

# Paired associative stimulation in spinal cord injury rehabilitation

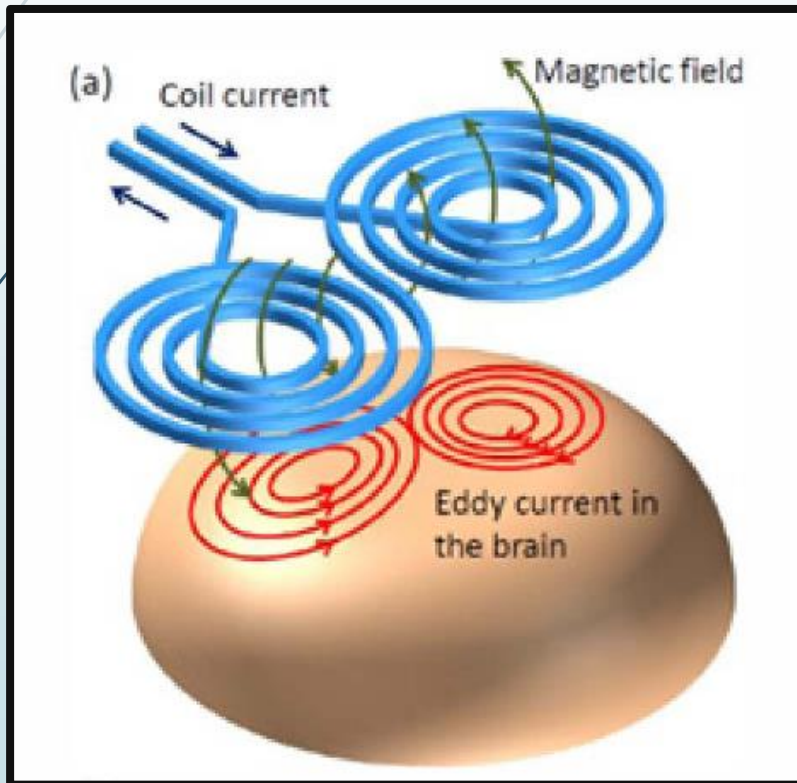
1

**Anastasia Shulga, MD, PhD, neurologist**

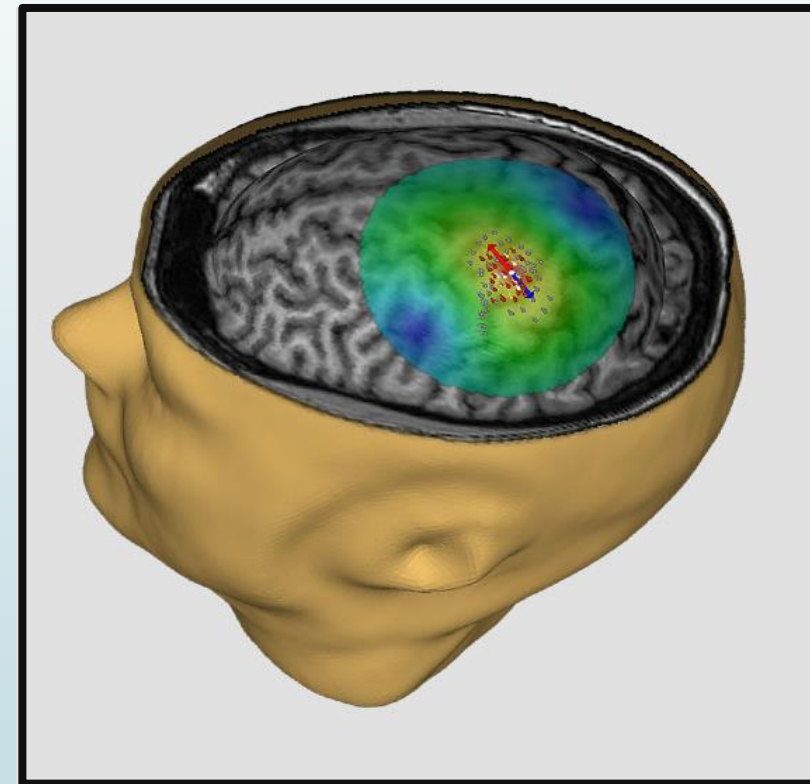
**Head of Department at Ward for Demanding Rehabilitation  
Helsinki University Hospital and BioMag laboratory  
Helsinki, Finland**

2

# TMS = transcranial magnetic stimulation



Sekino et al 2012  
Materials Science



Nexstim.com

3

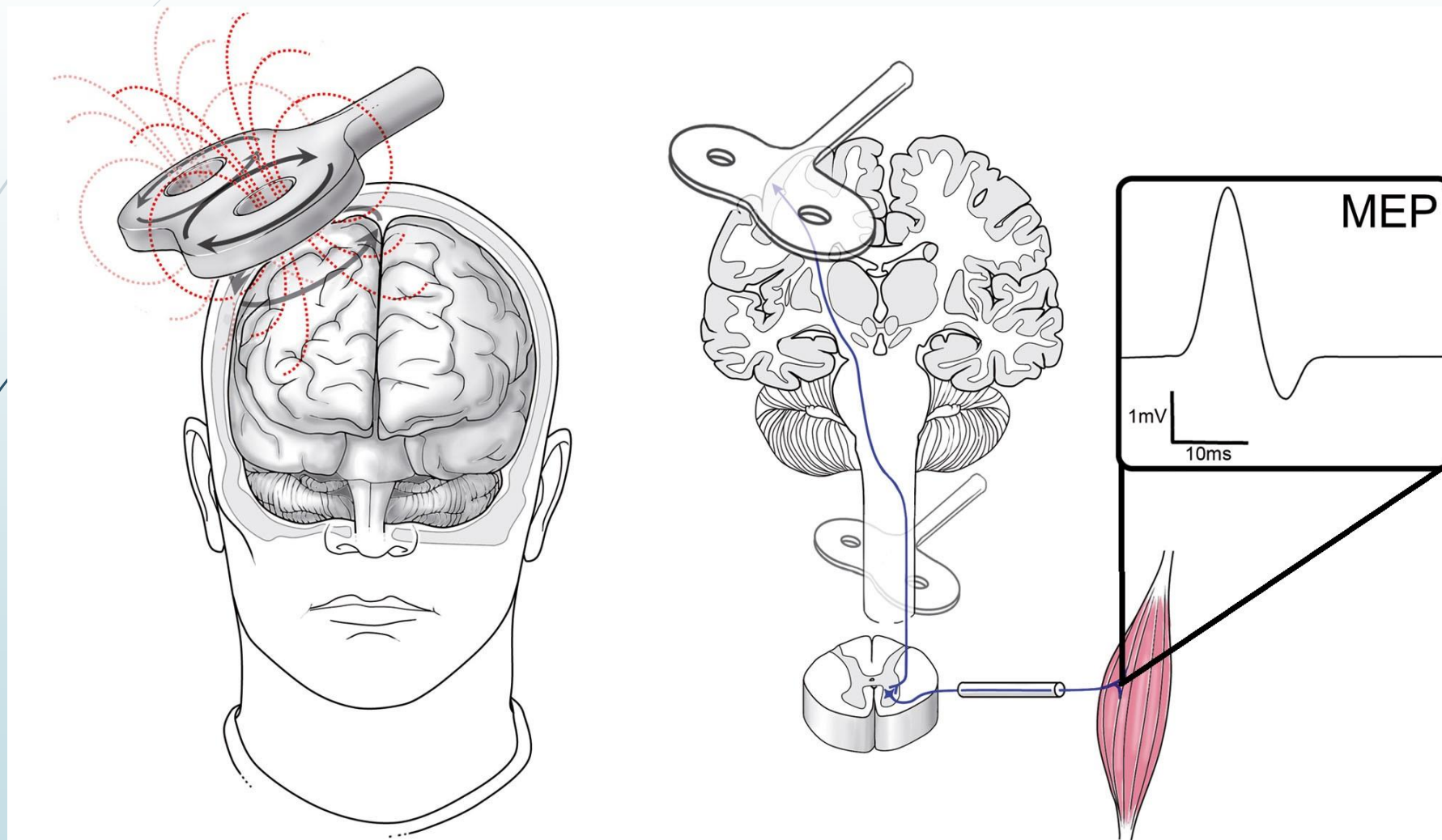
TMS = transcranial magnetic stimulation



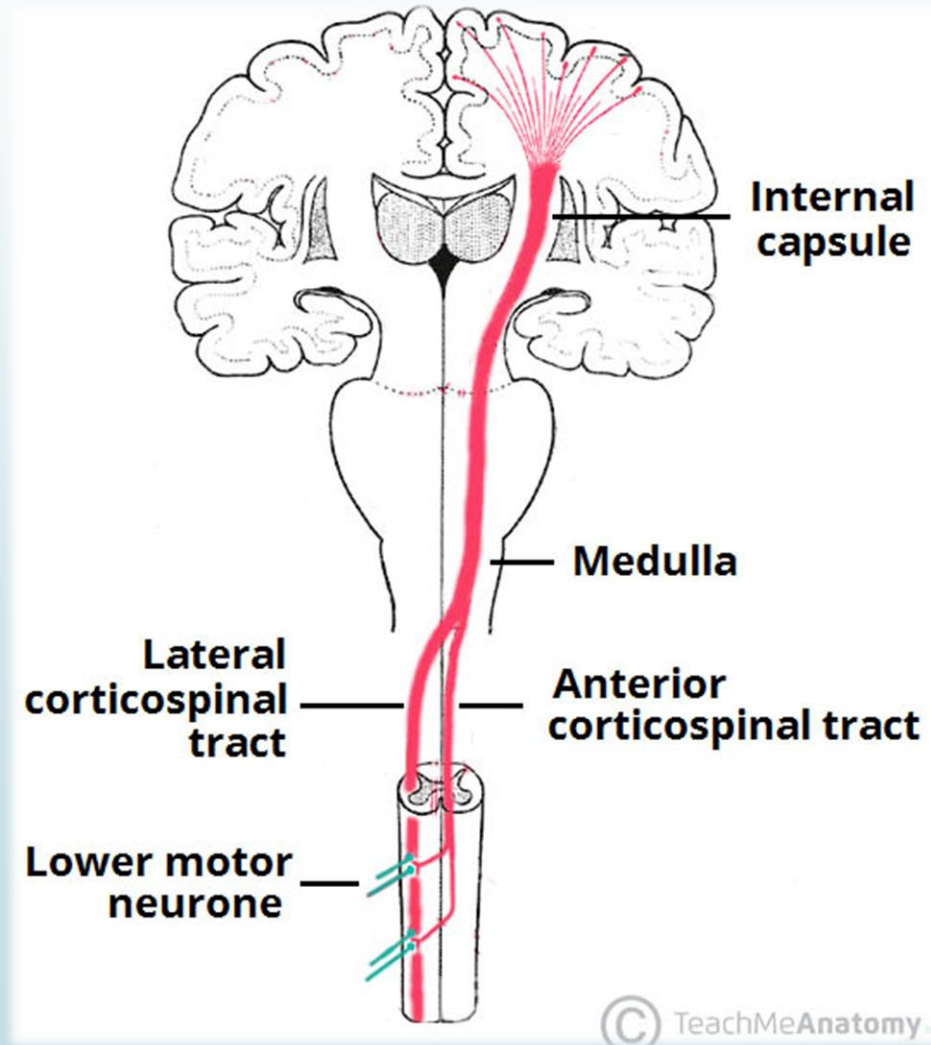
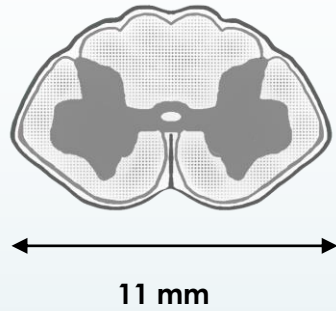
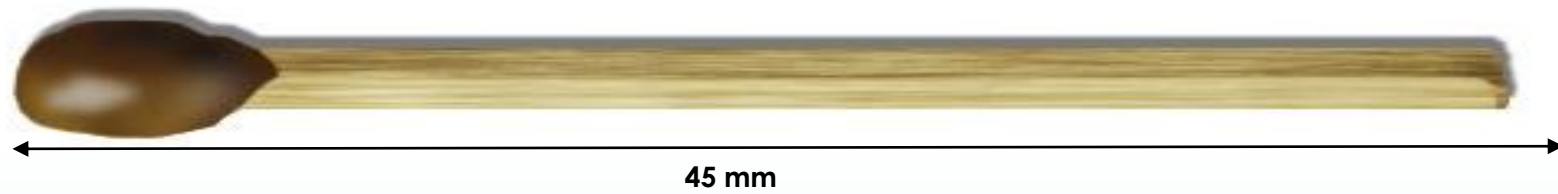


4

MEP = motor-evoked potential



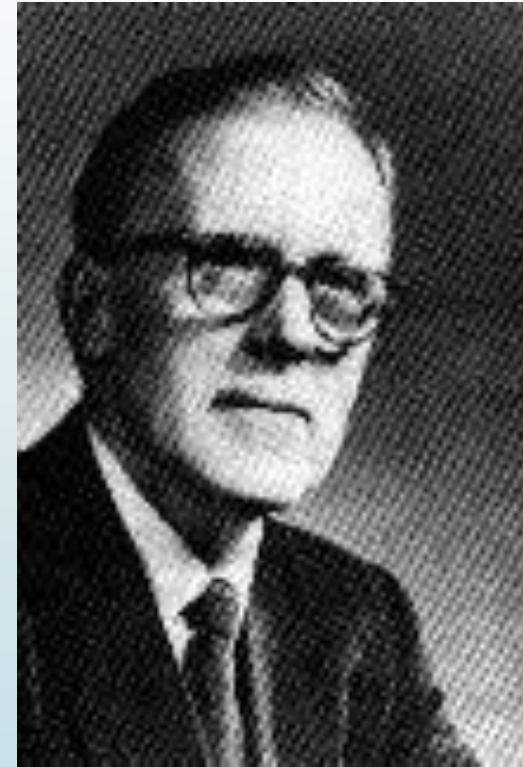
5



# Neurons that fire together wire together

“When an axon of cell *A* is near enough to excite a cell *B* and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficiency, as one of the cells firing *B*, is increased.”

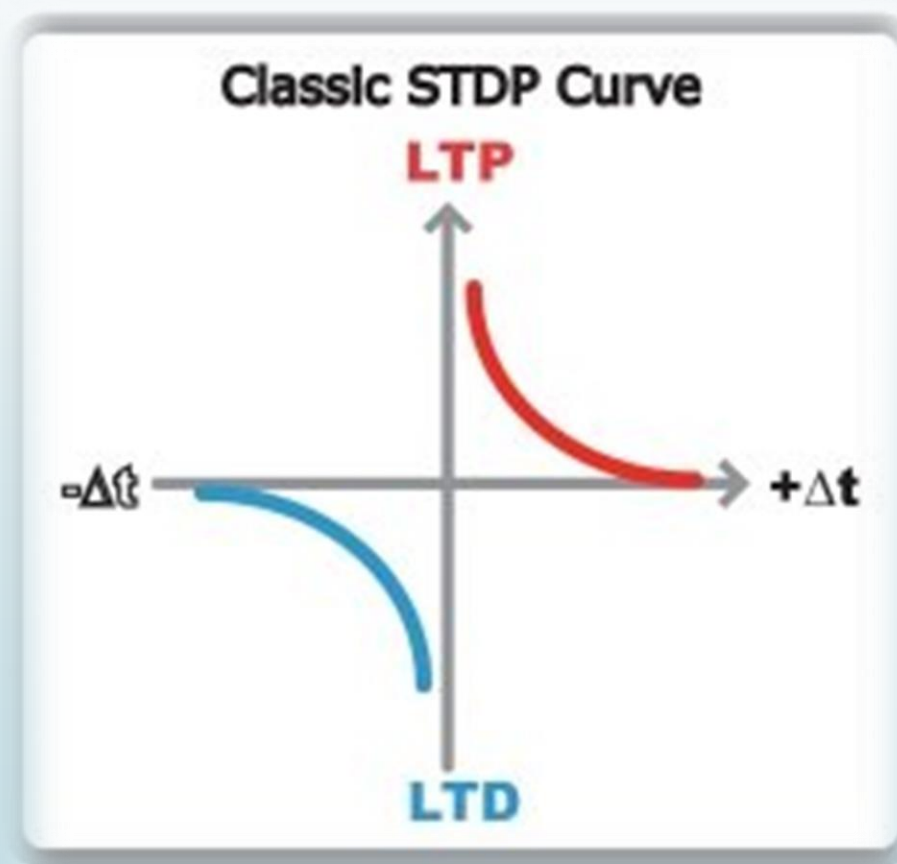
Donald Hebb, 1949



# STDP = spike-time dependent plasticity

LTP = long-term potentiation

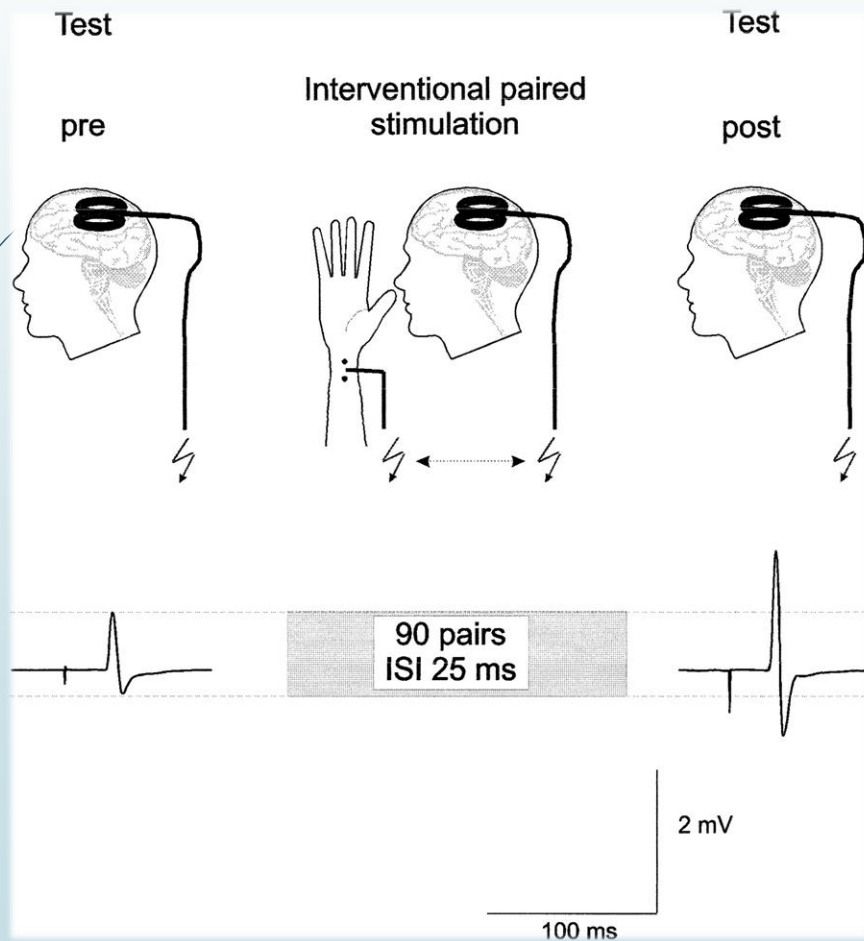
LTD = long-term depression



Brain 2000

## Induction of plasticity in the human motor cortex by paired associative stimulation (PAS)

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J.



- Upper and lower limbs
- Sensory and motor tracts
- Cortical and spinal level
- Plasticity marker and therapy



## Why long-term PAS for spinal cord injury?

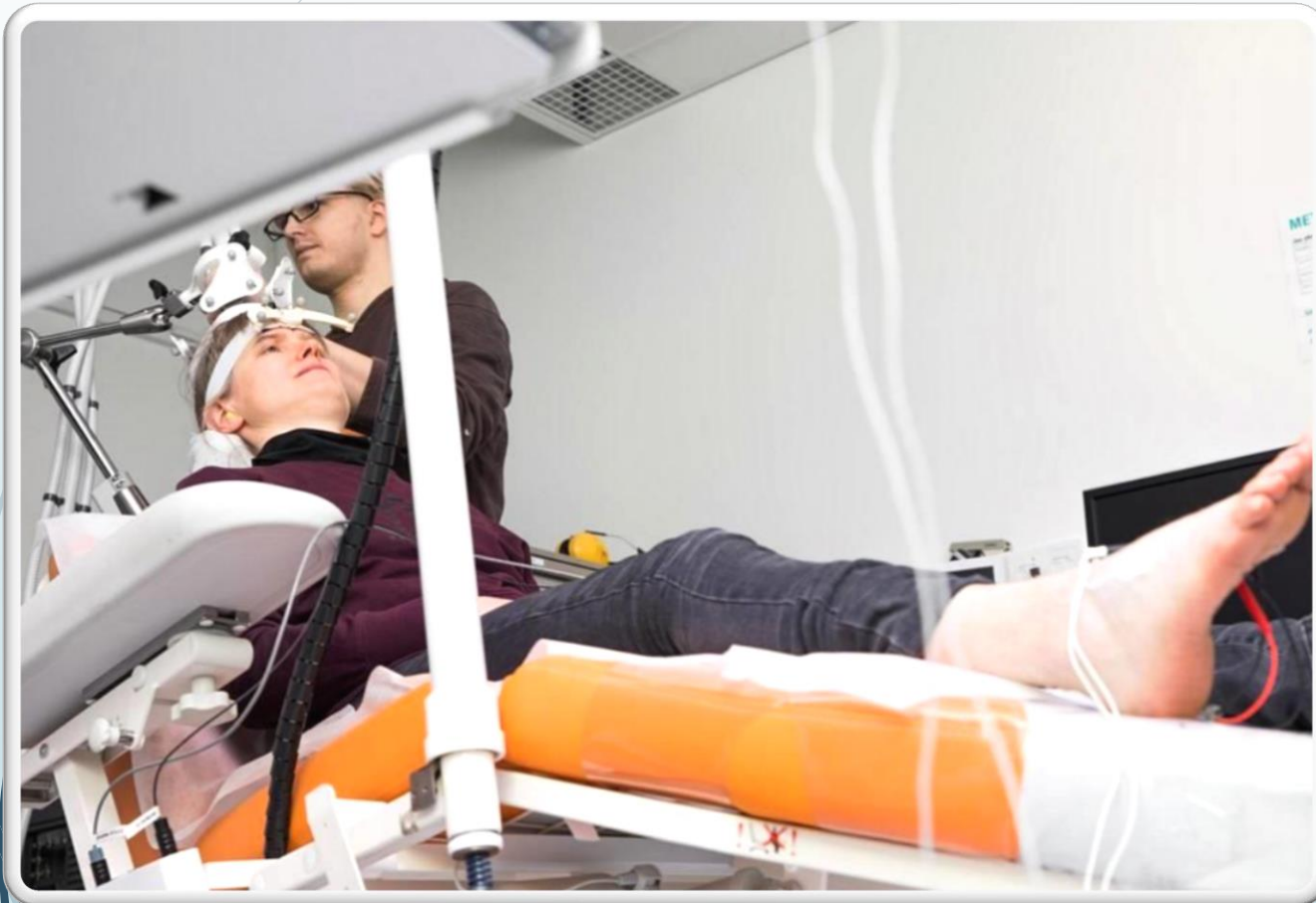
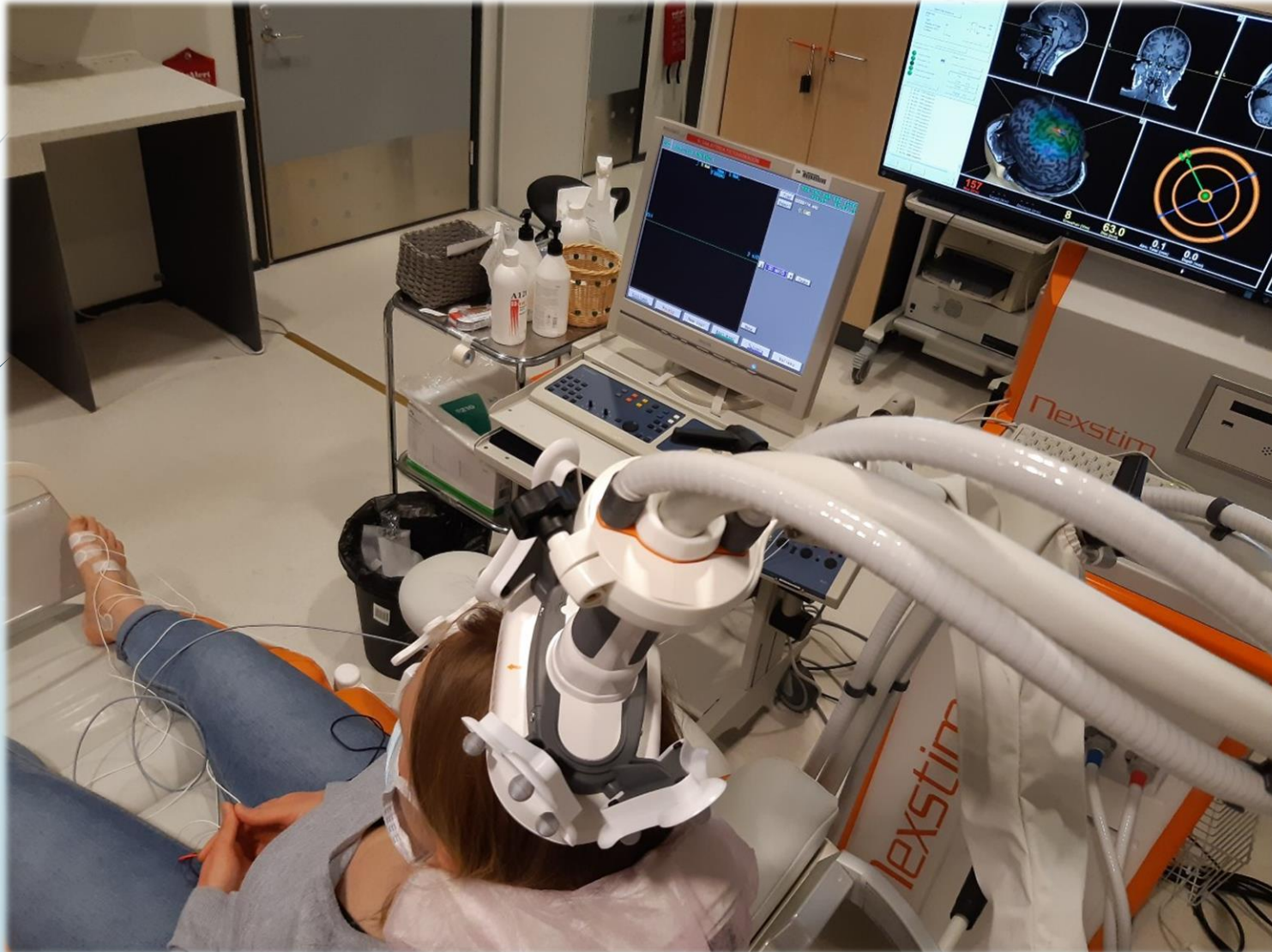


PHOTO: EMILIA ANUNDI / HS

- **Strengthens weakened connectivity simultaneously activating preserved upper and lower motor neurons**
- **Non-invasive**
- **Previously no works on therapeutically-oriented multiple PAS sessions applied for many nerves**

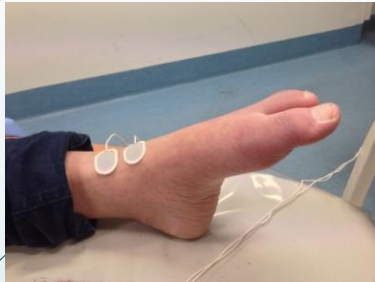
7.5 years after onset of symptoms  
before stimulation  
attempt to spread the fingers

## PAS setup – transcranial magnetic stimulation (TMS)



# PAS setup – peripheral nerve stimulation (PNS)

12



peroneal



tibial

(also femoral and gluteal)



ulnar

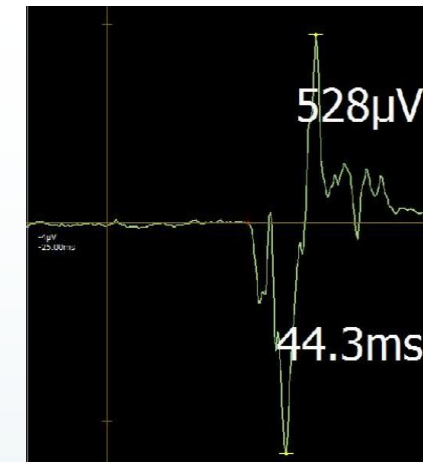
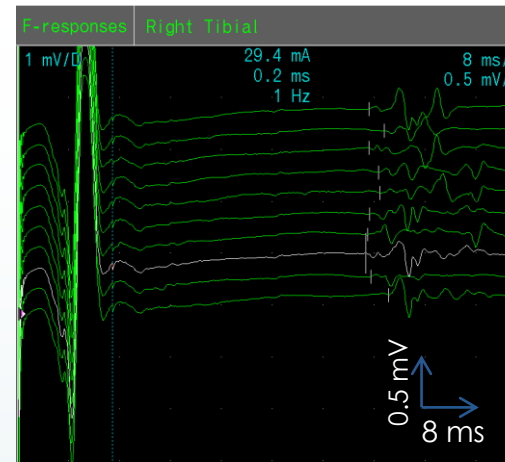
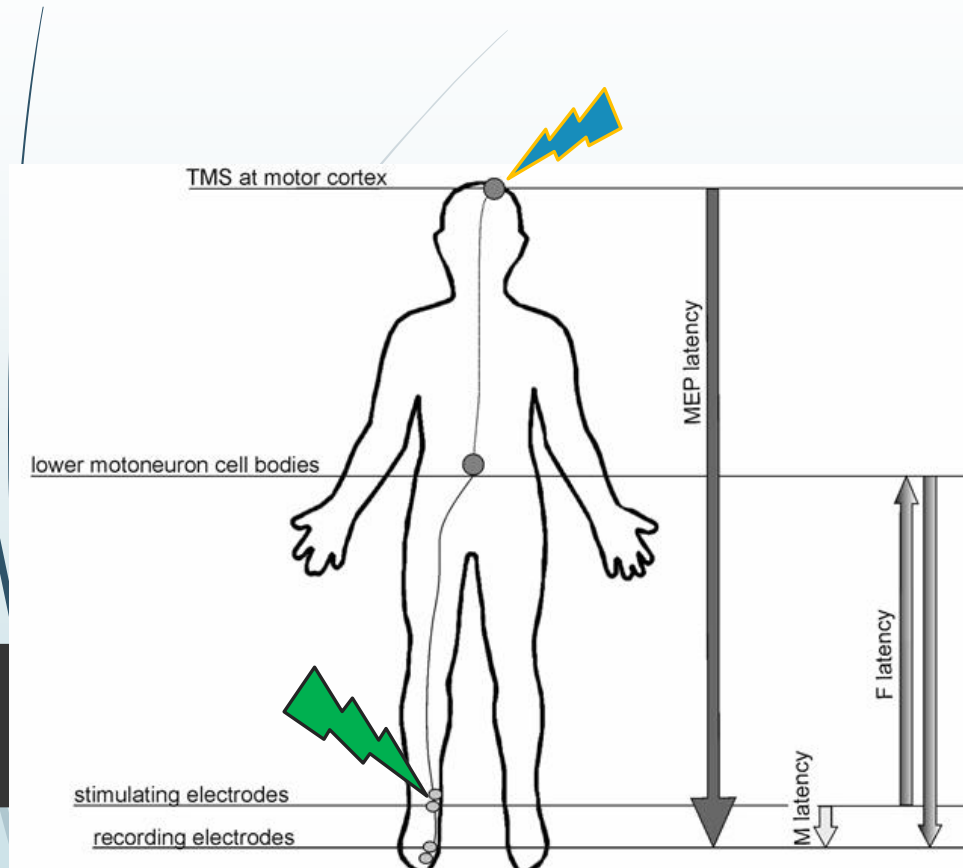


medial



radial

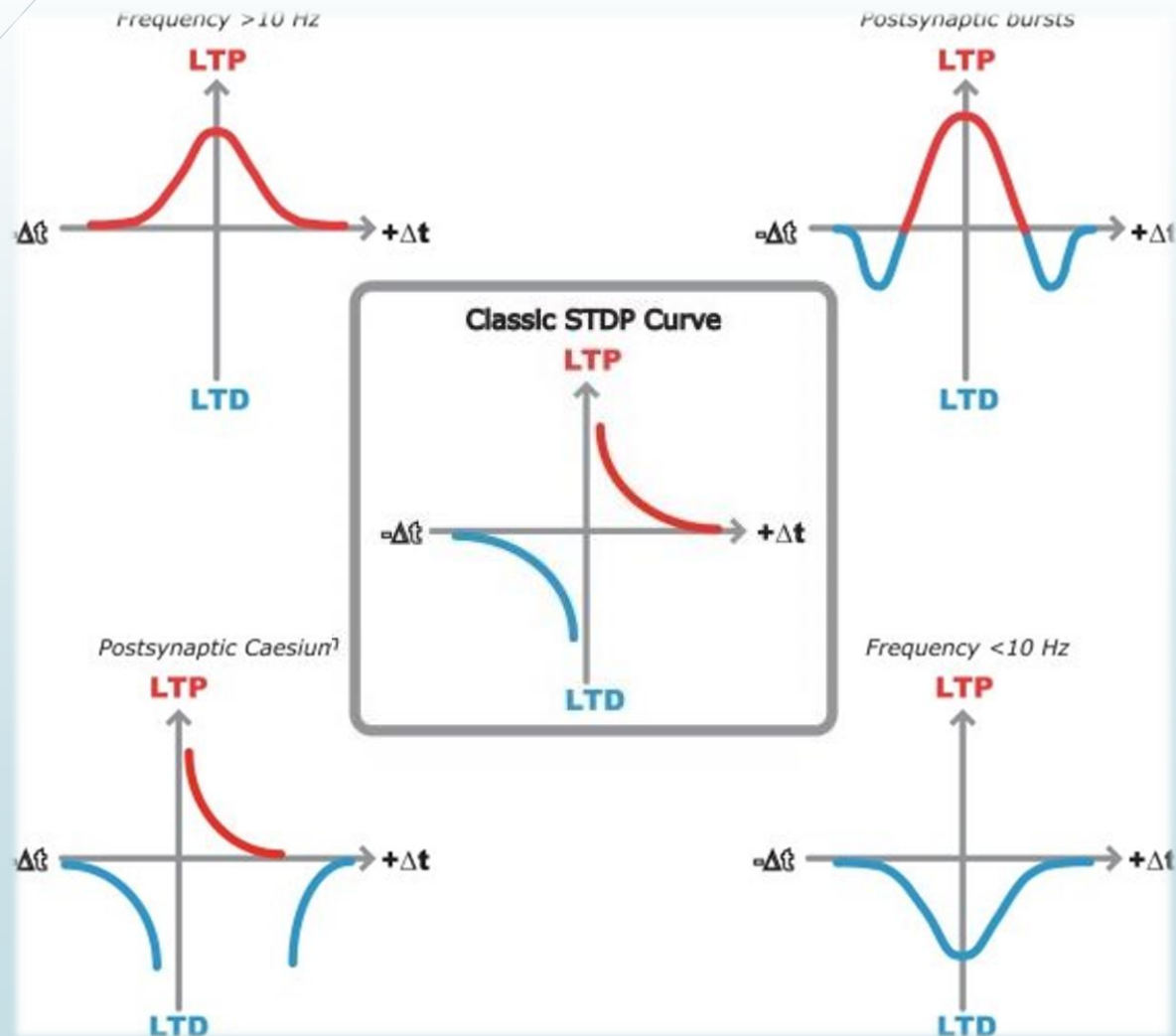




# We have applied PAS to chronic SCI patients for the first time ...

- ▶ in a long-term way (3-5 times per week, up to 20 weeks)
- ▶ using high-frequency peripheral component (conventional PAS utilizes single pulses or 10 Hz peripheral component)

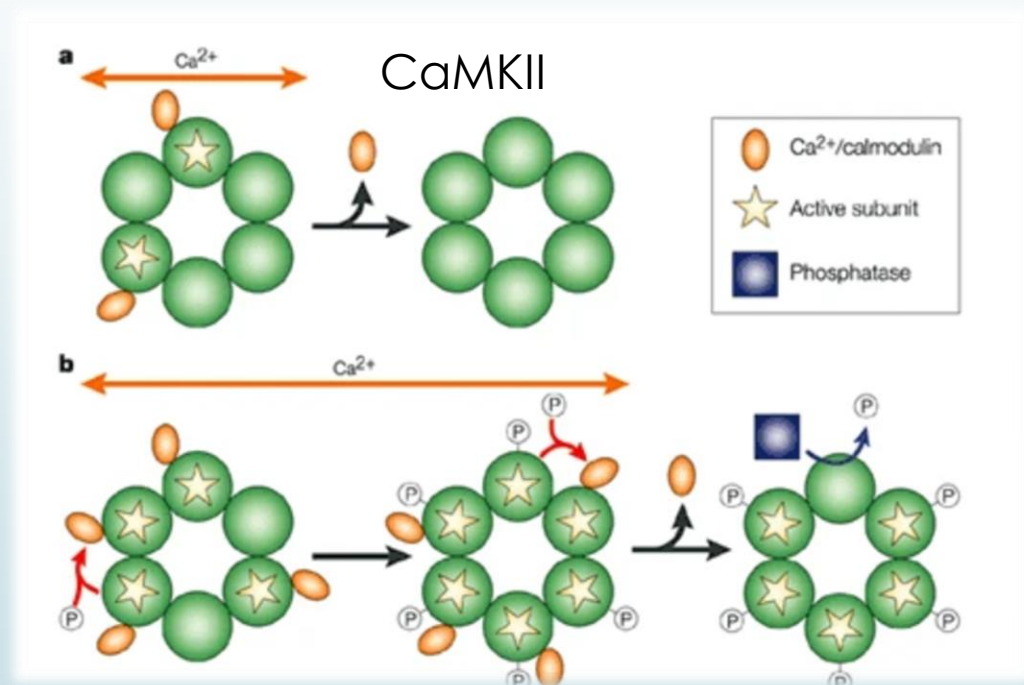
LTP = long-term potentiation  
LTD = long-term depression



# LTP wins over LTD when conditions favor both

We conclude from these modeling studies that LTP and LTD interactions occurring closely in time do not sum linearly, but that LTP wins over LTD.

Sjöström et al 2001 Neuron

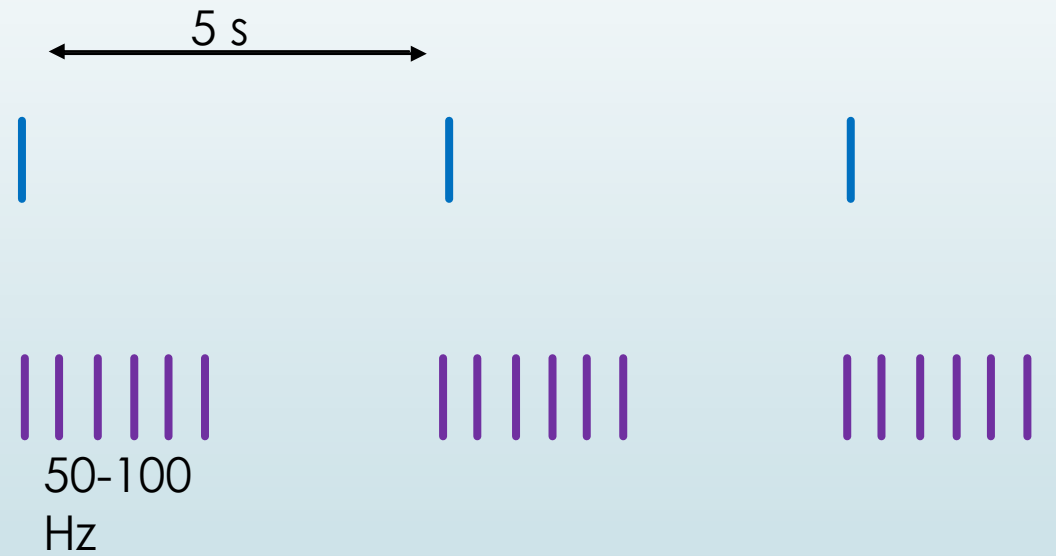


Lisman et al 2002



# "High-PAS"

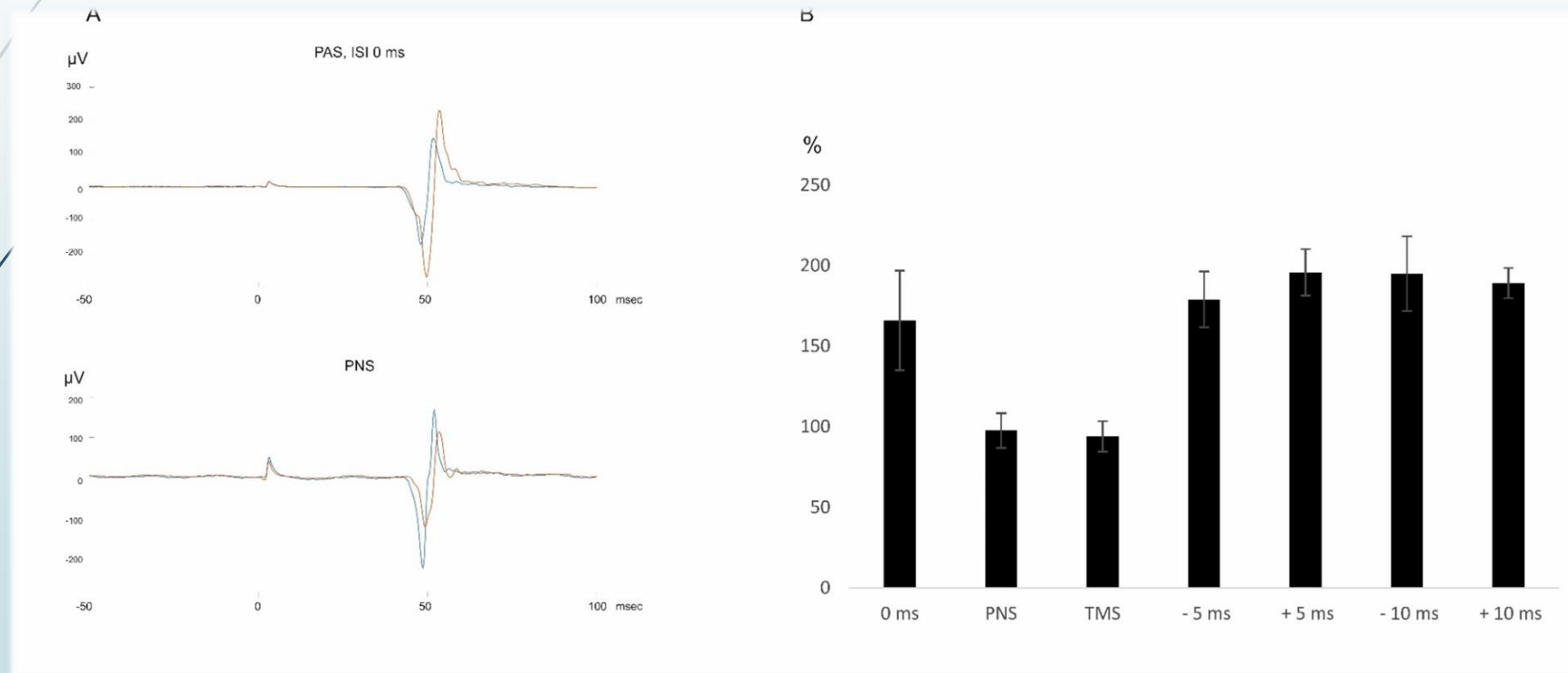
**High-intensity TMS**



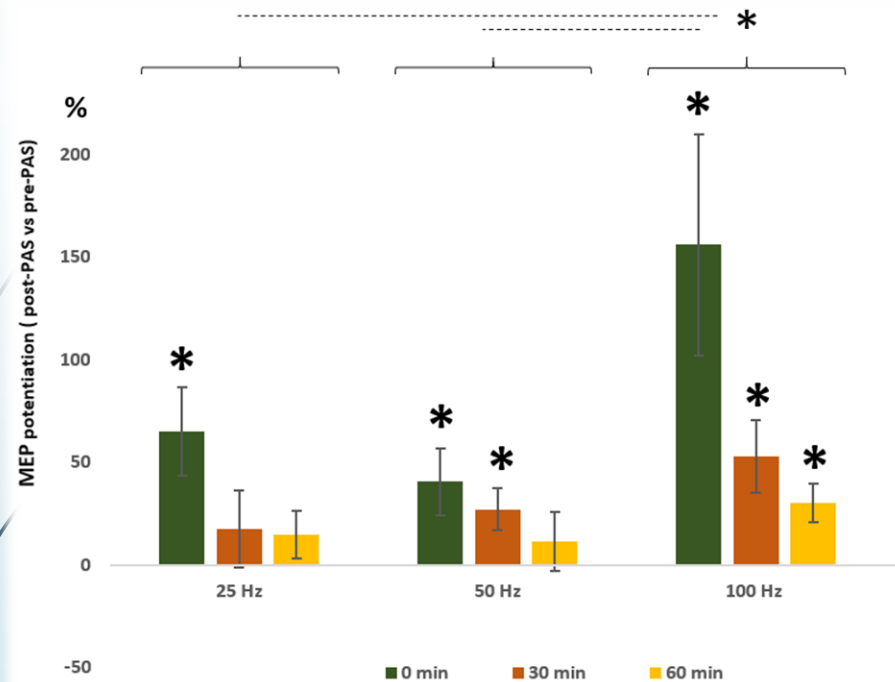
**High-frequency PNS**



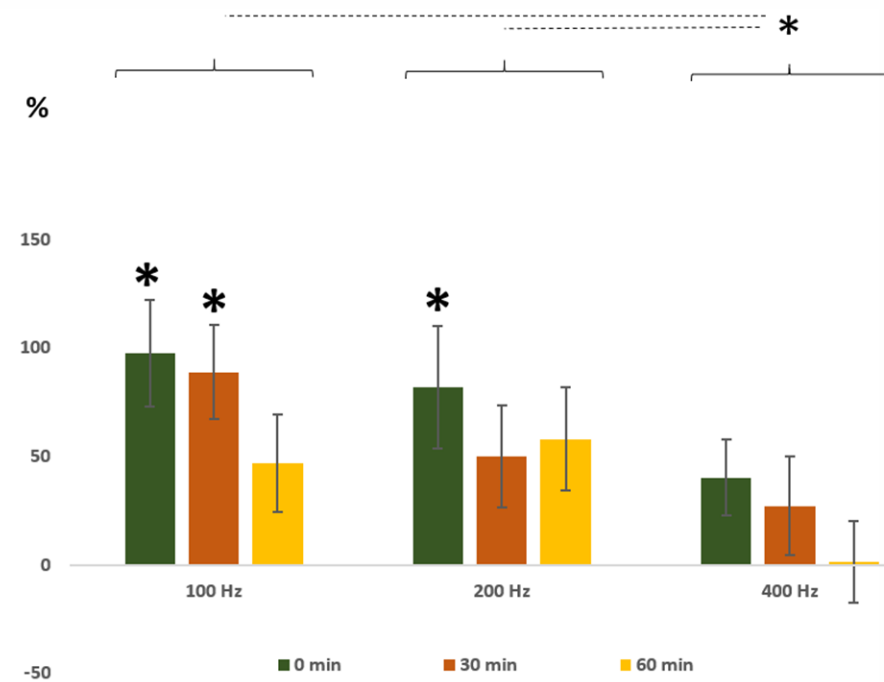
## PAS with high-frequency peripheral component induces MEP potentiation at wide range of interstimulus intervals



## High-PAS: 0.2 Hz TMS, 100 Hz PNS



Tolmacheva et al/Shulga 2019



Mezes et al/Shulga 2020

Optimal PAS-frequency is 0.2 Hz (every 5s.) (Mezes et al/Shulga 2020)

Optimal PNS intensity is the intensity required to elicit an F-response (Pohjonen et al/Shulga 2020)

# EVALUATION

## Manual Muscle Testing

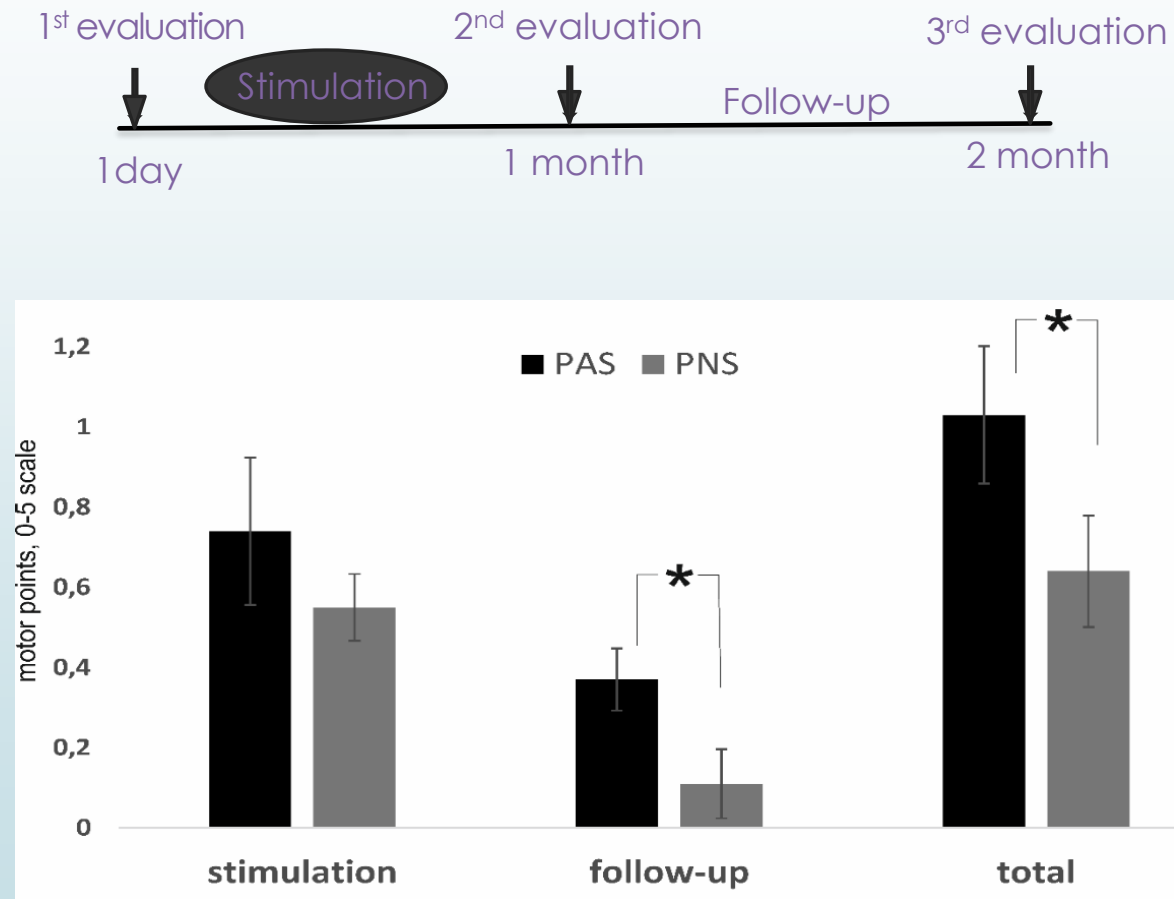
|   |                                                |
|---|------------------------------------------------|
| 0 | No visible or palpable contraction.            |
| 1 | Visible or palpable contraction.               |
| 2 | Full ROM gravity eliminated.                   |
| 3 | Full ROM against gravity.                      |
| 4 | Full ROM against gravity, moderate resistance. |
| 5 | Full ROM against gravity, maximum resistance.  |

Functional hand tests, SCIM, walking, spasticity...

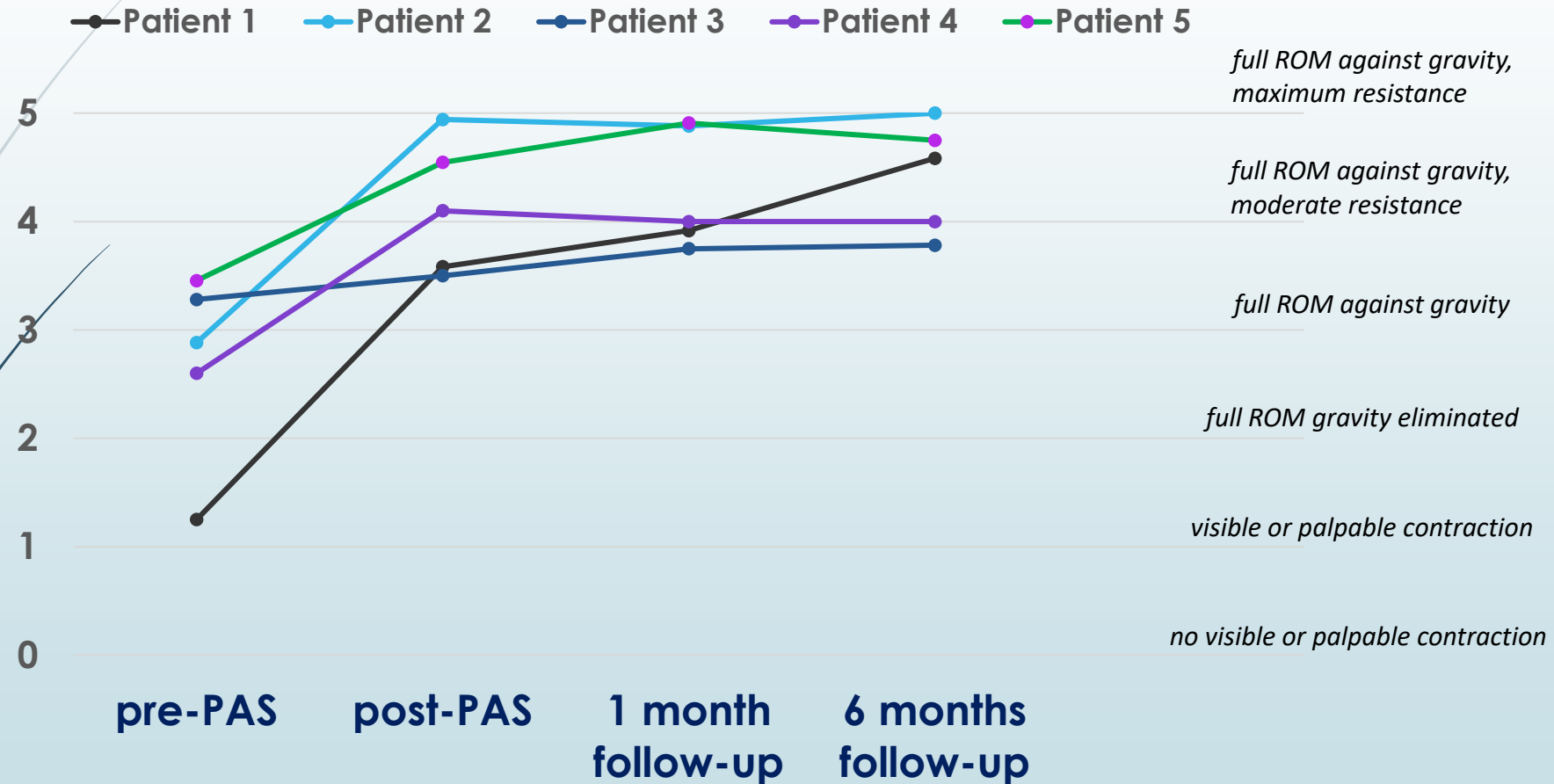
- Muscles with MMT less than 5 are taken into account
- Change is calculated separately for each muscle
- Average of change is reported for all muscles
- The physiotherapist is blinded always when it is possible



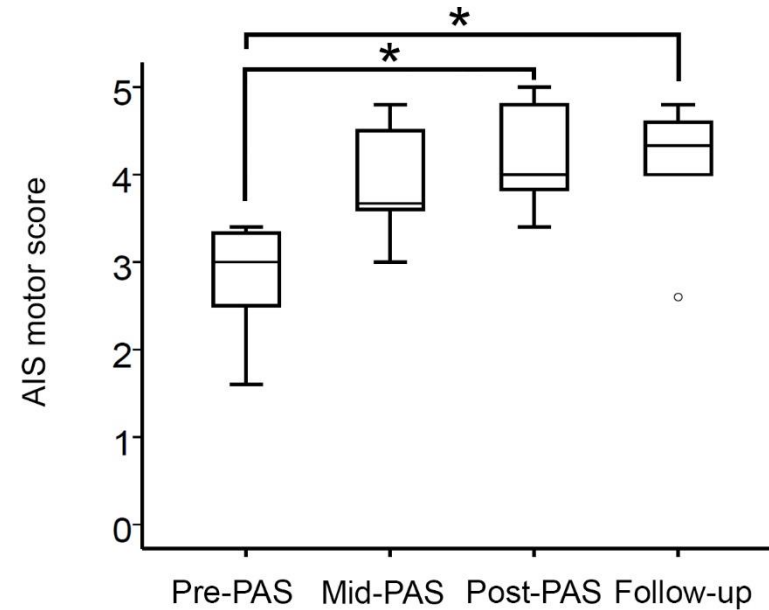
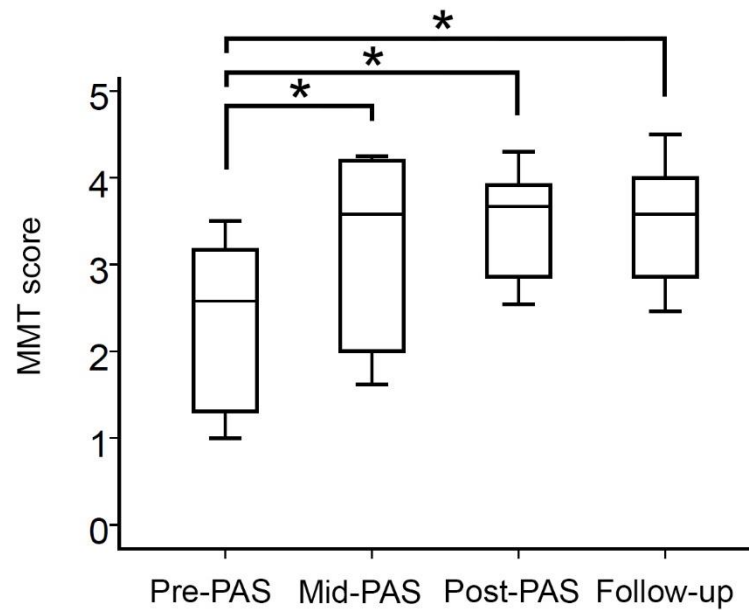
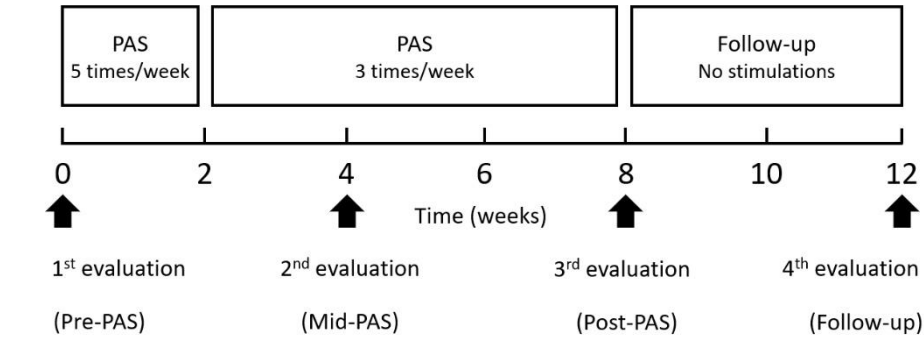
# Traumatic SCI: 5 patients



# Neurological SCI

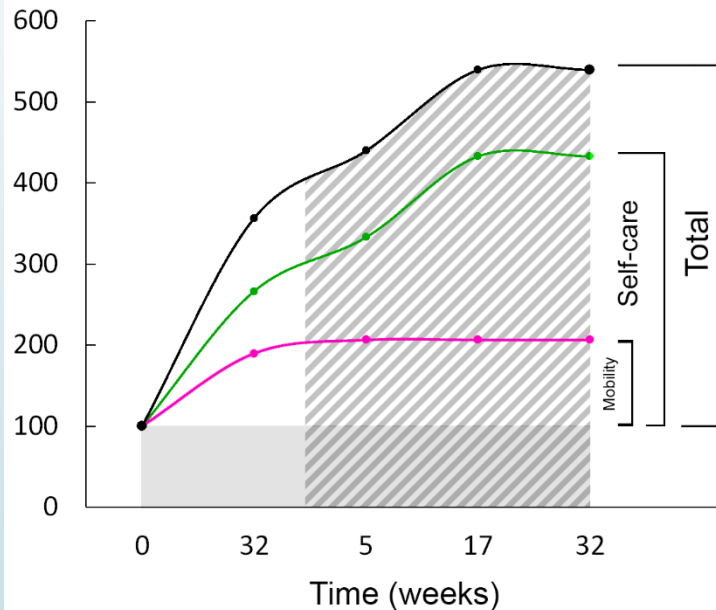


# Lower limbs, tetraplegic patients



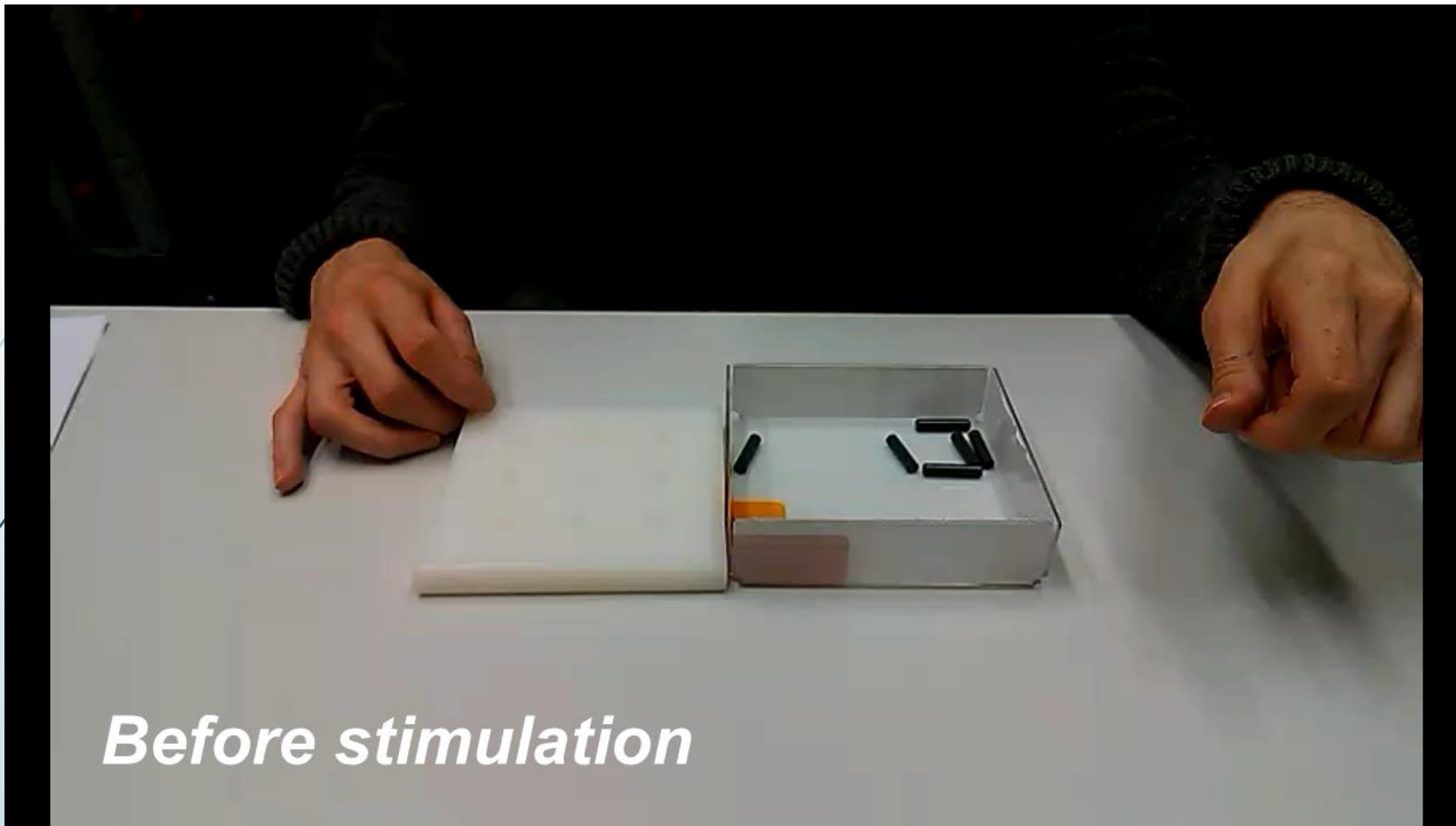
# Long-term stimulation

Spinal Cord Independence Measure (SCIM)



Rodionov et al Spinal Cord Series Cases 2020

| BEFORE (score and meaning)                                                                                                | AFTER (score and meaning)                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| 1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices                                   | 3. Eats and drinks independently; does not require assistance or adaptive devices                                     |
| 1. Requires partial assistance for bathing upper body (soaping, washing, drying body and head, manipulating water tap)    | 3. Washes independently; does not require adaptive devices or specific setting                                        |
| 0. Requires total assistance with dressing upper body (clothes, shoes, permanent orthoses: dressing, wearing, undressing) | 3. Independent with clothes without buttons, zippers or laces; does not require adaptive devices or specific settings |
| 0. Requires total assistance with transfer from bed to wheelchair                                                         | 2. Independent with transfer from bed to wheelchair                                                                   |
| 1. Requires partial assistance with grooming (washing hands and face, brushing teeth, combing hair, shaving)              | 3. Grooms independently without adaptive devices                                                                      |





1 year after  
thoracic SCI

Weight support  
40 kg

# Tolerability of high-PAS

- Possibility to use EMLA lidocaine-prilocaine cream
- Subjects and patients get used to stimulation quickly; sleepiness is more of a problem than discomfort
- None of the short-term results indicates activation of the sympathetic nervous system in healthy individuals. Observed changes in heart rate variability (HRV) indicate higher parasympathetic activity during stimulation, which is reversible (Haakana et al 2023 Front Rehabil Sci)
- Listening to music does not abolish the effect of high-PAS in healthy subjects or SCI patients measured by MEP potentiation. Music does however lead to greater variability in responses in SCI patients (Holopainen et al, manuscript in progress)

# Sham-controlled double-blind randomized clinical trial for subacute SCI



- 18/20 patients recruited
- Stimulation started 1-4 months post-injury
- Equipment installed to SCI rehabilitation ward
- Stimulation is lasting for 3 months
- Evaluations up to 1.5 years post-injury
- Primary endpoints: MMT and SCIM
- Goal: bringing high-PAS for SCI to clinical practice

# Some other ongoing projects

- **Mechanism, tolerability, indications, patients groups**
- High-PAS for neuropathic pain
- Combination of high-PAS with non-invasive vagus nerve stimulation
- Verification of spinal level in high-PAS therapeutic effect: H-reflex and TMS-EEG studies, spinal vs cortical PAS
- More patients where PAS is applied for as long as improvement is observed; differences between better and worse responders
- Children 10-18 years of age: ethical approval recieved

# Summary and clinical observations

**Para- and tetraplegic, traumatic and non-traumatic incomplete SCI patients are responsive to PAS.**

**The majority of incomplete injuries are asymmetric – PAS enables specifically strengthening the weakest connections in upper and lower limbs.**

**Reinforcing the connectivity of precisely defined motor cortex areas with corresponding nerves can be beneficial especially in hand rehabilitation where highly specific movements of small muscles are desirable.**

**Obtained improvement in MMT increases during follow-up period without stimulation at least up to 6 months.**

**Patients with more recent and milder injuries are more responsive than patients with more chronic and more severe injuries.**

**PAS requires equipment that is already available in many hospitals and laboratories worldwide.**

**PAS is effective at the chronic stage for at least up to 15 years after injury. It is plausible that starting PAS at subacute stage before irreversible changes in muscle tissue have occurred will result in even better outcomes.**



## TEAM

### Current members:

Anna Nätkynmäki  
Kirsi Holopainen  
Piia Haakana  
Markus Pohjonen  
Tommi Lehto  
Sarianna Savolainen

### Former members:

Aleksandra Tolmacheva  
Anna-Lena Nyman  
Andrey Rodionov  
Magdolna Mezes  
Roope Havu  
Ilida Suleymanova



## SENIOR COLLABORATORS

Erika Kirveskari  
Pantelis Lioumis  
Jyrki Mäkelä  
Jari Arokoski

## ACKNOWLEDGEMENTS

Our patients  
and healthy subjects

