EPFL

Advancing Closed-Loop Epidural Electrical Stimulation (EES) of the Spinal Cord for Gait Deficits in Parkinson's Disease

13/12/2024

Advanced methods for neuromodulation

NX-436

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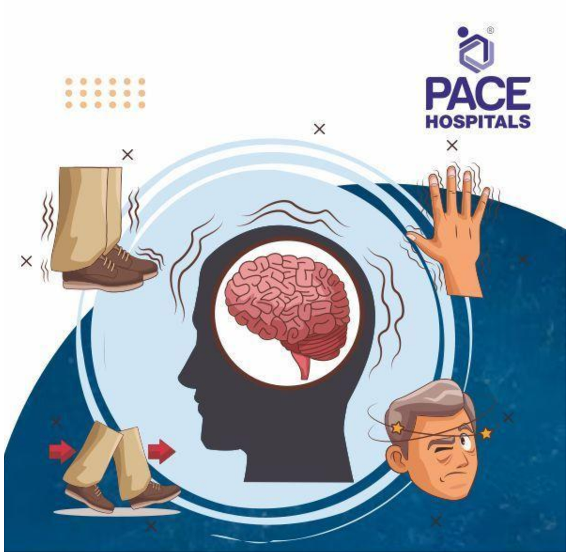
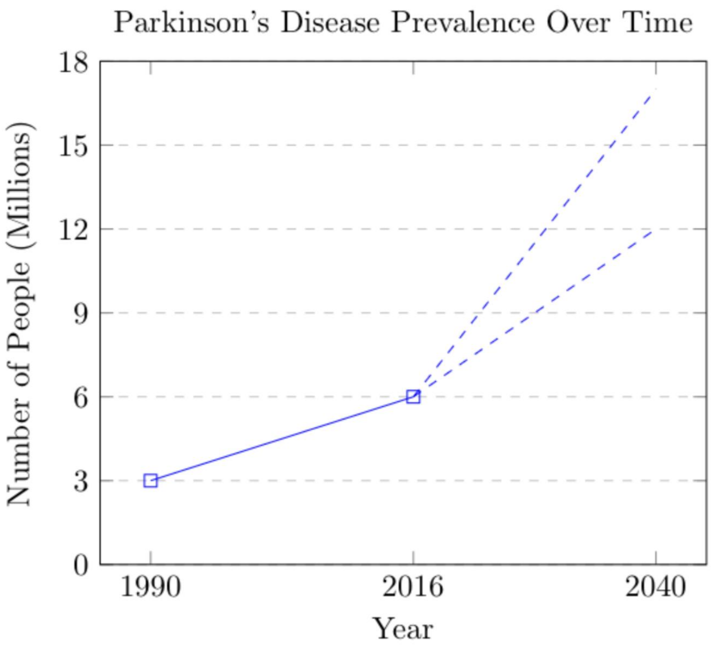


Fig.1

The problem?

Parkinson's Disease and Gait impairment

Parkinson's Disease (PD)



Fastest-growing neurodegenerative disorder

High economic burden

REF Fig.2 data from: Chaudhuri et al. - Drugs - Real World Outcomes - 2024; Gustavsson et al. - European Neuropsychopharmacology - 2011; Fig.3 - Castonguay et al. - Journal of Parkinson's Disease - 2021

Parkinson's Disease (PD)

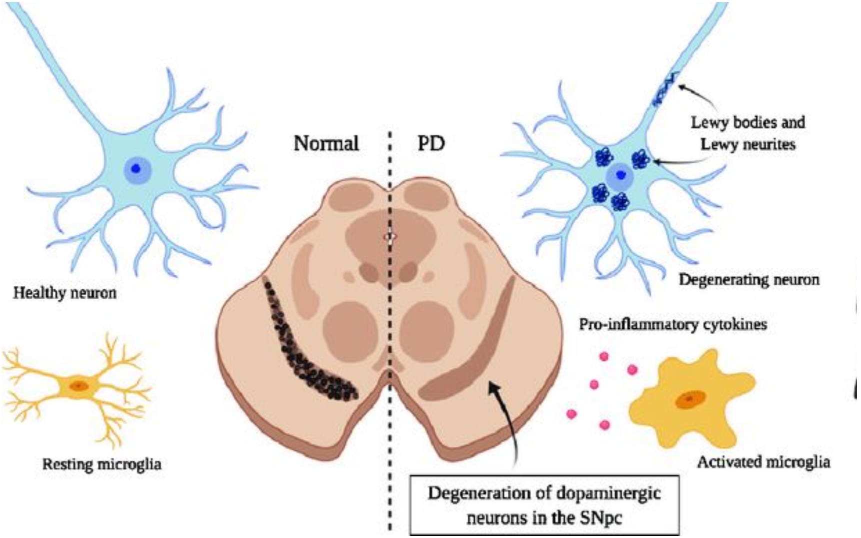
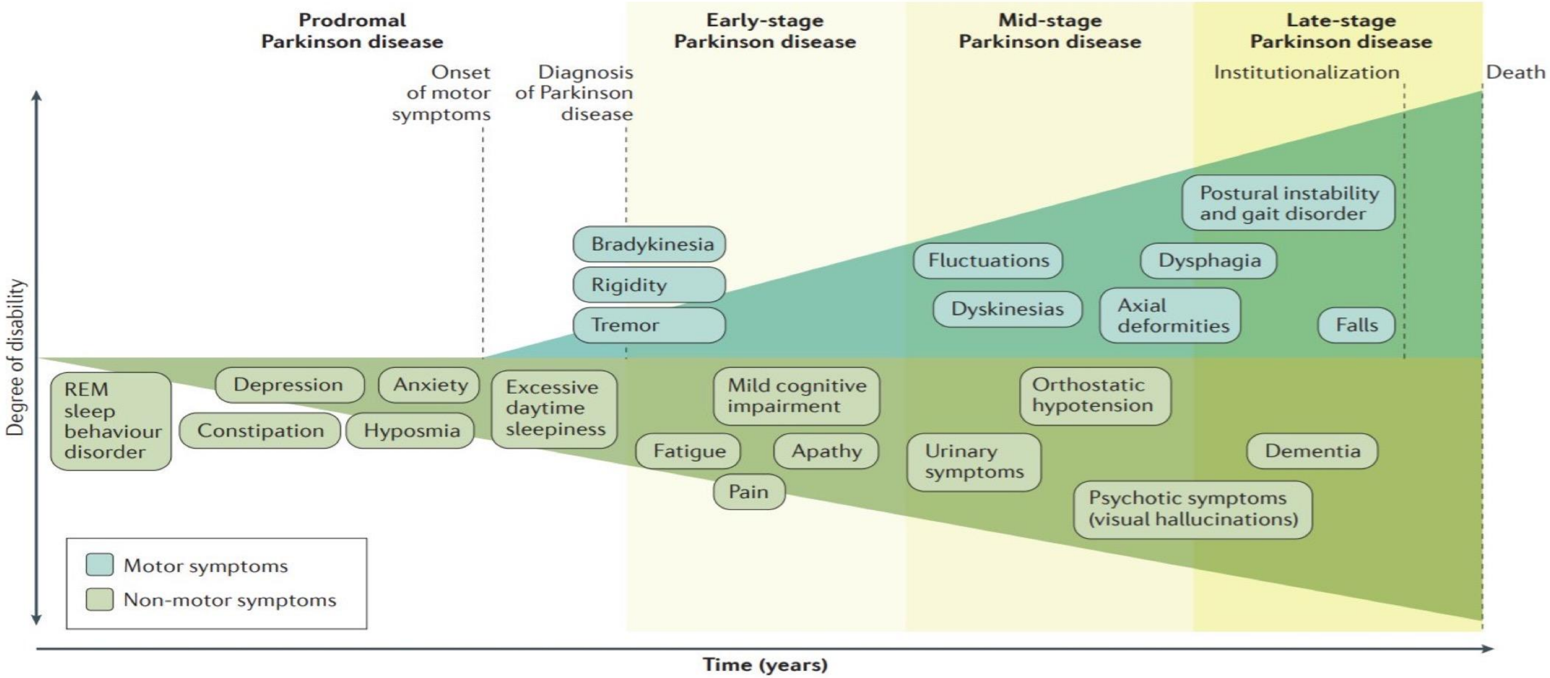


Fig.3

- Progressive loss of dopaminergic neurons in the Substantia Nigra
- Disruption of basal ganglia circuits

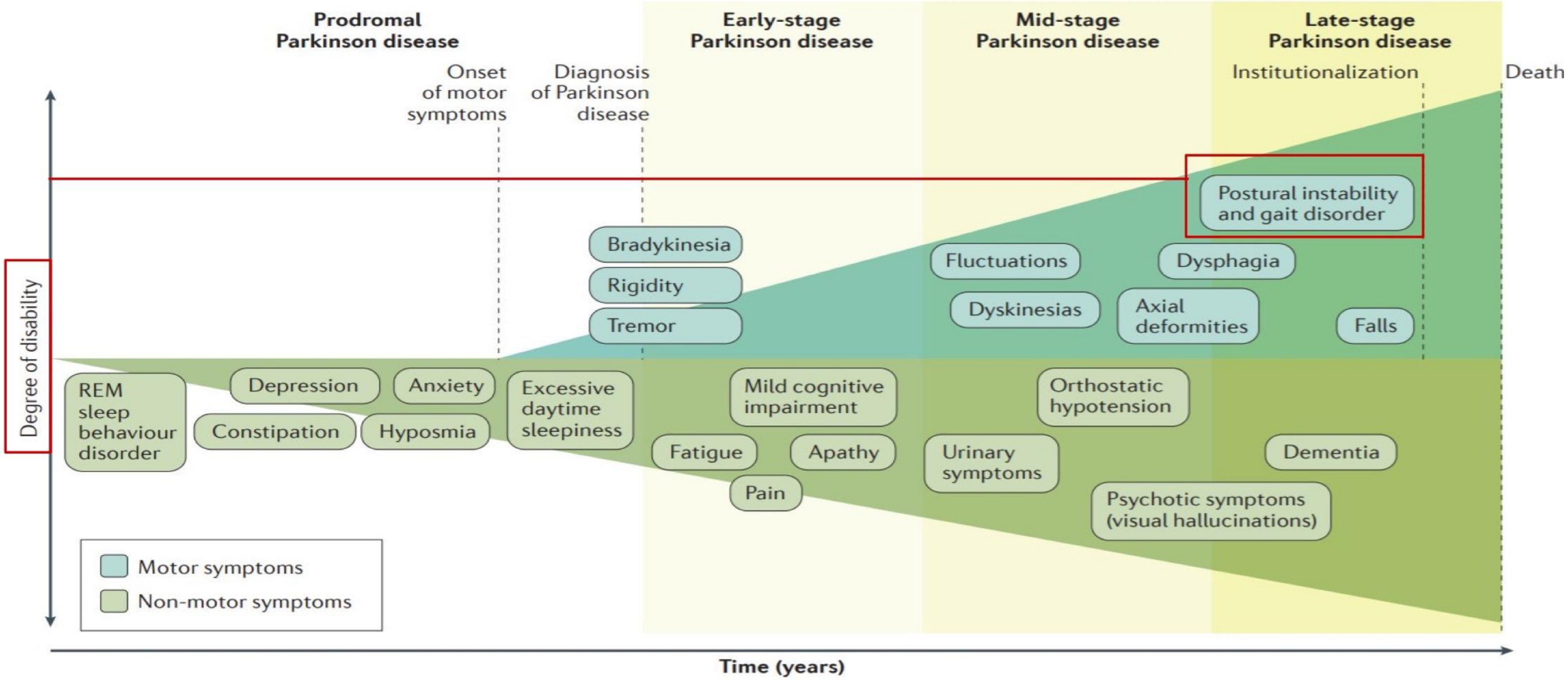
REF Fig.2 data from: Chaudhuri et al. - Drugs - Real World Outcomes - 2024; Gustavsson et al. - European Neuropsychopharmacology - 2011; Fig.3 - Castonguay et al. - Journal of Parkinson's Disease - 2021

Parkinson's Disease (PD)



REF Fig.4 - Slide NX 423, Translational Neuroengineering

Parkinson's Disease (PD)



REF Fig.4 - Slide NX 423, Translational Neuroengineering

Gait impairment

Gait pattern:

- Reduced leg speed and step length, (short shuffling step)
- Increased axial rigidity
- leg trembling,
- impaired rhythmicity
- Turning during change of direction,

REF Gilat et al. - Parkinsonism & Related Disorders - 2018; Mirelman et al. - The Lancet Neurology - 2019

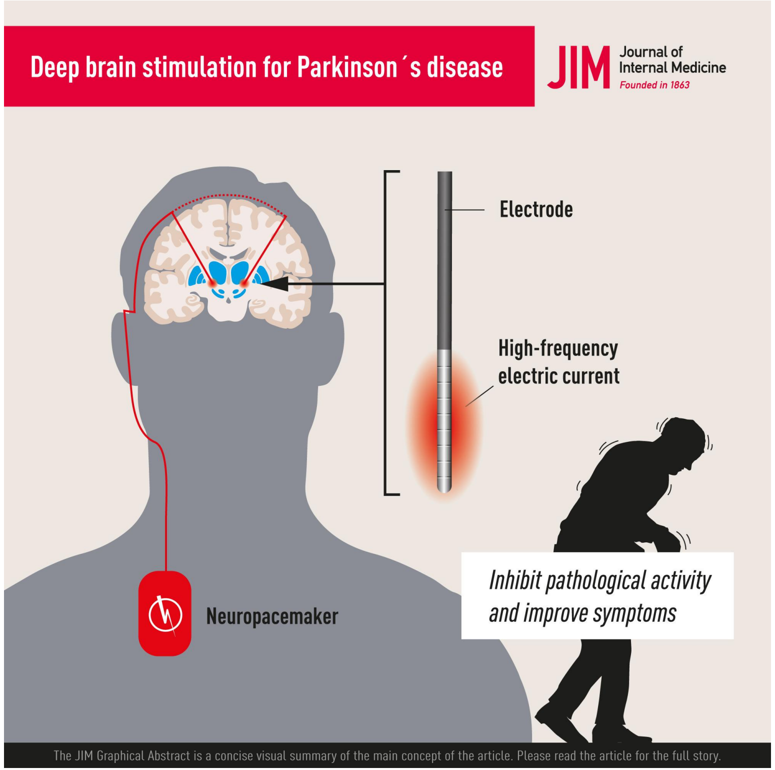
Gait impairment

FOG: sudden inability to initiate or continue walking.

Triggered by:

- certain movements (turning),
- mental tasks,
- emotions (stress),
- environmental constraints (narrow doorways).

REF Gilat et al. - Parkinsonism & Related Disorders - 2018; Mirelman et al. - The Lancet Neurology - 2019

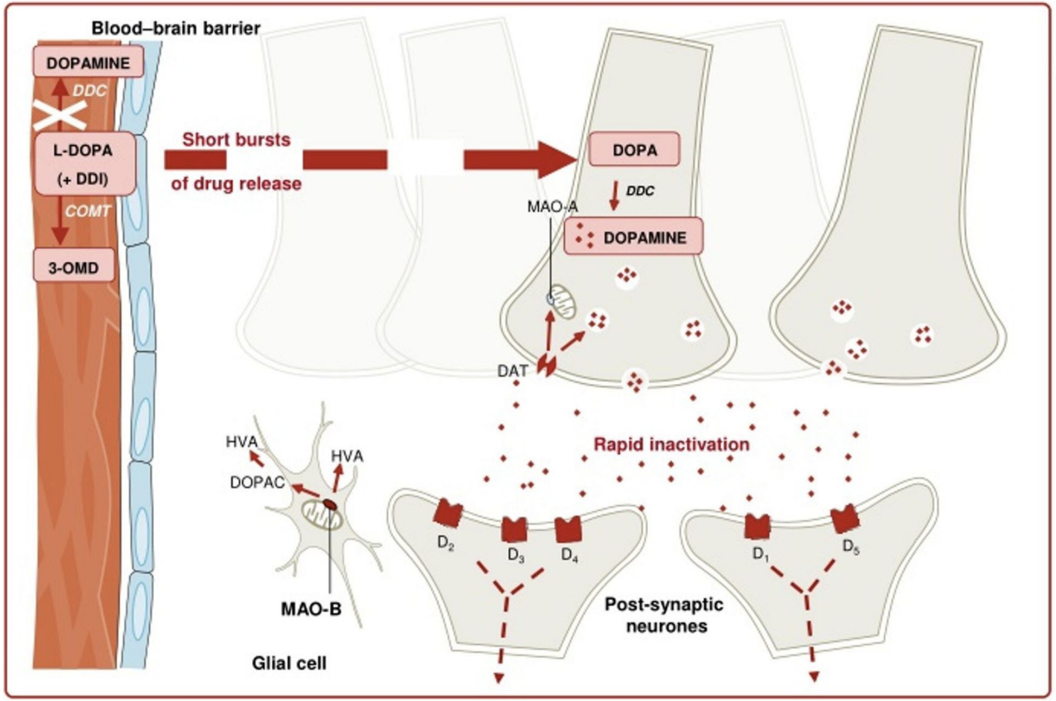


REF Fig.5 - Hariz & Blomstedt - Journal of Internal Medicine - 2022;;

How is the problem addressed?

Treatment approaches

Dopaminergic therapy



Gold standard

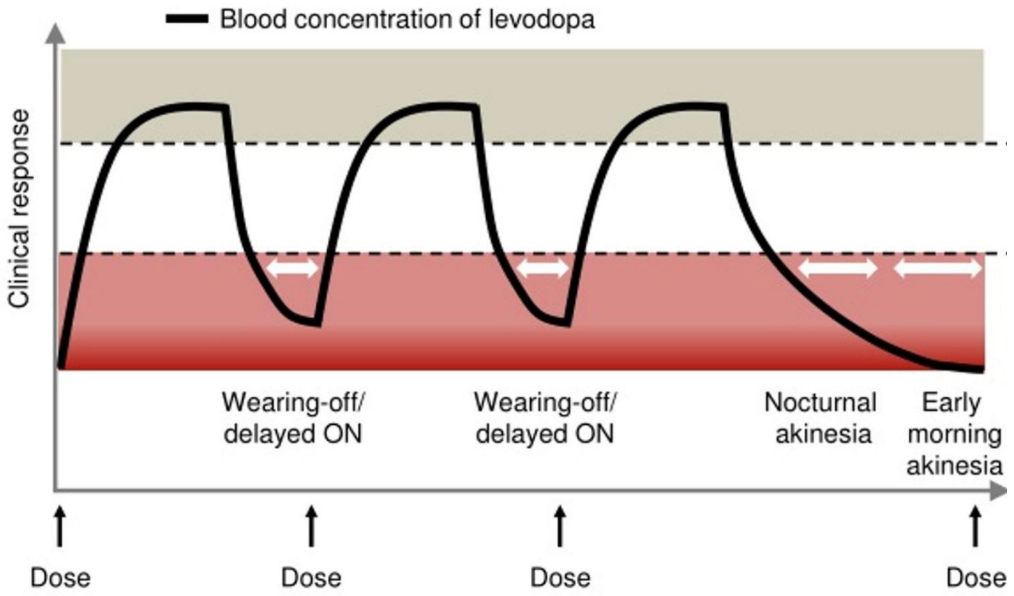
- L-DOPA
- Effective for most motor symptoms

Side effects

- Confusion
- Dyskinesia: involuntary movements

REF Beaulieu-Boire - Behavioral Effects of Levodopa;

Dopaminergic therapy

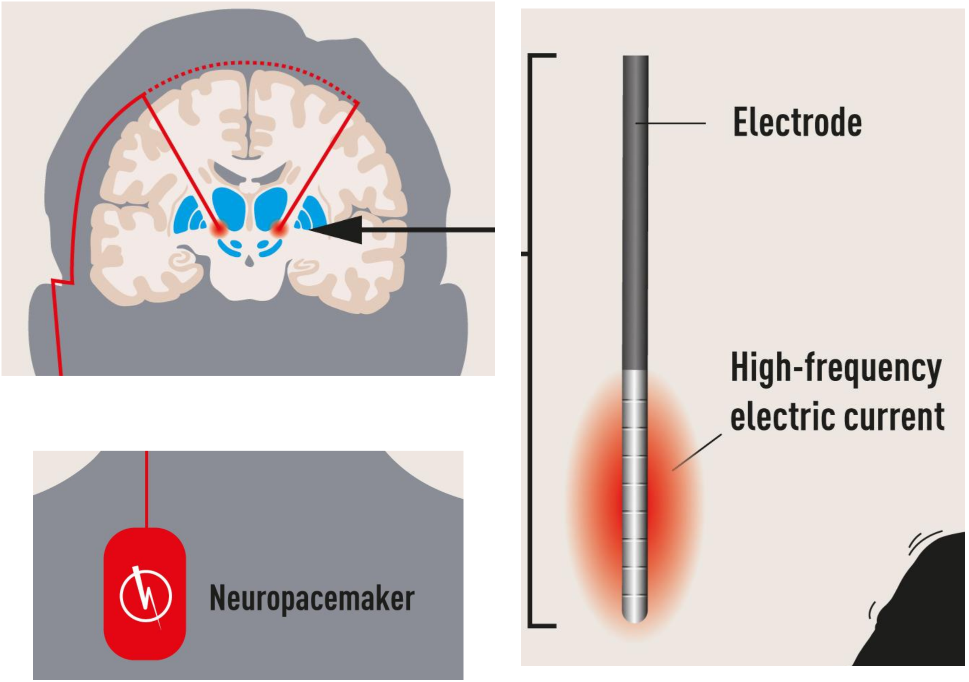


Fluctuations

- "**ON**" periods (good symptom control)
- "**OFF**" periods (symptom reemergence)

REF Beaulieu-Boire - Behavioral Effects of Levodopa;

Deep Brain Stimulation (DBS)



- Target STN (or GPi)
- Improves motor symptoms

However

- Gait disorders particularly resistant
- FoG episodes persist

REF Bloem et al. - Movement Disorders - 2004; Macellari, N., Closed-Loop Control of Epidural Electrical Stimulation in Patients with Spinal Cord Injury and Parkinson's Disease, EPFL, 2023

Epidural Electrical Stimulation (EES)

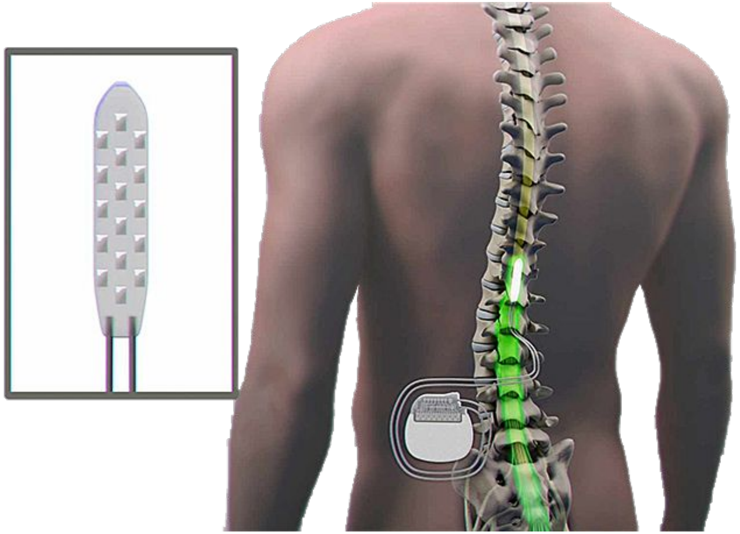
Electrode

Lumbar position for gait control

+ **IPG** (invasive pulse generator)

Power and settings for

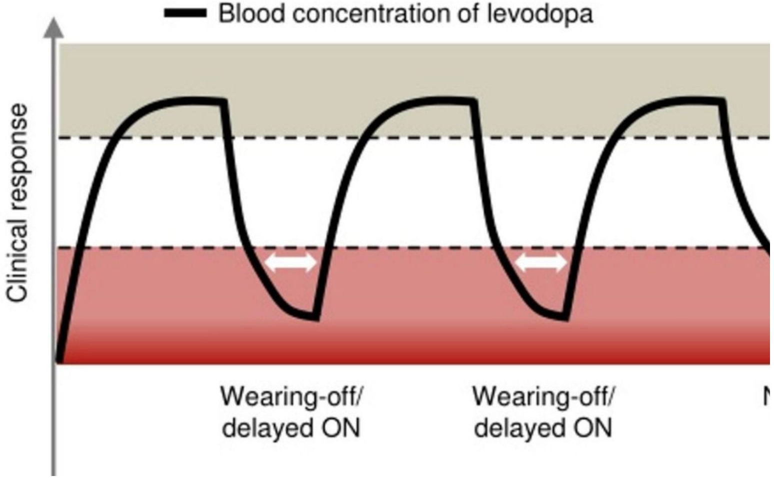
- amplitude
- frequency
- pulse width
- stimulation time



REF Bloem et al. - Movement Disorders - 2004

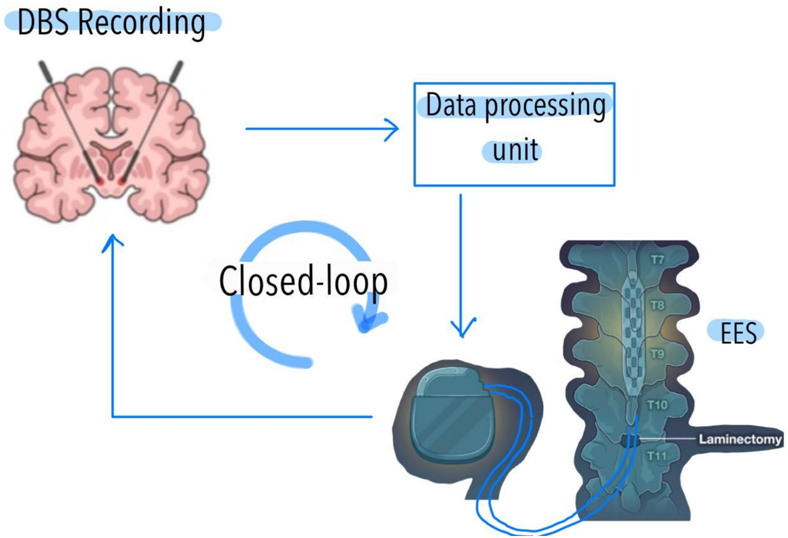
Summary: Target our problem!

- Drug-induced fluctuations and fast disease degeneration make each patient treatment needs unique
- EES Stimulation that doesn't take into account real-time patient state (medication, fatigue, performed activity in the moment)



Same stimulation in different conditions time would not be effective!

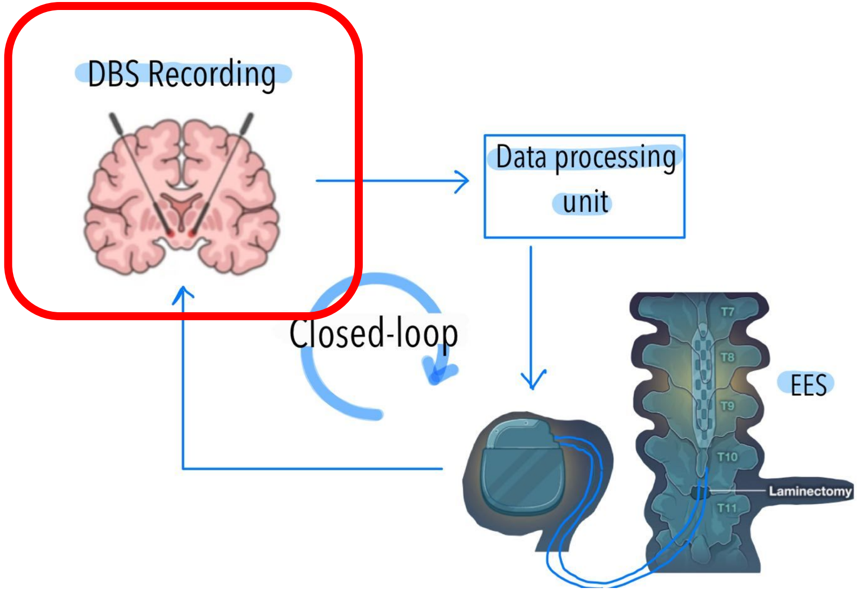
EPFL



Our solution

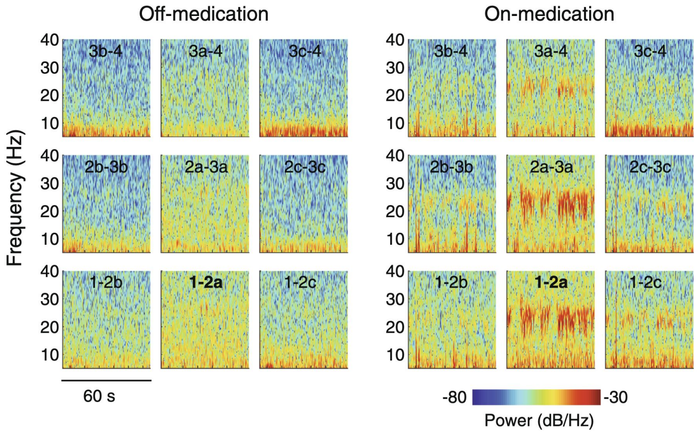
closed loop EES

Our solution - Overview



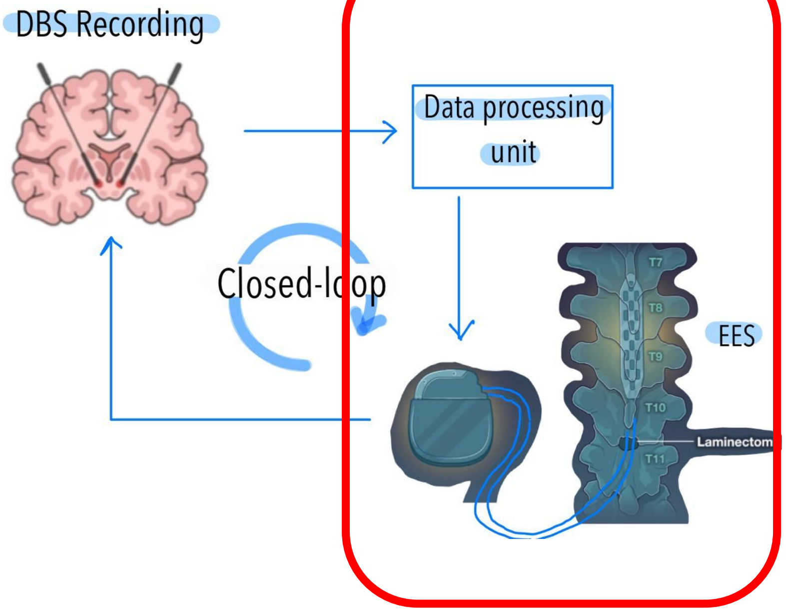
DBS is implanted in over 80.000 patients (⅔ are PD patients)

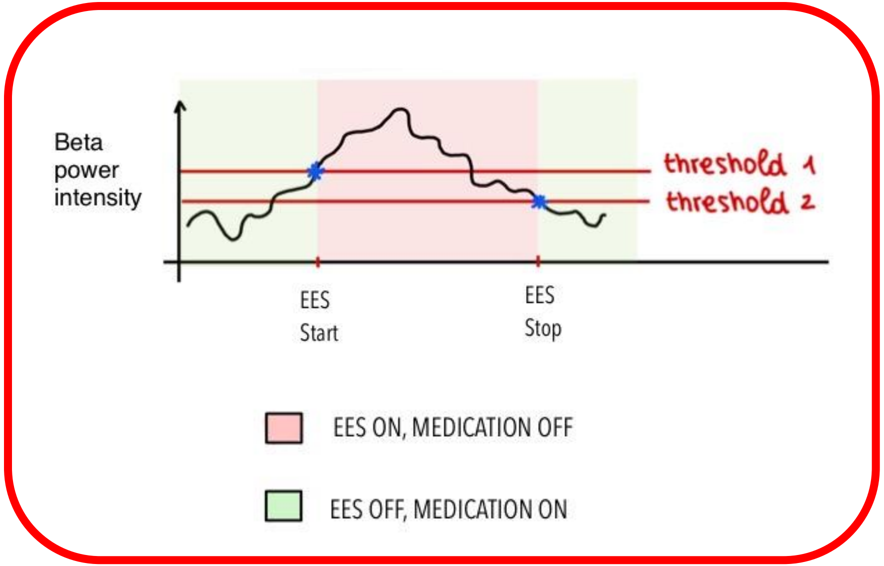
Beta band specifically, recorded in STN, strongly correlates with gait impairment and ON-OFF medication periods



REF van Wijk et al. - Journal of Neurology - 2022; Kestenbaum et al. - Movement Disorders Clinical Practice 2015; Hill et al. - Movement Disorders - 2023

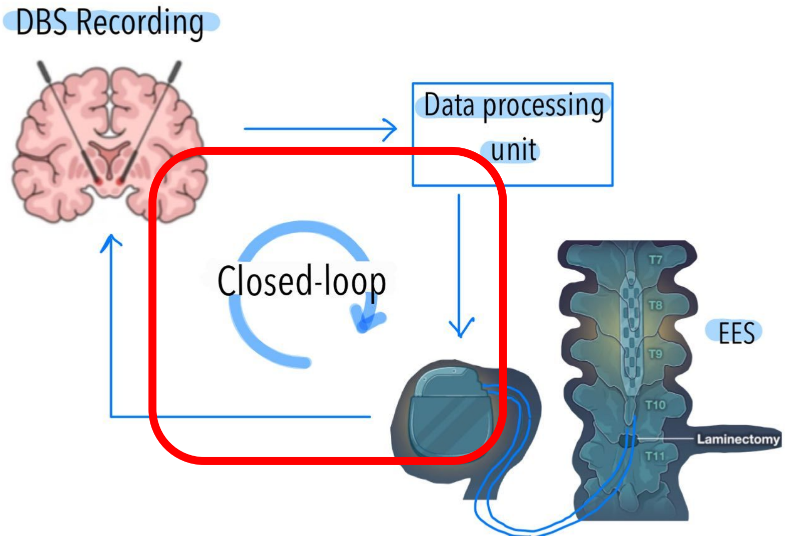
Our solution - Overview





REF van Wijk et al. - Journal of Neurology - 2022; Fuentes et al. - European Journal of Neuroscience - 2010

Our solution - Overview



Adjustment of EES parameters
based on EES-induced brain signal change

REF van Wijk et al. - Journal of Neurology - 2022; Fuentes et al. - European Journal of Neuroscience - 2010; Sandoval-Pistorius et al. - The Journal of Neuroscience - 2023

DBS biomarkers for FoG

Data from STN can be processed to extract relevant information related to gait dynamics (FoG episodes)

- Low-Beta power
- Beta burst duration
- Beta-Gamma PAC
- Alpha sample entropy
- Gait temporal dynamic

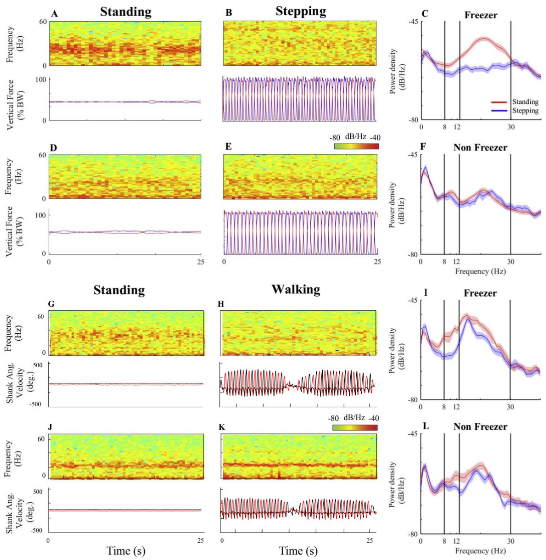
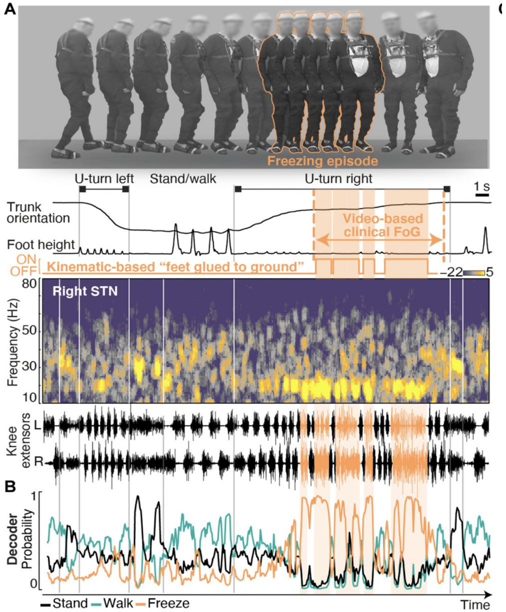
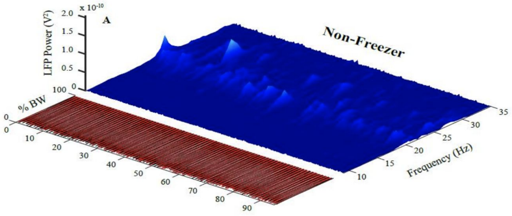
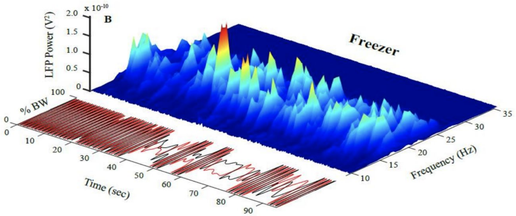


Fig. 3. Representative Freezer (A, B, C, G, H, I) and Non-Freezer (D, E, F, J, K, L) synchronized time-frequency STN LFP spectrograms, SIP cycles, FW cycles, and power spectral density diagrams (PSDs) during standing (red) and stepping or FW without FEs (blue). %BW = Percentage of bodyweight. * denotes subject turning around, not freezing.

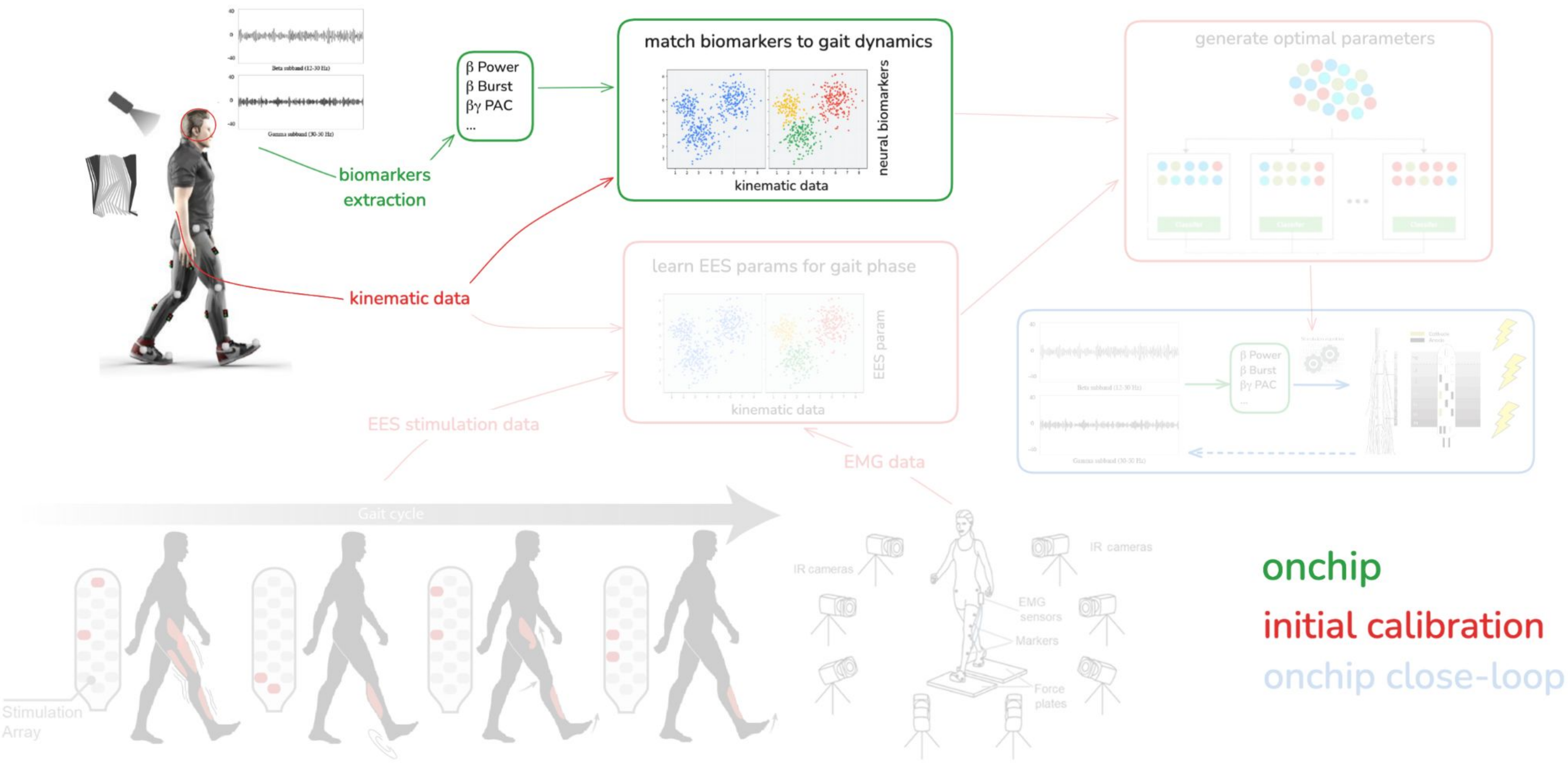




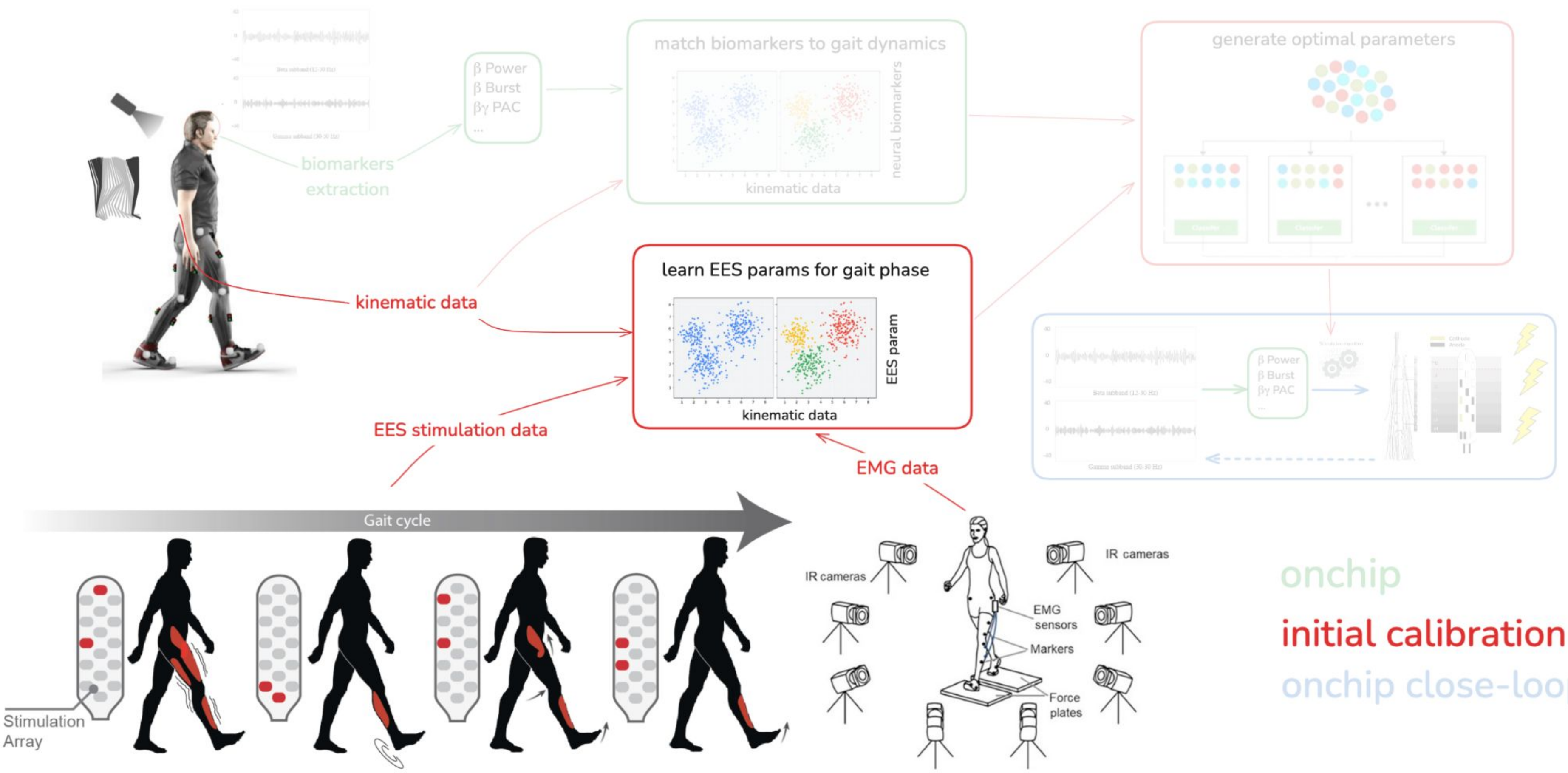


REF Anidi et al. - Neurobiology of Disease - 2018; Thenaisie et al. - Science Translational Medicine - 2022; Syrkin-Nikolau et al. - Neurobiology of Disease - 2017; Farokhniaee et al. - Scientific Reports - 2024

Initial tuning - DBS-Gait



Initial tuning - Gait-EES

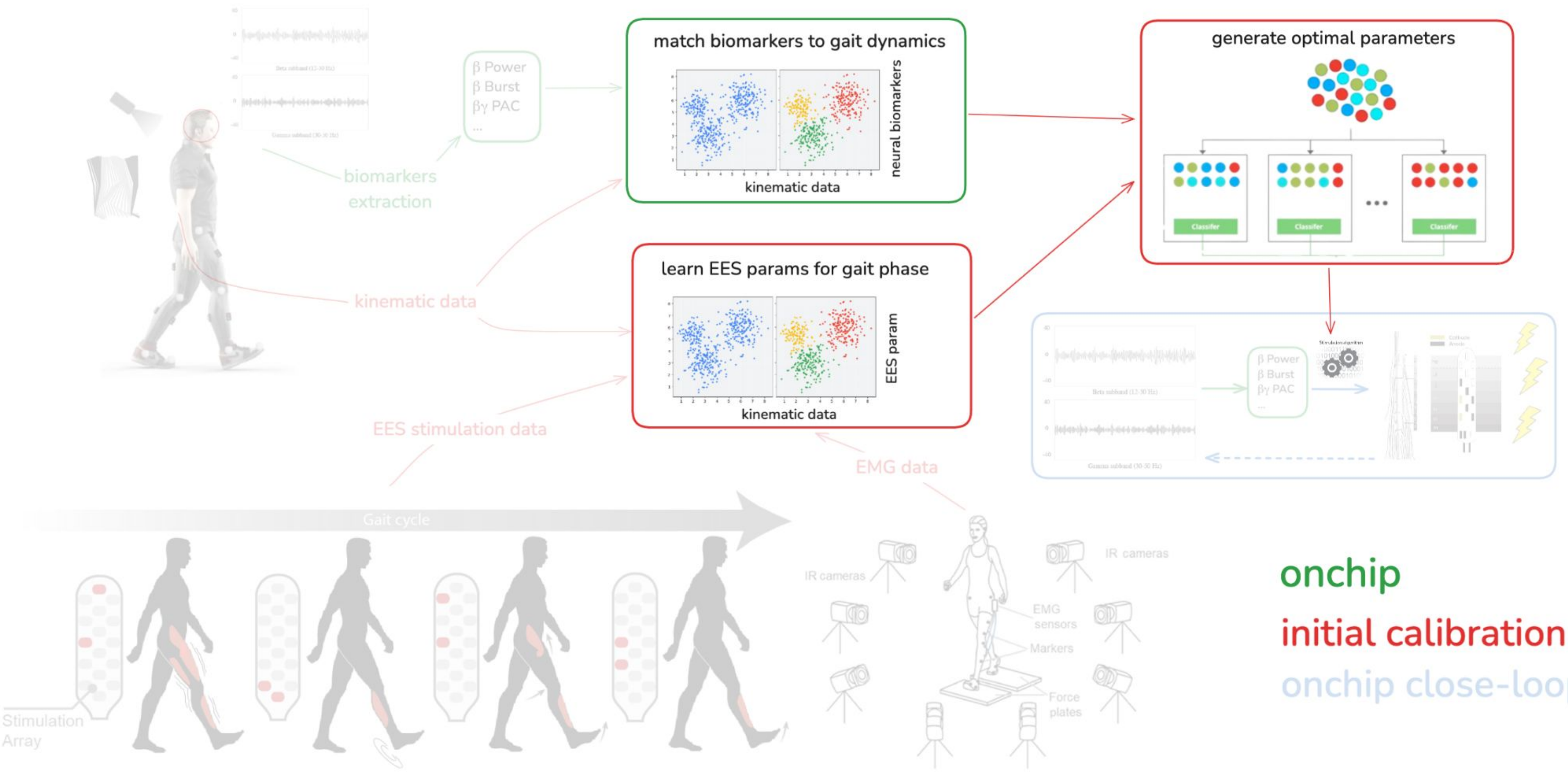


onchip

initial calibration

onchip close-loop

Initial tuning - DBS-EES

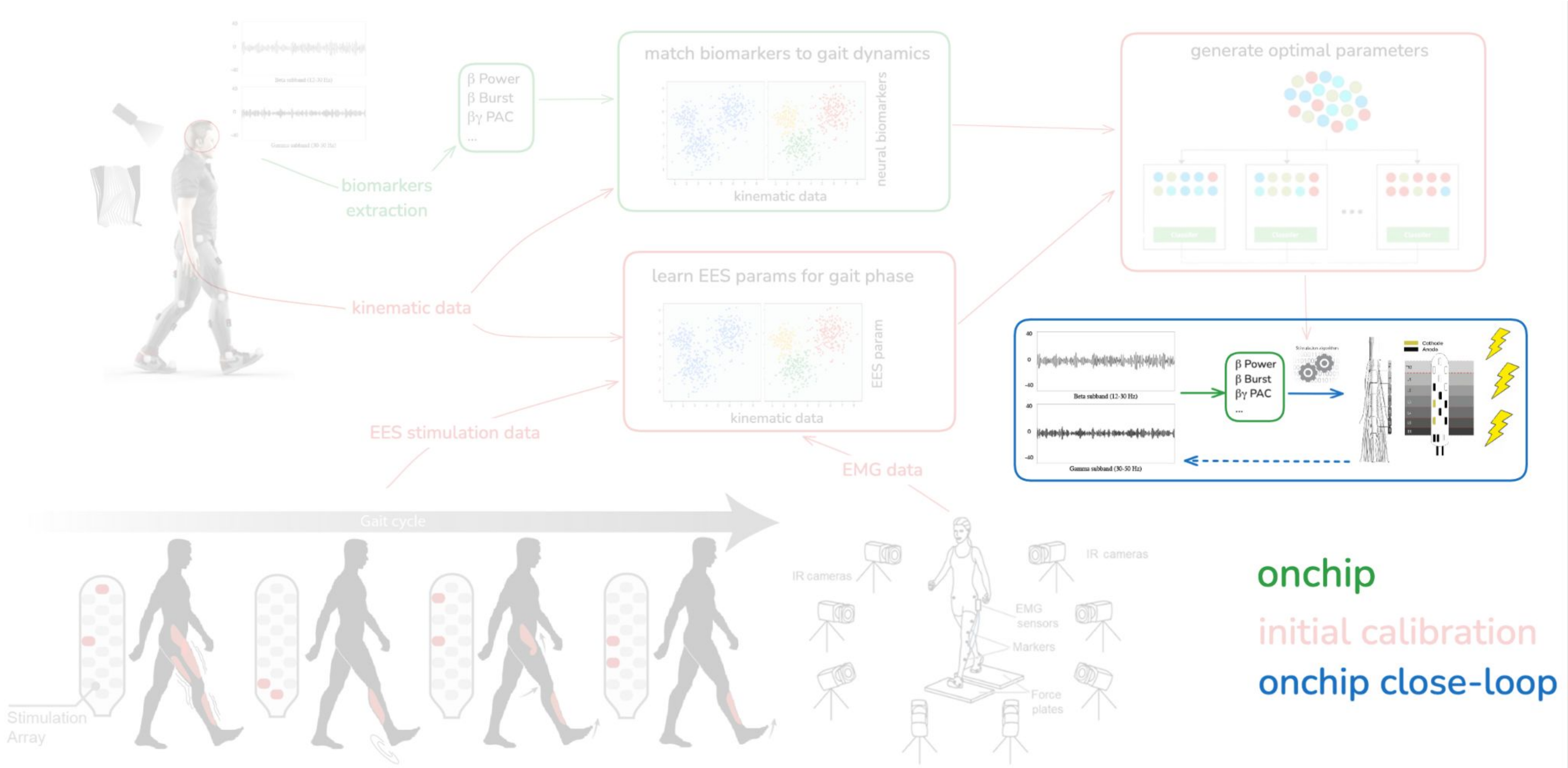


onchip

initial calibration

onchip close-loop

Closed loop



β Power
β Burst
βγ PAC
...
biomarkers extraction
match biomarkers to gait dynamics
neural biomarkers
kinematic data
generate optimal parameters
kinematic data
learn EES params for gait phase
EES param
kinematic data
EES stimulation data
EMG data
Gait cycle
Stimulation Array
IR cameras
IR cameras
EMG sensors
Markers
Force plates
Beta subband (12-30 Hz)
Gamma subband (30-50 Hz)
β Power
β Burst
βγ PAC
...
Cathode
Anode
onchip
initial calibration
onchip close-loop

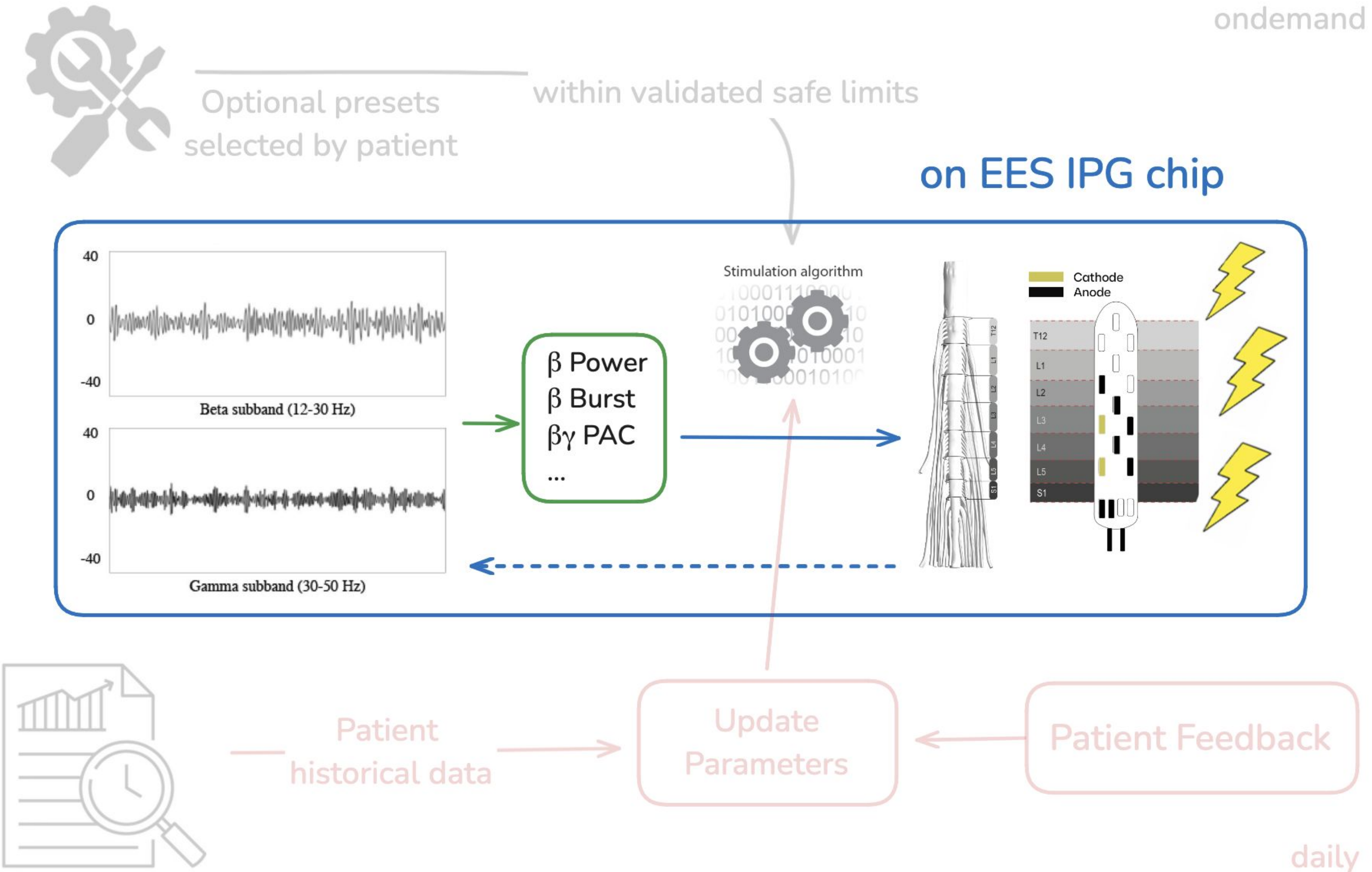
Closed loop in details

Calibration Phase & Initial Learning

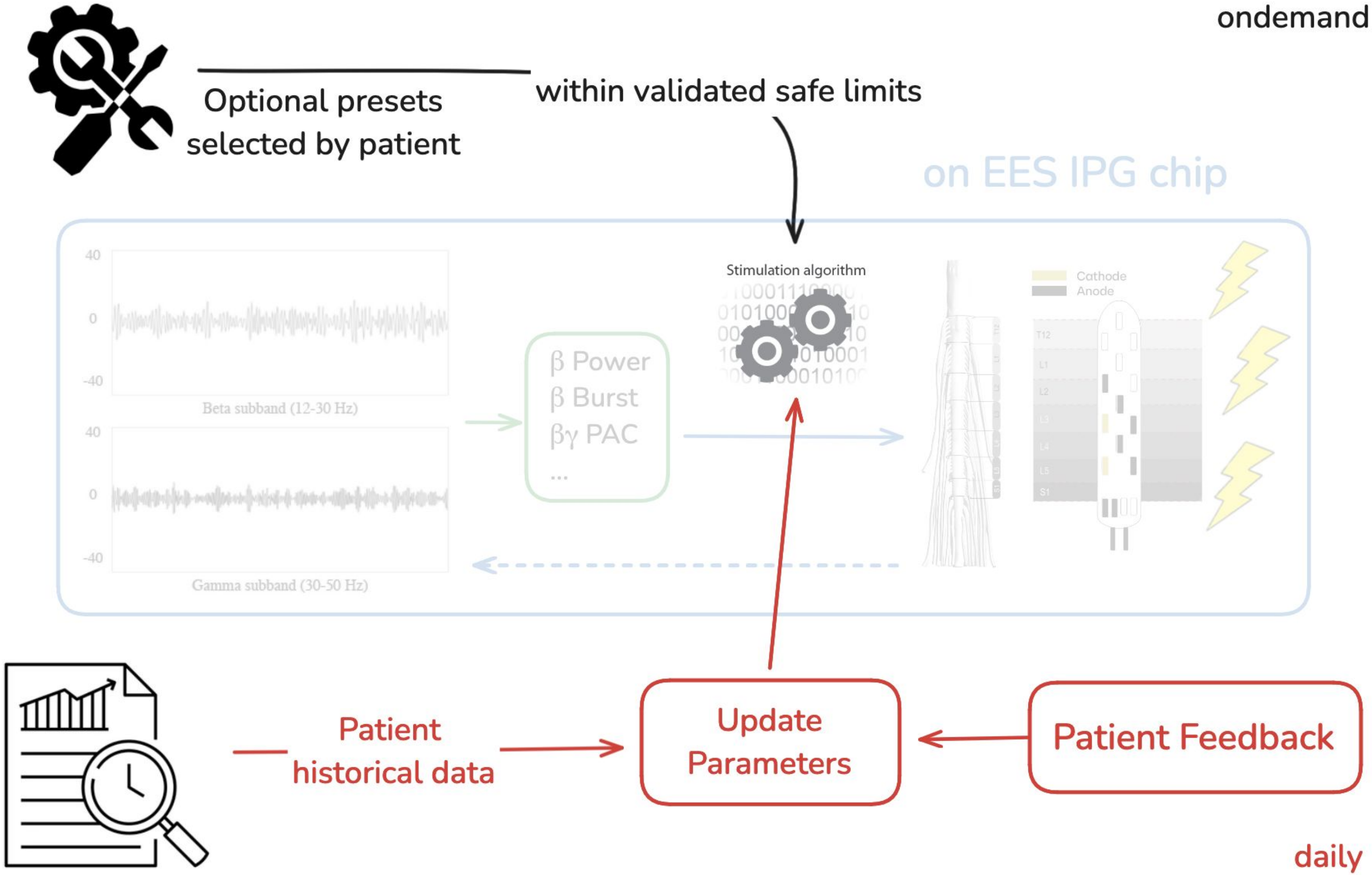
- Neural signals is processed on chip for feature/biomarker extractions
- Neural biomarkers matched to kinematic data to understand gait dynamics from DBS alone
- EES is tuned with the help of EMG recordings
- Kinematic data is matched to EES parameters to learn optimal stimulation settings for each gait phase/condition

The system integrates neural recordings, kinematic measurements, EES stimulation settings, and EMG data during gait cycles to establish these foundational mappings. Mappings are store as LUT on the EES chip for fast retrieval

Adaptive optimization



Adaptive optimization

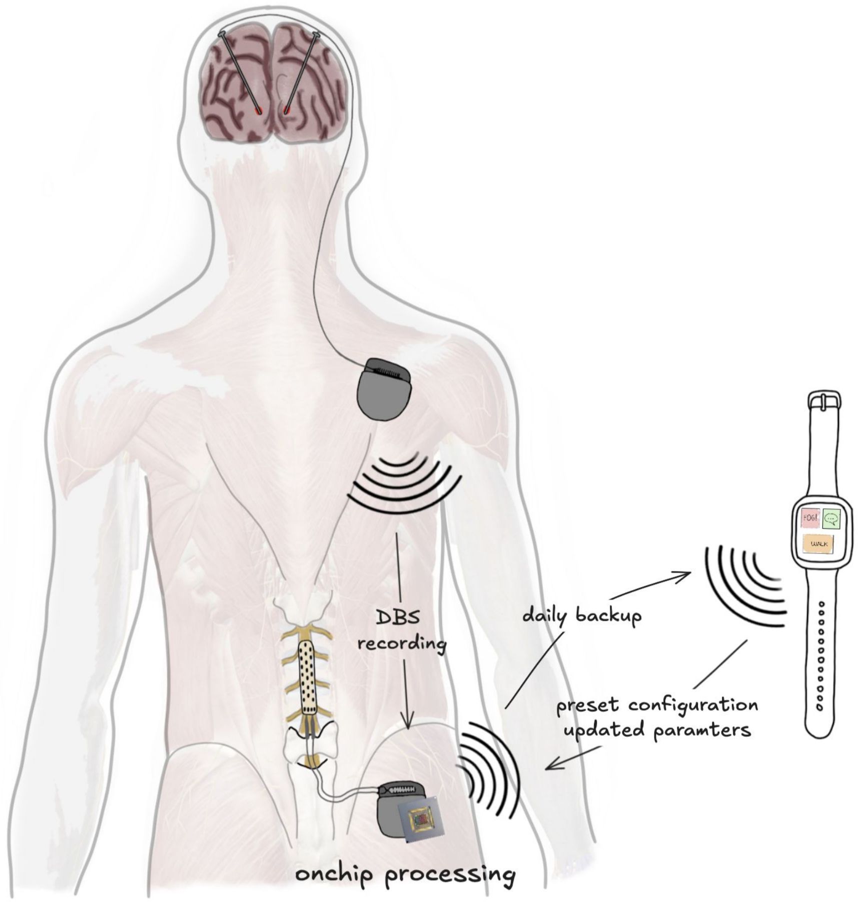


Adaptive optimization

Adaptive Optimization Process

- Continuous learning system where stimulation parameters are refined using patient feedback and historical performance data
- The system allows patients to select optional presets within validated safety limits
- Monitors beta (12-30 Hz) and gamma (30-50 Hz) frequency bands, extract features and updates the stimulation algorithm accordingly.

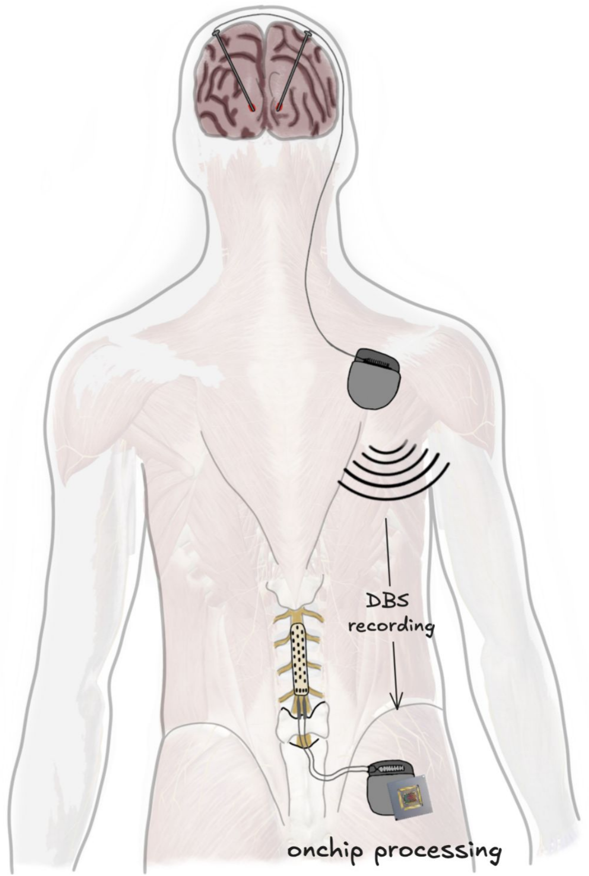
This creates a closed-loop system where parameters are continuously optimized based on real-world use while maintaining safety constraints.



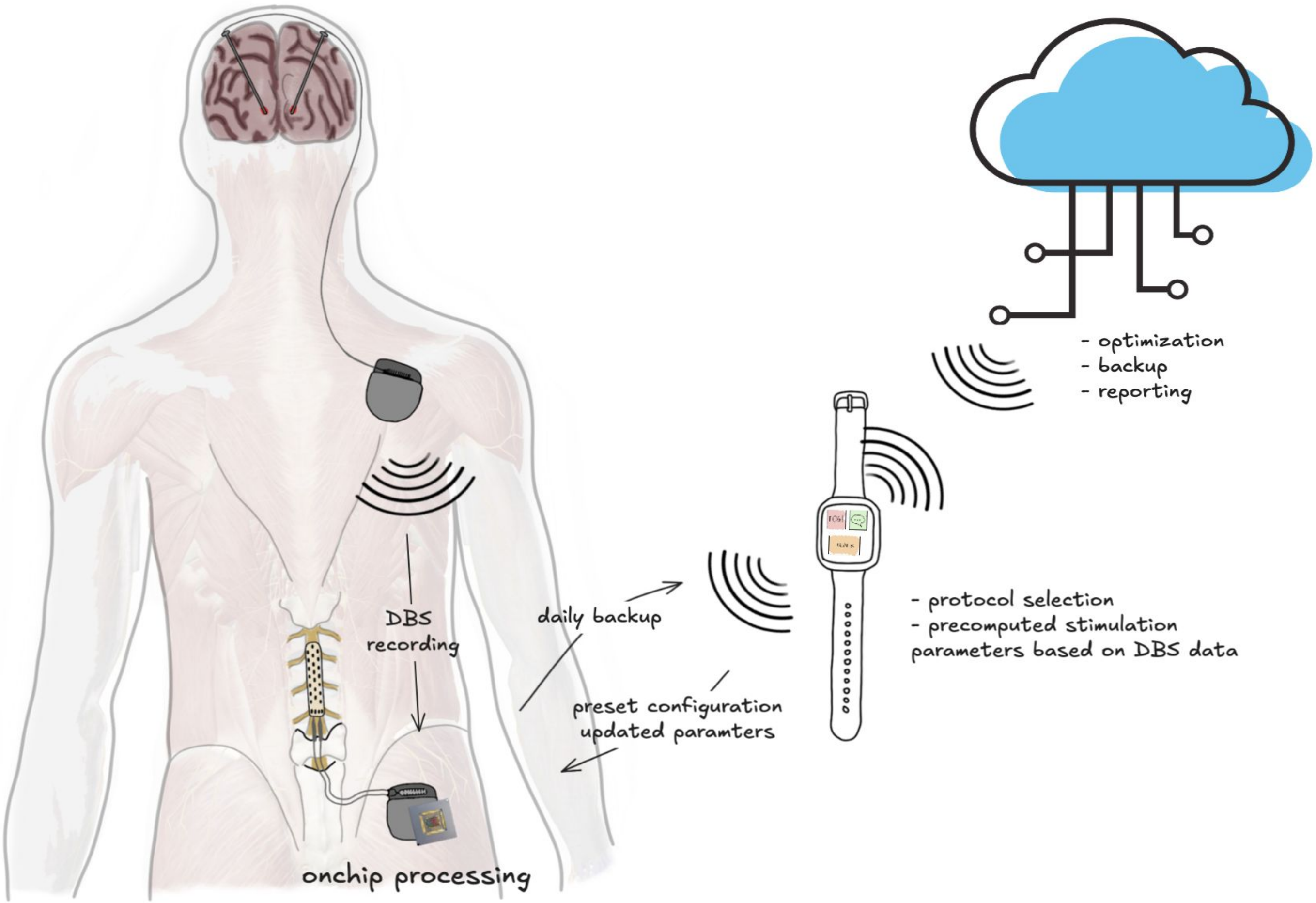
DBS and EES communication

EES-DBS communication

- Link 2 IPGs: EES and DBS
  - Long-time solution, non-cumbersome
  - Internet connection for storage
- DBS unchanged because already implanted
- EES IPG
  - Received from DBS
  - Determination of stimulation signal explained before



The system


- optimization
- backup
- reporting
- protocol selection
- precomputed stimulation
parameters based on DBS data
DBS
recording
daily backup
preset configuration
updated paramters
onchip processing

Reporting the data

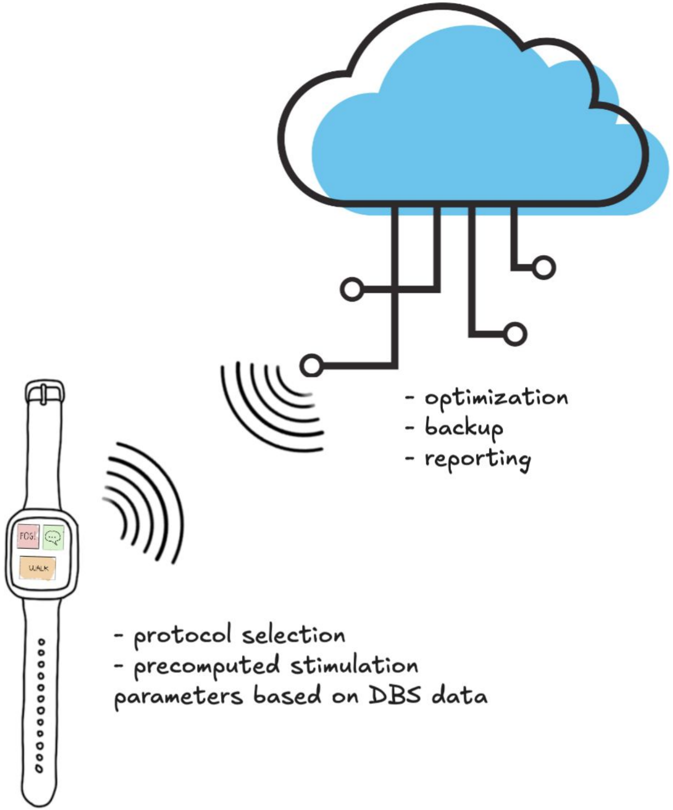
External connected watch

Uploaded on cloud when connection

- Health report
- Follow advance of disease
- Regulation if required (after certain period of time)

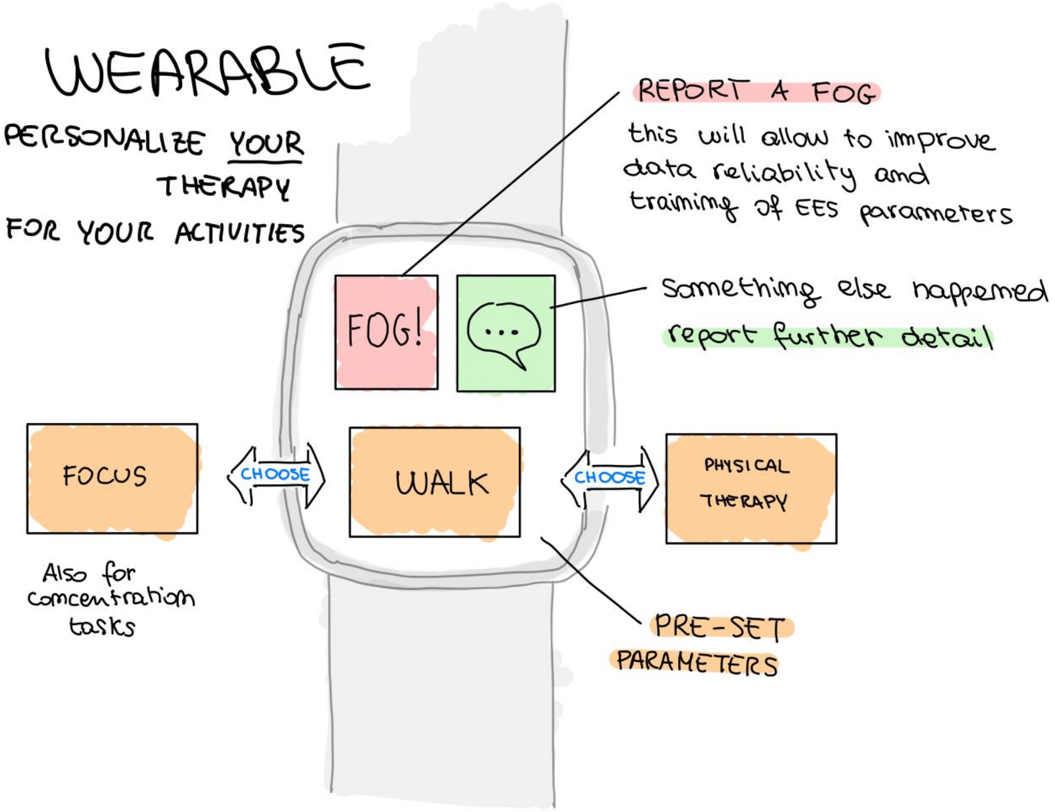
Useful for Healthcare providers

- Call to the hospital
- Change of treatment

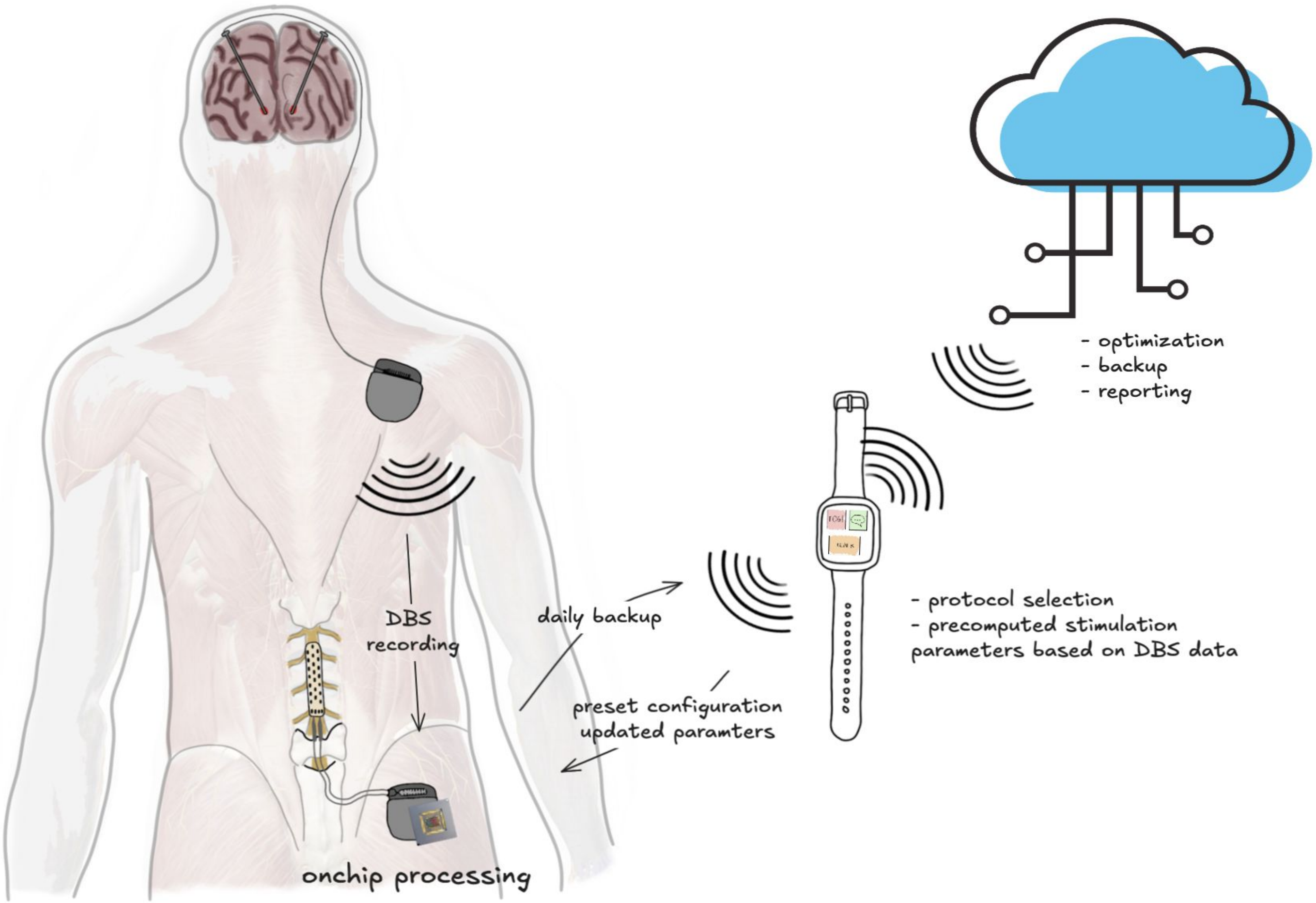


REF Kremen et al. - IEEE Journal of Translational Engineering in Health and Medicine - 2018

Scheme watch



The system


- optimization
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parameters based on DBS data
DBS
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Clinical validation and beyond

- Selection of Patients
- Calibration of the system
- Multi-Task Validation
- Identification of FoG
- Self-calibration

REF Syrkin-Nikolau et al. - Neurobiology of Disease - 2017

Selection of patients

Standard “Freezing of Gait Questionnaire” assessment across PD patients

- In all-day life
- Experiencing gait deficits or Freezing of Gait

Selection of Patients

Calibration of the system

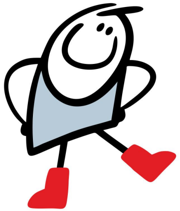
Multi-Task Validation

Identification of FoG

Self-calibration

REF Syrkin-Nikolau et al. - Neurobiology of Disease - 2017

Calibration of the system in the clinic



Initial tuning (in hospital)

- External sensors
- Identifying hierarchy most predictive biomarkers
- For example: EMG sensors/socks, floor pressure mat, smart pressure/IMU insoles

Tasks selection (**blinded ON/OFF**)

- Turning and Barrier Course (TBC)
- Timed Stepping in place (SIP) - well established
- Forward walking assessment

Selection of Patients

Calibration of the system

Multi-Task Validation

Identification of FoG

Self-calibration

Multi-Task Validation

Attention Division Strategy

- Dual-task conditions to challenge attention during gait
  - Auditory odd balls for distraction
- Environmental manipulations

Data Collection

- Continuous neural recording
- **Movement sensors**
- Real-time **patient feedback**

Selection of Patients

Calibration of the system

Multi-Task Validation

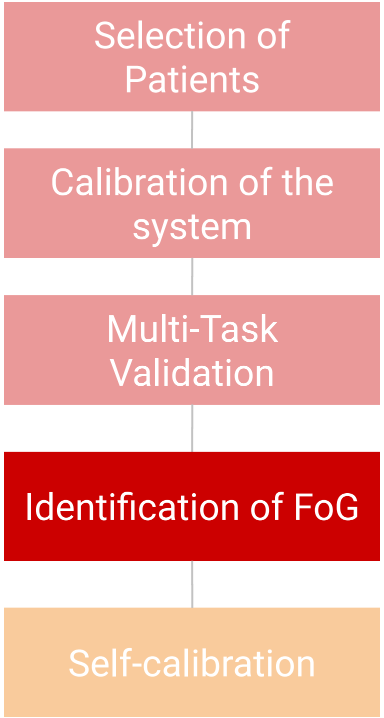
Identification of FoG

Self-calibration

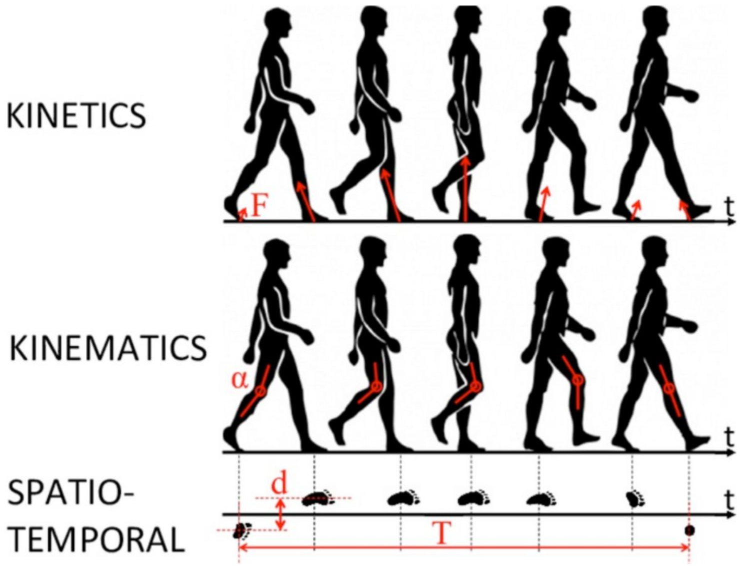
EPFL

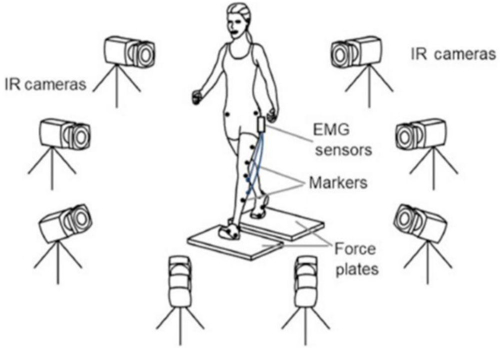
Identification of FoG episode during clinical setting

- Tuning to recognize and proactively act on onset of FoG episodes
- Standard Approach
  - Videotaping during walking (analysis by neurologists)
  - Sensors: inertial motions or pressure
  - Body markers for computational gait analysis



Identification of FoG episode during clinical setting





Selection of Patients

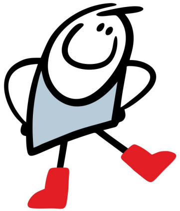
Calibration of the system

Multi-Task Validation

Identification of FoG

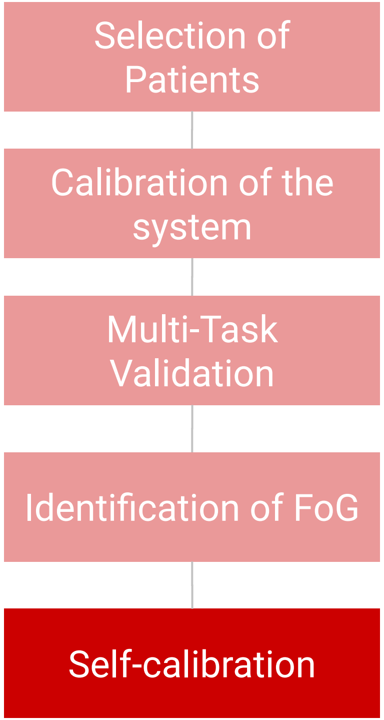
Self-calibration

Self-Calibration of the system



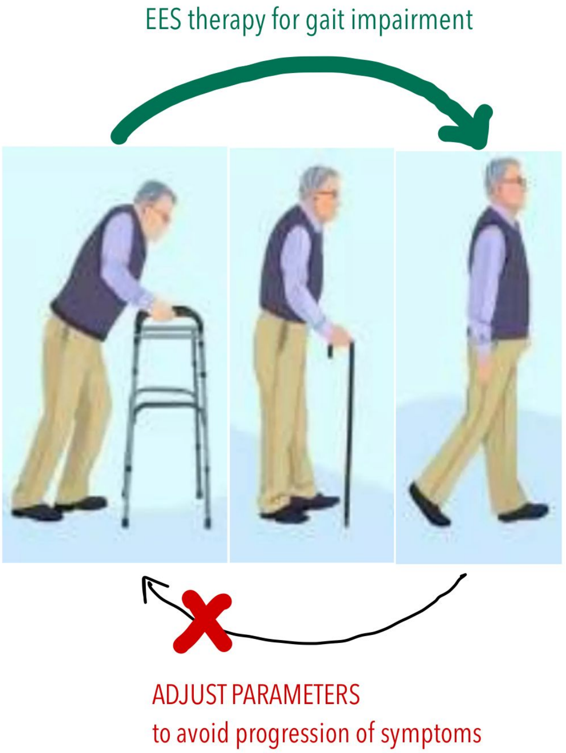
- Self - calibration period
  - Maintain accurate prediction
  - Depending patient feedback
  - Combination of easy-to-install sensors
- Hypothesis
  - Neural activity changes over time
  - Not just patient symptoms but need to recalibrate step 1

1. neural-activity -> detected-event
2. detected-event -> stimulus



Our solution is THE solution

- Regain QUALITY of life
- Little WEARABLE WATCH instead of a cumbersome computer
- Independent and ease of use for patient
- RELIABILITY compared to non-invasive signal
- PERSONALIZATION with patient's needs
- Reproducibility
- Energy-efficient in a way that there is only stimulation when needed



Limitations

- Not all patients with DBS have the new generation recording electrodes
- Precise timing for stimulation, and real-time data analysis required. No clear failsafe mechanism (stimulation happening at wrong time)
- Long term instability of neural signature might decrease the accuracy of the stimulation due to progression of the disease
- Accurate application needs a often control with the doctor
- Ethical consideration wrt data reporting system that must guarantee patient privacy

However, we are confident that with more research, data collection and test of this system, the reliability can be maximized

References:

Fig.1: Parkinson’s Disease - Causes, Symptoms, Treatment and Prevention

Chaudhuri et al. - Drugs - Real World Outcomes - 2024
https://doi.org/10.1007/s40801-023-00410-1

Castonguay et al. - Journal of Parkinson's Disease - 2021

A.-M. Castonguay, C. Gravel, M. Lévesque, Journal of Parkinson’s Disease 2021

Mizrahi-Kliger & Ganguly - Nature Medicine - 2023 https://doi.org/10.1038/s41591-023-02604-0

Hariz & Blomstedt - 2022 https://doi.org/10.1111/joim.13541

Bloem et al. - Movement Disorders - 2004 - https://doi.org/10.1002/mds.20115

Wang et al. 2018 https://doi.org/10.1109/ICASSP.2018.8462472

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Thenaisie et al. 2022 https://doi.org/10.1126/scitranslmed.abo1800

Syrkin-Nikolau J et al. 2017 - https://doi.org/10.1016/j.nbd.2017.09.002

Farokhniaee et al. 2024 https://doi.org/10.1038/s41598-024-57252-2

Hausdorff et al. - 2003 https://doi.org/10.1007/s00221-002-1354-8

Thank you

Extra Slides

Cardinal symptoms

TREMORS

BRADYKINESIA

POSTURAL INSTABILITY

RIGIDITY

Cardinal symptoms

TREMORS

BRADYKINESIA

POSTURAL INSTABILITY

RIGIDITY




Cardinal symptoms

TREMORS

BRADYKINESIA

POSTURAL INSTABILITY

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Cardinal symptoms

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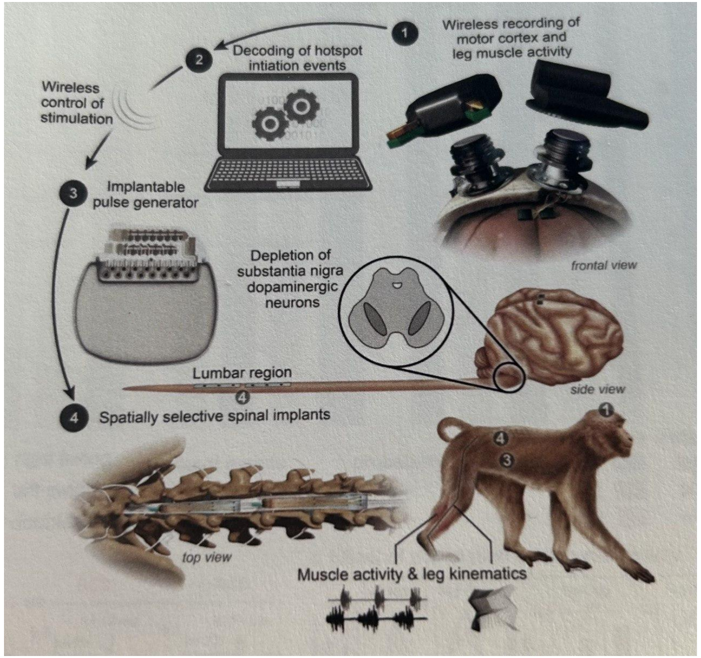
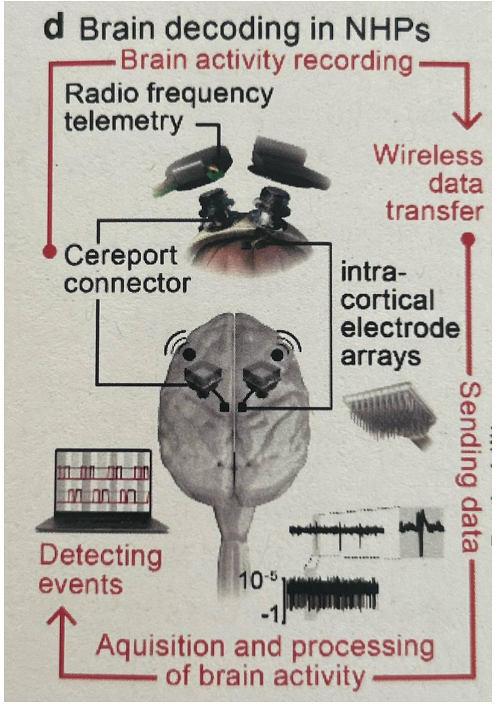
Ongoing research on EES to solve gait impairment in PD - at EPFL



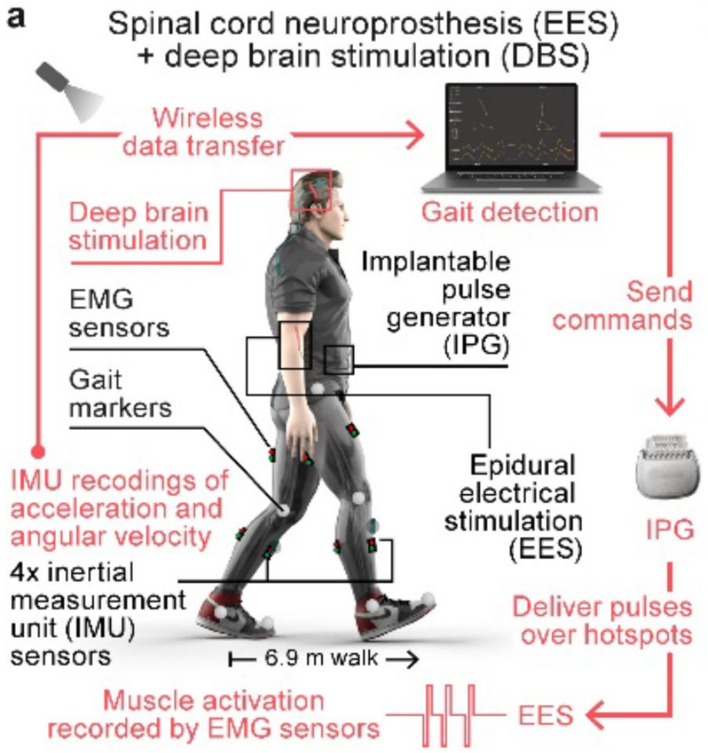


- Brain-spine interface (BSI) for alleviating gait impairments in a non-human primate (NHP) model of PD induced by MPTP.
- *Recorded signal:* **<u>microelectrode arrays</u>** <u>in the motor cortex</u> to decode locomotor intentions
- *Stimulation:* EES stimulation of motor neurons in the spinal cord
- *Results:* This approach reduced FOG and enhanced gait quality.

- all necessary implantable technologies were undergoing clinical evaluation for human application. (2019)

REF Doctoral thesis Raschella, F. Brain-spine interface technologies to alleviate gait deficits after Parkinson's disease, EPFL, 2019

Ongoing research on EES to solve gait impairment in PD - at EPFL



- Neuroprosthesis centered on closed loop EES
- *Recorded signal:* wearable sensors attached to the legs (IMUs) were used to synchronize EES with ongoing movement.
- *Data processing unit:* software running on a tablet. This software detected gait events related to hotspot activation and transmitted updated sequences of EES bursts to the IPG of EES.
- *Stimulation:* EES modulation of the lumbosacral spinal cord compensates in real time for the abnormal activation of leg motor neurons caused by PD
- *To validate:* compared gait patterns registered, against those of both PD and healthy controls using a linear discriminant analysis (LDA) classifier
- *Results:* (EES on) the majority steps were classified as resembling those of healthy individuals.

REF Doctoral thesis Macellari, N., Closed-Loop Control of Epidural Electrical Stimulation in Patients with Spinal Cord Injury and Parkinson's Disease, EPFL, 2023

Offline computational modeling

Offline processing needs to solve and optimize

- DBS signal X to gait impairments Y
  - Supervised classification with data collected during validation protocol
- EES parameters P to improve Y
  - Computational modeling + simulation (paired with EMG for tuning of the stimulation parameters) with confidence intervals
- Learn f(X) = P
  - LSTM / autoencoder / ??

Ideally we'd like to have interval around the predicted stimulation that the patients can auto tune. Considering `latency`, `duration` and `amplitude`, allow patients to choose `P ± k` based on `low/normal/high` intensity preset

EPFL EXTRA SLIDES

Why a comparison to SPI patients

- In some studies of Spinal Cord Injury they did already link EES and DBS IPGs
    - SPI-patients can walk again
    - BUT not exactly the same as Parkinson Disease
- In studies over Spinal Cord Injury use of a computer
    - PD-patient won’t re-establish connections as SPI-patients
    - Need of “long-time solution” while computer is heavy and cumbersome
    - Possible solution: watch or phone app for making an external communication and storing of data
        - Connect to internet and store there for higher capacity of stockage

Rehabilitation Program

Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis

EPFL

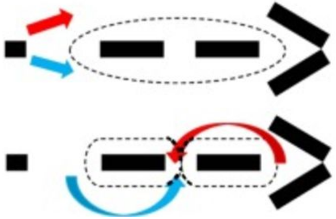
Task - Validation Protocol in details

STEPPING IN PLACE

C

TURNING AND BARRIER COURSE

D



Task	*Description*	Average timing
Forward Walking	Walk forward 10m, turn around and walk back Back and forth until have walked approximately 40m	27.29 s
Stand in Place	Alternating stepping on dual forceplates, measure of the ground forces captured at 100 or 1000 Hz	100s
Turning and Barrier Course	*Novel FW*: subject is instructed to walk around room dividers in form of ellipse twice, then walk in figure of eight twice and then through the gaps between the dividers Little resting break Subject starts repeats task in opposite direction but four times (not the gaps part)	140.08s
	All tasks started with resting state of 30s	

REF Syrkin-Nikolau et al. - Neurobiology of Disease - 2017

Identification of Freezing of Gate

Beta frequencies: 12-30 Hz

*Figure 3 Representative Freezer (A, B, C, G, H, I) and Non-Freezer (D, E, F, J, K, L) synchronized time-frequency STN LFP spectrograms, SIP cycles, FW cycles, and power spectral density diagrams (PSDs) during standing (red) and stepping or FW without FEs (blue). %BW = Percentage of bodyweight. * denotes subject turning around, not freezing.*

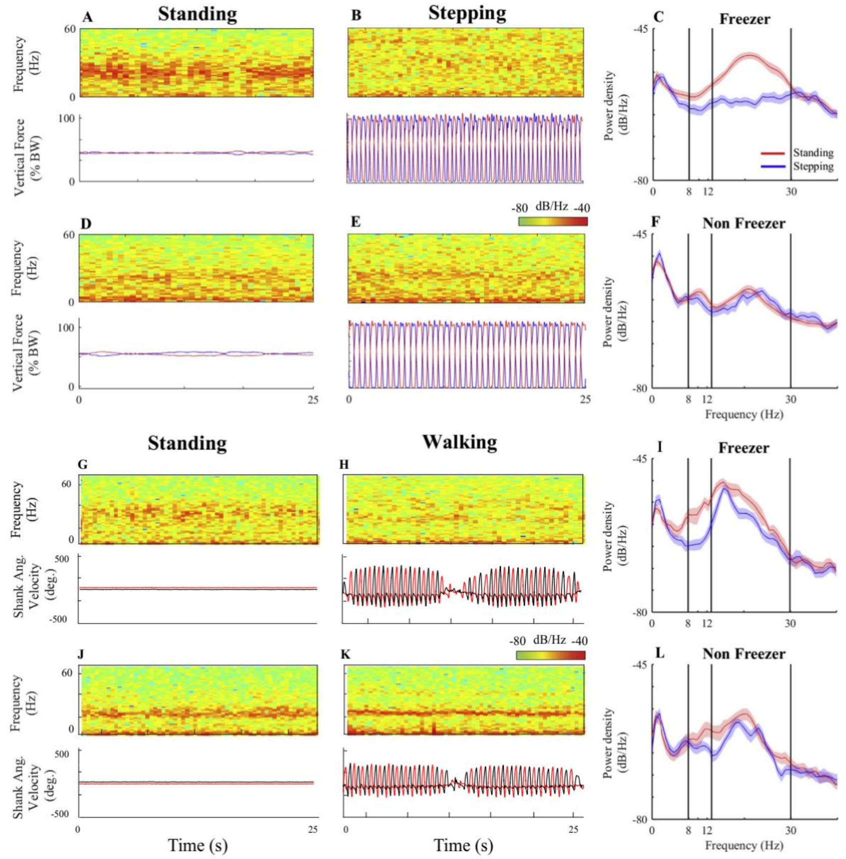


Fig. 3. Representative Freezer (A, B, C, G, H, I) and Non-Freezer (D, E, F, J, K, L) synchronized time-frequency STN LFP spectrograms, SIP cycles, FW cycles, and power spectral density diagrams (PSDs) during standing (red) and stepping or FW without FEs (blue). %BW = Percentage of bodyweight. * denotes subject turning around, not freezing.

Speaker

Beta Burst Characteristics

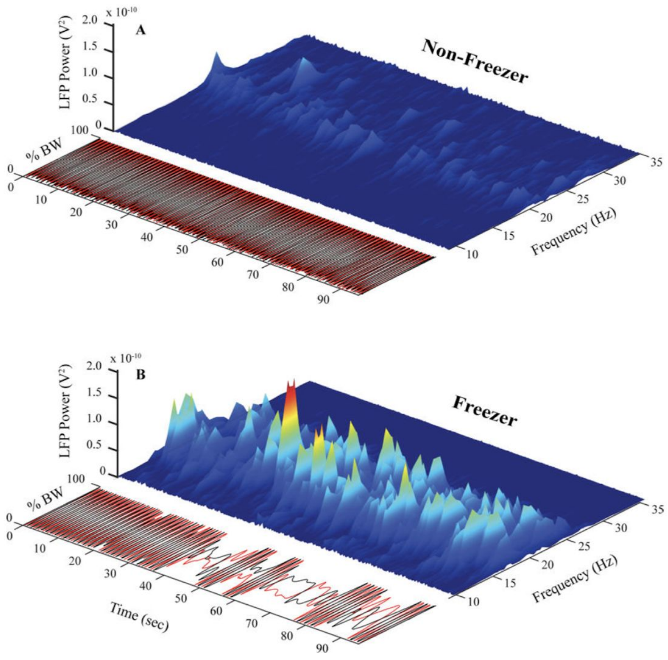
Temporal patterns of beta activity:

Key Findings

- **Longer burst durations** in Freezers vs Non-Freezers
- **Even longer during active FOG** events
- Independent from resting state measurements

Clinical Relevance

- Minimal computational cost
- Potential predictive value



Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease

EPFL

Low-Beta Power Trends

Spectral changes during freezing events:

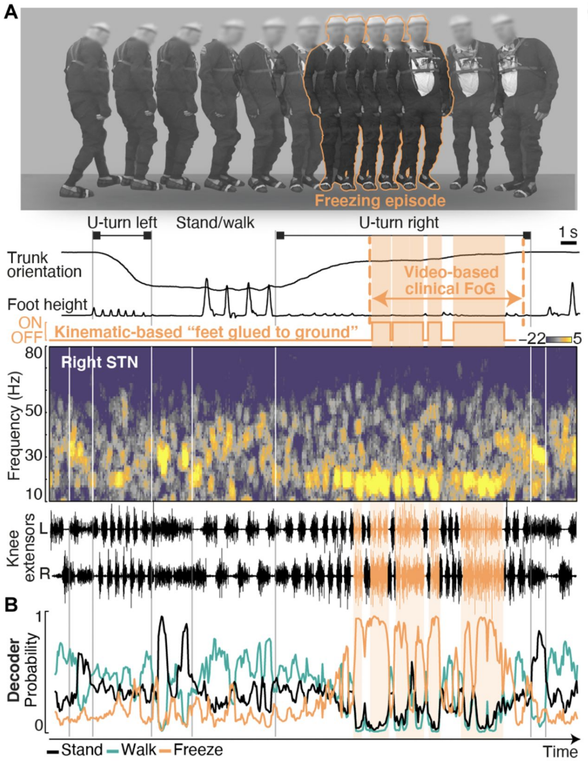
Key Findings

- **Increased low beta power (13-20 Hz) during freezing** vs walking
- Signal strength mirrors freezing severity
- Bilateral STN activation patterns to decode **right/left striking events***

Clinical Relevance

- Real-time detectability in STN recordings
- Correlation with muscle activation patterns

**this might be critical for a proper solution*



Principles of gait encoding in the subthalamic nucleus of people with Parkinson's disease

Sample Entropy Analysis

Information content in neural signals:

Key Findings

- Higher alpha Sample Entropy during FOG
- Changes specific to freezing episodes
- Distinct from regular walking patterns

Clinical Relevance

- Indicator of motor inhibition
- Real-time computation using specialized hardware

Subthalamic Neural Entropy is a feature of Freezing of Gait in freely moving people with Parkinson’s disease

Beta-Gamma PAC

Key Findings

- Beta-Gamma (1) phase amplitude coupling could also be used to classify the current motor state of the patient during.

Clinical Relevance

- Real-time decoding through specialized neural hardware (2)

Gait-related beta-gamma phase amplitude coupling in the subthalamic nucleus of parkinsonian patients (1)
A 16-Channel Low-Power Neural Connectivity Extraction and Phase-Locked Deep Brain Stimulation SoC (2)

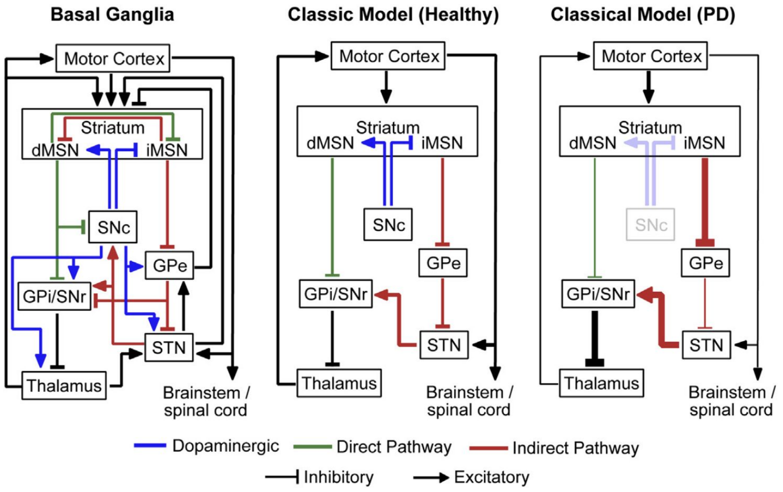
Basal ganglia - motor circuit

Primary Pathophysiology

- Progressive loss of dopaminergic neurons
- Disruption of basal ganglia circuits

BG movement planning and initiation:

- The basal ganglia receive inputs from many brain areas, especially the motor cortex
- They have two main pathways:
  - Direct pathway ("go" signal): Promotes desired movements
  - Indirect pathway ("stop" signal): Inhibits unwanted movements
- When working properly, these pathways maintain a careful balance that allows smooth, controlled movement



Dopamine's Role:

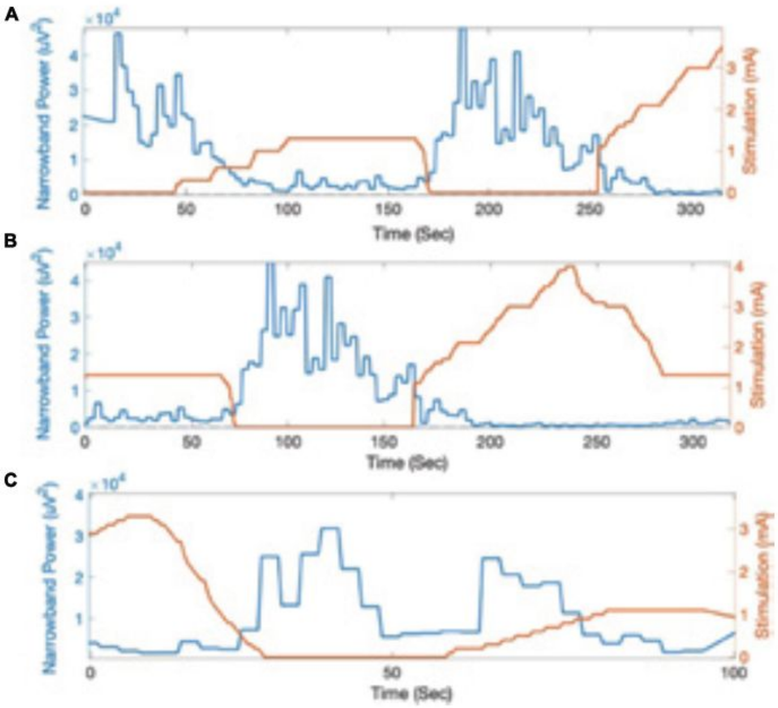
- Dopamine from the substantia nigra helps activate the "go" pathway
- It also helps suppress the "stop" pathway
- This balance allows proper motor functioning

In Parkinson's disease, this system breaks down:

- The dopamine-producing cells in the substantia nigra die off
- Without enough dopamine:
  - The "go" pathway becomes too weak
  - The "stop" pathway becomes too strong
- This creates the classic PD symptoms: difficulty initiating movement (bradykinesia), muscle rigidity, tremor at rest, balance problems

REF Galvan et al. - Frontiers in Neuroanatomy - 2015; Rubin et al. - European Journal of Neuroscience - 2012

Recordings from DBS



This is an example of the type of data that can be recorded with BrainSense™ (Medtronic)

REF Medtronic – Scientific compendium, Research on brain sensing and BrainSense™ technology

Hidden

EES influence on DBS signal

Need for a procedure to ensure that the **data processing unit remain reliable during EES**, despite **cortical responses to EES bursts**.

It is possible to use a two-step calibration procedure, optimized for PD.

Recorde several trials and calibrate the data processing unit, based on the data recorded without and with EES.

2-step decoder successfully compensated for stimulation induced changes in motor cortex activity. [result of REF]

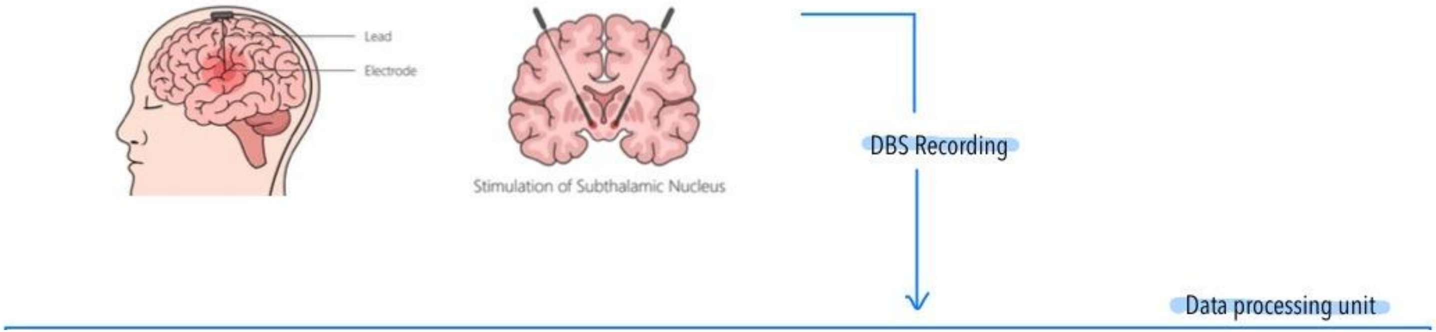
Our calibration should compensate for responses to EES in the STN

REF Doctoral thesis Macellari, N., Closed-Loop Control of Epidural Electrical Stimulation in Patients with Spinal Cord Injury and Parkinson's Disease, EPFL, 2023

Our solution - Overview

DBS is implanted in over 80.000 patients (⅔ are PD patients)

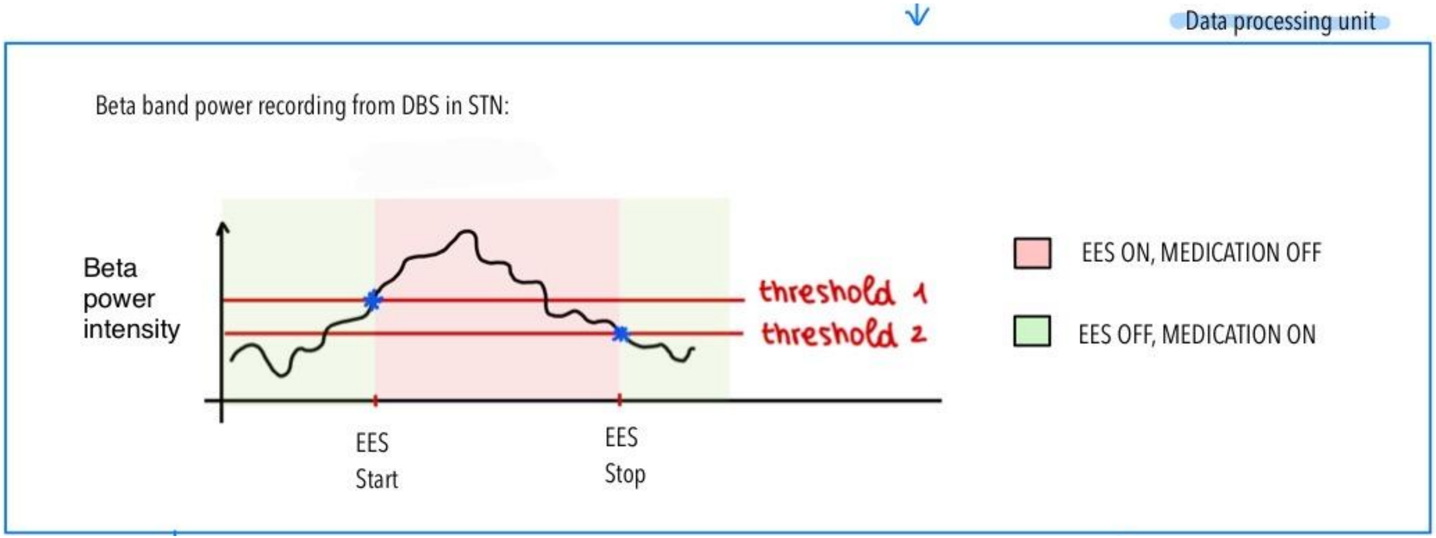
Beta band specifically, recorded in STN, strongly correlates with gait impairment and ON-OFF medication periods



Our solution - Overview

Data acquired from STN, are sent to a data processing unit, that calculates and select appropriate EES parameters in real-time in relation to the neural state (medication, fatigue) of the patient

Thus, making the therapy personalized for the patients



Our solution - Overview

Data acquired from STN, are sent to a data processing unit, that calculate and modifies the EES parameters in real-time in relation to the medication state of the patient

Thus, making the therapy personalized for the patients