# Neural interfaces for the management of movement disorders

Alejandro Pascual Valdunciel, Imperial College London

July 10th, Summer School on Neural Interfaces, Maribor, Slovenia

Funded by the European Union
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Universitat Politècnica de Catalunya BarcelonaTech
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# Overview

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1. Introduction
2. Basis of neurophysiology and motor control
3. Neural interfaces: operant conditioning and human-machine-interfaces
4. Neural interfaces: management of pathological tremor
5. Neural interfaces: study spinal circuits
6. Discussion

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# I am a Young Researcher

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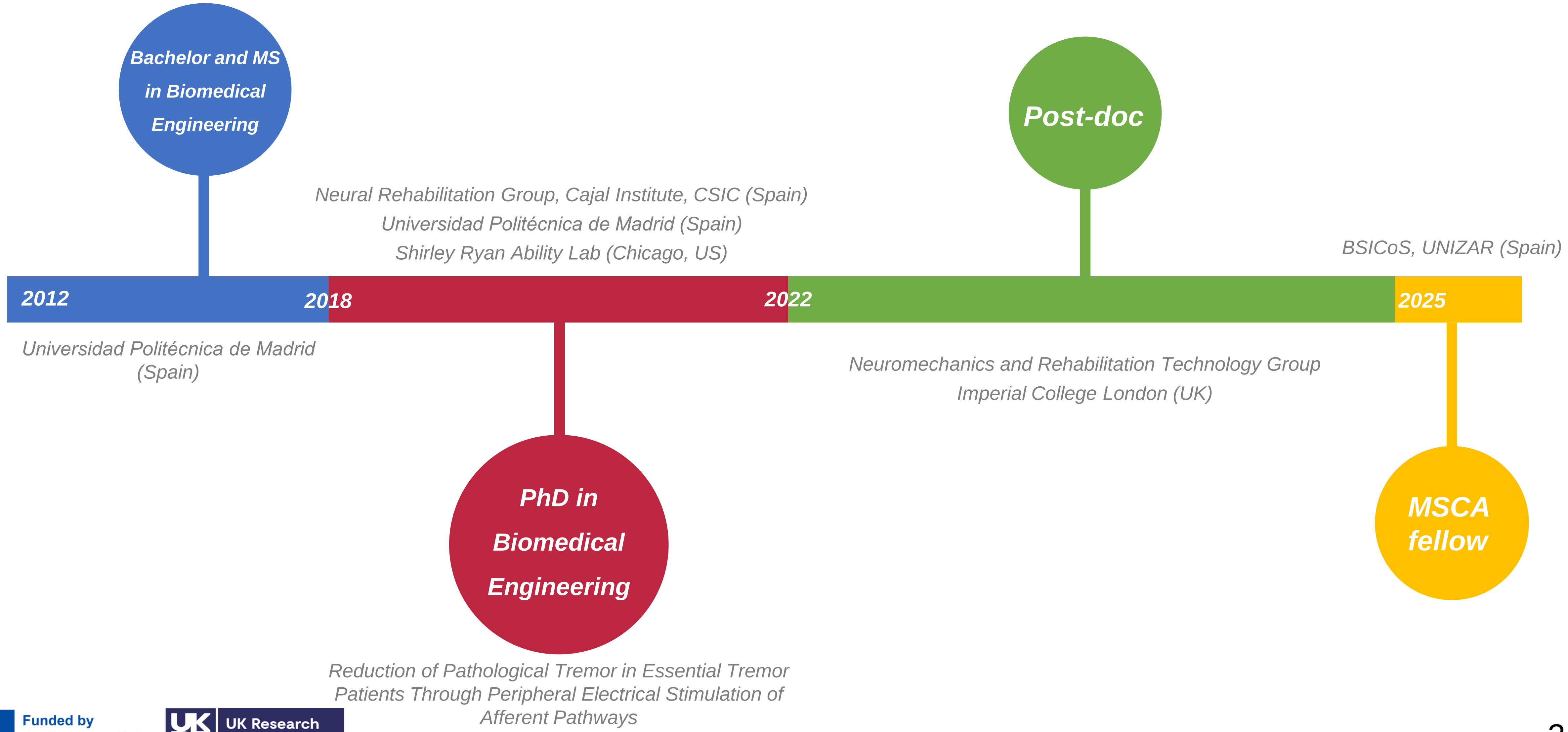



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# Neural interfaces

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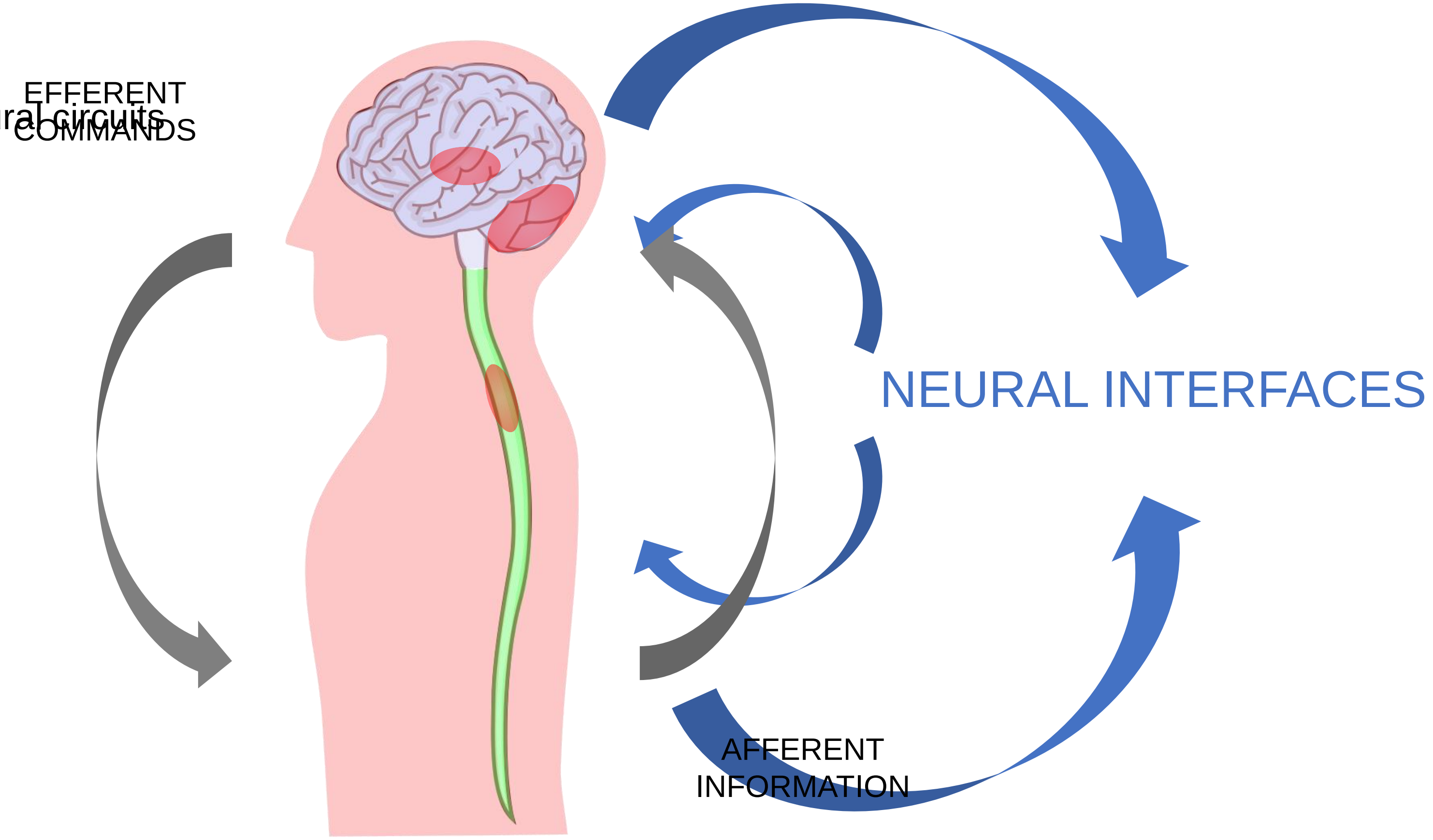
Aberrant neural circuits




*Stroke*

*Pathological Tremor*

*Pain*

*SCI*

*Other neural disorders*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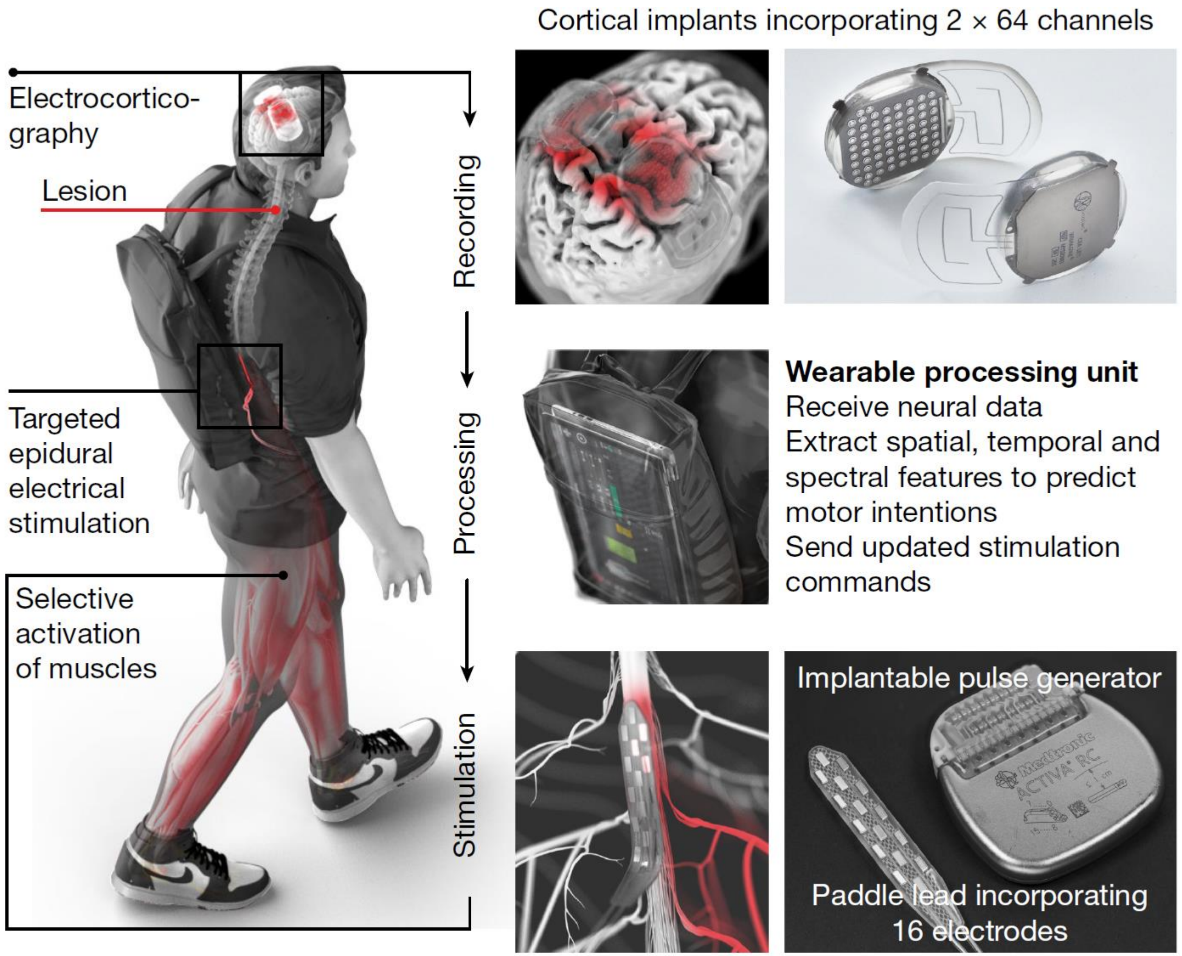
# Neural interfaces




*Lorach et al., Nature, 2024*

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# Neural interfaces: EXTEND project

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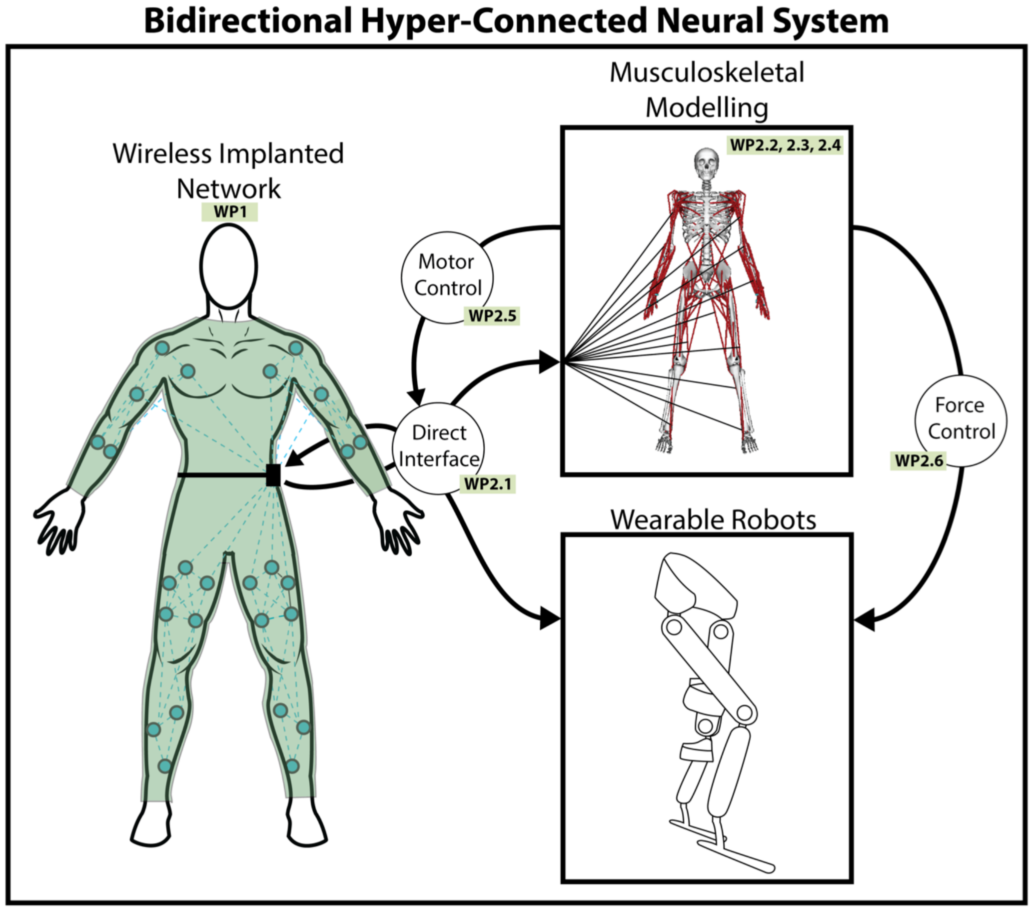


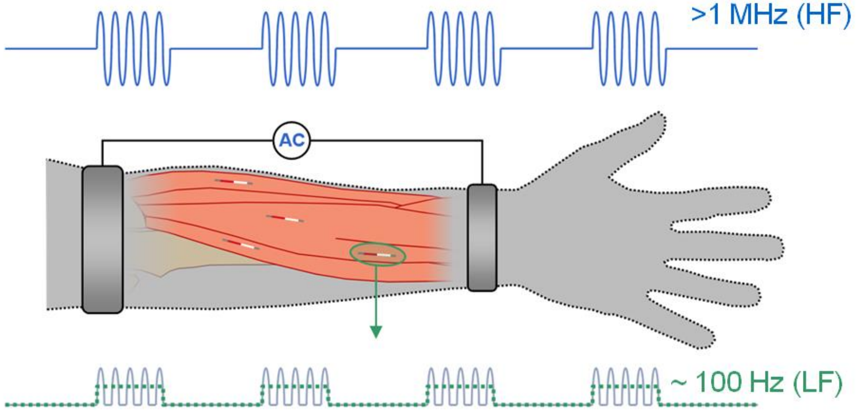


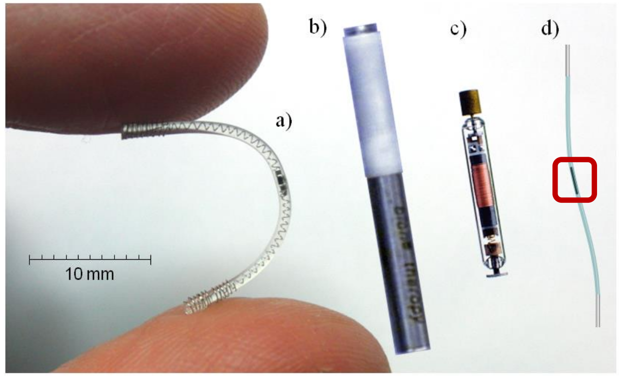


INSTITUTO CAJAL CSIC | upf. Universitat Pompeu Fabra Barcelona | Fraunhofer | SaludMadrid | sescam | Imperial College London | ÖSSUR | Shirley Ryan Abilitylab

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# Movement disorders

Movement disorders are a group of neurological conditions that cause abnormal voluntary or involuntary movements. Causes can range from genetic mutations, neurodegenerative diseases, infections, injuries, metabolic issues, and exposure to toxins or certain medications.

## Hyperkinetic Disorders (Excessive Movement)

1. **Tremor**
    1. **Essential Tremor**: Commonly affects the hands, head, and voice.
    2. **Parkinsonian Tremor**: Associated with Parkinson's disease, usually at rest.
2. **Chorea**
    1. **Huntington's Disease**: Genetic disorder causing progressive breakdown of nerve cells.
3. **Dystonia: Cervical Dystonia:** Affects the neck muscles.
4. **Myoclonus:** Characterized by sudden, brief involuntary muscle jerks.
5. **Tics: Tourette Syndrome**: Characterized by motor and vocal tics.
6. **Ballism: Hemiballismus**: Violent flinging movements of one side of the body.
7. **Athetosis** Typically seen in **Cerebral Palsy**: Slow, writhing movements, especially in the hands and feet.
8. **Ataxia.** Coordination and balance issues due to cerebellar damage.

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# Movement disorders

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## Hypokinetic Disorders (Reduced or Slow Movement)

**Parkinson’s Disease**

- Characterized by bradykinesia, rigidity, and resting tremor.

**Other disorders**
**Spasticity**

- Increased muscle tone leading to stiffness and difficulty in movement, often seen in conditions like **Multiple Sclerosis** and **Stroke**.

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# Basis of neurophysiology and motor control

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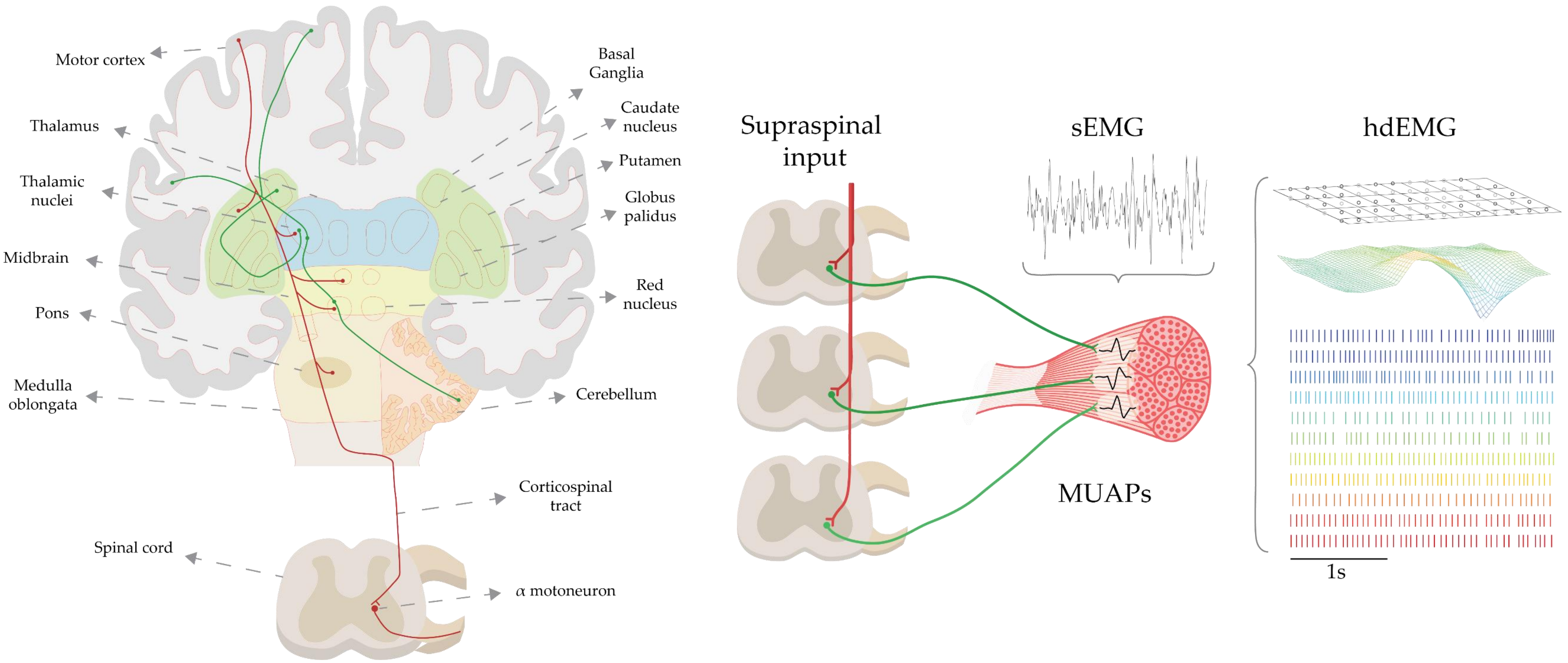
# The basis of motor control





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# Motoneurons

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## Alpha Motoneurons

•Innervate extrafusal muscle fibers, which are responsible for generating force.

•Larger in size, high conduction velocity.

## Gamma Motoneurons

•Innervate intrafusal muscle fibers where the muscle spindles are located, which are involved in maintaining muscle tone and proprioception. They do not contribute to force.

•Smaller in size, have lower conduction velocity, and regulate the sensitivity of muscle spindles.

## Beta Motoneurons

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# Motoneurons

A Motor Unit (MU) consists of a single motor neuron and all the muscle fibers it innervates.

**Slow (S, Type I)**

- Slow-twitch, low force output, fatigue-resistant.

**Fast Fatigue-Resistant (FF, Type IIa)**

- Fast-twitch, moderate force output, fatigue-resistant, faster contraction than Type I.

**Fast Fatigable (FF, Type IIb)**

- Fast-twitch, high force output, quick to fatigue.

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# Question time!

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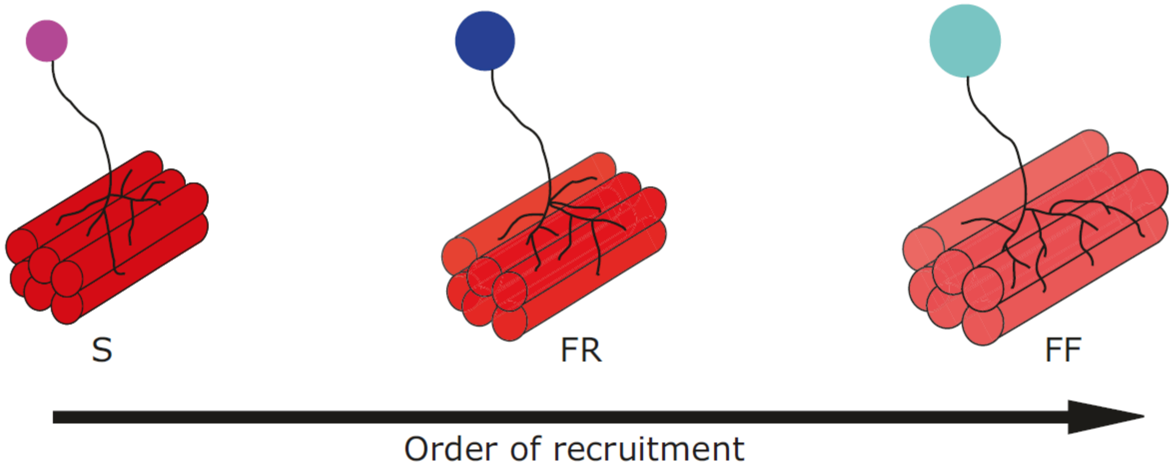
# Motoneurons




*Henneman's principle*

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# Afferent pathways

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| Receptor type | Fiber group[1] | Fiber name | Modality |
|---|---|---|---|
| Cutaneous and subcutaneous mechanoreceptors | | | Touch |
| Meissner corpuscle | Aα,β | RA1 | Stroking, flutter |
| Merkel disk receptor | Aα,β | SA1 | Pressure, texture |
| Pacinian corpuscle[2] | Aα,β | RA2 | Vibration |
| Ruffini ending | Aα,β | SA2 | Skin stretch |
| Hair-tylotrich, hair-guard | Aα,β | G1, G2 | Stroking, fluttering |
| Hair-down | Aδ | D | Light stroking |
| Field | Aα,β | F | Skin stretch |
| C mechanoreceptor | C | | Stroking, erotic touch |
| Thermal receptors | | | Temperature |
| Cool receptors | Aδ | III | Skin cooling (<25°C [77°F]) |
| Warm receptors | C | IV | Skin warming (>35°C [95°F]) |
| Heat nociceptors | Aδ | III | Hot temperature (>45°C [113°F]) |
| Cold nociceptors | C | IV | Cold temperature (<5°C [41°F]) |
| Nociceptors | | | Pain |
| Mechanical | Aδ | III | Sharp, pricking pain |
| Thermal-mechanical (heat) | Aδ | III | Burning pain |
| Thermal-mechanical (cold) | C | IV | Freezing pain |
| Polymodal | C | IV | Slow, burning pain |
| Muscle and skeletal mechanoreceptors | | | Limb proprioception |
| Muscle spindle primary | Aα | Ia | Muscle length and speed |
| Muscle spindle secondary | Aβ | II | Muscle stretch |
| Golgi tendon organ | Aα | Ib | Muscle contraction |
| Joint capsule receptors | Aβ | II | Joint angle |
| Stretch-sensitive free endings | Aδ | III | Excess stretch or force |

*Kandel et al. , Principles of Neuroscience, McGraw Hill 2005*

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# Spinal cord circuits

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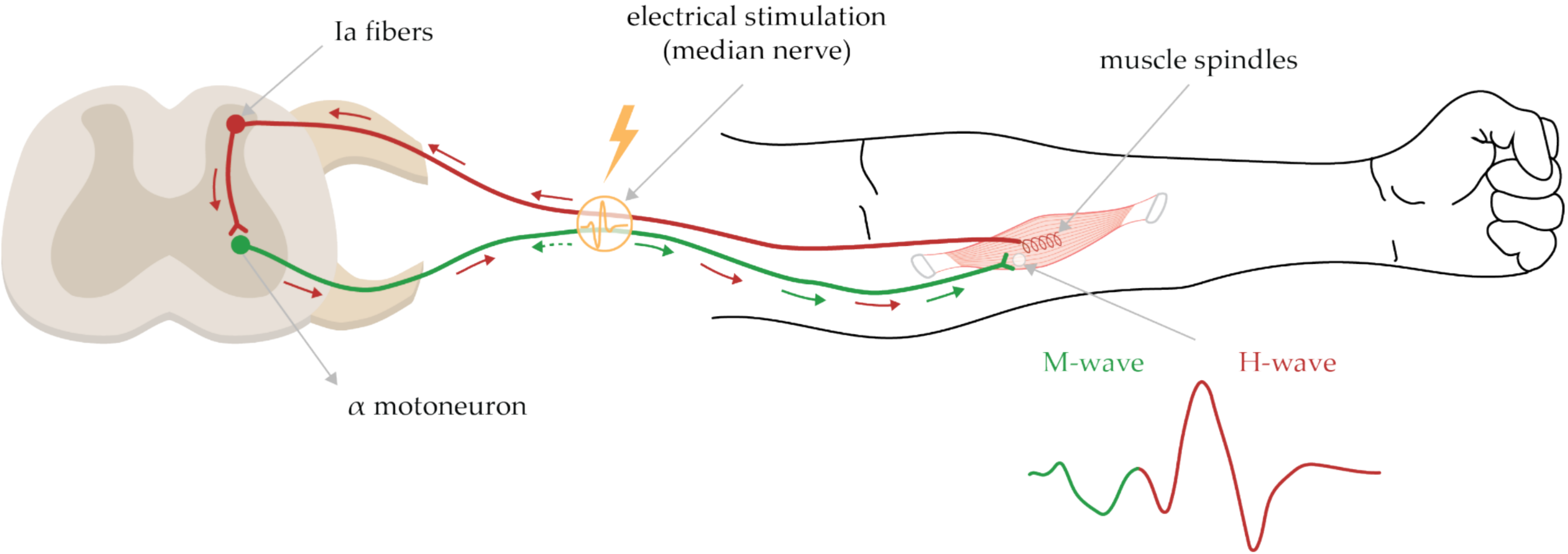
## Stretch reflex / H reflex





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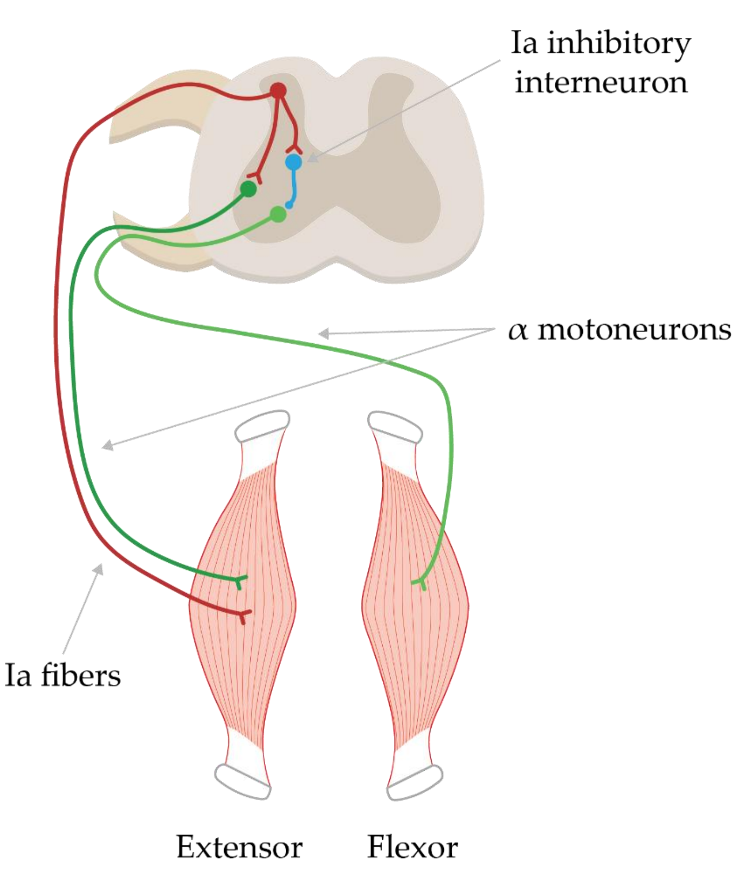
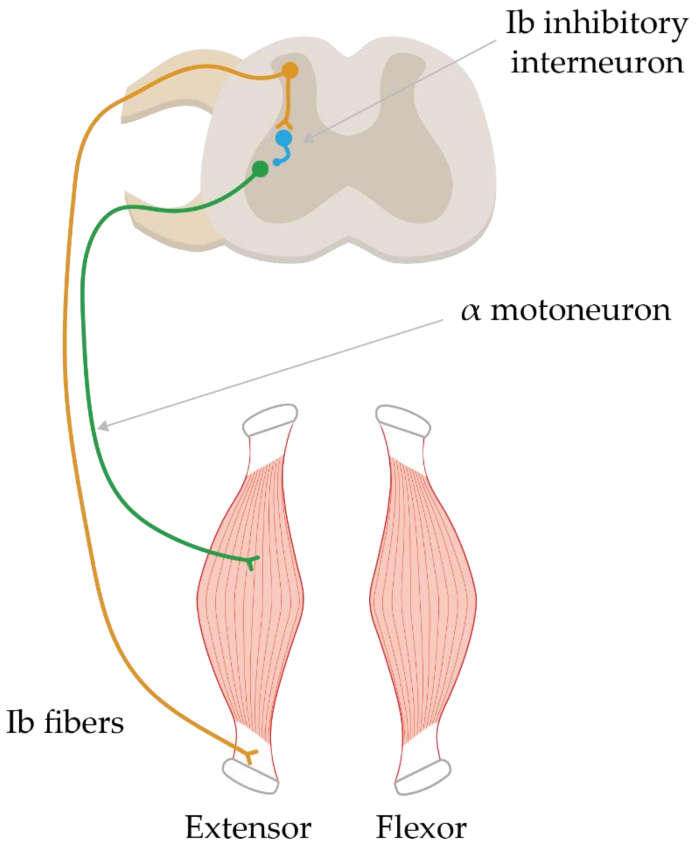
# Spinal cord circuits

## Reciprocal inhibition




## Autogenic inhibition (Ib)

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# Spinal circuits and adaptive behaviours

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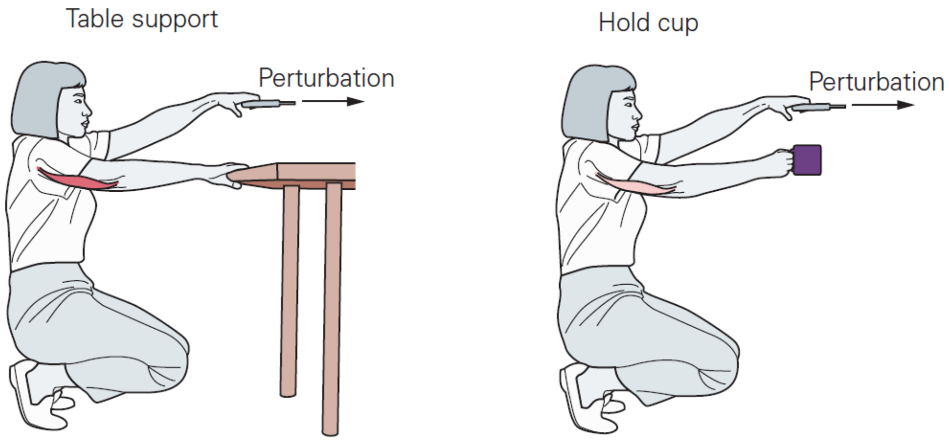
- **Spinal circuits are not hard-wired behaviours.**




*Kandel et al., 2005*

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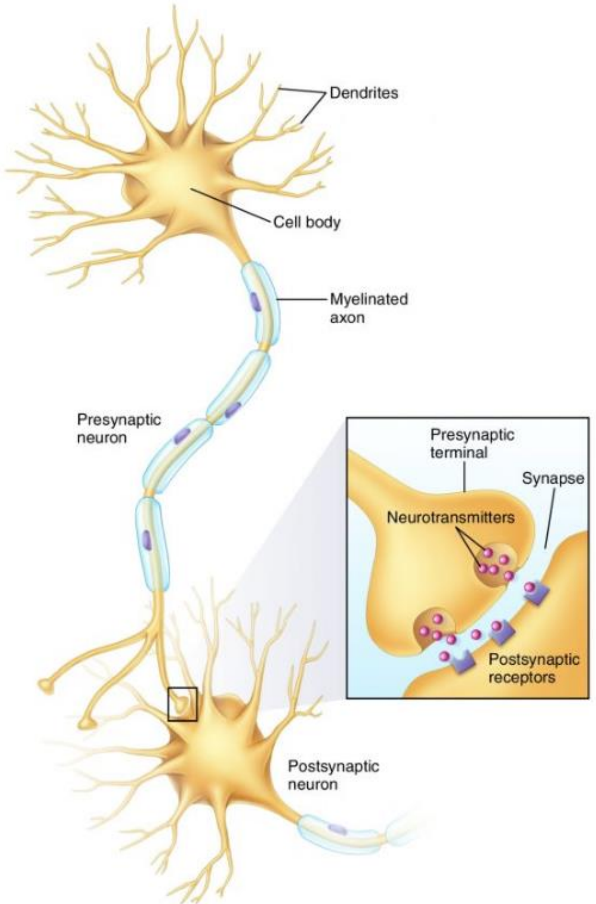
# Neural plasticity

"Neural plasticity" refers to the capacity of the nervous system to modify itself, functionally and structurally, in response to experience and injury. *Bernhardi et al., Adv Exp Med Biol., 2017*

⬇

**Repetitive paired activation of a synapse or circuit leads to plasticity mechanisms (Hebb 1949).**

Goal: to increase or decrease the excitability of a synapse or neural circuit → facilitate neural adaptations → promote functional recovery

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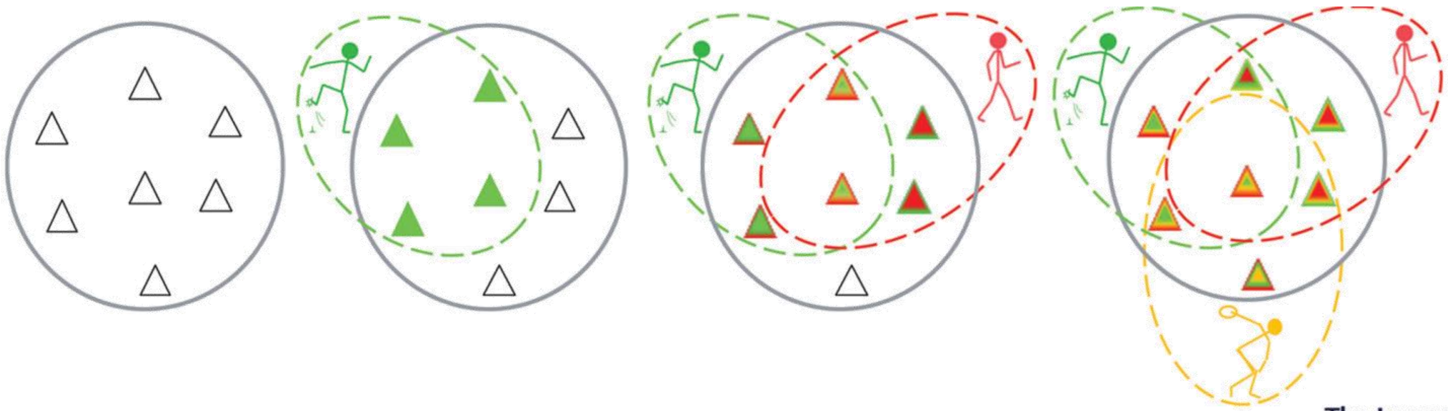
*Joseph E. Muscolino and Giovanni Rimasti*

# Spinal circuits and adaptive behaviours

- **Spinal circuits are not hard-wired behaviours.**

- **Heksor:** A *heksor is a widely distributed network of neurons and synapses that produces an adaptive behaviour and changes itself as needed in order to maintain the key features of the behaviour, the attributes that make the behaviour.*

- Heksors negotiate the properties of the CNS neurons and synapses that they all use. Through this process, they establish and maintain an equilibrium satisfactory to all of them.



Wolpaw and Kasemar, 2022, J. Physio

The Journal of Physiology

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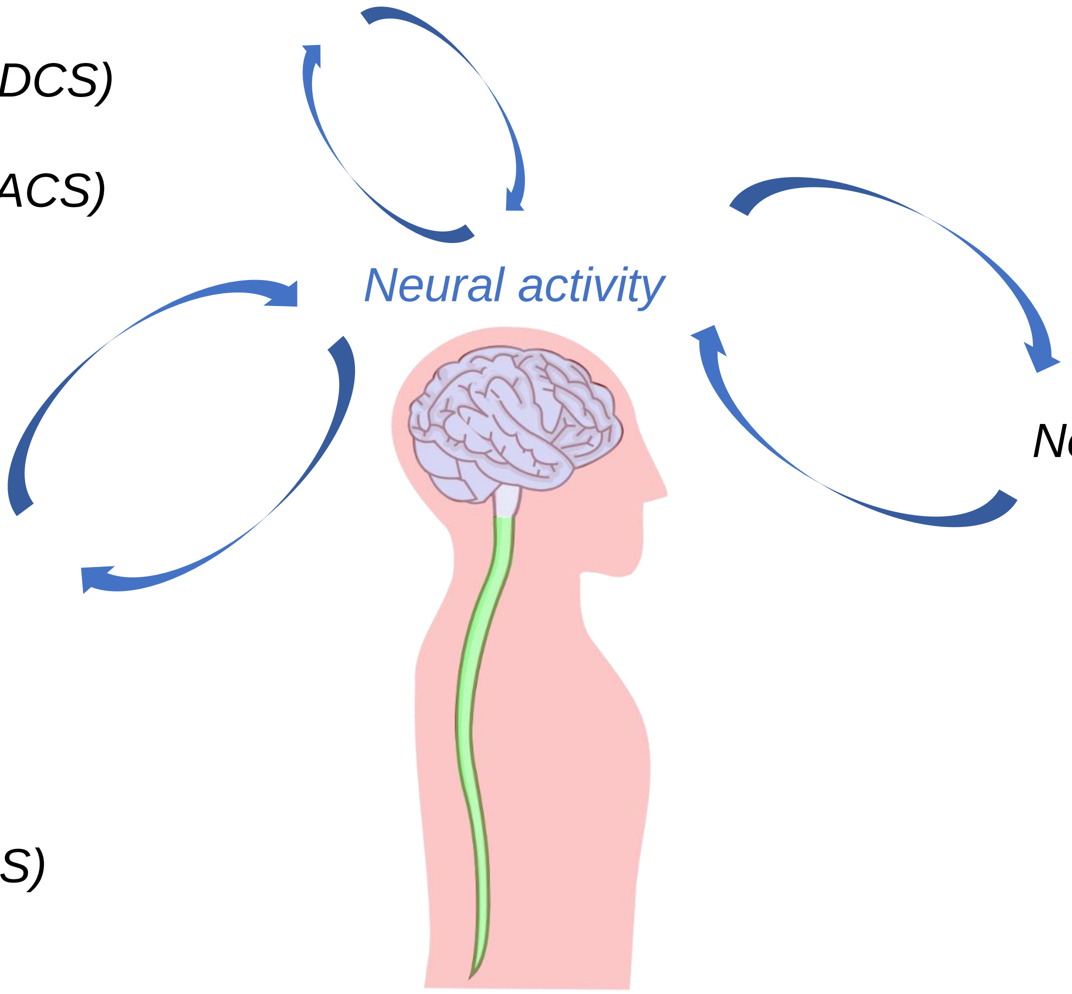
# Neuromodulation

*Transcranial magnetic stimulation (TMS)*

*Transcranial direct current stimulation (tDCS)*

*Transcranial alternating current stimulation (tACS)*




*Spinal Cord Stimulation (SCS)*

*Neurofeedback*

*Peripheral Nerve Stimulation (PNS)*

*Functional Electrical Stimulation (FES)*

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# Neuromodulation

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## Acute effect

- Neuromodulation effect measured relative to pre-stimulation levels, that is present while stimulation is applied
- No neural plasticity
- E.g., DBS, eSCS

## Lasting (short-term/prolonged) effect

- Neuromodulation effect  measured relative to pre-stimulation levels, that persists for minutes or > hours after the stimulation ends.
- Neural plasticity.
  - Long-term potentiation (LTP): increase in the excitability of the target circuit.
  - Long-term inhibition (LTI): decrease in the excitability of the target circuit.

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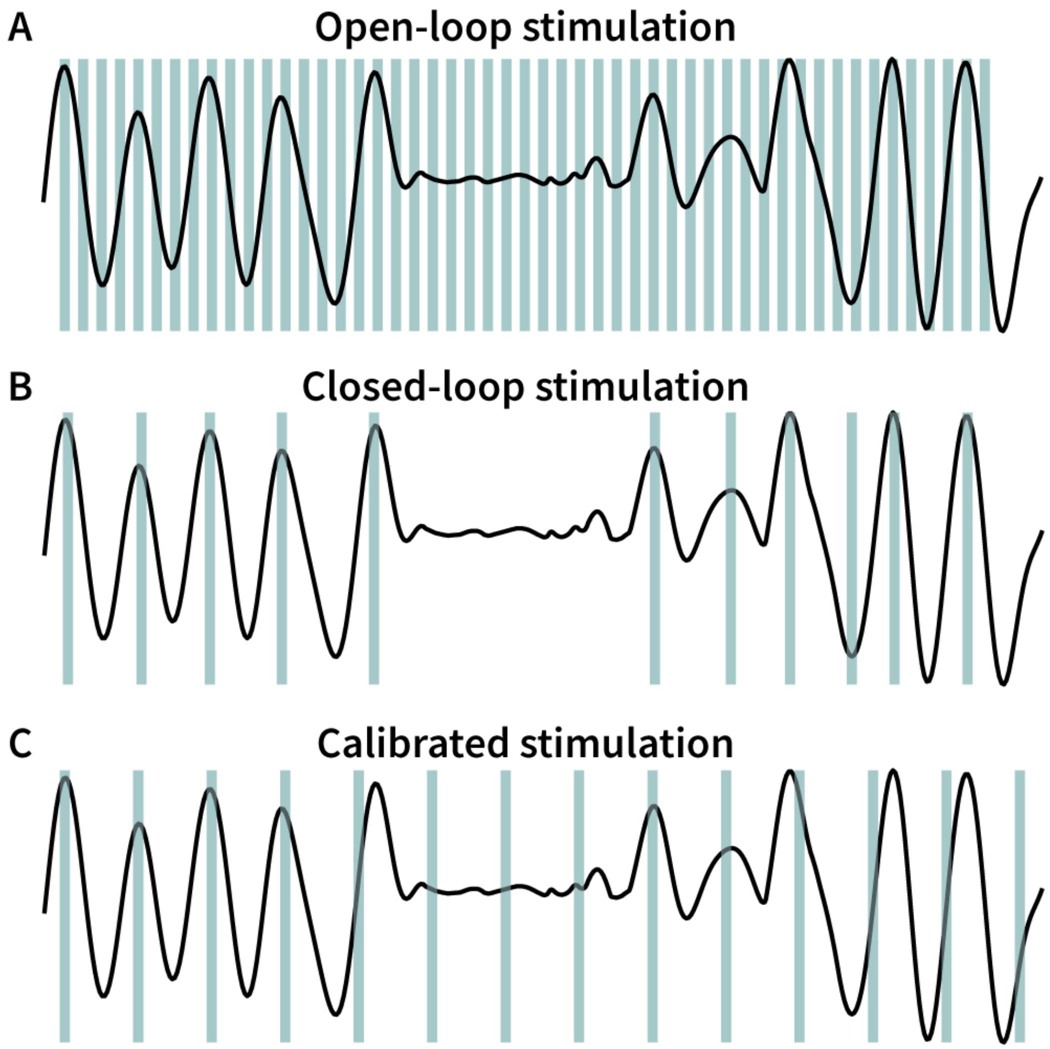
# Stimulation strategies

- **Open-loop stimulation:** Stimulation that is delivered with a predetermined waveform that is independent of any characteristic of the physiological/biomechanical events (TENS).
- **Closed-loop stimulation:** Stimulation whose waveform is adjusted in real-time based on continuous sensing of physiological/biomechanical events.
- **Calibrated open-loop stimulation:** Stimulation with a waveform that is tuned (once, or repeatedly) to match characteristics (e.g., frequency-locked) of physiological/biomechanical events.

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# Neuromodulation: operant conditioning



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# Operant conditioning

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- The subject learn to associate a certain behaviour with a consequence.
- The spinal cord plays a key role in motor control and learning.
- Proprioception (afferent/sensory information) is essential in motor learning.
- Brain states and supraspinal inputs can modulate spinal reflexes (preset behaviours)

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# Neuromodulation of the H-reflex

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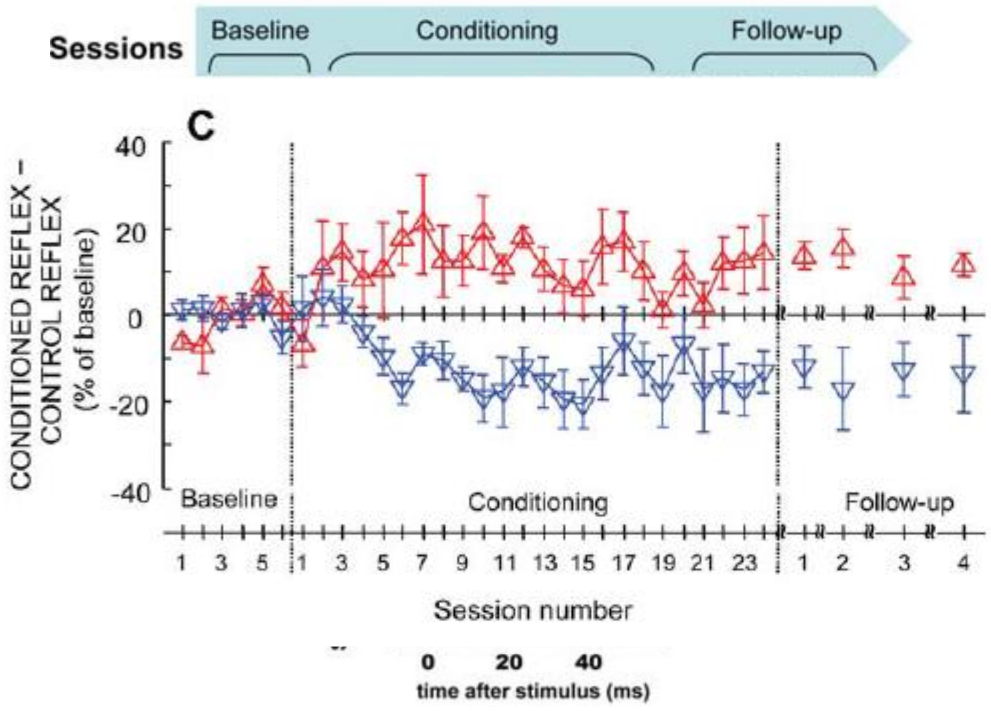
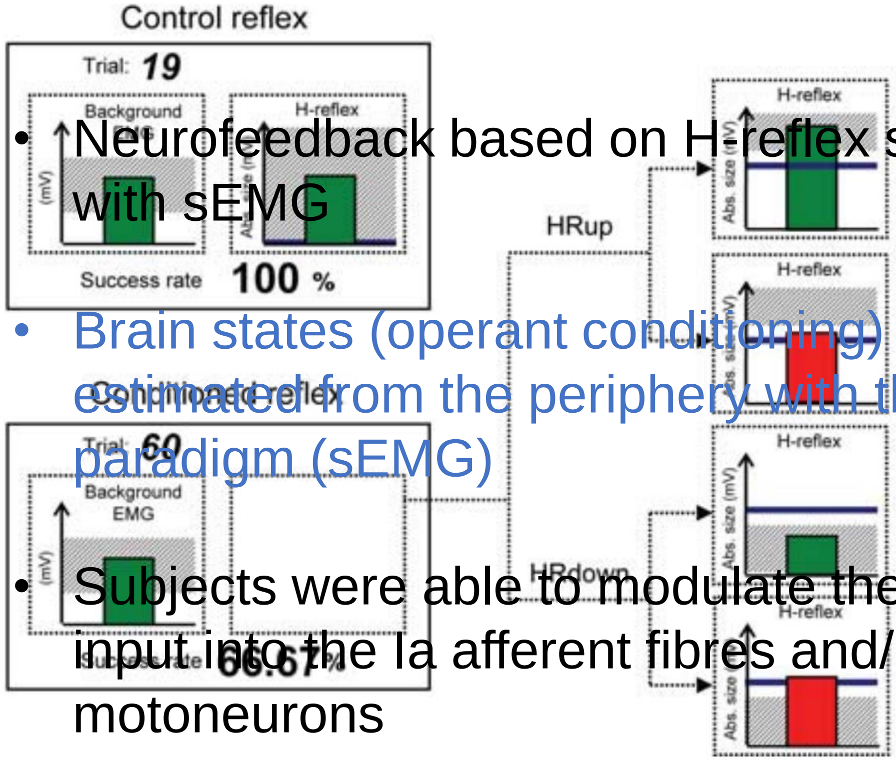



*Wolpaw et al.,*
*Thompson et al., J of Neuroscience, 2008*




- Neurofeedback based on H-reflex size measured with sEMG
- Brain states (operant conditioning) can be estimated from the periphery with the H-reflex paradigm (sEMG)
- Subjects were able to modulate the supraspinal input into the Ia afferent fibres and/or $\alpha$ motoneurons
- Are neural adaptations specific from the H-reflex circuit or they happen widespread in the CNS and lead to functional improvement?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# Question time!

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# Neuromodulation of the H-reflex

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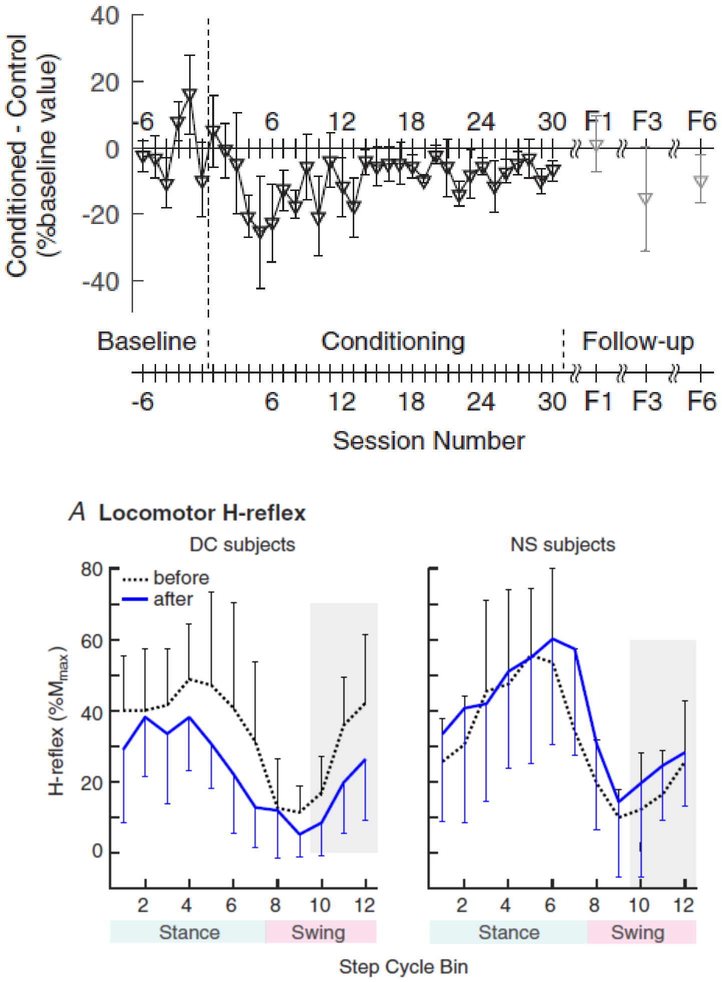


*Thompson et al., J Physiology, 2021*

- Operant conditioning can be mixed with brain states and spinal cord states (gate cycles)
- Specific paradigms for specific circuits: hyperreflexia in Spinal Cord Injury patients or spasticity in stroke.
- Intensive training can lead to long-term plasticity
- Neural adaptations (plastic changes) are widespread in the CNS and shared by different behaviours


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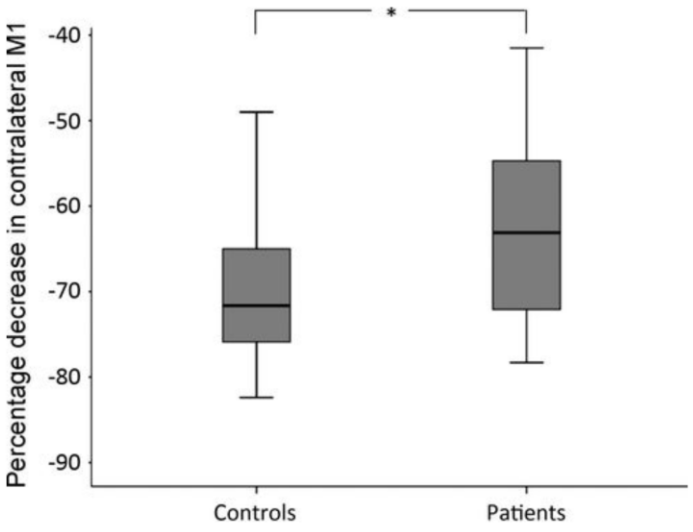
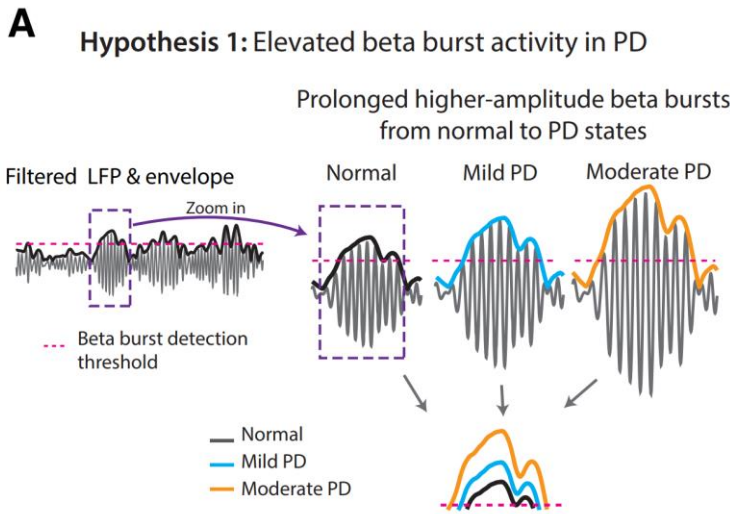
# Beta oscillations

- Beta band (13-30 Hz) are involved in sensorimotor processing.
- Beta band activity is typically characterized in brain recordings (EEG, invasive electrodes)
- Beta band is altered in several neurological conditions:
  - Decrease of Event Related Desynchronization (ERD) in stroke patients
  - Increased beta activity in Parkinson's Disease




*Rossiter HE, et al.J Neurophysiol. 2014*




*Yu et al., J Neurosc, 2021*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# Decoding brain activity from the periphery

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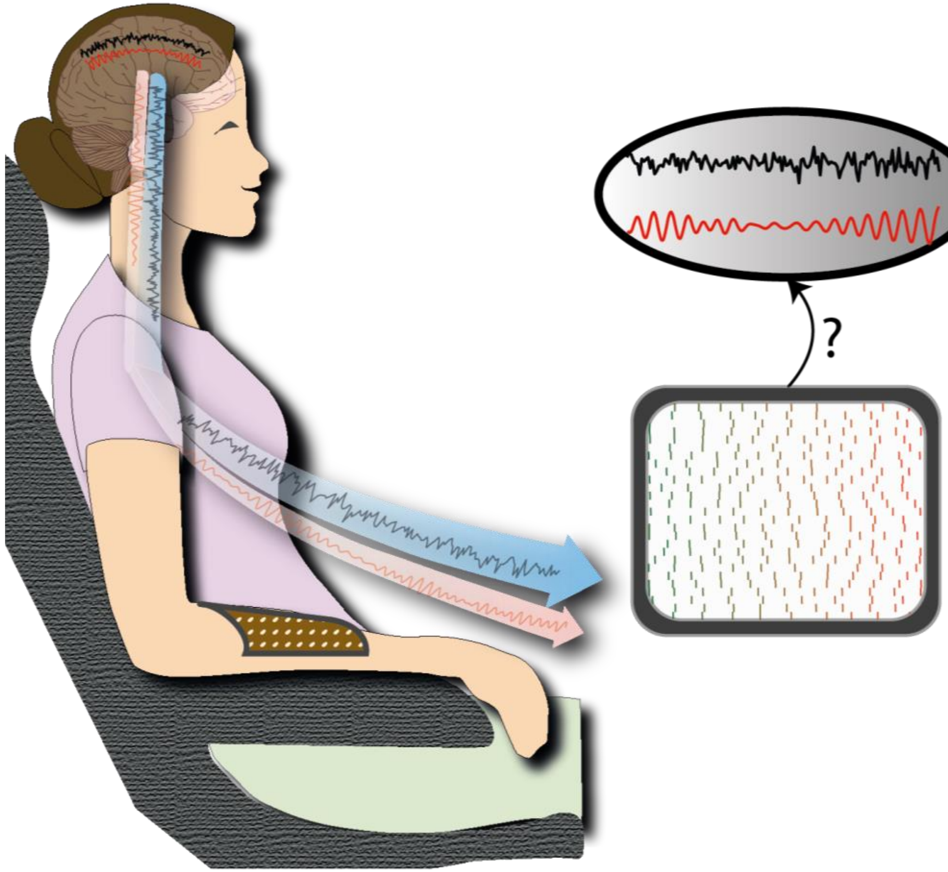


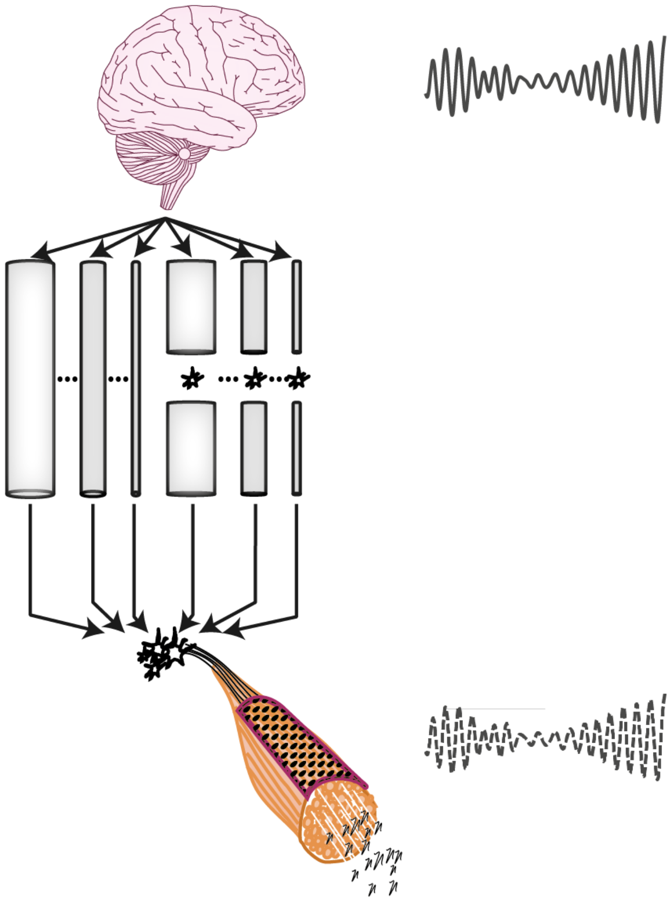

*Ibáñez and Farina et al.*

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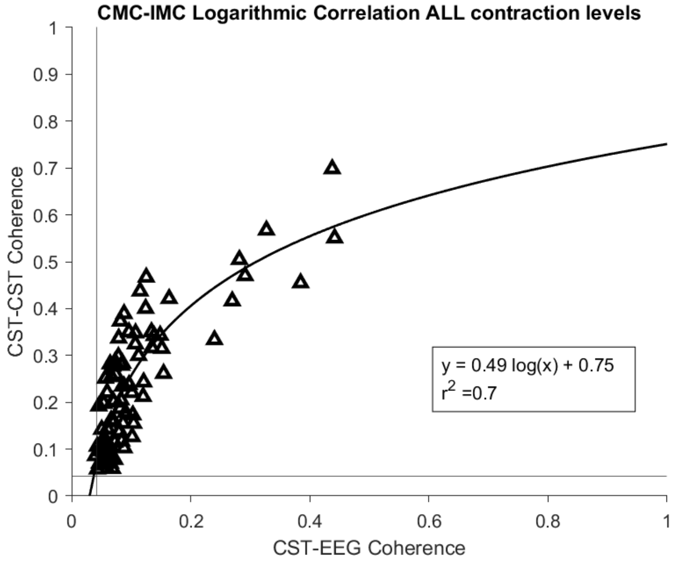
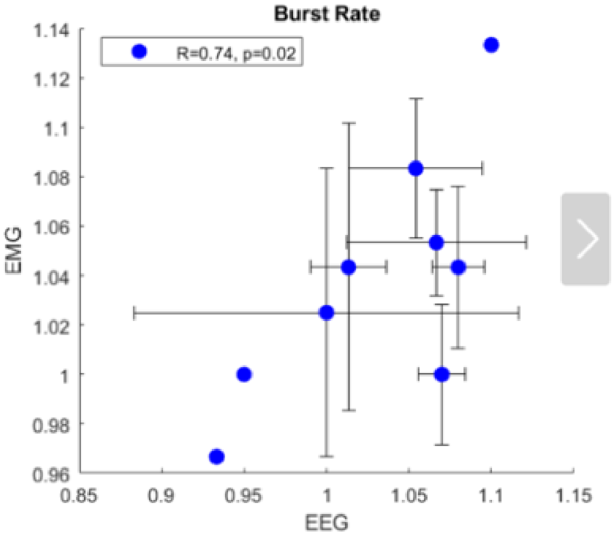
# Decoding brain activity from the periphery

- Beta band (13-30 Hz) brain activity can be characterized from the muscle electrical activity (HDEMG)
- Applications: movement augmentation, biomarker of disease state or rehabilitation progress




Intramuscular coherence (IMC) can be an estimator of corticomuscular coherence (CMC) in healthy subjects
*Emanuele Abbagnano et al. (manuscript under preparation)*




Beta bursting activity measured from the ECR (wrist extensors) can predict cortical bursting features
*Cosima Graef et al. (manuscript under preparation)*

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# Decoding brain activity from the periphery

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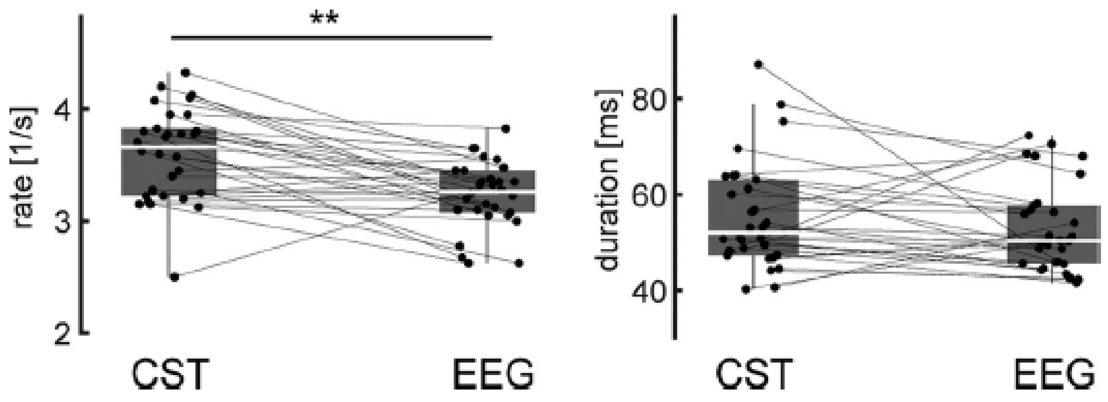
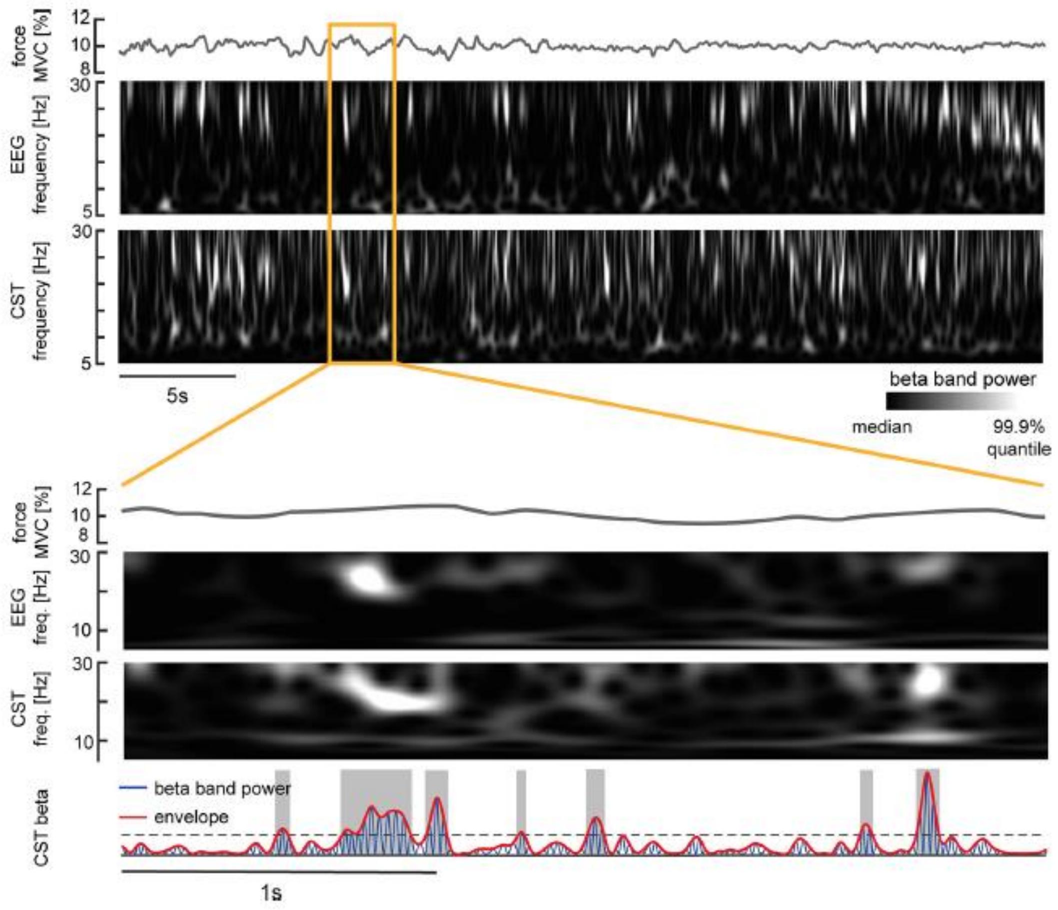
*Ibáñez et al., J of Neuroscience, 2022*

- Beta events can be detected in the CST. These estimations are more accurate compared to sEMG.
- The fastest corticospinal fibres contribute to beta burst transmission from the cortex to the muscles.




*Bräcklein et al., J of Neuroscience, 2022*

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# Question time!

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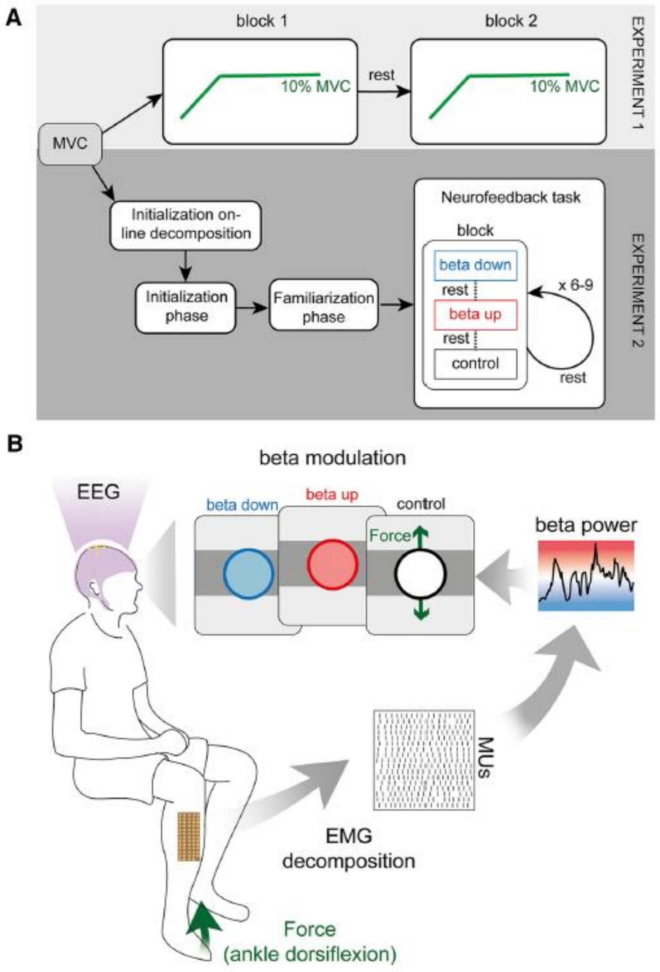
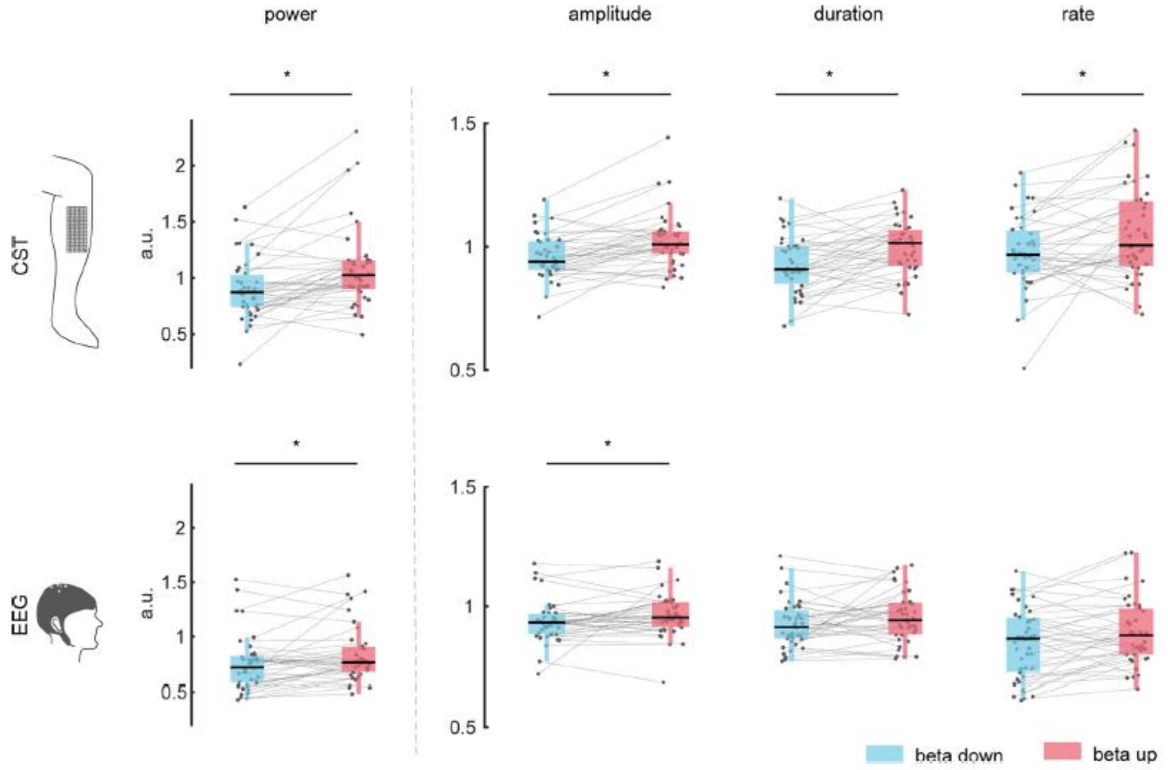
# Neuromodulation of beta band




*Bräcklein et al., J of Neuroscience, 2022*




- Healthy subjects were able to modulate the supraspinal input into $\alpha$ motoneurons in the beta band.
- No changes in force while modulation occurred.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# Neural interfaces: operant conditioning and human-machine-interfaces

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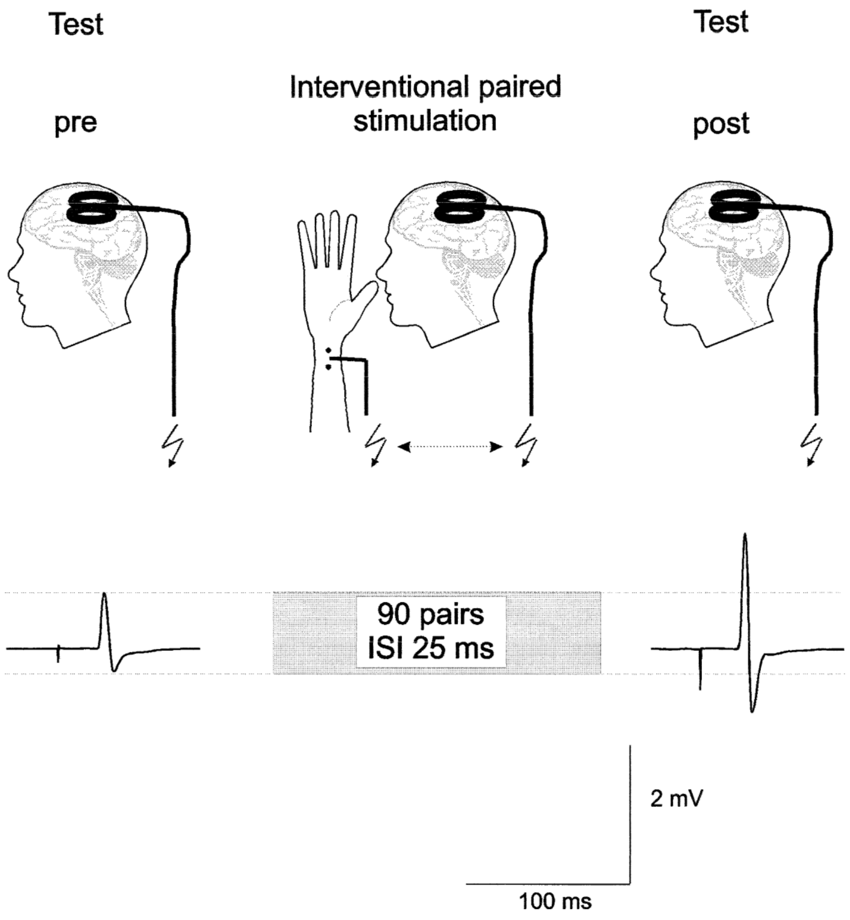
# Paired Associative Stimulation (PAS)




*Stefan et al., Brain, 2000*

- Induction of plasticity through pairing TMS and PNS
- Precise timing is essential to activate target brain circuits.
- When the activity elicited via TMS and PNS converge in the same synapses the synapsis is strengthened.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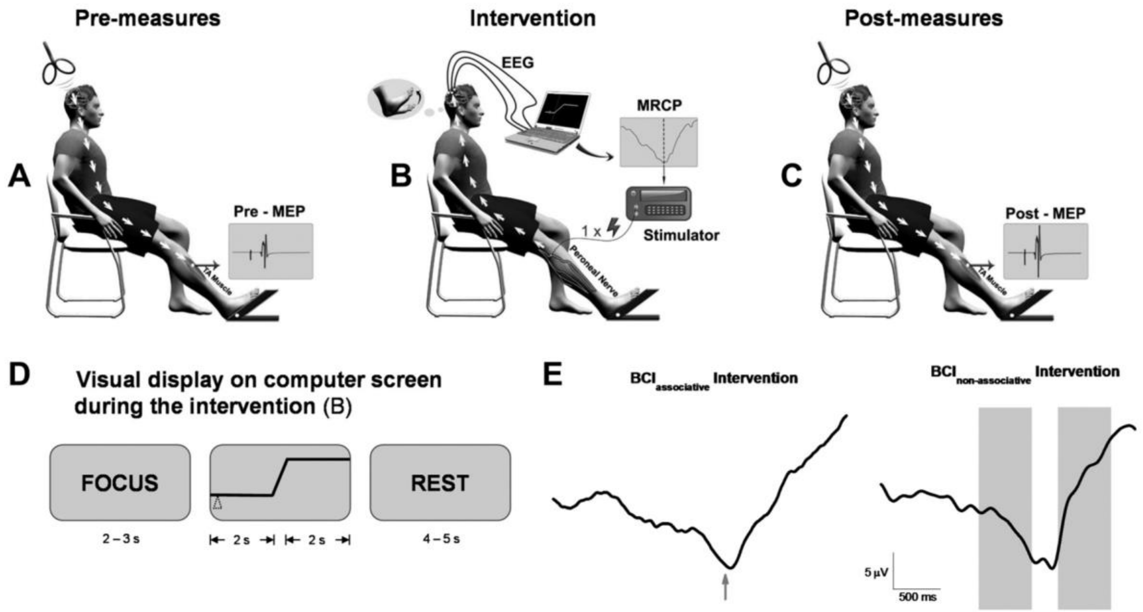
# PAS (Brain Computer Interface)

- Movement related cortical potentials (MRCP)
  CNV – Cue-based (Contingent Negative Variation)
  BP – Self-paced (Bereitschaftspotential)




*Mrachacz-Kersting et al., J Neurophysiol, 2015*

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# Question time!

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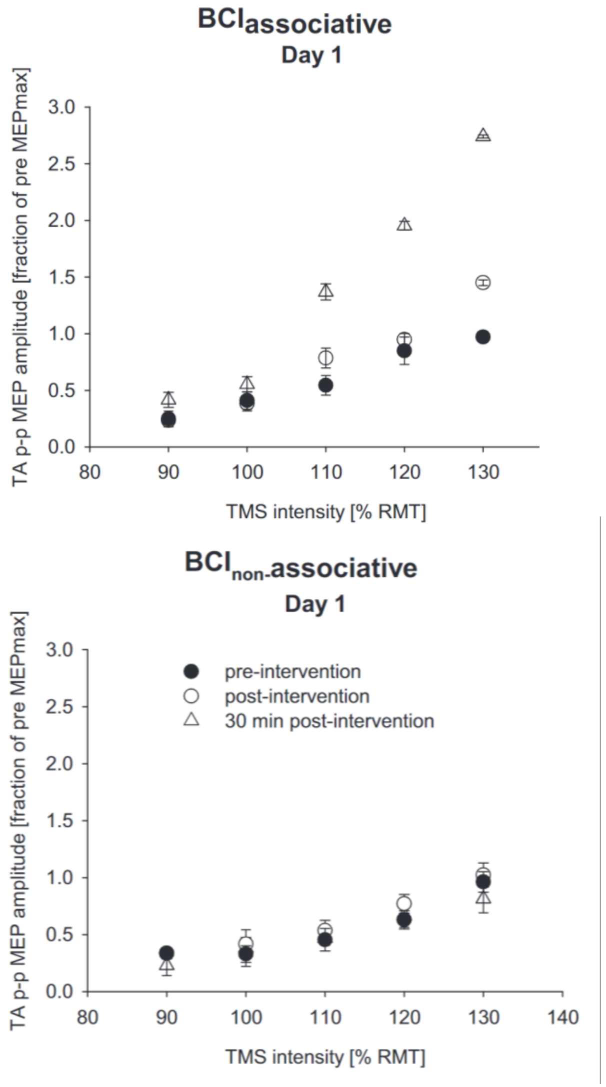
# PAS (Brain Computer Interface)

- Increase in corticospinal excitability
- Increase in functional outcomes
- Precise timing is essential to activate target CNS circuits
- Does not require residual muscle activation (motor imagery)




*Mrachacz-Kersting et al., J Neurophysiol, 2015*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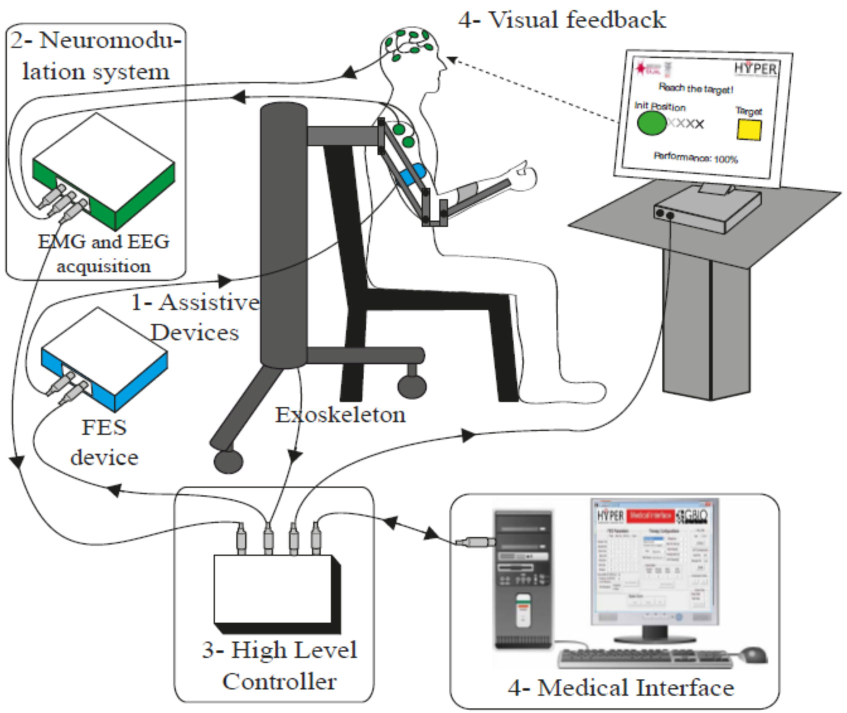
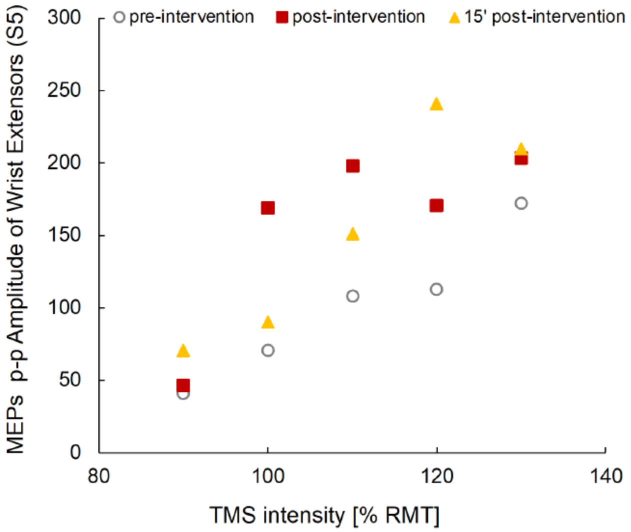
# PAS (BCI + Assistive devices)

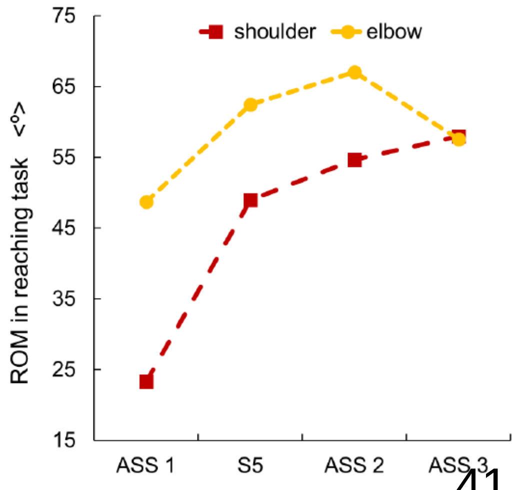



*Herrero et al., ICNR, 2018*

- Assistive devices: Armeo Spring + FES
- FES adaptive control strategy based on FEL
- Reaching task guided by Visual Feedback

*Chronic stroke case study*



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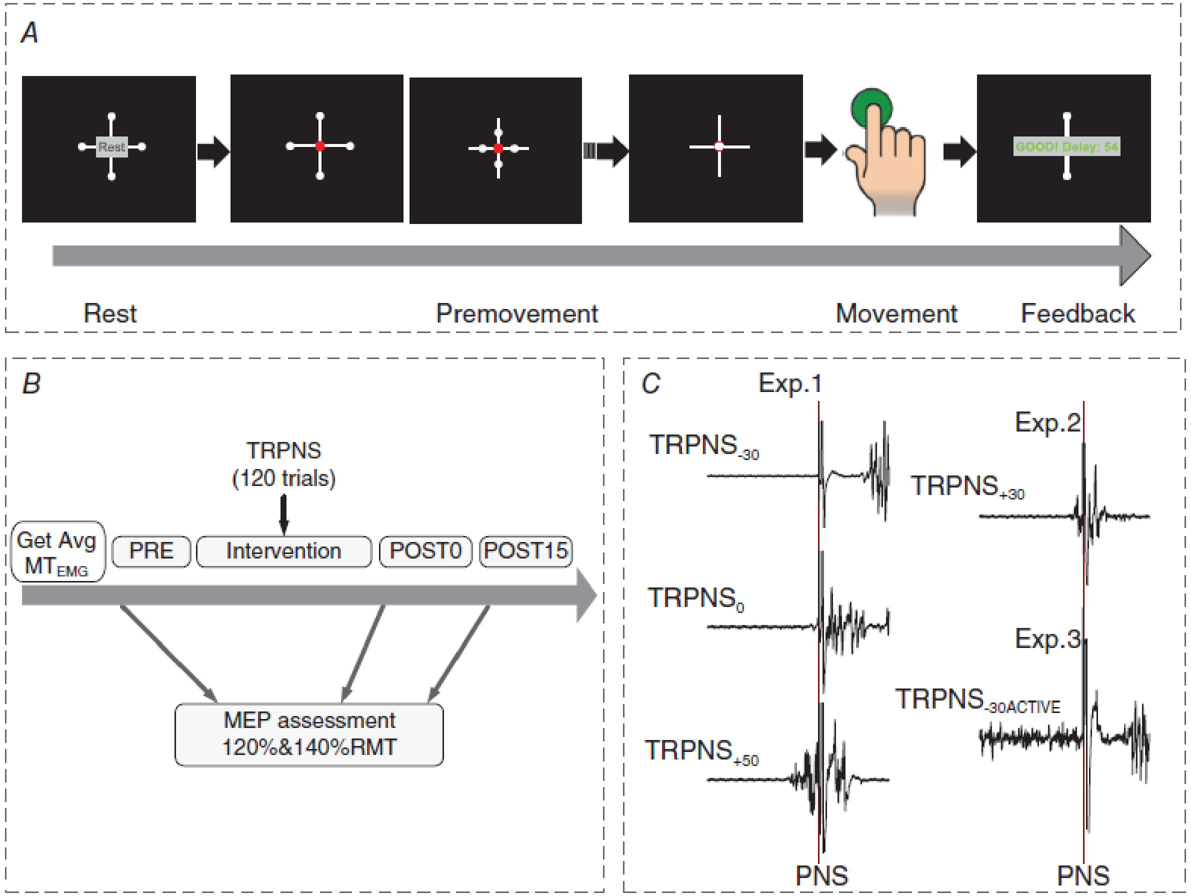
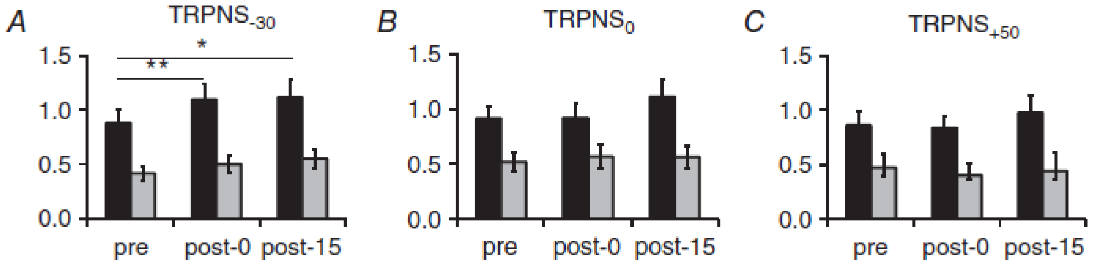
# PAS (brain state estimated from the periphery)




*Fu et al., J Physiology, 2021*




- **Brain state (CNV) is estimated via sEMG**
- Avoid limitations from EEG:
  - Training
  - Mental fatigue
  - Complex EEG setup
- **Timing is fundamental:** afferent brain stimuli must reach M1 circuits during movement initiation phase



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# Neural interfaces: management of pathological tremor

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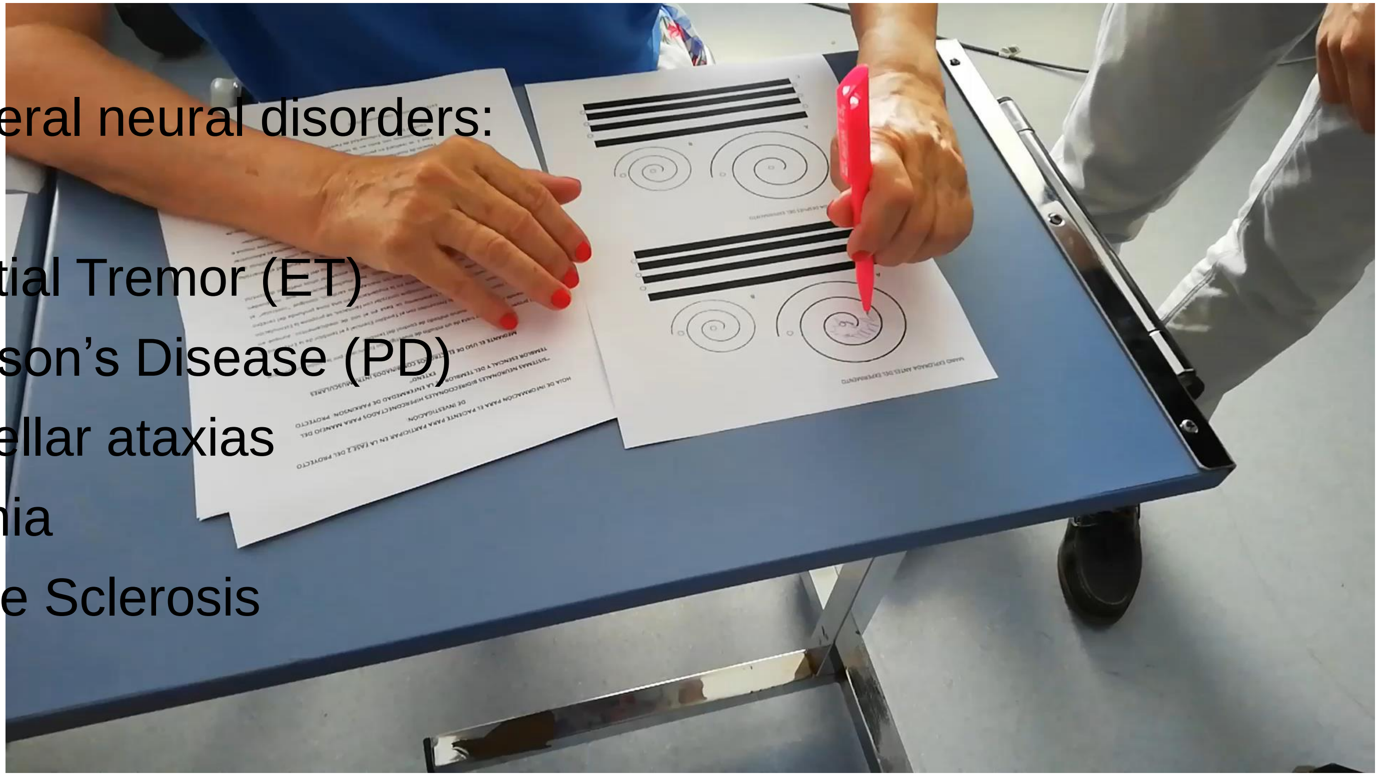
# Pathological tremor

Oscillatory and unvoluntary movement of one or more body parts (typically 3-12 Hz)



Caused by several neural disorders:

- Essential Tremor (ET)
- Parkinson’s Disease (PD)
- Cerebellar ataxias
- Dystonia
- Multiple Sclerosis

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# Parkinson's Disease

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PD is a neurodegenerative disease caused by gradual loss of dopaminergic cells in the substantia nigra (basal ganglia).

- Affecting ~10% million people in the world

- **Symptoms:**
  - Tremors (rest)
  - Bradykinesia
  - Muscle rigidity
  - Postural instability, freezing of gate
  - Non-motor symptoms (depression, cognitive changes)

- **Treatment (no cure available):**
  - Pharmacotherapy (L-dopa), botulin toxin, Deep Brain Stimulation (DBS), physical exercise

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# Essential Tremor

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- A global neural disorder: 4-5% of population > 65 years
- Physiopathology not completely understood (no clear evidenced of neurodegenerative component)
- Around 50% patients do not receive an effective treatment (Louis et al., 2012)
    - Pharmacotherapy, alcohol??, botulin toxin, Deep Brain Stimulation (DBS), HIFU
- A disabling condition: physical and psychological consequences

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# Question time!

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# Pathological tremor

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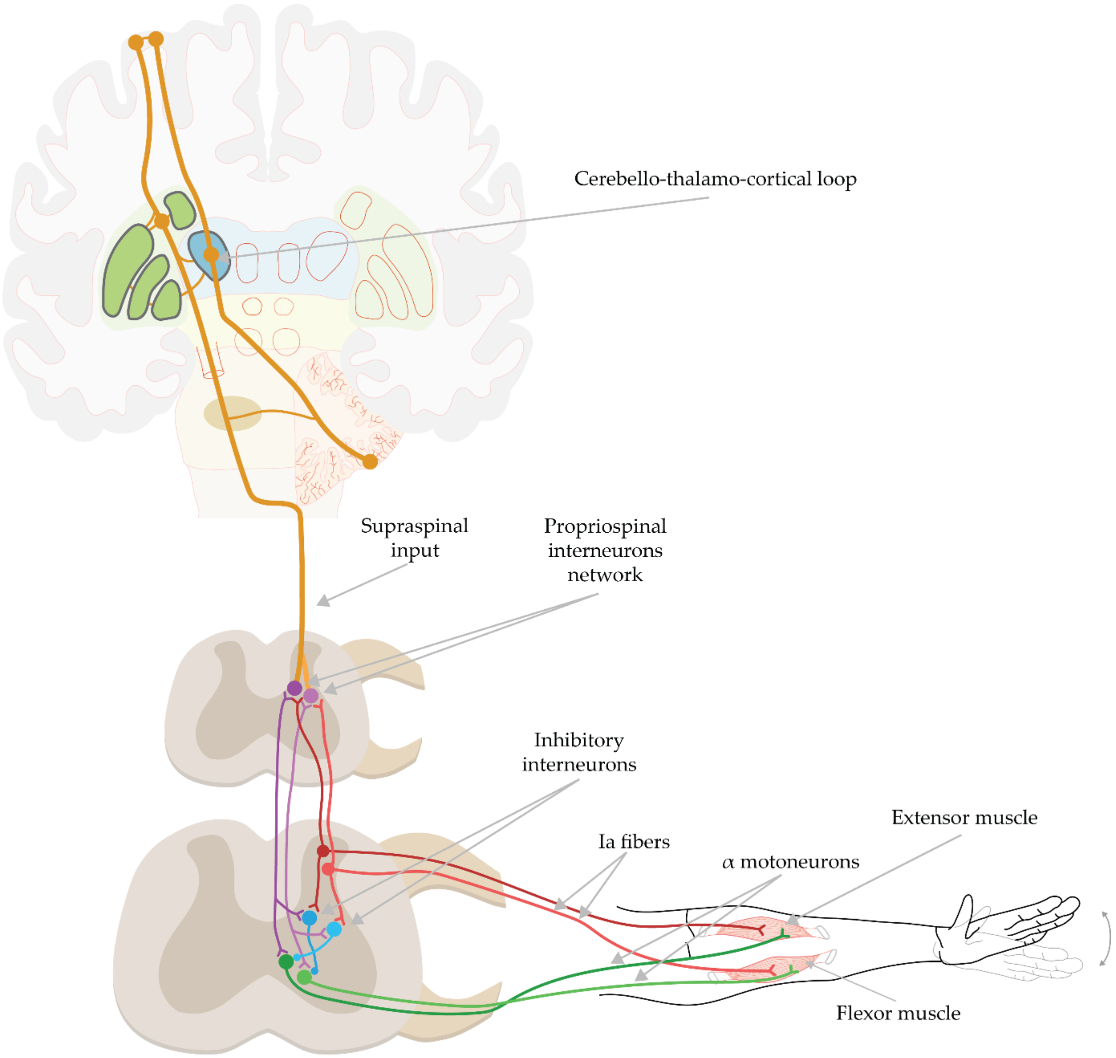


**Supraspinal**: Thalamus, cerebellum, basal ganglia

**Spinal**: propriospinal system

**Spinal**: reflex loops


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# DBS

**Deep Brain Stimulation (DBS):** stimulation of sub-cortical regions of the brain) to mitigate the symptoms of several movement disorders:

- Parkinson's Disease (tremor, bradykinesia)
- Essential Tremor
- Dystonia
- Epilepsy, choreas, etc.

First invasive stimulation of the brain (epilepsy)

Penfield, 1936

First DBS (tremor and PD symptoms)

Benavide, 1987

First closed-loop DBS study, 2012

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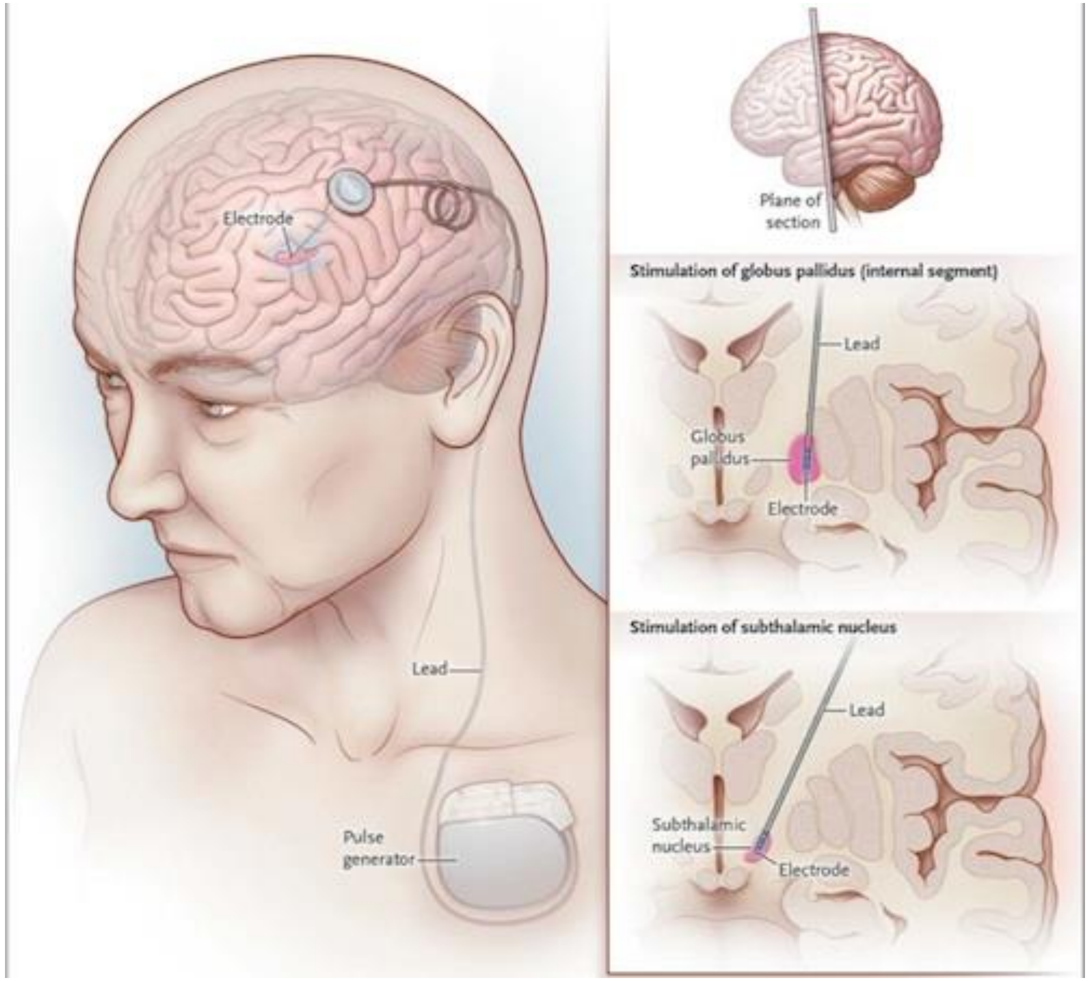
# DBS




*Okun 2012, N. Engl*

- Electrode placement and stimulation parameters vary on the target
- Mechanism not completely understood: disruption of pathological rhythms.
- Most effective treatment option for mitigating symptoms in severe cases of PD, ET, dystonia
- Limitations: invasive procedure, limited to patients without co-morbidities, tolerance development

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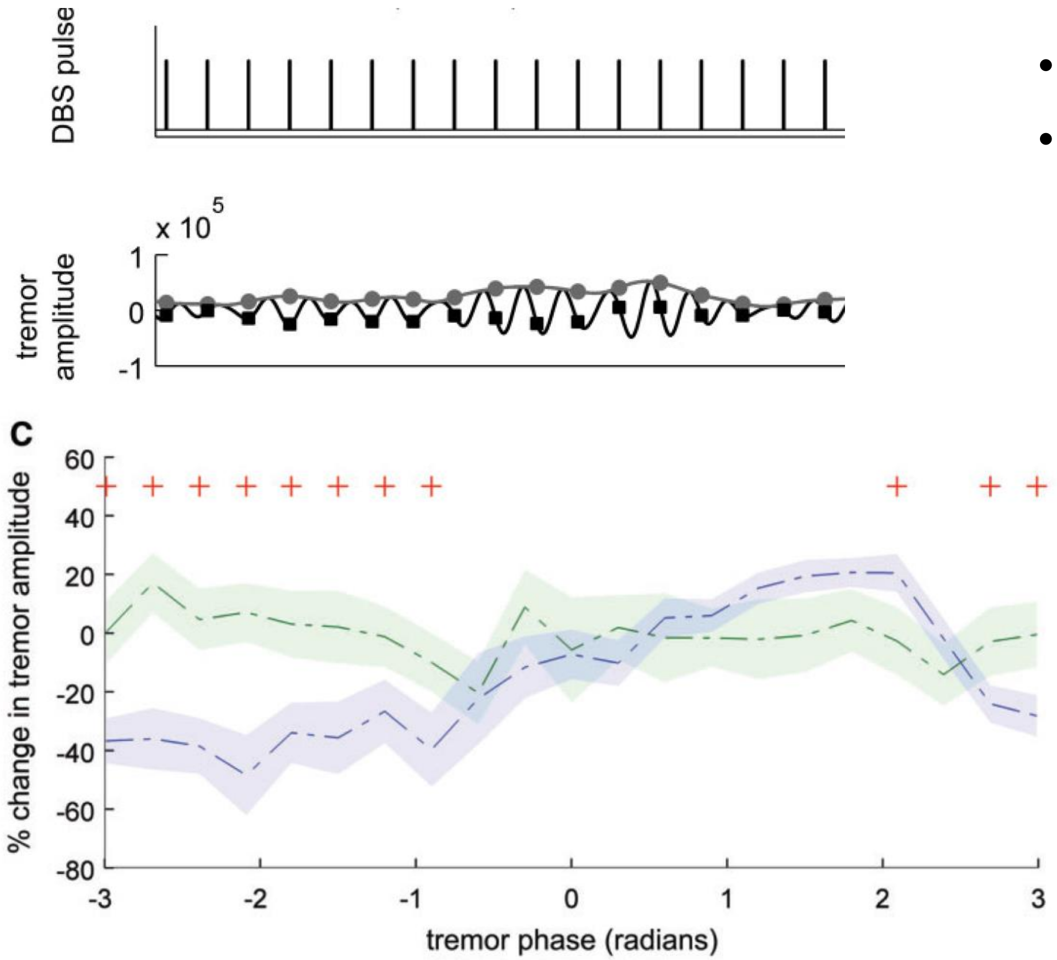
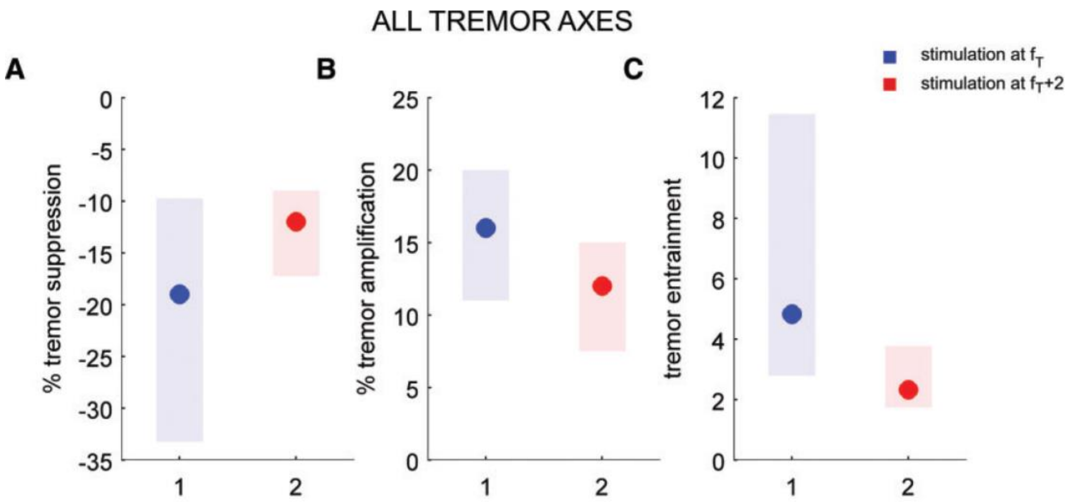
# DBS

*Cagnan et al., Brain, 2013*




- DBS at the tremor frequency can entrain tremor
- Stimulation at frequencies far from tremor frequency are less effective





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# EMG to characterize tremor

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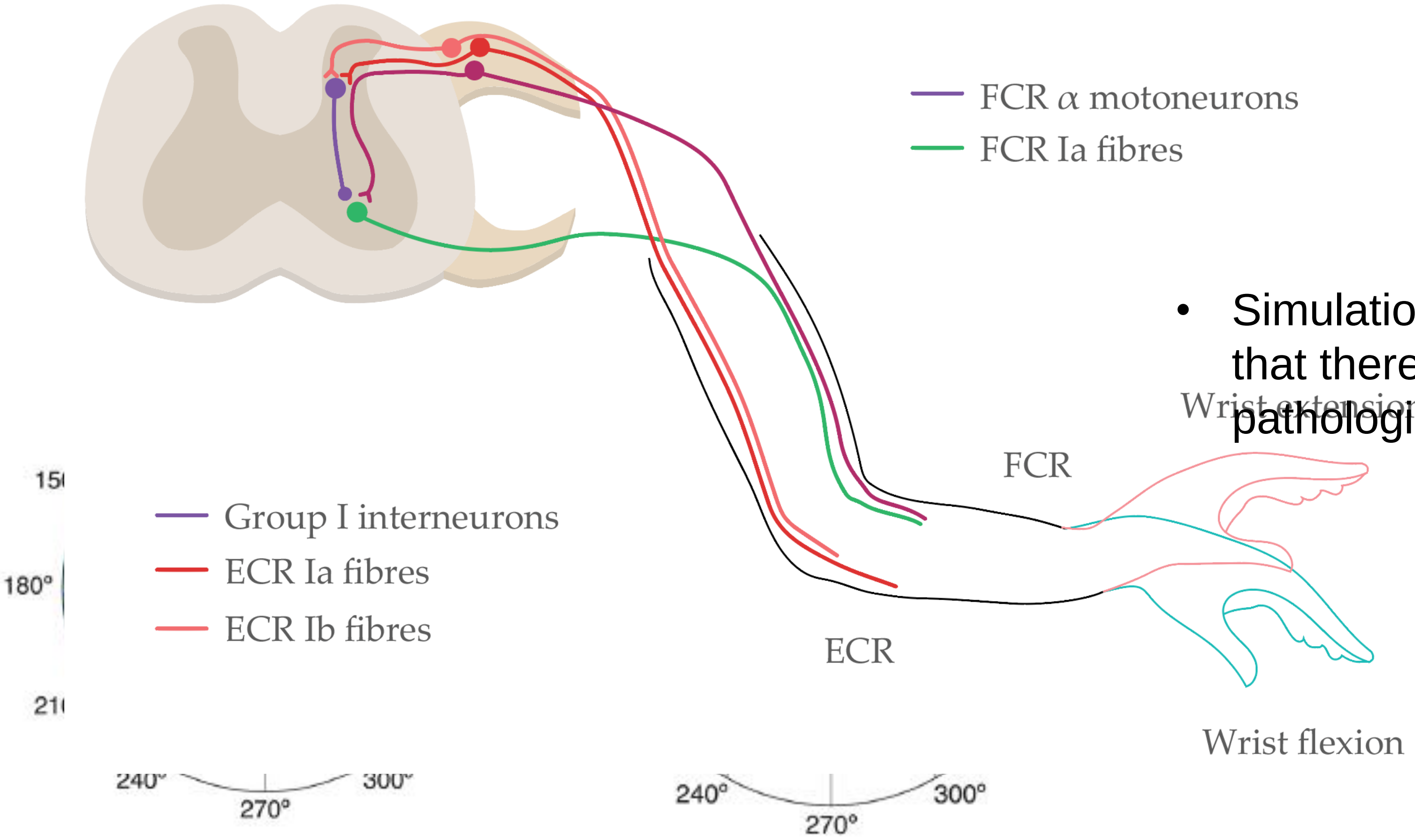
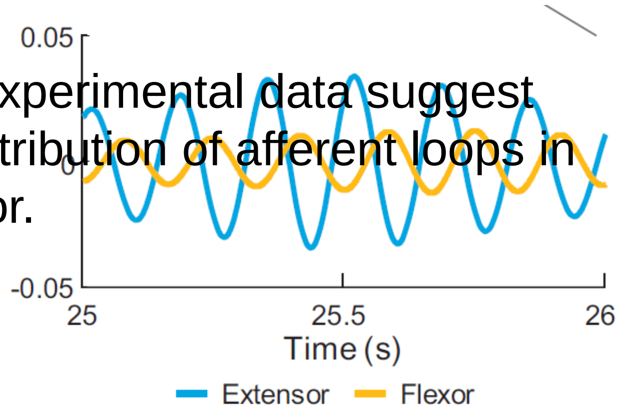



Posture

Rest

ı Essential Tremor Is Associated with

*Puttaraksa et al., IEEE TBME, 2019*




- Simulations and experimental data suggest that there is a contribution of afferent loops in pathological tremor.

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# Phase-dependent neuromodulation

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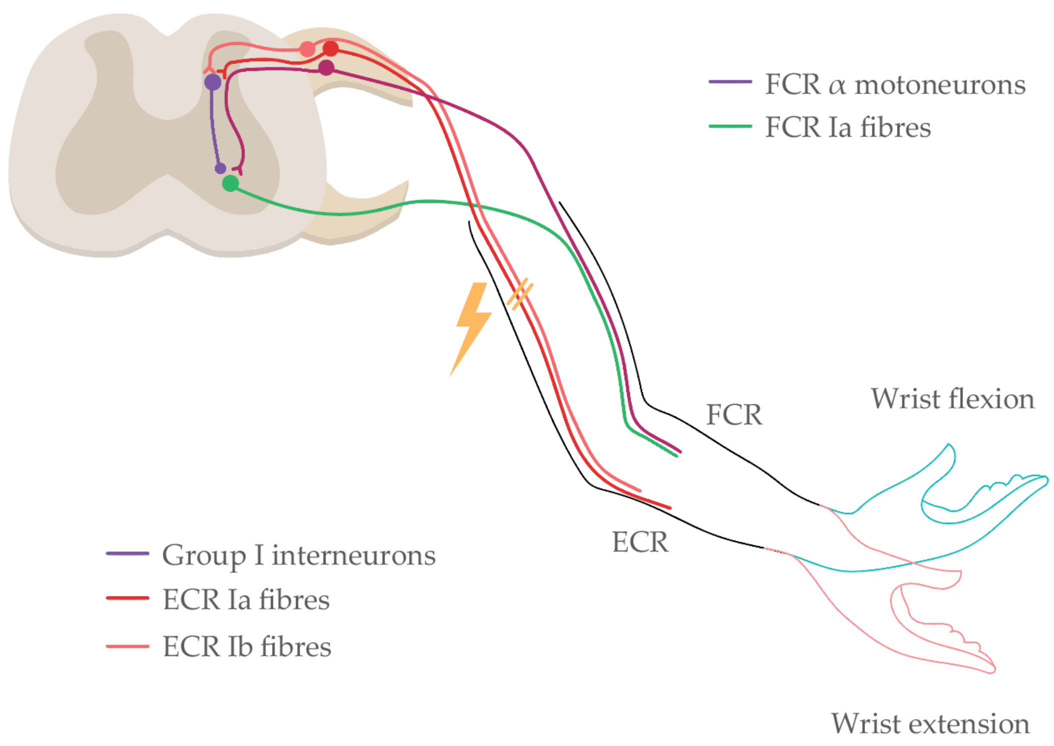


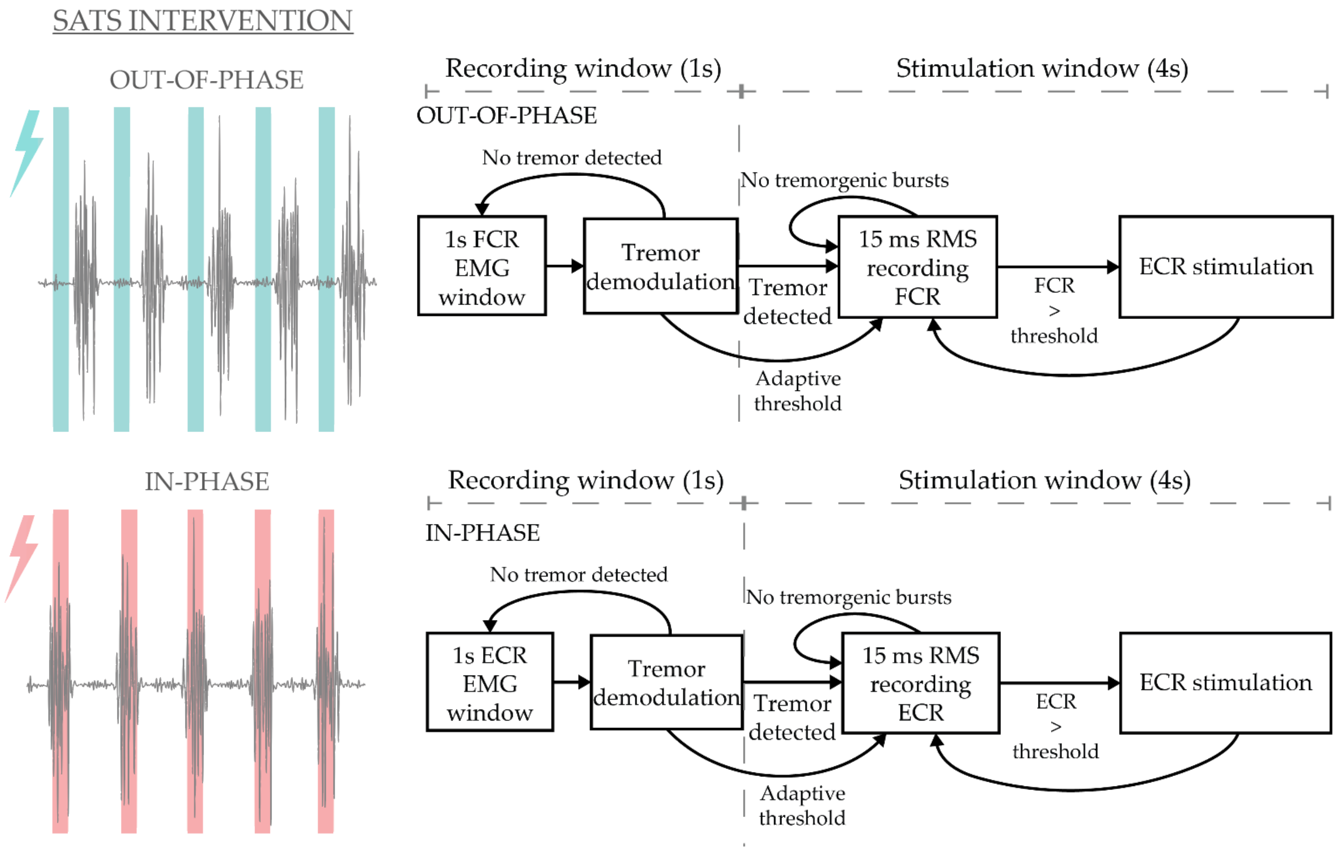


- Healthy subjects (n = 11)
- Mimicked wrist tremor


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# Question time!

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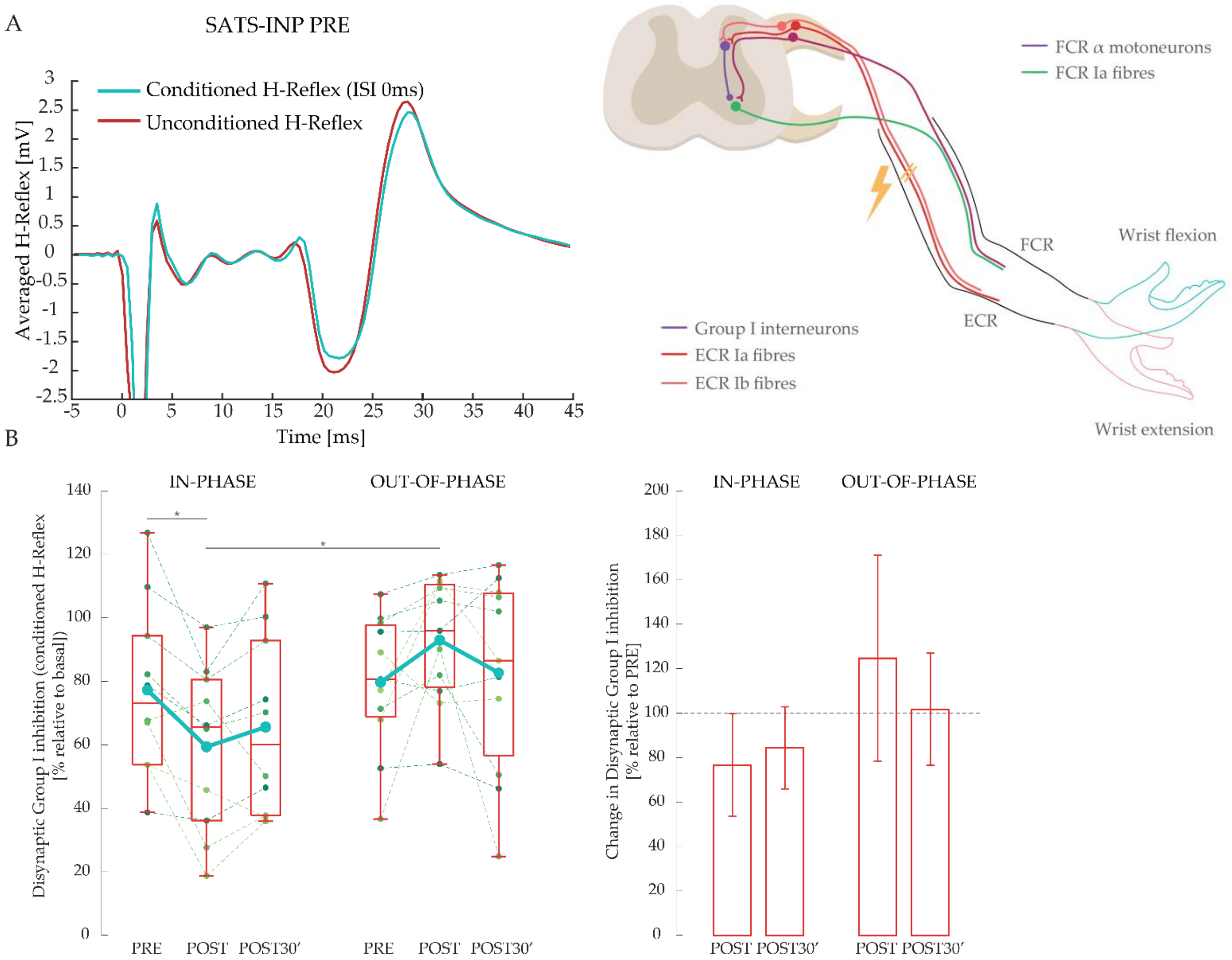
# Phase-dependent neuromodulation




- Disynaptic Group I inhibition increases after SATS-INP
- Disynaptic Group I inhibition decreases after SATS-INP
- Specific phases of stimulation synced with neural activity lead to specific neural adaptations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# Afferent stimulation to reduce tremor

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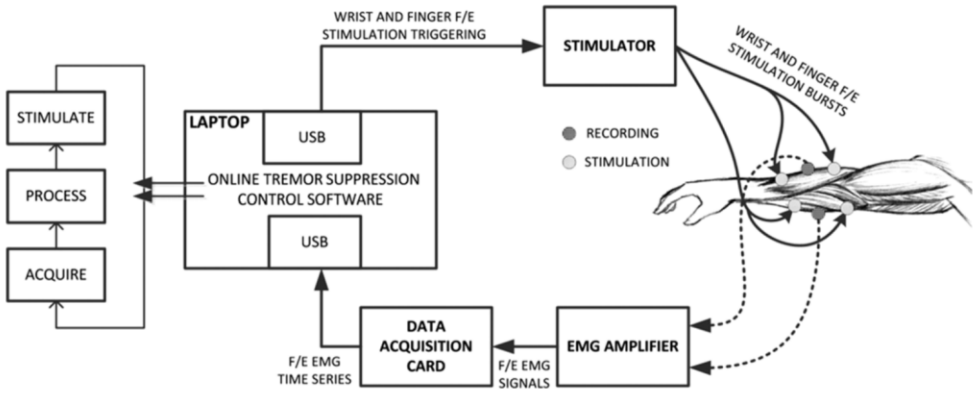
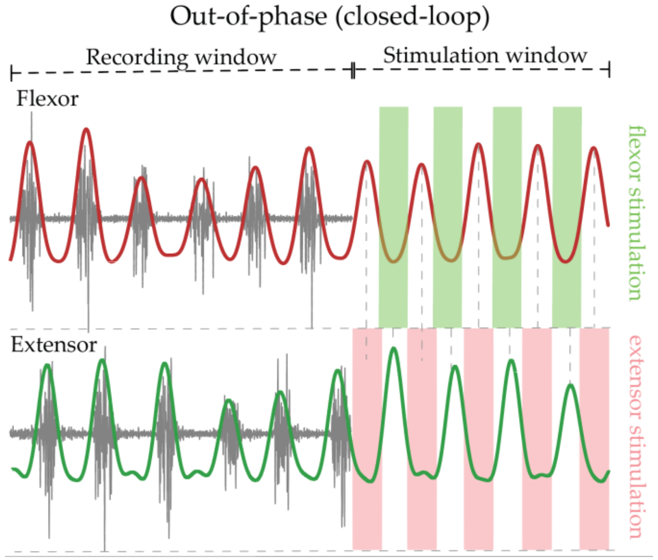
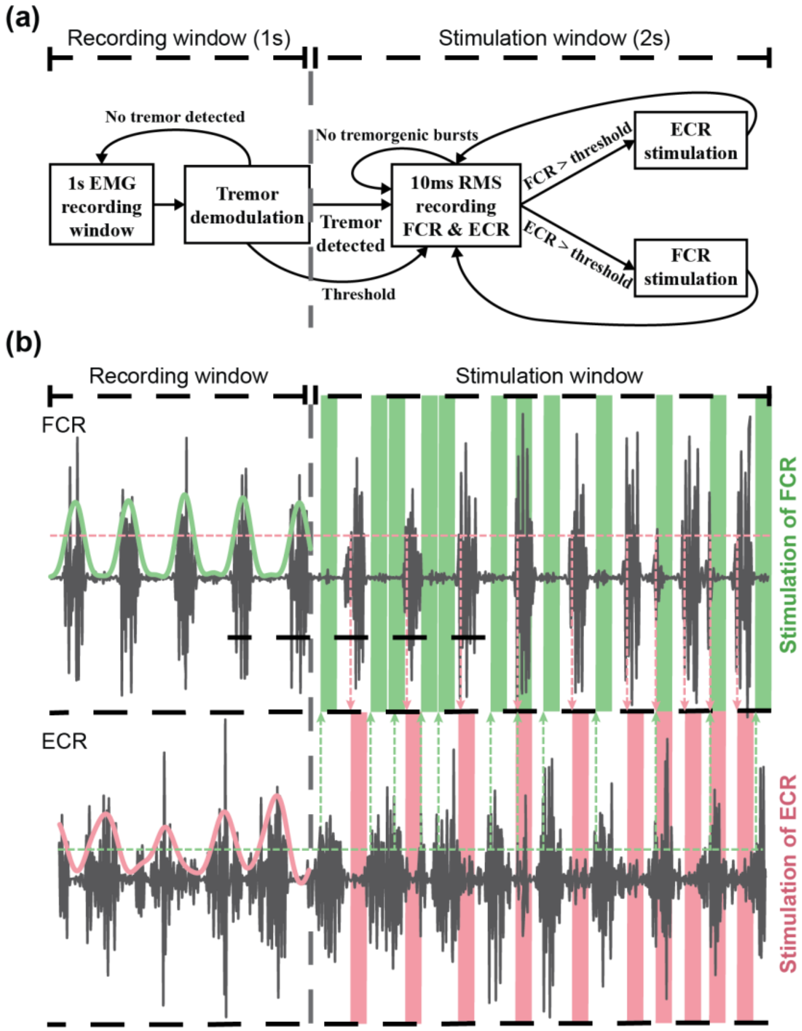



*Dosen et al., IEEE TNSRE 2015*
*Dideriksen, Frontiers in Neurosc, 2017*




*Pascual-Valdunciel et al., TBME, 2021 (SATS)*

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# Afferent stimulation to reduce tremor

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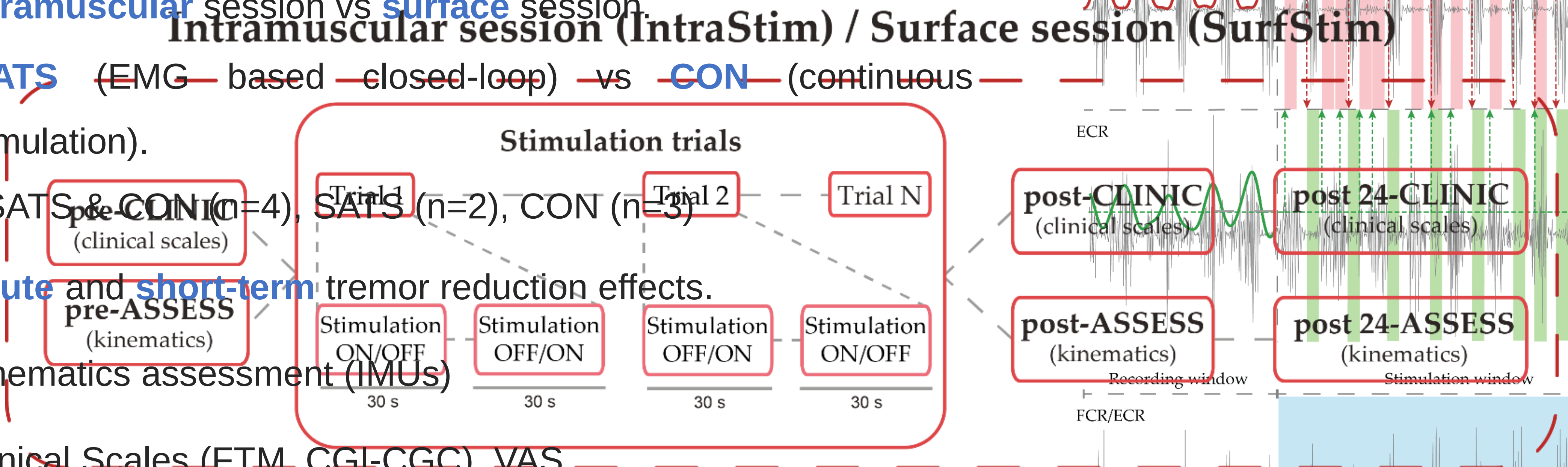
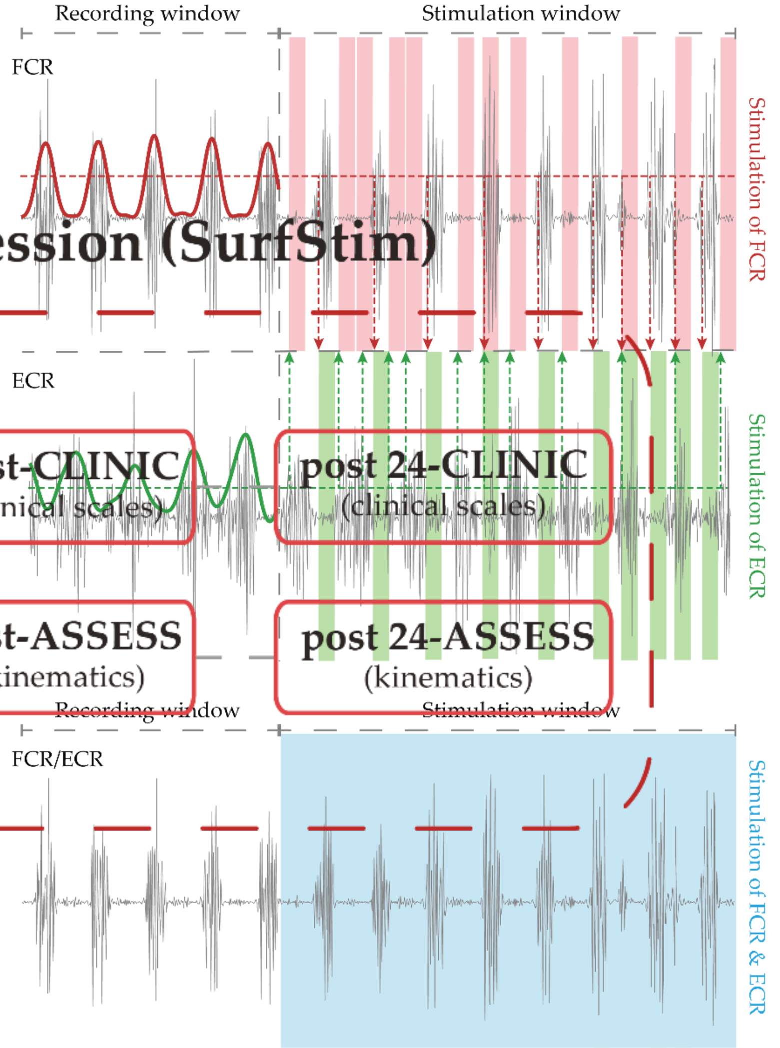
- 11 ET patients (HGM) → 9 patients selected for final analysis.
- **Intramuscular** session vs **surface** session.
- **SATS** (EMG based closed-loop) vs **CON** (continuous stimulation).

  SATS & CON (n=4), SATS (n=2), CON (n=3)
- **Acute** and **short-term** tremor reduction effects.
- Kinematics assessment (IMUs)
- Clinical Scales (FTM, CGI-CGC), VAS




*Pascual-Valdunciel et al., TBME, 2021*

SATS vs CON



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# Afferent stimulation to reduce tremor

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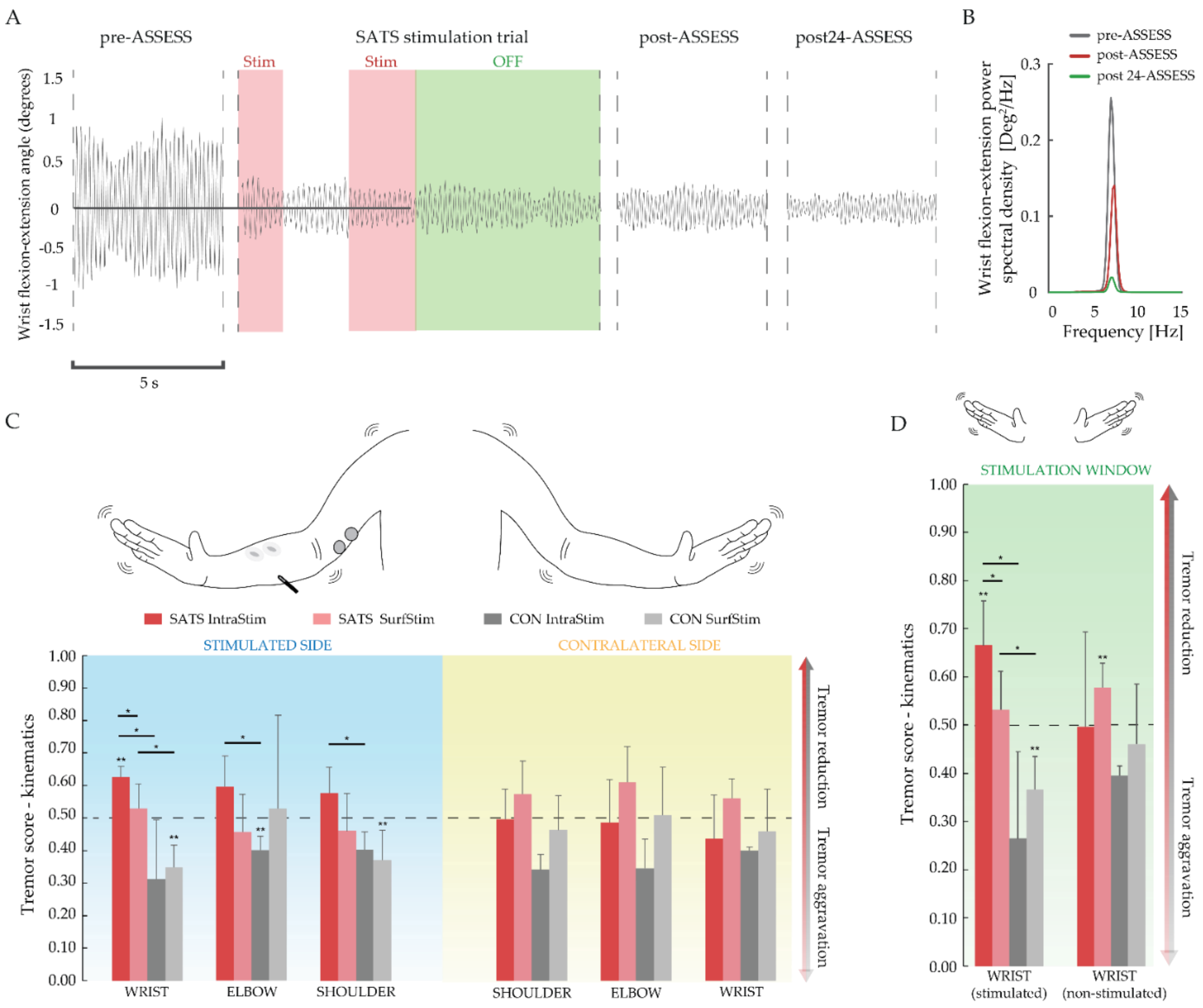
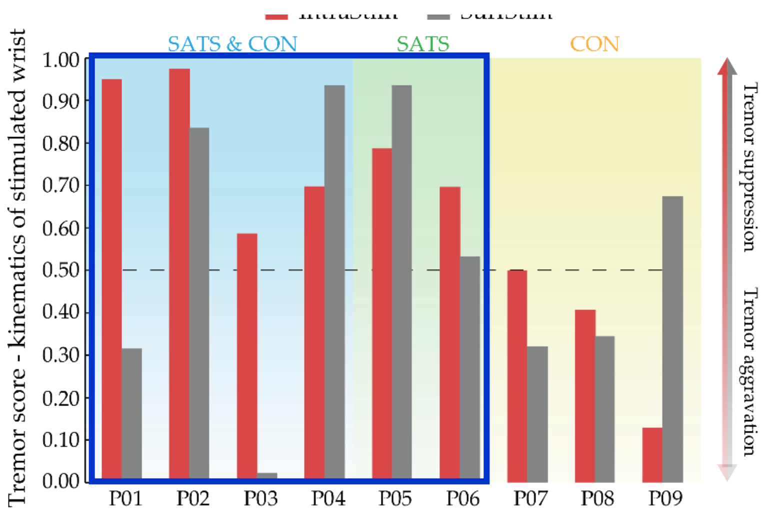
# Afferent stimulation to reduce tremor




- Acute tremor reduction
- SATS (Closed loop) >>> CON (Open loop)
- Intramuscular stimulation





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# Afferent stimulation to reduce tremor

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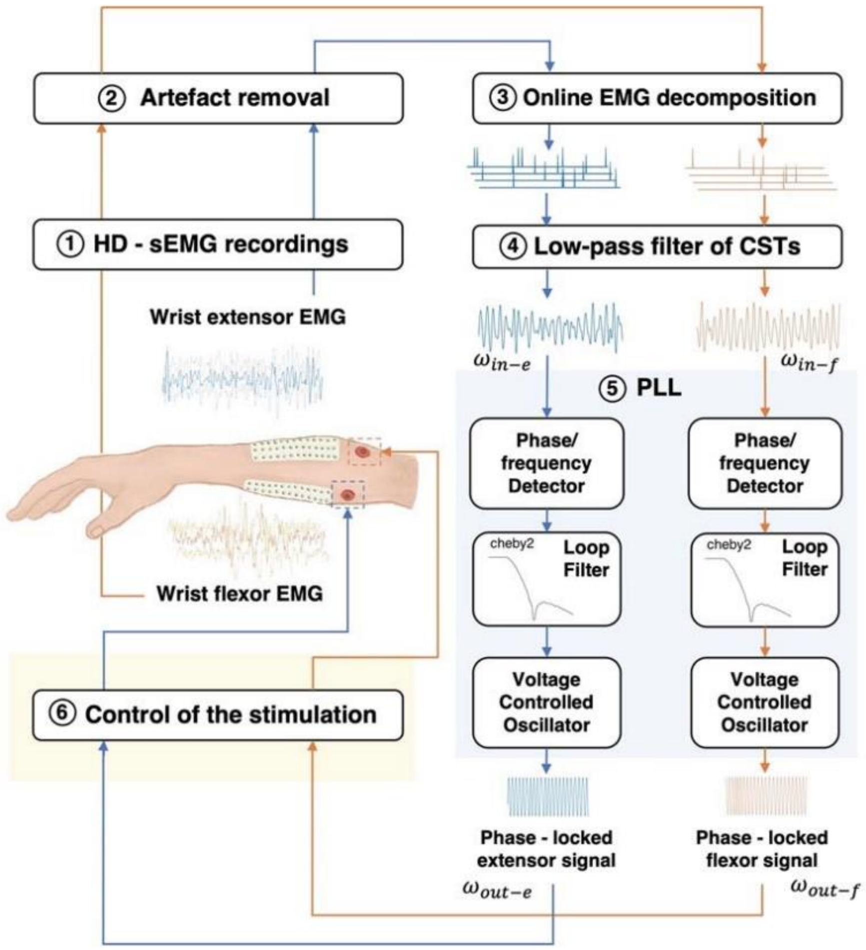
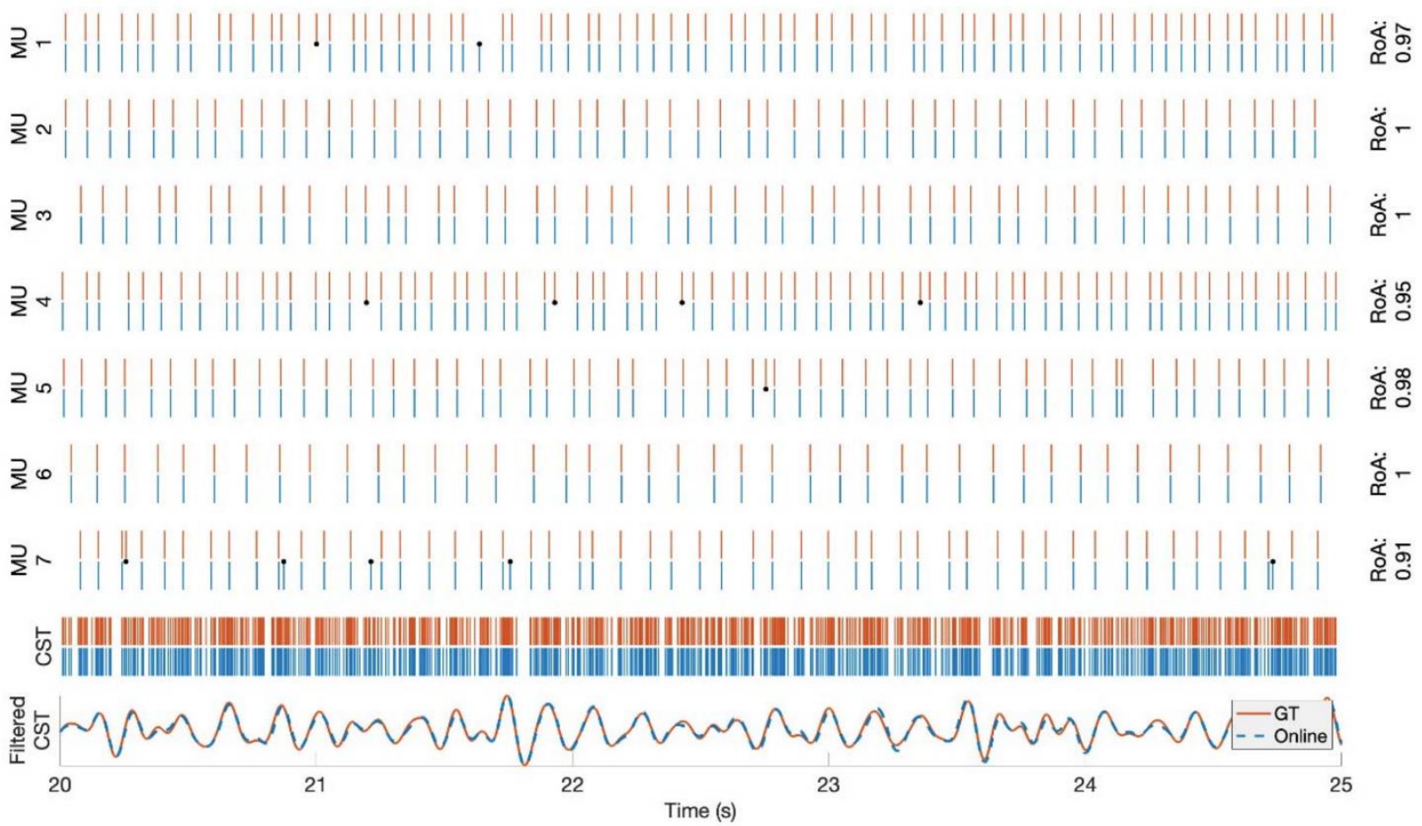
# Neural interfaces: closed-loop MU




*Puttaraksa et al., IEEE TNSRE 2022*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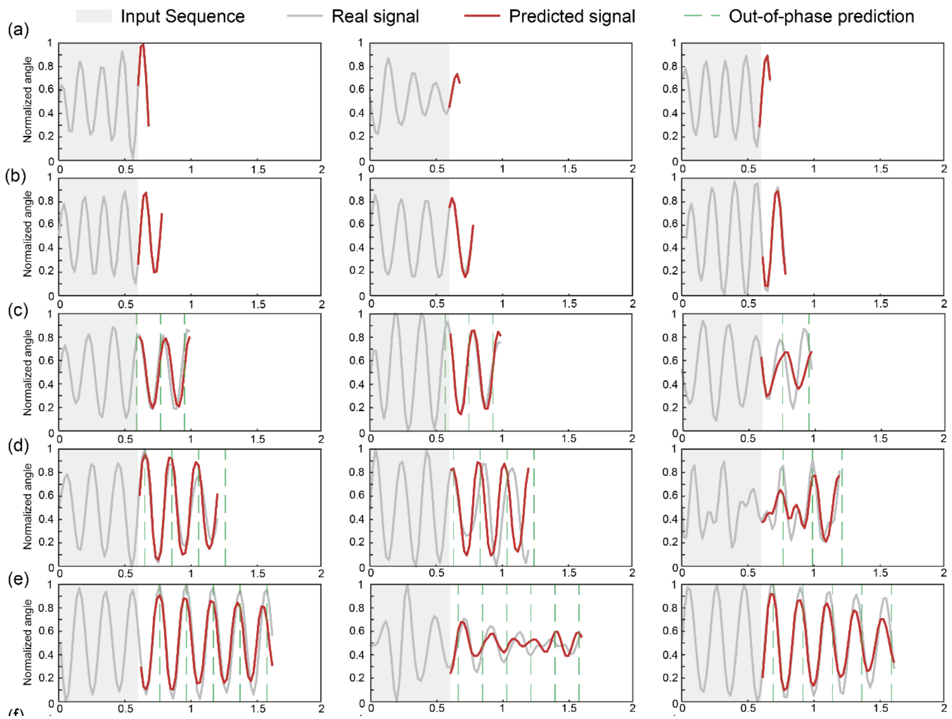
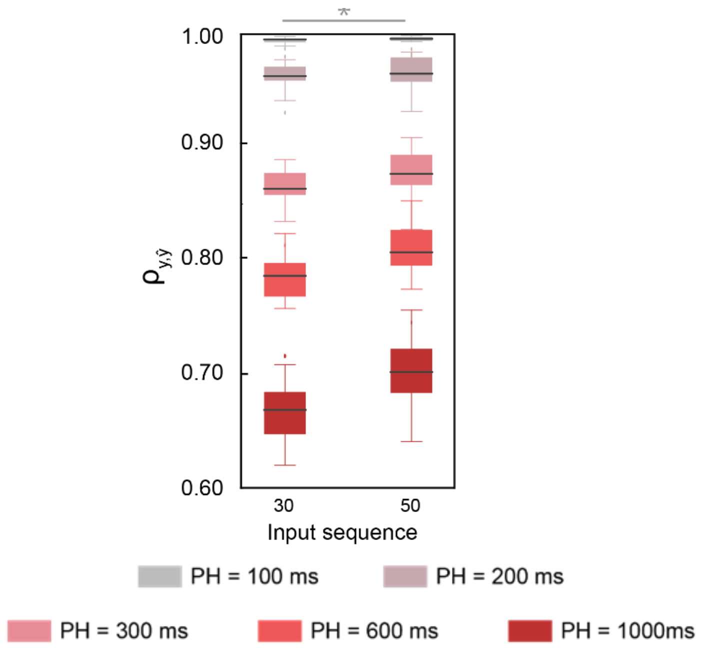
# Neural interfaces: tremor prediction

- Long short-term memory neural network (LSTM) Pascual-Valdunciel et al., IEEE JBHI, 2022
- Prediction of tremor phase and amplitude of the next tremor cycles

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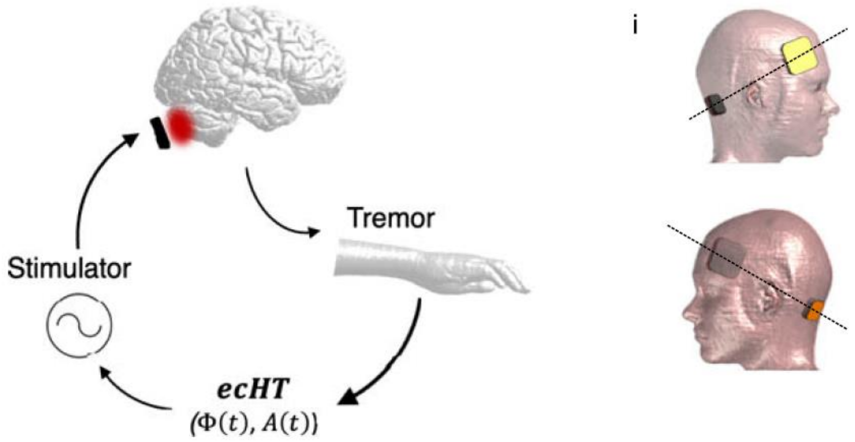
# Non-invasive CNS stimulation

**Transcranial electrical stimulation of the cerebellum**




Schreglmann et al., Nat Comm, 2020

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# Question time!

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# Non-invasive CNS stimulation

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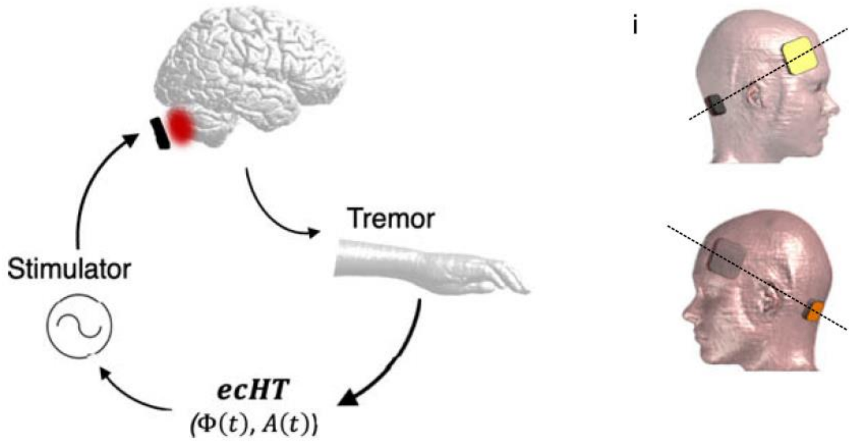
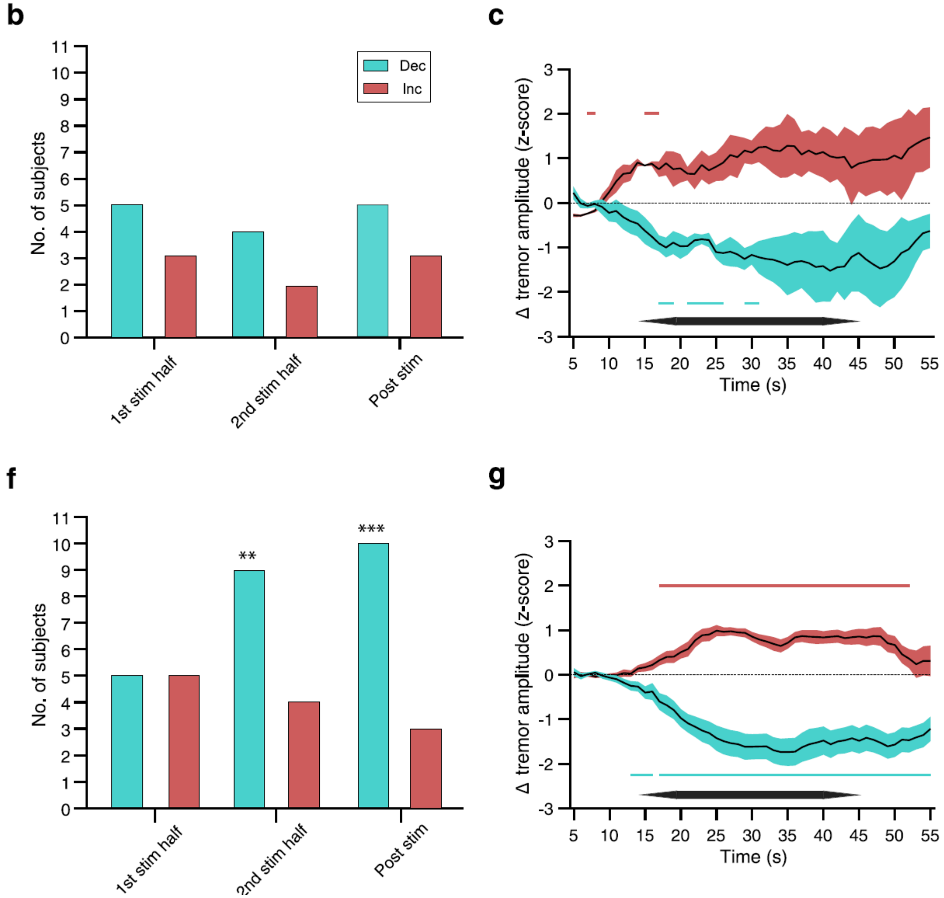
## Transcranial electrical stimulation of the cerebellum

- Cerebellar stimulation disrupt tremor
- Phase-locked (closed-loop) increases efficacy compared to frequency-locked (calibrated open-loop)




Schreglmann et al., Nat Comm, 2020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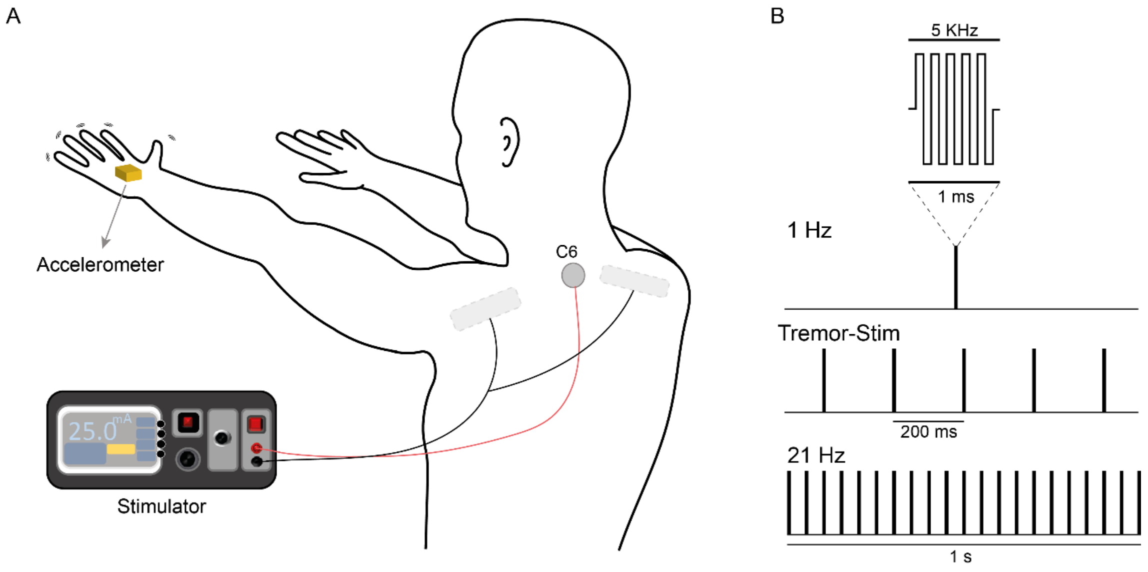
# Non-invasive CNS stimulation: tSCS

## Transcutaneous spinal cord stimulation (tSCS)




*Pascual-Valdunciel and Ibáñez et al., (almost in) Mov Disorders, 2024*

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# Question time!

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# Non-invasive CNS stimulation: tSCS

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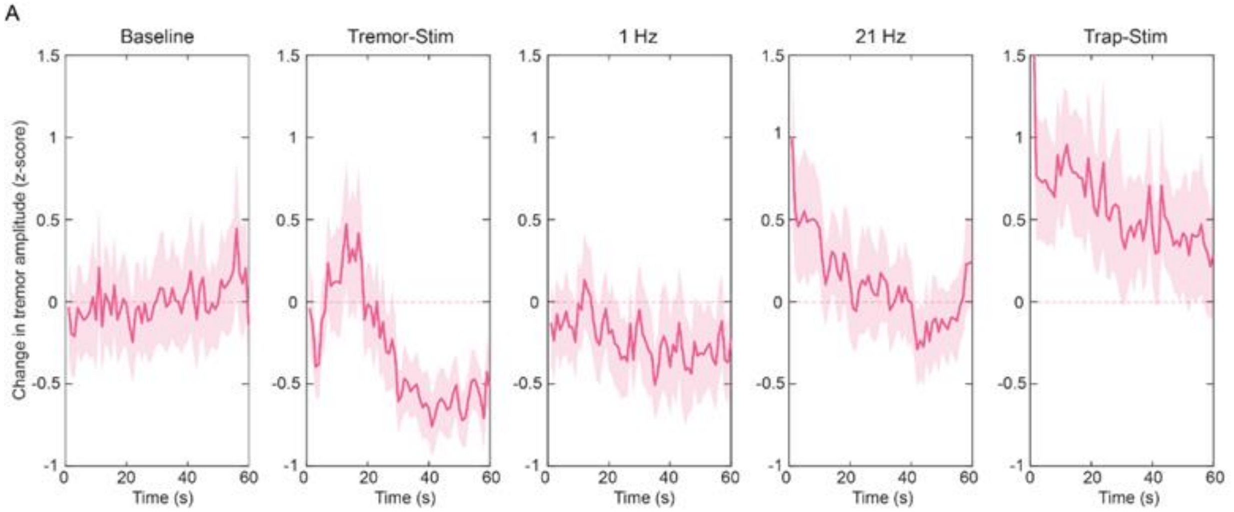
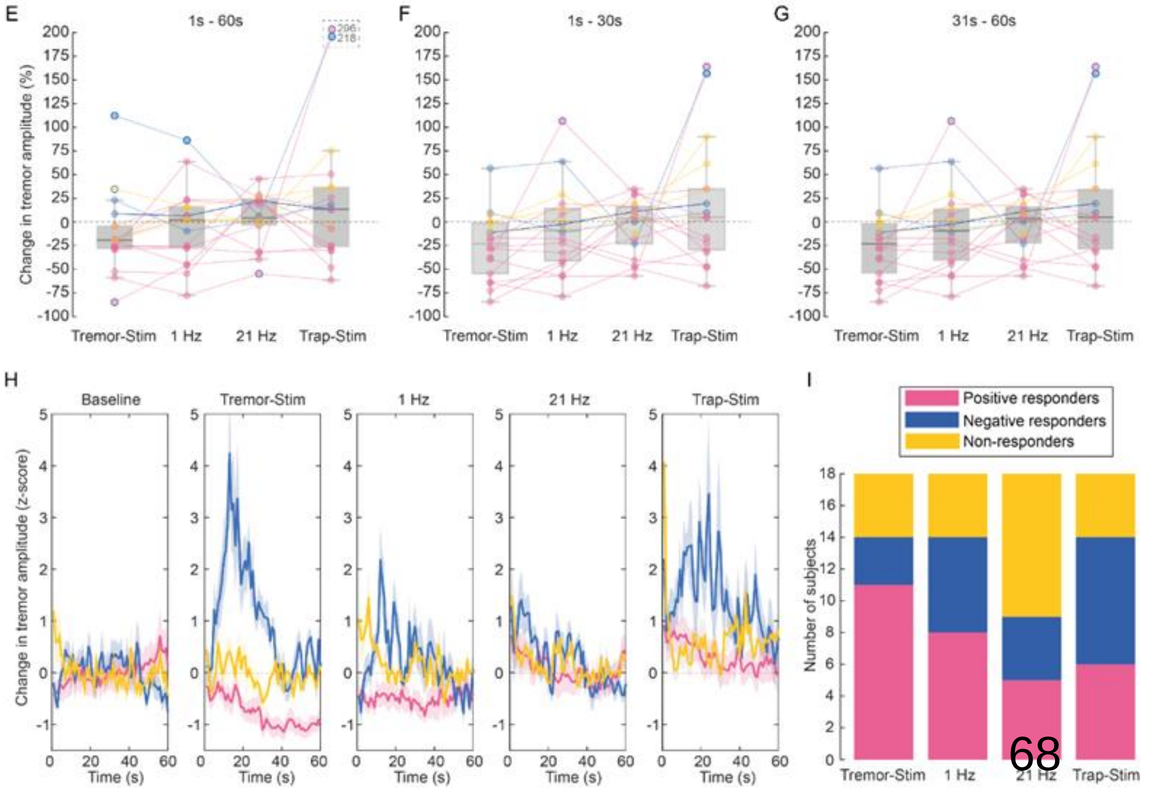
## Transcutaneous spinal cord stimulation (tSCS)

- tSCS recruit afferent and interneurons in the spinal cord
- tSCS-locked to the tremor frequency disrupts tremor
- Other frequencies (1Hz or 21Hz) does not reduce tremor

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# Non-invasive CNS stimulation: tSCS

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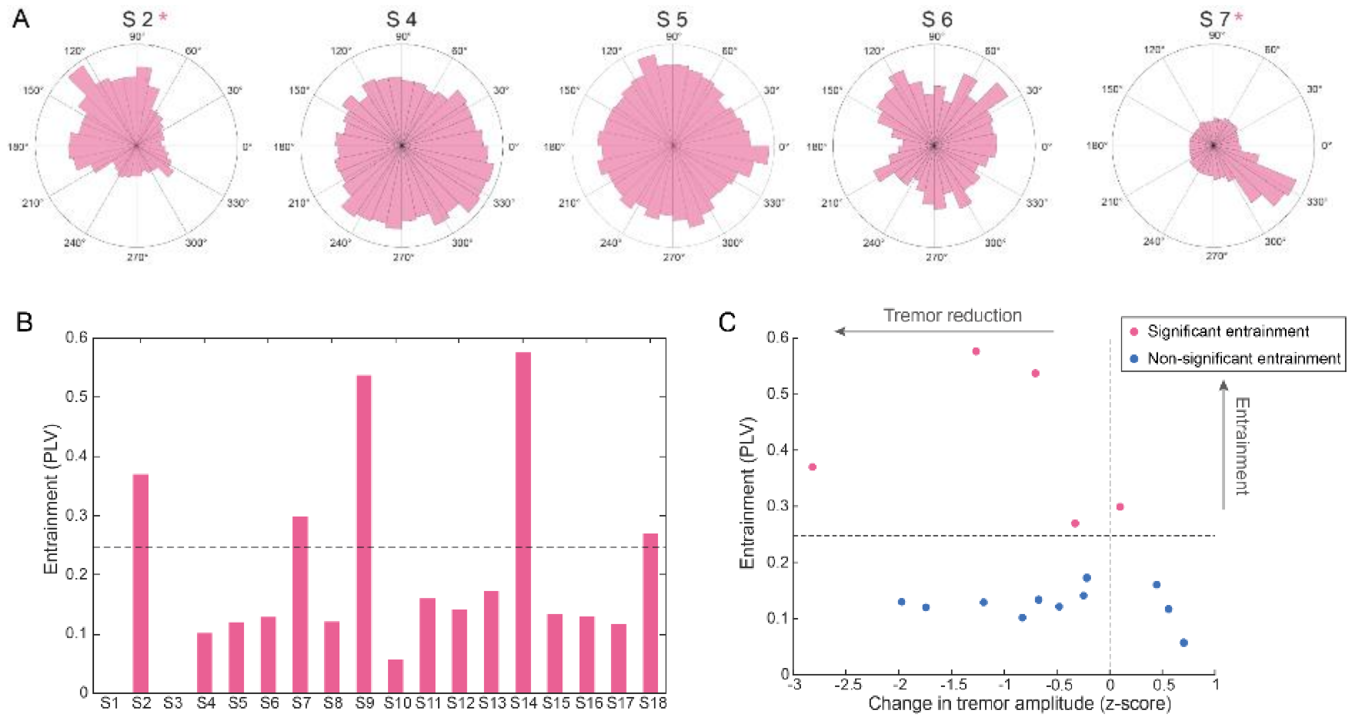
## Transcutaneous spinal cord stimulation (tSCS)

- Entrainment: tSCS drives the tremorgenic phase for some patients
- Future works: exploration of tSCS effects, circuits implied

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# Neural interfaces: study spinal circuits

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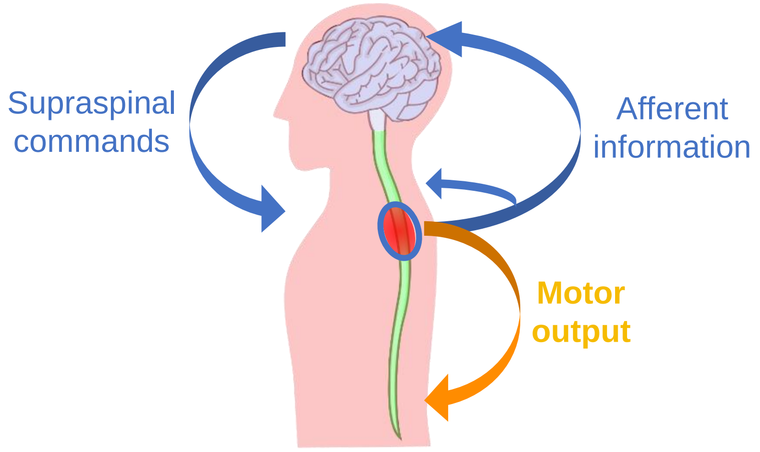
# Spinal circuits

**The motoneurons in the spinal cord are the final integration centres involved in motor control.**

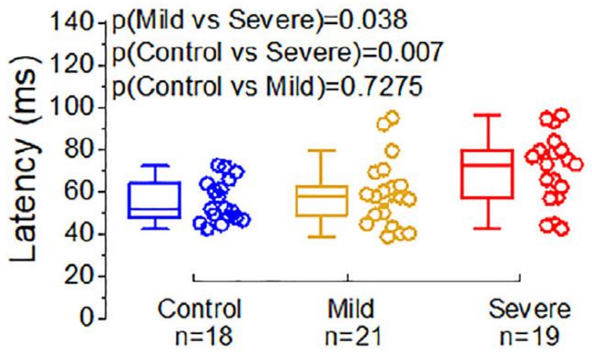
<u>Electromyography allow to study spinal circuit properties from the periphery</u>

Understanding their role in motor control
Biomarkers of the disease state/progression




## Spinal circuits can be altered in neural diseases

- Cutaneous Silent Period (CSP) in Amyotrophic Lateral Sclerosis (ALS)




*Topkara and Özyurt et al., Clin. Neurophysiol., 2024*

- Recurrent inhibition in ALS (Özyurt et al., Clinical Neurophysiology, 2020)
- Reciprocal inhibition in Parkinson's Disease (Meunier et al., Brain, 2000)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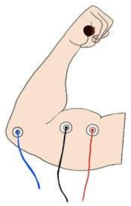
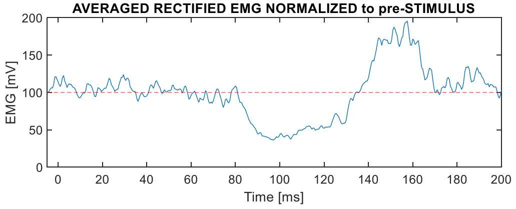
# Spinal circuits

### Surface EMG

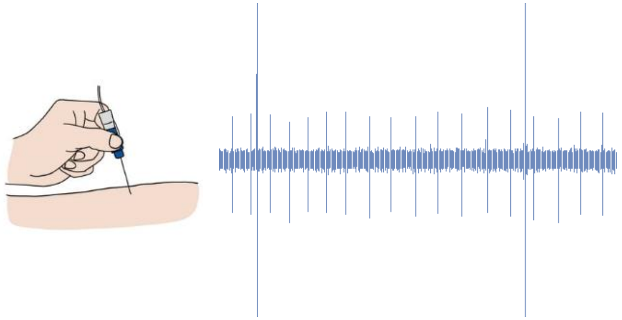
- ✔ Fast
- ✔ Non-invasive
- ✘ Low resolution
- ✘ No single MU






### Intramuscular EMG

- ✘ Time consuming
- ✘ Invasive
- ✔ High resolution
- ✘ Typically limited to 1 MU

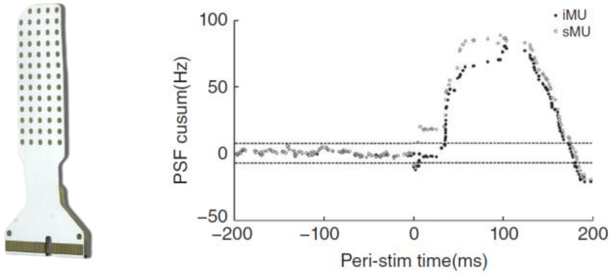


### High-Density EMG

- ✘ Time consuming
- ✔ Non-invasive
- ✔ High resolution
- ✔ Large sample of MUs
- ✔ Reflex amplitudes in the TA and SOL

*Yavuz et al. 2015, 2018*

- ✘ No validation on inhibition features for single MUs




✘ *Cons* ✔ *Pros*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# hdEMG as a neural interface

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## Characterization of spinal circuits with high density surface electromyography (HDsEMG)

- HDEMG can be used to study the properties of spinal circuits in individual MNs

Alejandro Pascual-Valdunciel, M. Görkem Özyurt, Filipe Nascimento, Marco Beato, Rob Brownstone, Dario Farina; *International MotoNeuron Society Meeting 2024 and ISEK 2024; article under preparation*

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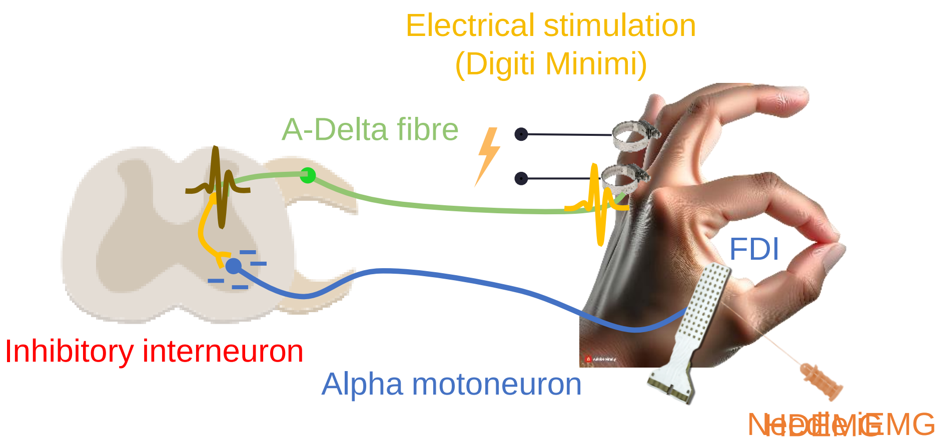
# Cutaneous Silent Period




## CSP latency and duration are altered in ALS

- 200 s isometric contraction at 10% MVC (≈ 160 pulses)
- Stimulation (ISI = 1.8± 0.2 s)
  - x7.5 sensory threshold
  - x10 sensory threshold
- HDEMG (4mm IDE grids) on the FDI and APB
- 8 healthy subjects

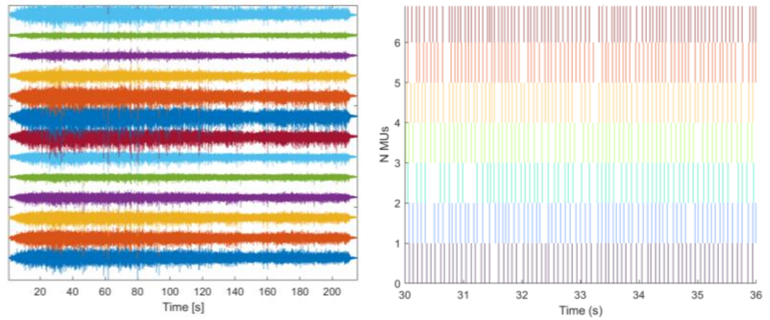
**Decomposition into individual MUs**
(Convolutive Blind Source Separation)

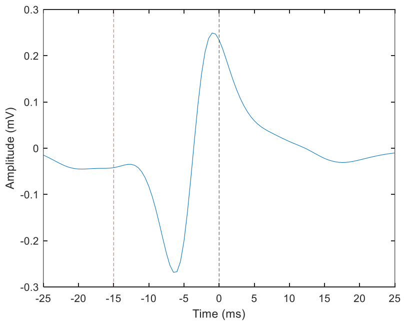
→

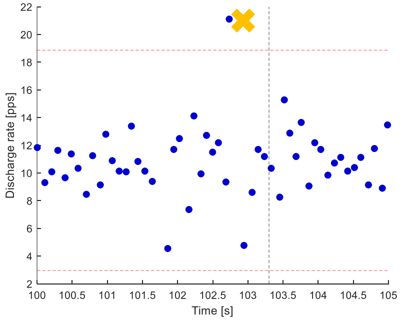
**Motor Unit Amplitude Potential onset**
**Automatic MU cleaning**
(Removing outlier iDR)

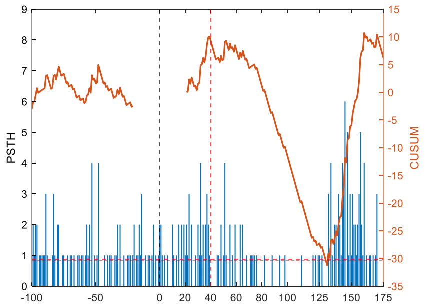
→

**PSTH** (latency, duration)
**PSF** (latency, duration)





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*article under preparation*

# Peristimulus Time Histogram (PSTH)

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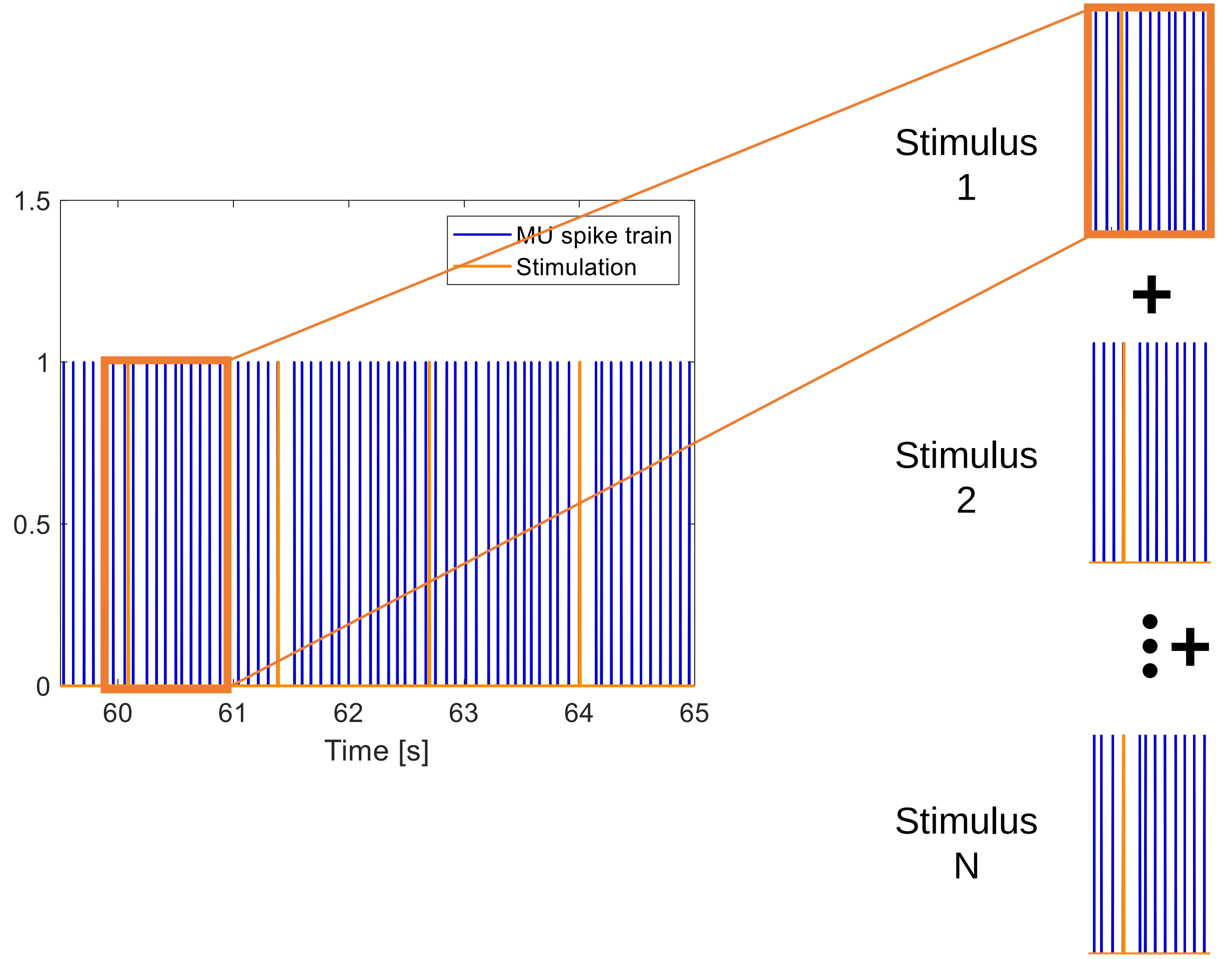


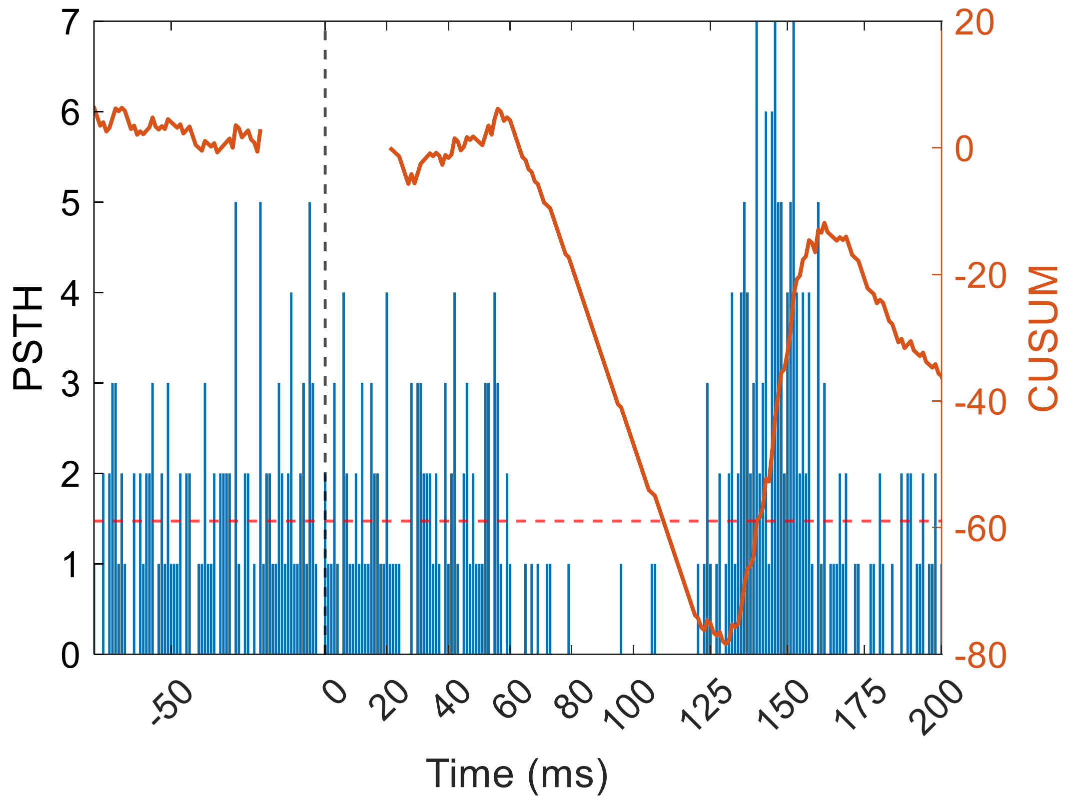


CUSUM = Cumulative sum of MU firing occurrence


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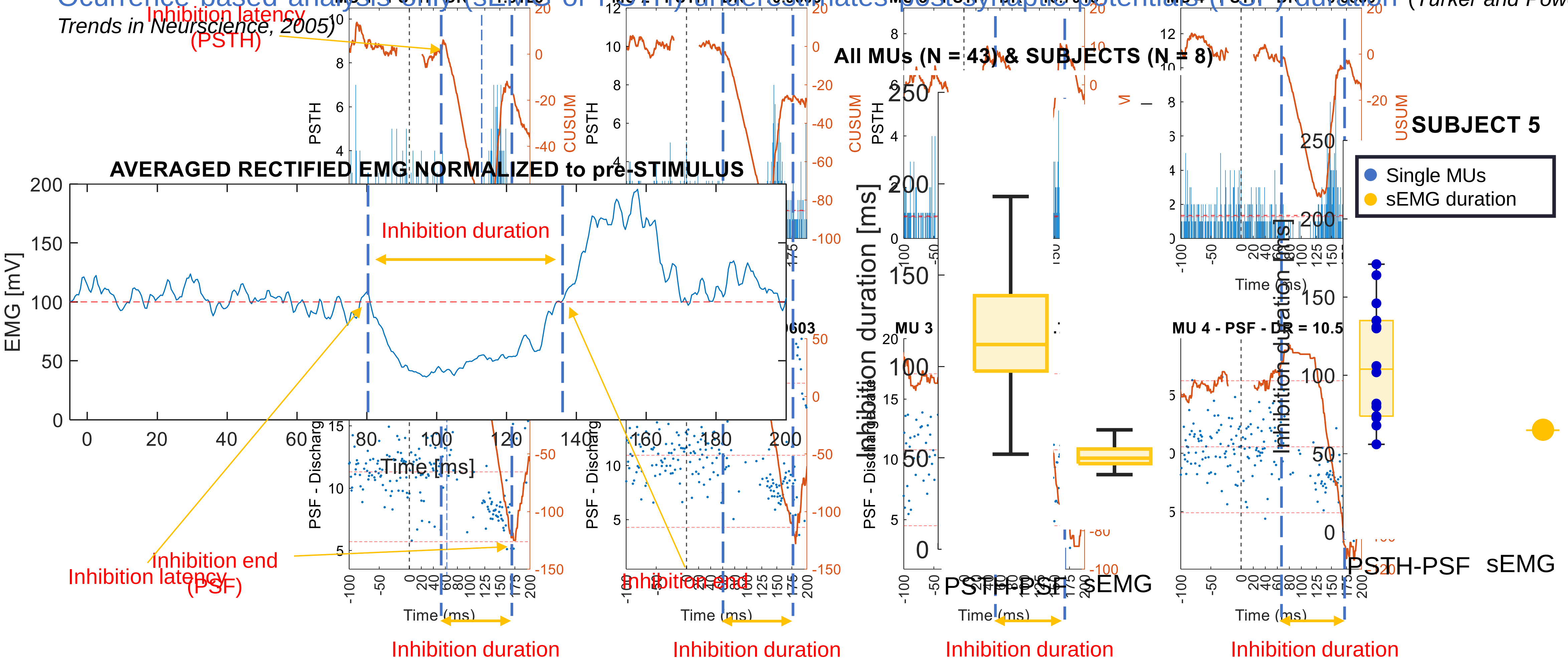
# Cutaneous Silent Period

HYBRID NEURO

Ocurrence based analysis only (sEMG or PSTH) underestimates post-synaptic potentials (PSP) duration *(Türker and Powers, Trends in Neurscience, 2005)*





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*article under preparation*

# Cutaneous Silent Period

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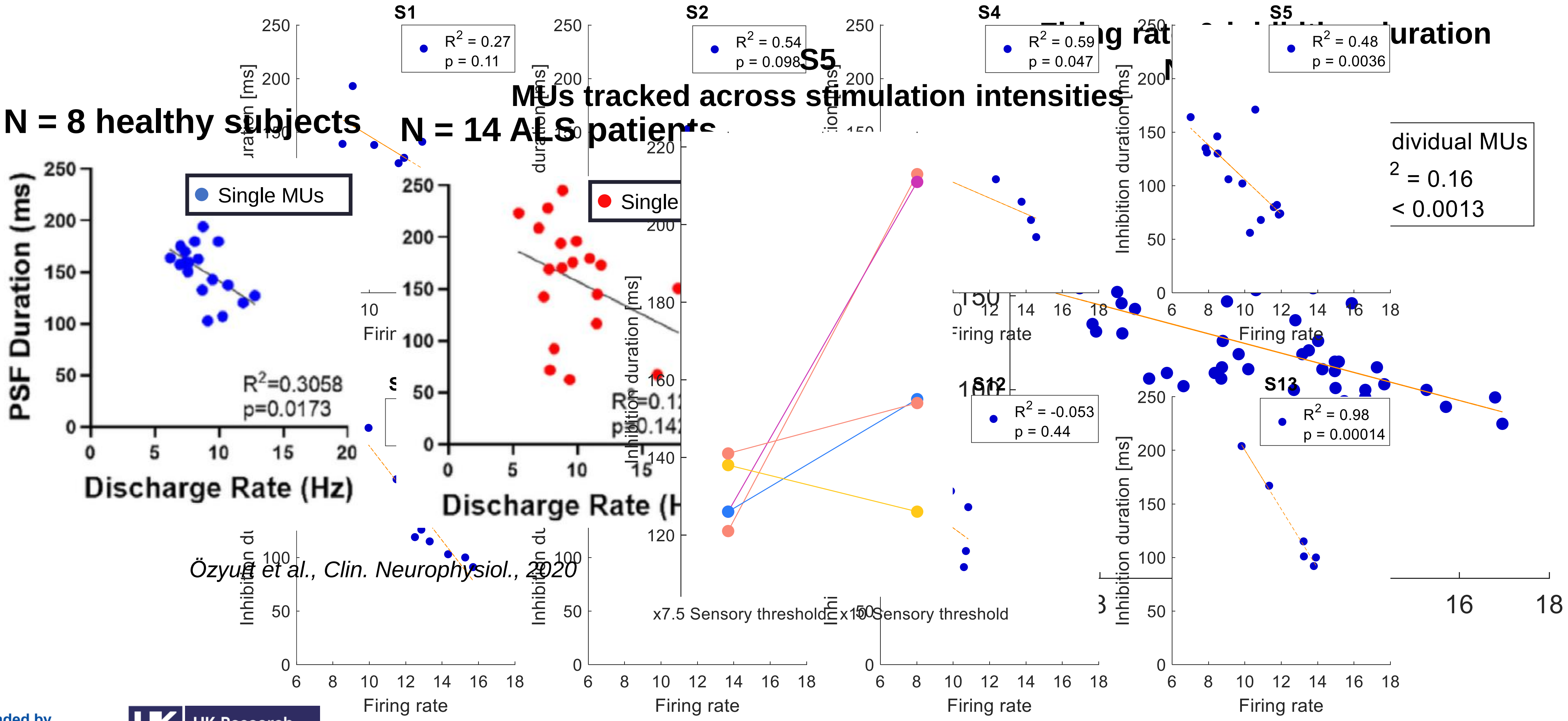
N = 8 healthy subjects

N = 14 ALS patients

MUs tracked across stimulation intensities




*Özyurt et al., Clin. Neurophysiol., 2020*

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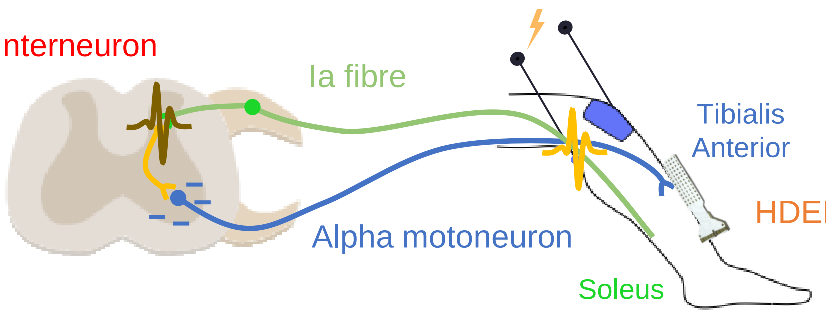
# Reciprocal inhibition




**TA RECIPROCAL INHIBITION**

- 300 s isometric dorsiflexion at 10% MVC (≈ 150 pulses)
- Stimulation of Tibial Nerve (ISI = 2.0 ± 0.2 s)
- HDEMG (4 x 4mm IDE grids) on the TA
- Healthy subjects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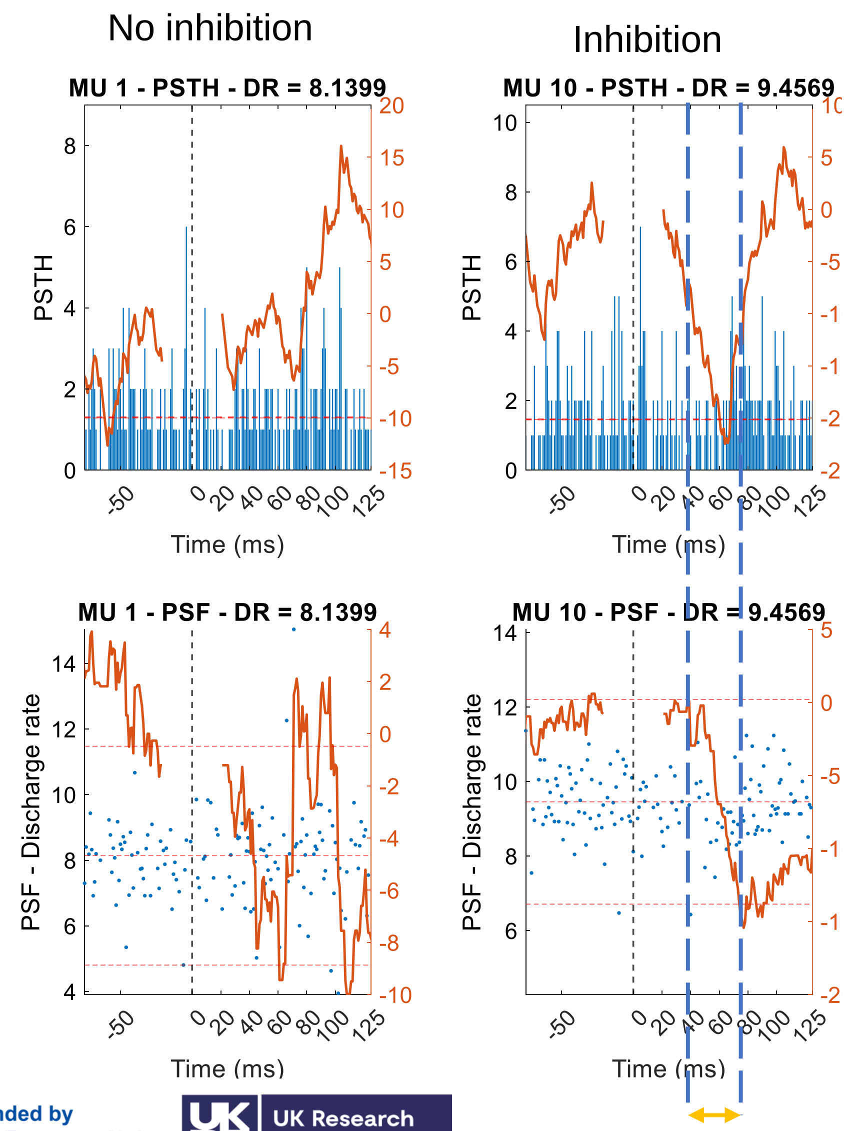
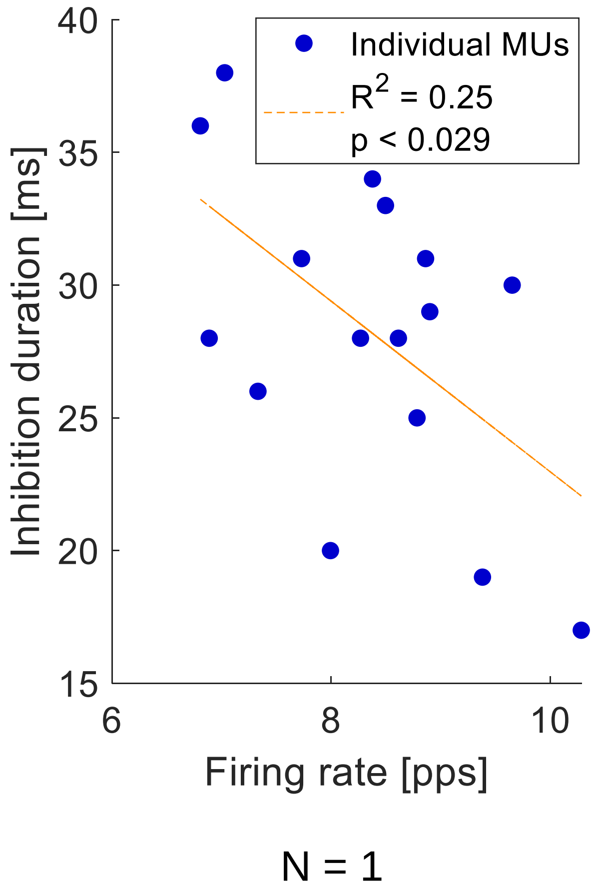
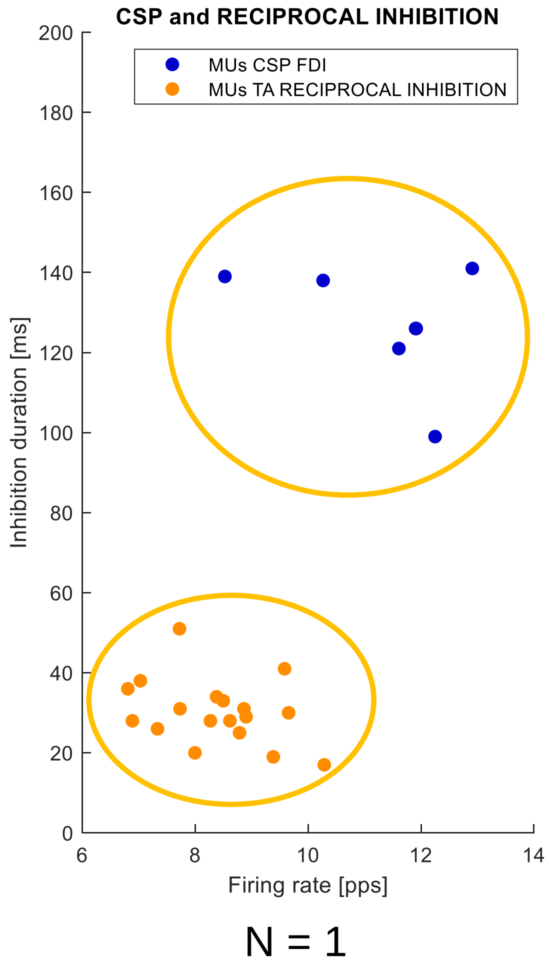
# Reciprocal inhibition




*article under preparation*

**HDEMG is sensitive to different inhibition circuits**

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# Neural interfaces Applications

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- Neural rehabilitation: modulating neural activity towards the restoration physiological rhythms in neural disorders
  - Parkinson’s Disease, Essential Tremor, Dystonia
  - Stroke, SCI, cerebellar ataxias

Identification of aberrant neural rhythms → Design neuromodulation paradigm → Target neuromodulation → Functional recovery

- Diagnosis/Monitoring: identifying biomarkers to understand disease pathophysiology and diagnosis/prognosis

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# Thank you

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**Imperial College London**
Dario Farina
Emanuele Abbagnano
Cosima Graef
Rita Kharboush
…

**Cajal Institute**
Filipe Barroso
José Luis Pons
Cristina Montero Pardo

**SRAlab**
José Luis Pons
Nish Mohit Kurukuti

**UCL**
Anna Latorre
Gorkem Ozyurt
Filipe Nascimento

**UPM**
Álvaro Gutiérrez
Alberto Beltrán
Victor Lopo

**UNIZAR**
Jaime Ibáñez

**Chalmers University**
Silvia Muceli

**HGM**
Francisco Grandas
Miguel González
Javier Pérez

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