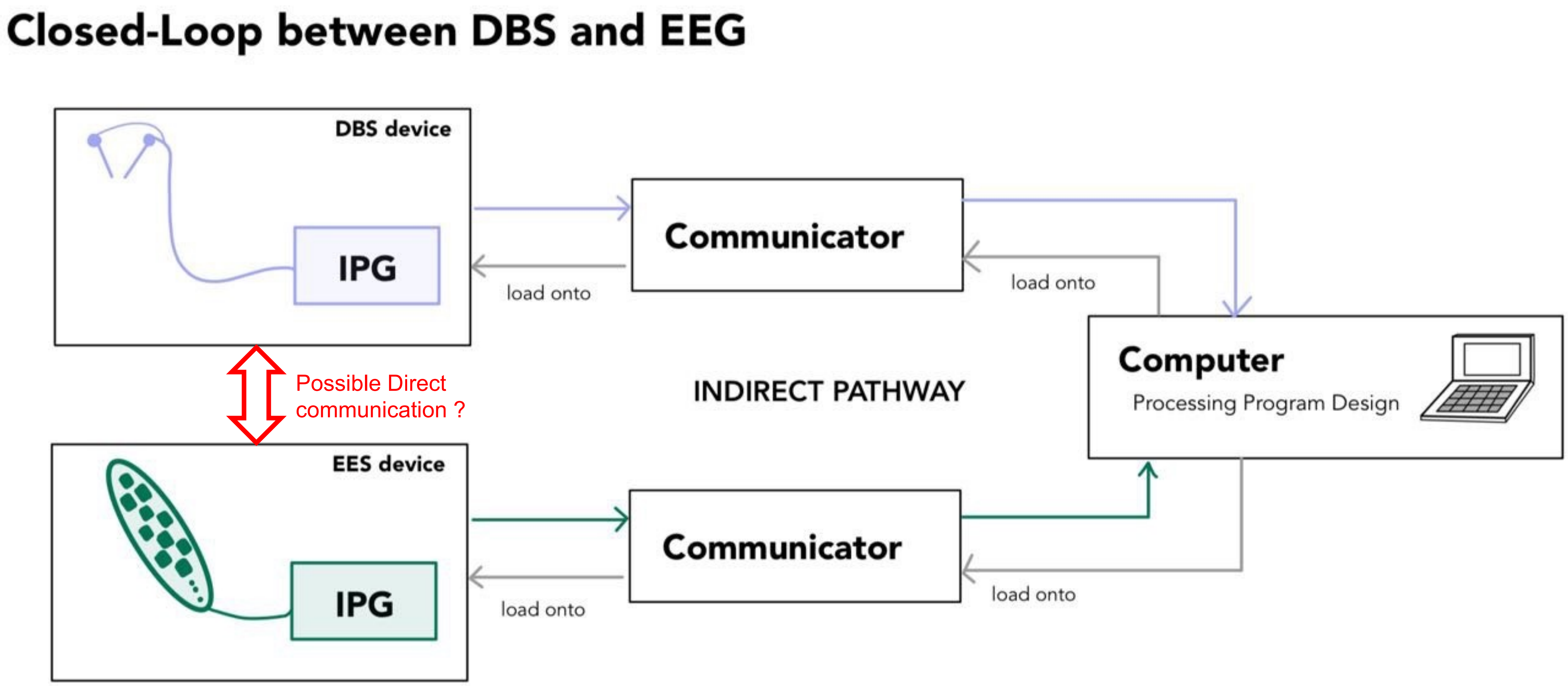
- Current IPG (eg. Percept PC system by Medtronics) allow the **recording of LFPs trough the same electrodes used for stimulation**
- Further processing can be integrated **by using the communicator intermediate,** to load the processing program from a computer



Wireless communication of LFP recordings from DBS (Yin et al., 2021)

Technical Challenges – Communication to EES device (1)

- How can we transmit the signal from DBS-IPG to EES-IPG?



Technical Challenges – Communication to EES device (2)

Three possibilities

1. Integrate EES-IPG in the chest next to DBS-IPG
   - ✓ **Pros**: small distance between the two IPGs, reducing delay
   - ✗ **Cons**: long wire from the chest to the EES device
2. Integrate EES-IPG in the hip
   - ✓ **Pro**: small wire from the IPG and the EES
   - ✗ **Cons:** long wire from the DBS-IPG and the EES-IPG
3. Wireless Connection from DBS-IPG to EES-IPG
   - ✓ **Pro:** no long wire throughout the body
   - ✗ ***« Cons »:*** *not done for now*

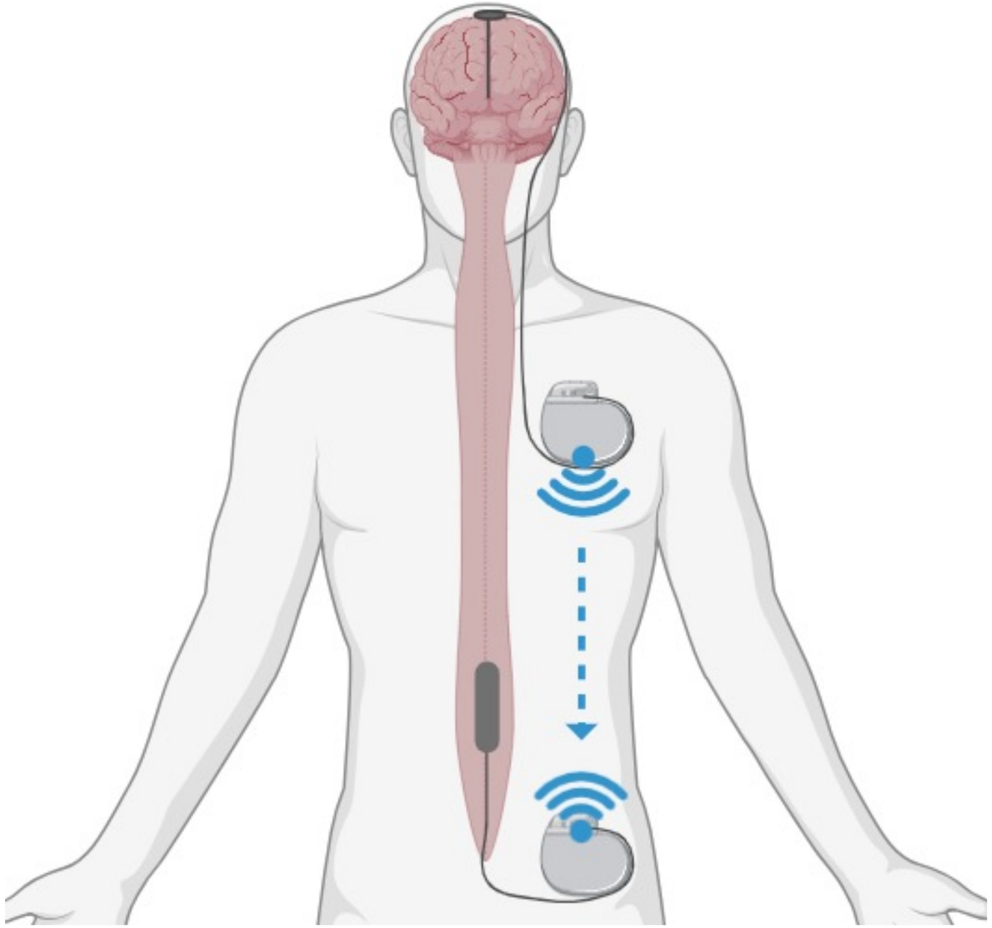
Technical Challenges – Communication to EES device (3)

- **Wireless Connection from DBS-IPG to EES-IPG**

- Percept PC IPG (Medtronic) for **DBS** : stimulation + brain sensing (Jimenez, 2021)

- Activa RC IPG (Medtronic) for **EES** :
  - Upgraded with wireless communication modules inspired by Milekovic et al., 2023 and Capogrosso et al., 2016 to receive signals directly from DBS IPG

- Novelty : **SPU** (Processing module) directly in the IPG
  - Embedded SPU: Directly within the EES IPG (e.g., ~2–5 mm² microprocessor)
  - Interprets DBS signals and adjusts EES parameters (Amplitude + Frequency (Pulse Width), Wenger et al., 2014) to activate spinal locomotor circuits in real time.



Clinical Application and Trials

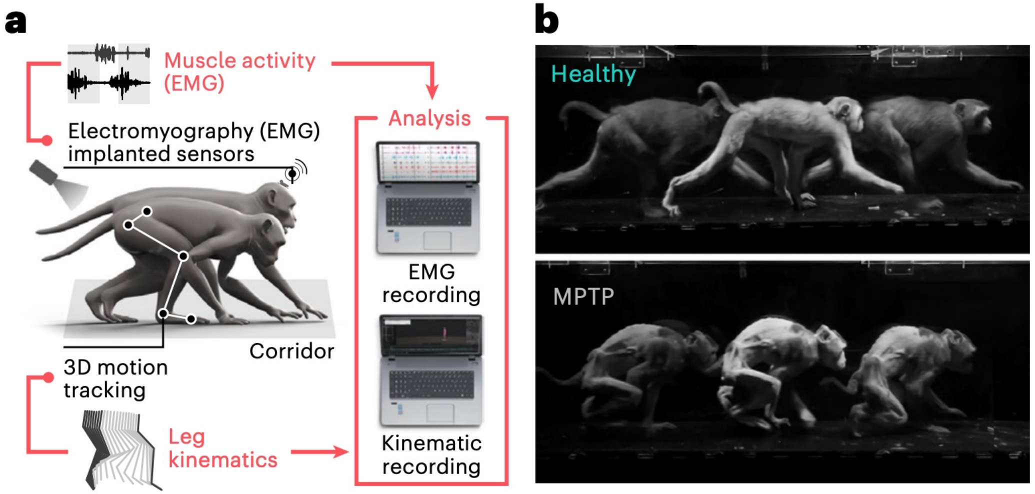
- Eligibility
- Surgery (EES implementation)
- Configuration Optimization
- Evaluation of the Closed-Loop

Pre-Clinical Studies

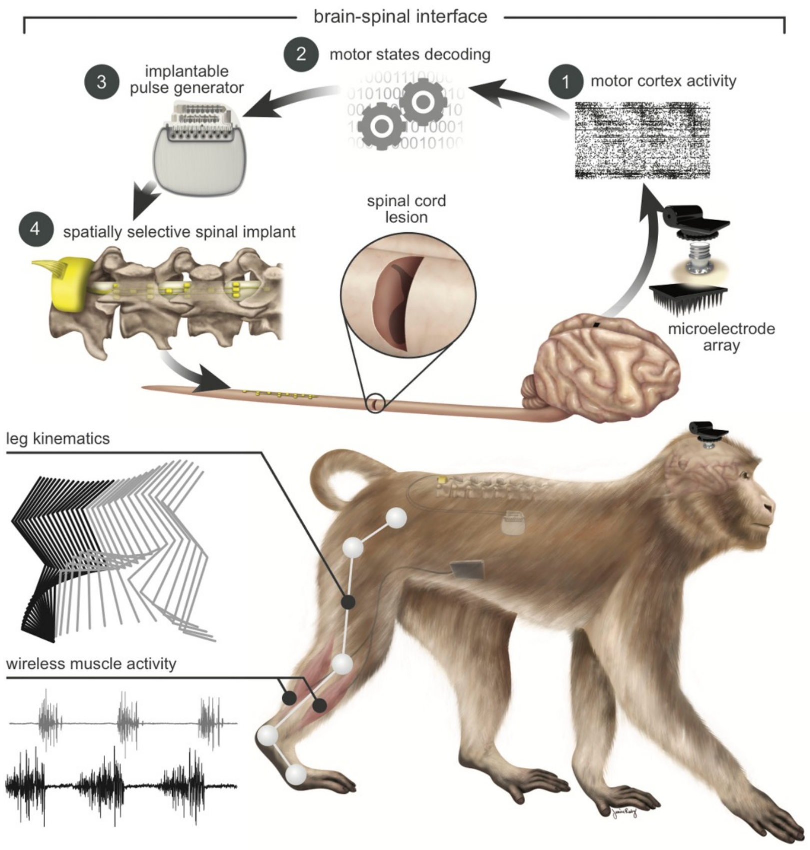
Pre-Clinical Studies – (Animal Models)

For validation, the closed loop can be tested in non-human primate (NHP).

- NHP treated with MPTP as PD clinical model (Milekovic et al., 2023)
- Combination of DBS stimulation and EES models in MPTP-treated animals for the entire closed-loop



Parkinson's Disease Model by treating Non-Human-Primate with MPTP (Milekovic et al., 2023)

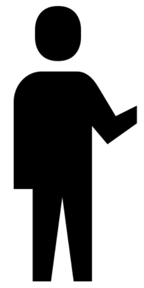


Brain-Spinal Interface in Monkeys (Capogrosso et al., 2016)

Eligibility (1)

Eligibility

1. Is **beta band** the right frequency band to consider?
2. How are these fluctuations varying with **medication state?**
3. What are the **gaits deficits** the patient is suffering from?



Patient Personalized Approach

Eligibility (2)

Eligibility → Surgery (EES implementation) → Configuration Optimization → Evaluation of the Closed-Loop

Real-Time Monitoring of Beta Fluctuations and Medication State

1. Beta Fluctuations
LFP recordings with DBS

2. Medication State
Wearable sensors and ML tools

Reliability of Beta Power
- Does it rise with worsening gains or impairements?
- Does the beta power align with other motor symptoms?

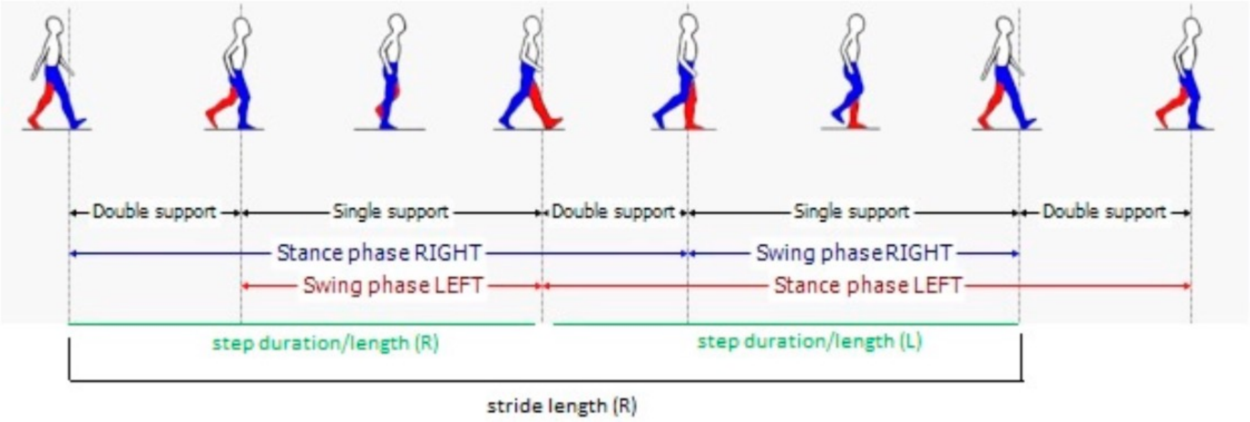
Medication-Driven Variability

Eligibility (3)

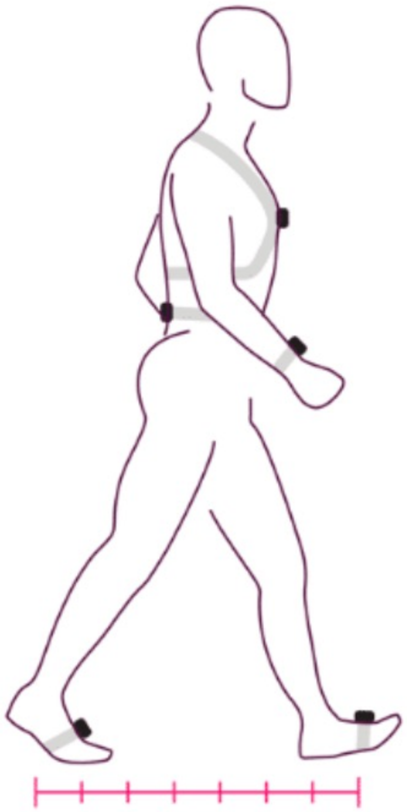
3. Gaits Quality Analysis

LFP recordings with DBS

- **GAITRite System** (Bryant et al., 2011)
- **3D Motion Capture** (Molina et al., 2021)
- **APDM MobilityLab System** (Antoniades et al., 2020)
- **Inertial Measurement Units (IMU) with Wearable Motor Sensors** (Brognara et al., 2019)

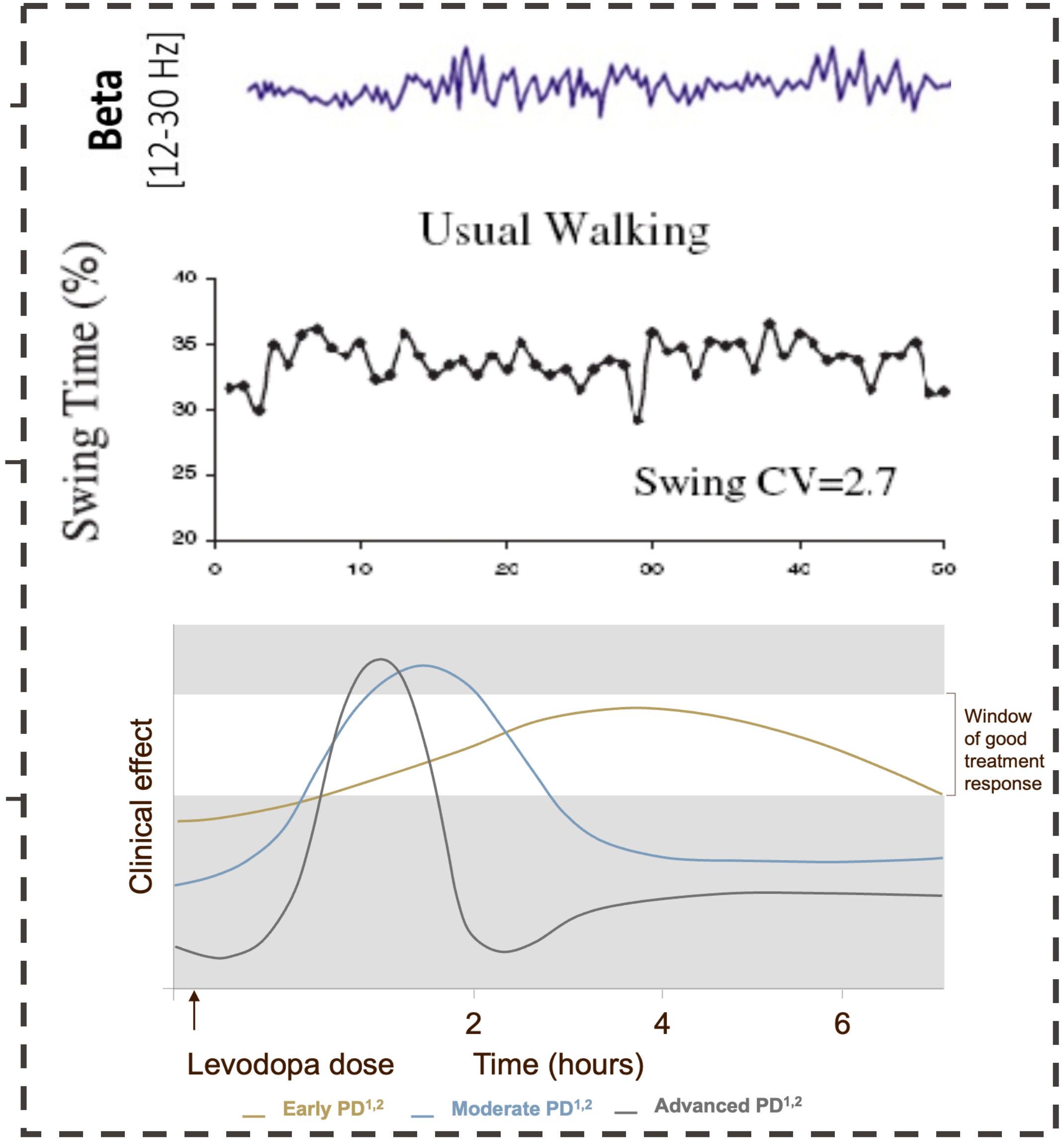


Gait Phases (Antoniades et al., 2020)



https://clario.com/solutions/precision-motion-for-research/

Eligibility Step



Simultaneous Comparison

(Nambiar et al. 2023)

Neurotorium, 2019

Surgery (EES)

Eligibility

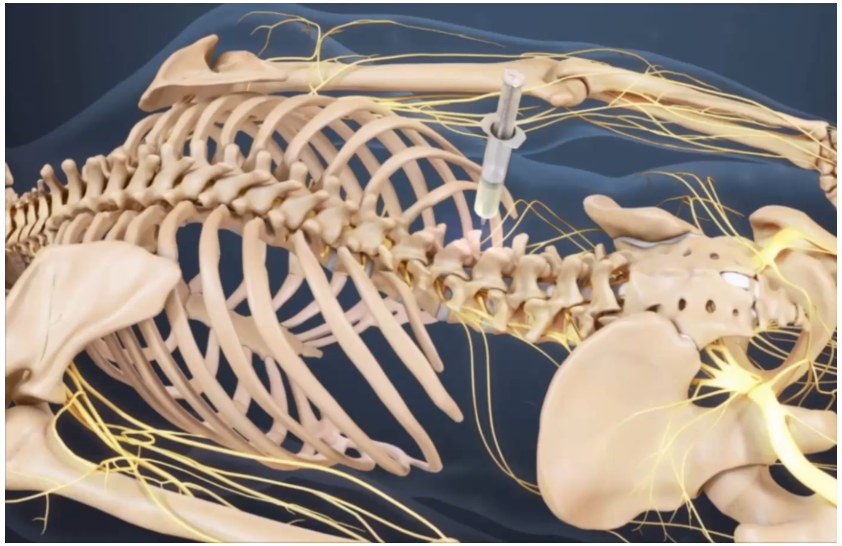
- Already implanted with DBS and who have not achieved sufficient gait improvement from DBS alone
- Primary symptoms include gait freezing and postural instability.
- **Stable enough** for an additional invasive procedure.

Duration of Surgery

- 1-2 Hours

Rehabilitation

- **2-3 weeks** before starting again light activities
- **6 weeks** for full recovery
- Avoid certain type of physical activities to avoid displacement of the leads for **the first three months**



EES Implantation Surgery

https://www.spine-health.com/treatment/pain-management/spinal-cord-stimulator-implantation-surgery-step-step?

Configuration Optimization

EES Program Optimization

WARNING: Parkinson's Disease patients typically don't have spinal cord injury (SCI)

- Thus, they can feel EES stimulation → **potential pain**

In Bed – Patient's Feedback:

- Try several set of parameters
- Find the pain threshold

Gaits Tasks

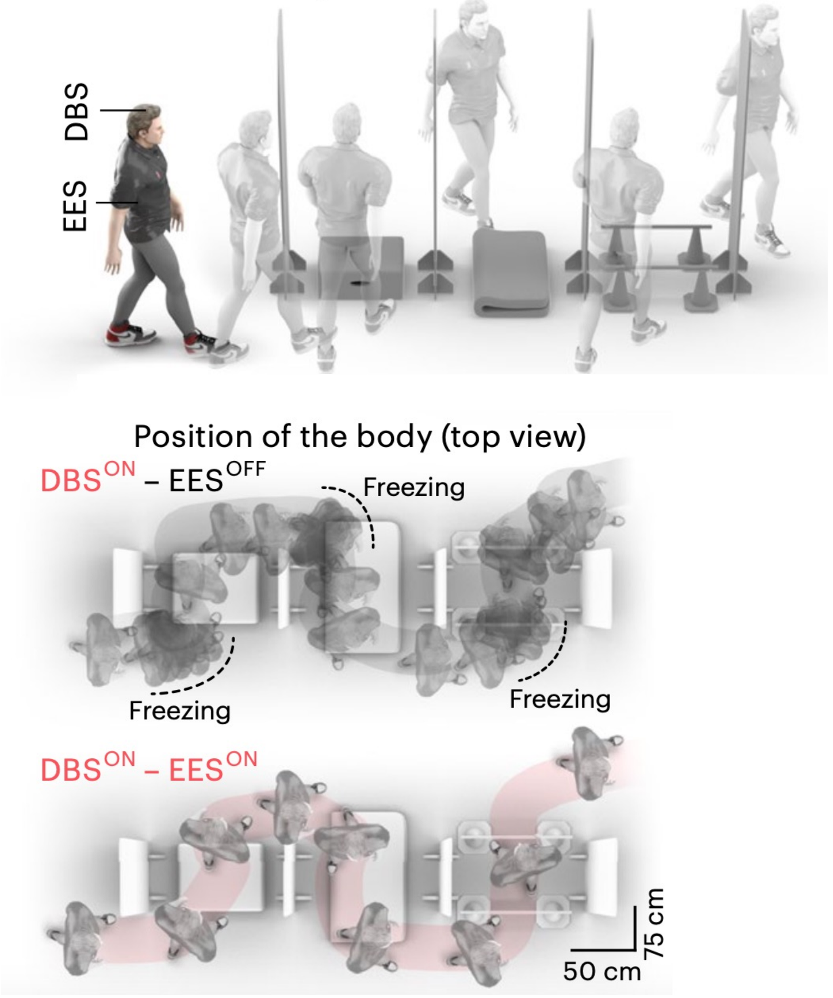
- Try several set of parameters during gaits tasks using motion recording tools
- Find the optimal parameters when using the device

Closed-Loop Evaluation (1)

How can we assess whether the Closed-Loop works?

In Lab:

- Specific Circuits that can induce gaits freezing to assess closed-loop efficacy
- Likewise before the surgery, gaits analysis with simultaneous recordings



Freezing Gaits Inducing Circuit
(Milekovic et al., 2023)

Closed-Loop Evaluation (2)

At Home

- For patient's comfort
- Long-term validation of the closed loop
- Use some tri-axial accelerometers coupled with some symptom diaries (Fisher et al., 2016)
- Get the **patient's feedback**

3-Axis Logging Accelerometer
(Axivity: https://axivity.com/product/ax3)

- Wear one on each wrist
- Sense for 12 days without needing to charge
- Use some tri-axial accelerometers (Fisher et al., 2016)

Limitations of our device

DBS Limitations

- This closed-loop does not overcome DBS limitations
- DBS stimulation would remain constant

Surgery Risks and Pain

- Invasive device
- EES can be painful
- Risk of infection or foreign body reaction (Eldabe et al., 2016)

Loss of Therapeutic Effects Over Time

- Epidural electrodes can diminish in efficiency (Taccola et al., 2020)
- Electrodes can migrate over time and require a subsequent surgery (Garg et al., 2023)

Battery Duration

- Even with adaptive stimulation, battery life remains finite, requiring periodic replacements.

Ethical, Regulatory, and Practical Considerations

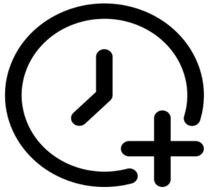
Need to address the broader implications of deploying the device

Ethical:
- Informed consent for the surgery and procedure
- Accessibility

Regulatory:
- Compliance with FDA and EMA guidelines
- Safety and efficacy benchmarks

Practical:
- **Wireless** communication
- **Costs of the device** and surgery

Future Directions



Longitudinal Studies to assess durability, safety and functional outcomes

Integrate real-time feedback and adapt **DBS** as a closed-loop to overcome its limitations

Extend the application of the closed-loop to **other motor impairments**

Conclusion – Empowering Gaits Restoration with an EES Closed-Loop

Innovation

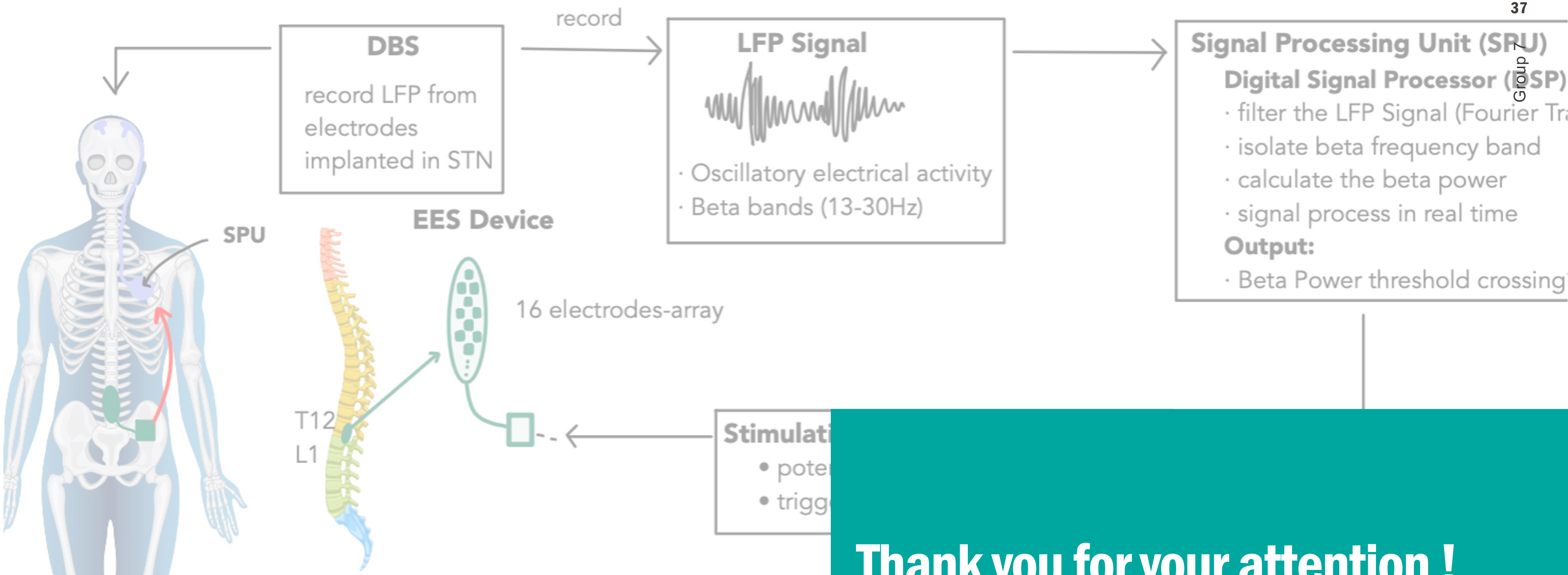
- Closed-Loop adressing **criticial limitations** of existing PD therapies
- Real-time adaptation to neural activity and medication state
- **Aim to restore gait and improve quality of life for PD patients**

Benefits

- Tailored solution to manage gait fluctuations
- Paves the way for **functional independance**

Feasibility

- Grounded in validated technologies (LFP recording, EES, …) and build on a foundation of scientific advancements
- Some technical challenges
- Both practical and impactful



Thank you for your attention !

And a special thanks to Paula for her help during this project !

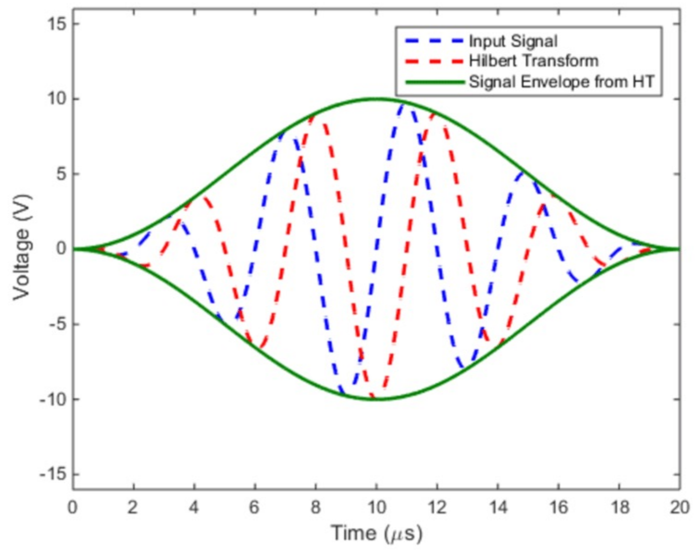
Complementary: Algorithm in more details (1)

The Algorithm of detection would include :

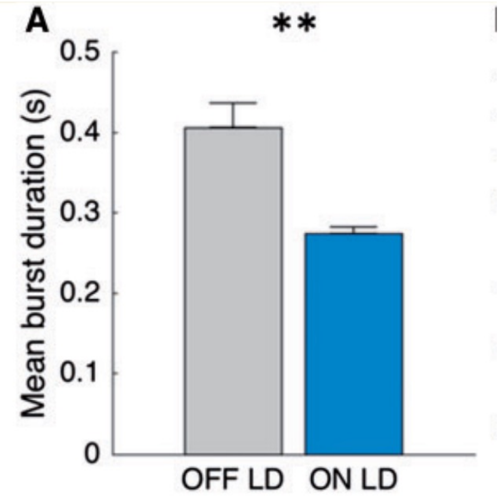
(1) To adapt threshold based on medication state → **Dual Threshold Algorithm** with ON medication representing the lower threshold and OFF medication the upper one

- Threshold at the 20th percentile of beta fluctuations (Fleming et al., 2020)

(2) As beta bursts do not have the same duration (Tinkhauser et al., 2017) → **Hilbert transform** to extract beta power envelope and detect bursts exceeding a predefined amplitude threshold



https://www.researchgate.net/figure/The-Hilbert-transform-of-a-5-cycle-Hanning-modulated-toneburst-signal_fig4_341231532



Differences in Peaks between ON and OFF medication (Tinkhauser et al., 2017)

Complementary: Algorithm in more details (2)

Raw LFP

LPF processing

Determine Bursts Duration

longer → **OFF Medication State**
Upper Threshold

smaller → **ON Medication State**
Lower Threshold

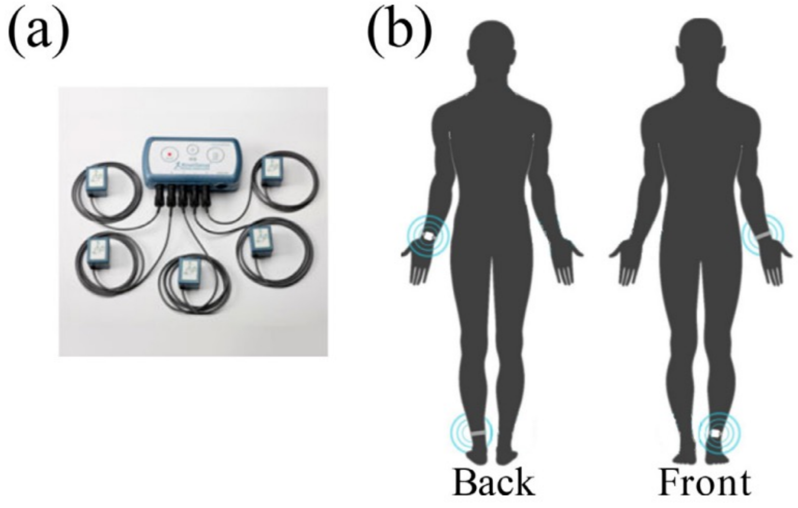
Dual Threshold Algorithm
Determien two thresholds at the 20th percentile of the beta burst during Eligibility

Complementary:
Stimulation Based on Medication Intake

Need real-time recording of ON and OFF medication states

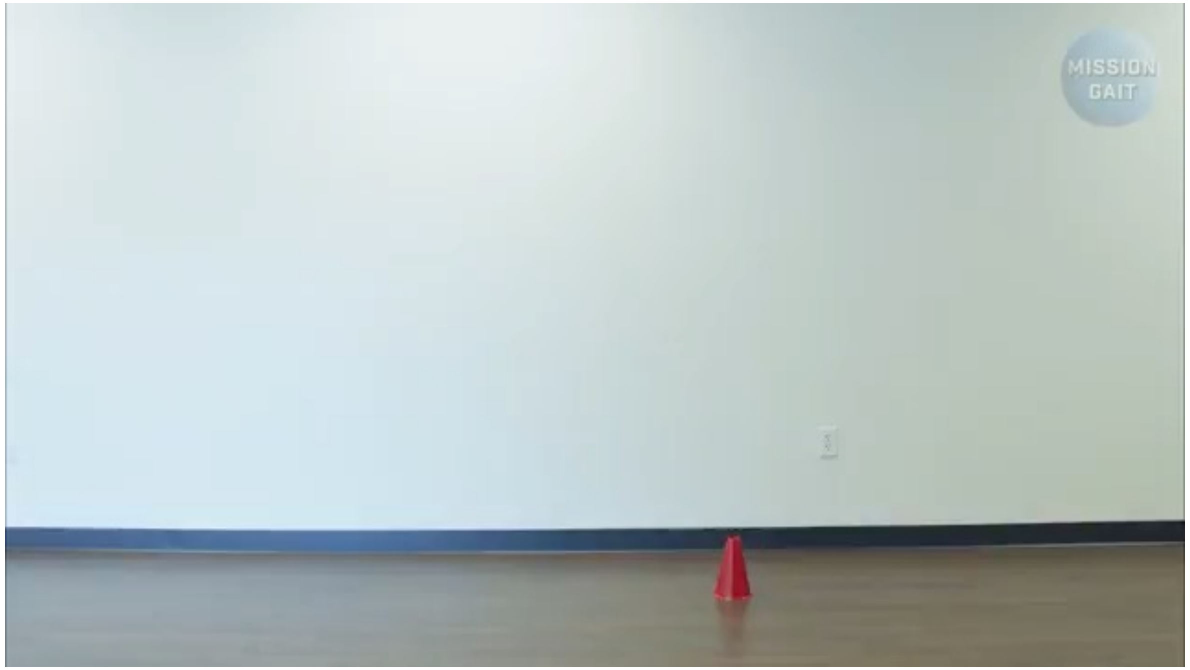
Combination of sensors and Machine Learning Tools

- Use wearable sensors – **wrist and ankle wearable** with accelerometers and gyroscopes (Hssayeni et al., 2019)
- **Adaptive classification of medication states (ON/OFF)** with Reinforcement Learning (RL) framework combined with a Long Short-Term Memory (LSTM) neural network (Shuqair et al., 2024)

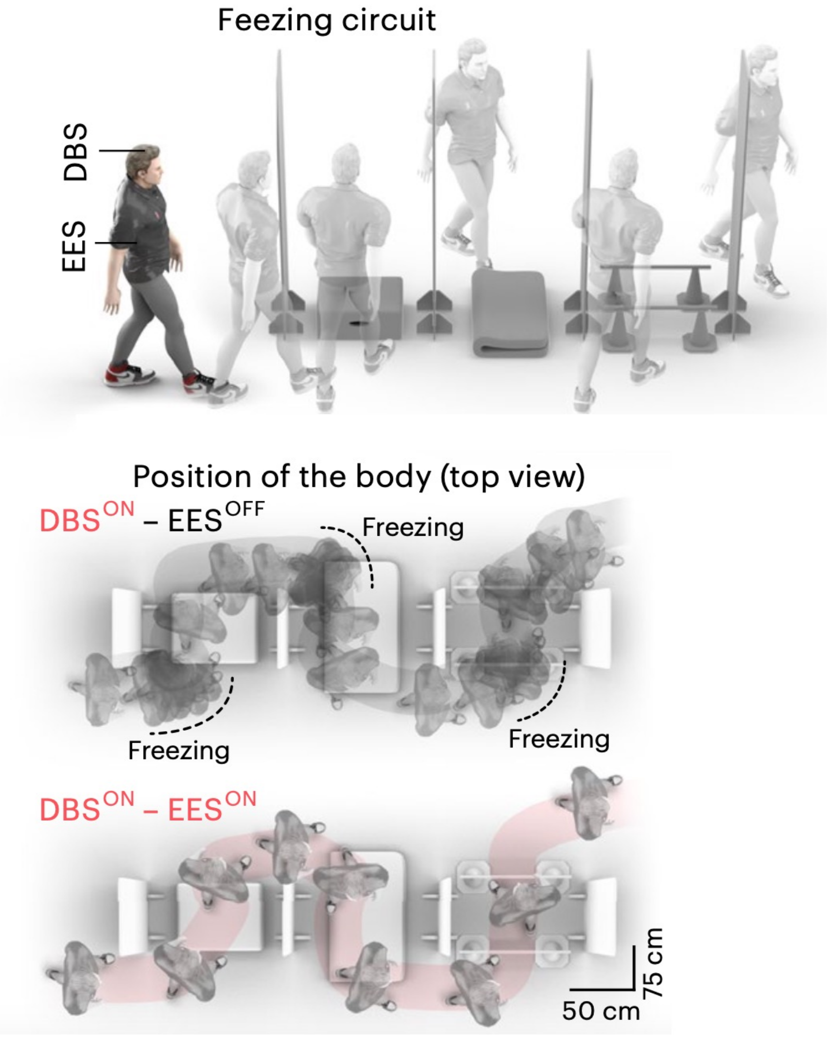


(a) KinetiSense Motion sensor unit and (b) the locations of the wearable sensors (Hssayeni et al., 2019)

Complementary:
Specific Focus on Freezing of Gaits



https://www.youtube.com/watch?v=EQ0HG16EC3g



Freezing Gaits Inducing Circuit
(Milekovic et al., 2023)

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