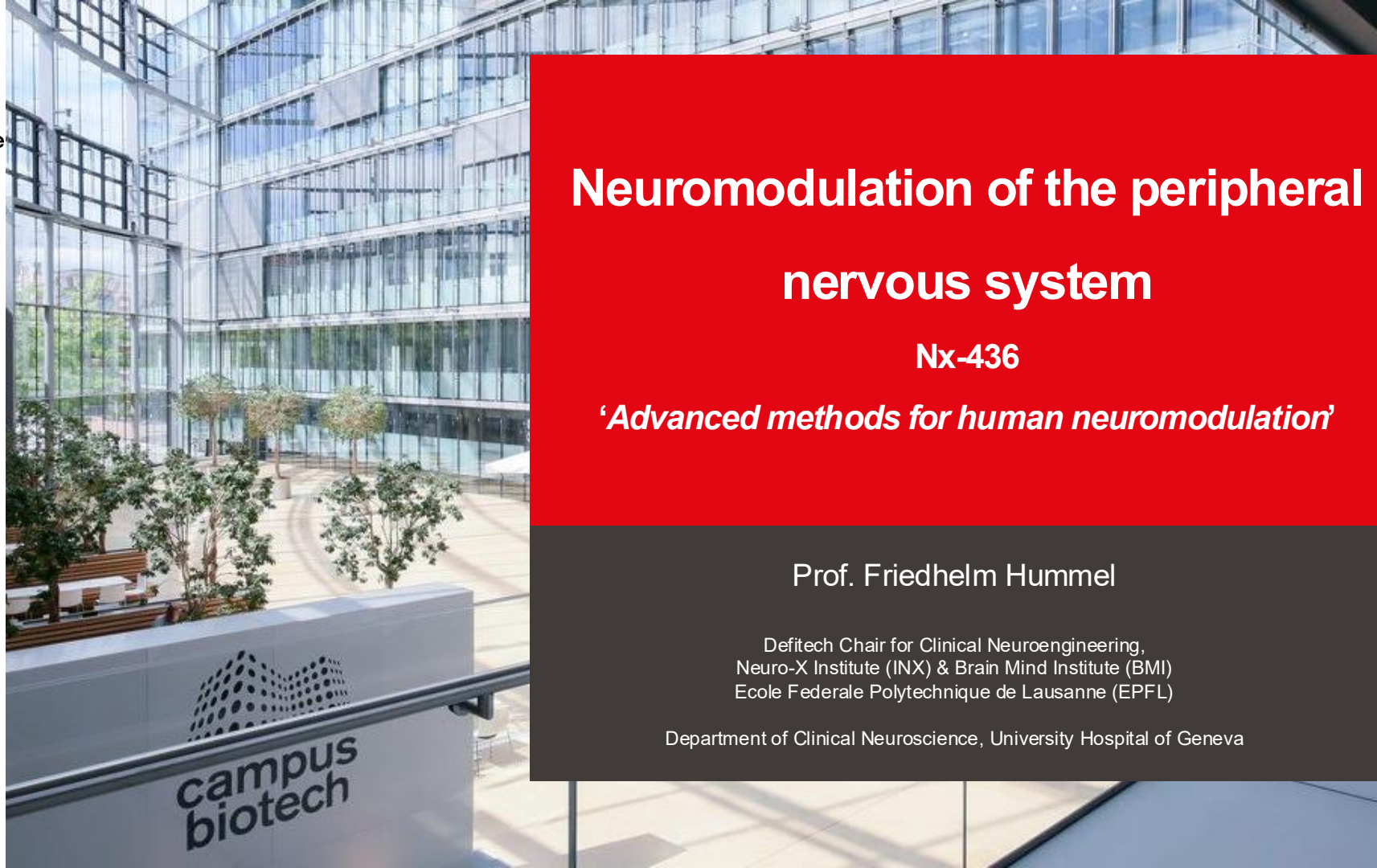
EPFL

Neuro X Institute



Neuromodulation of the peripheral nervous system

Nx-436

'Advanced methods for human neuromodulation'

Prof. Friedhelm Hummel

Defitech Chair for Clinical Neuroengineering,
Neuro-X Institute (INX) & Brain Mind Institute (BMI)
Ecole Federale Polytechnique de Lausanne (EPFL)

Department of Clinical Neuroscience, University Hospital of Geneva

Nx-436
24/09/2025

Objectives

Provide (brief) information about the physiology of sensory systems

Description of neurotechnologies/approaches to modulate somatosensory processing

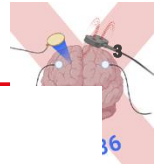
- Peripheral nerve stimulation
- Paired associative stimulation
- Functional electrical stimulation

Description of neurotechnologies/approaches to restore sensory information

- Tactile/proproceptive/temperature feedback for amputees

Description of neurotechnologies/approaches to restore sensory-motor function

- Multitechnology to enhance stroke recovery



NERVOUS SYSTEM

CENTRAL NERVOUS SYSTEM

BRAIN

SPINAL CORD

PERIPHERAL NERVOUS SYSTEM

SOMATIC

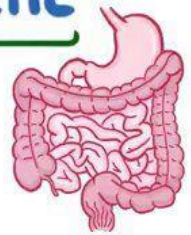
Voluntary movement of skeletal muscle

AUTONOMIC

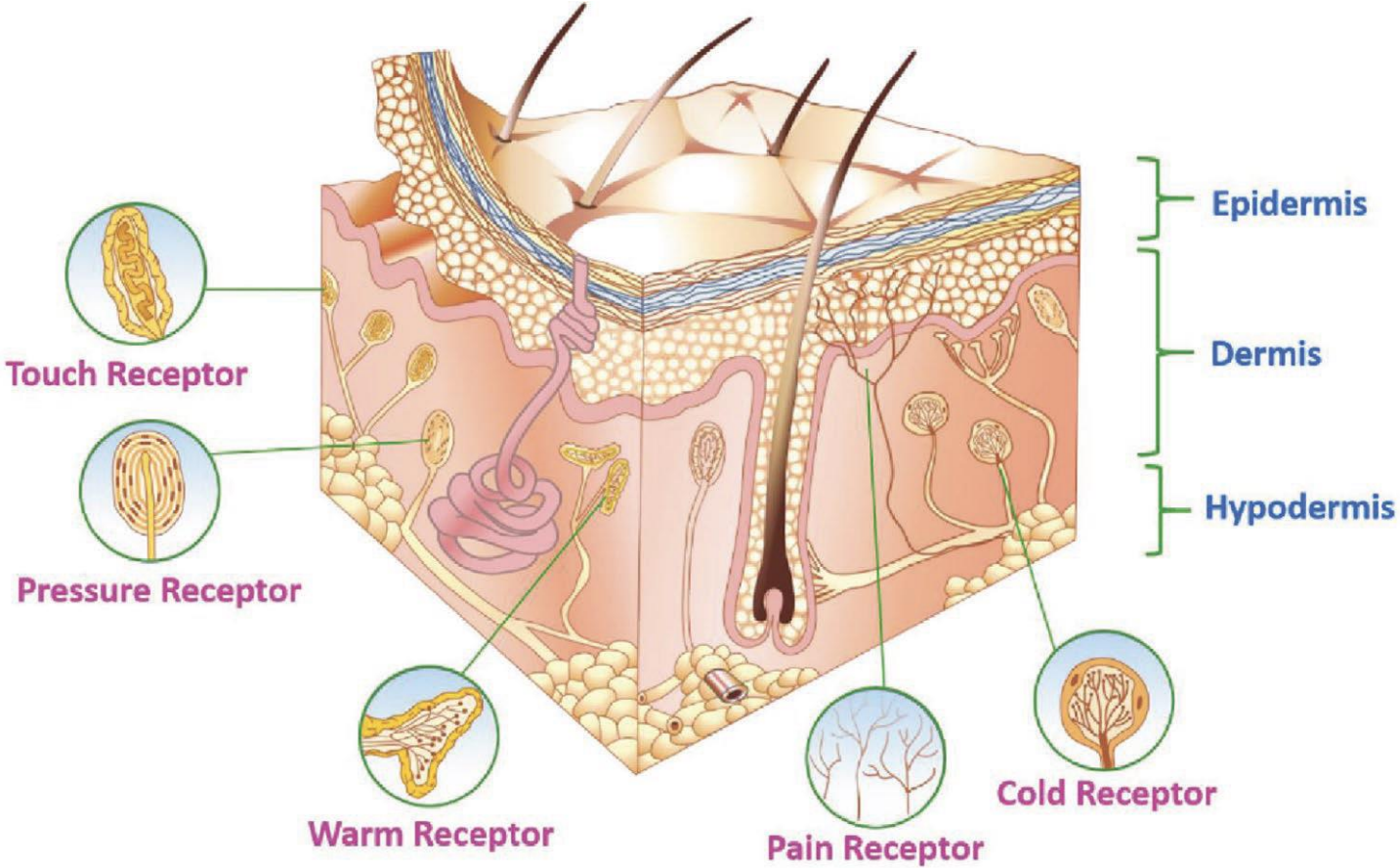
SYMPATHETIC PARASYMPATHETIC

Involuntary movement of

* Smooth muscles
* Glands of organs



The peripheral nervous system (PNS)



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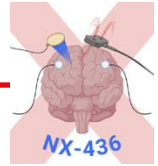
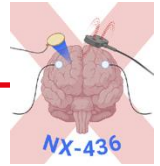


1. **Mechanoreceptors**:
   - **Meissner's corpuscles**: Found in the upper dermis, they are responsible for detecting light touch and changes in texture.
   - **Merkel cells**: Located in the basal layer of the epidermis, these receptors detect sustained pressure and texture.
   - **Pacinian corpuscles**: Situated deeper in the dermis, they are sensitive to deep pressure and vibration.
   - **Ruffini endings**: Found in the dermis, these receptors detect skin stretch and contribute to the perception of sustained pressure.

2. **Thermoreceptors**:
   - **Cold receptors (Aδ fibers)**: Activated by cooler temperatures, typically below 25°C (77°F), and can be found closer to the skin surface.
   - **Warm receptors (C fibers)**: Detect temperatures above 30°C (86°F), with maximum sensitivity around 40-45°C (104-113°F).

3. **Nociceptors** (Pain receptors):
   - These free nerve endings respond to potentially harmful stimuli, such as extreme temperatures, mechanical damage, or chemical irritants. There are different types, including thermal nociceptors for extreme heat or cold and mechanical nociceptors for physical damage.

The peripheral nervous system (PNS)



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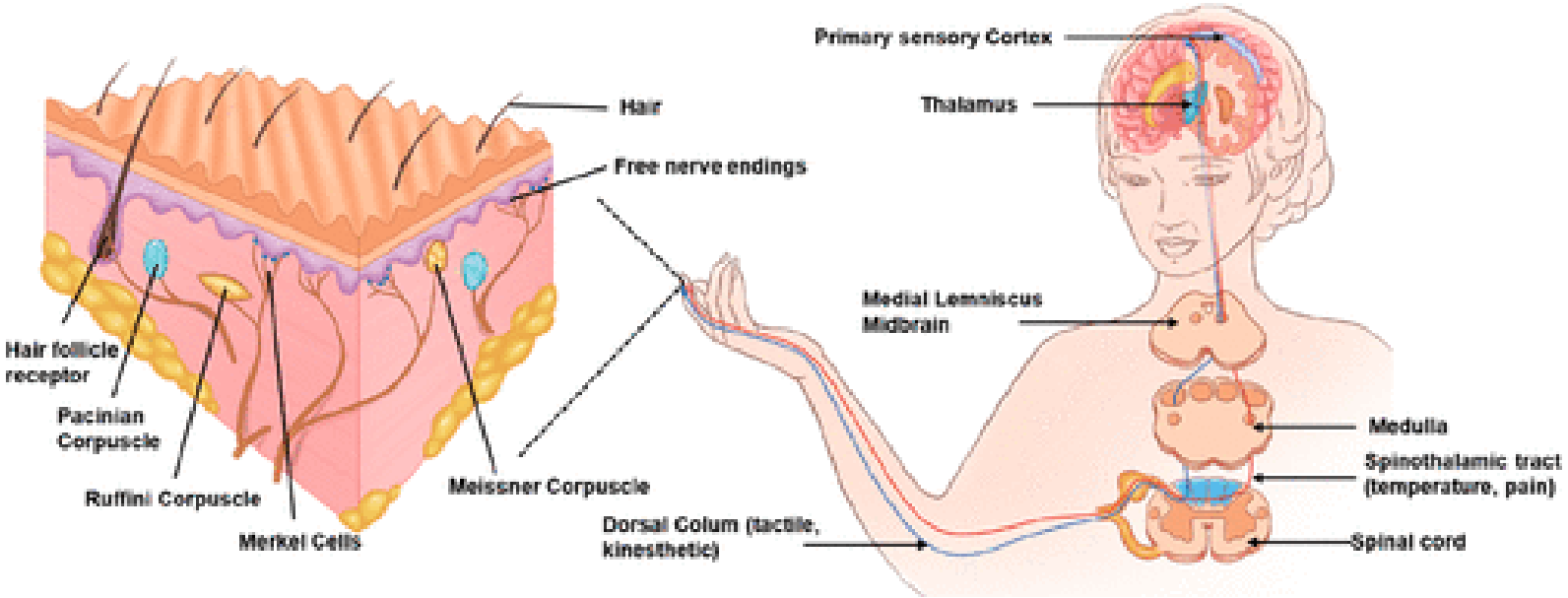
A-δ fibers
Diameter: 2–6 µm (thinly myelinated)
Conduction velocity: ~5–40 m/s (usually quoted around 10–30 m/s)
Stimulation threshold: lower than C fibers (because of myelination → more excitable, lower rheobase/current needed)
Function: “first pain” (sharp, pricking, well localized), temperature

C fibers
Diameter: 0.4–1.2 µm (unmyelinated)
Conduction velocity: ~0.4–2 m/s (very slow)
Stimulation threshold: higher than A-δ fibers (need stronger current/longer pulses to activate; chronaxie much longer)
Function: “second pain” (burning, dull, poorly localized), temperature, autonomic functions

Summary:
A-δ fibers: **faster conduction, lower threshold**
C fibers: **slower conduction, higher threshold**

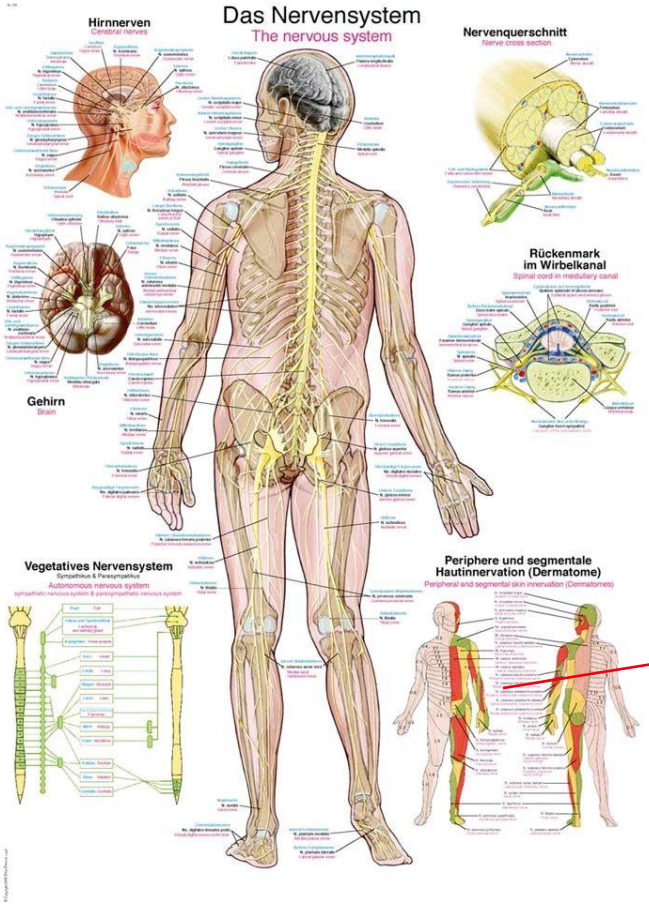
The peripheral nervous system (PNS)

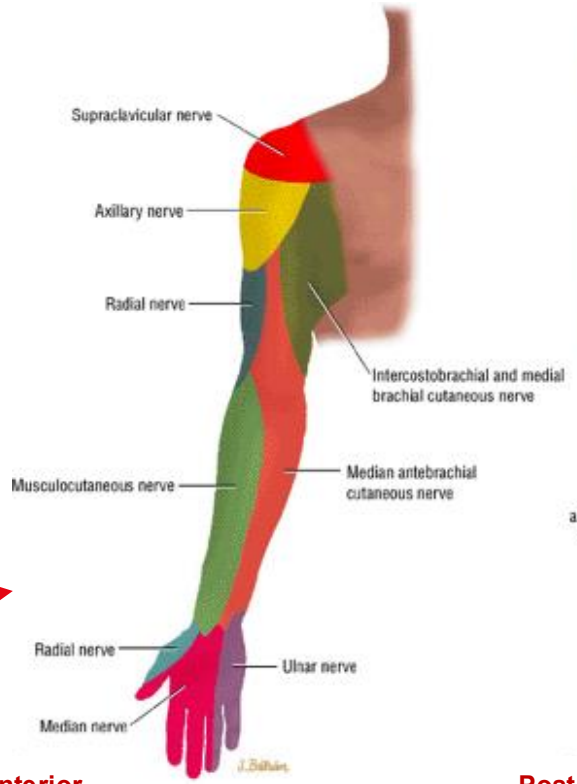


pressure (**touch**), pain (**nociception**), **vibration**, **temperature**, position sense (**proprioception**), and body movement (**kinesthesis**)

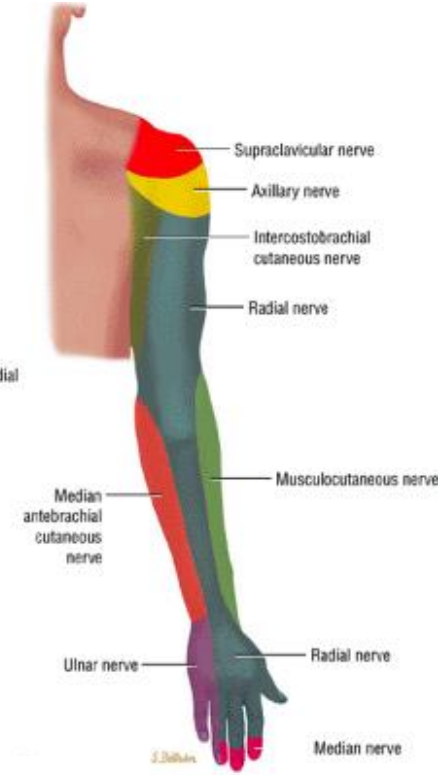
Zheng 2021

The peripheral nervous system (PNS)



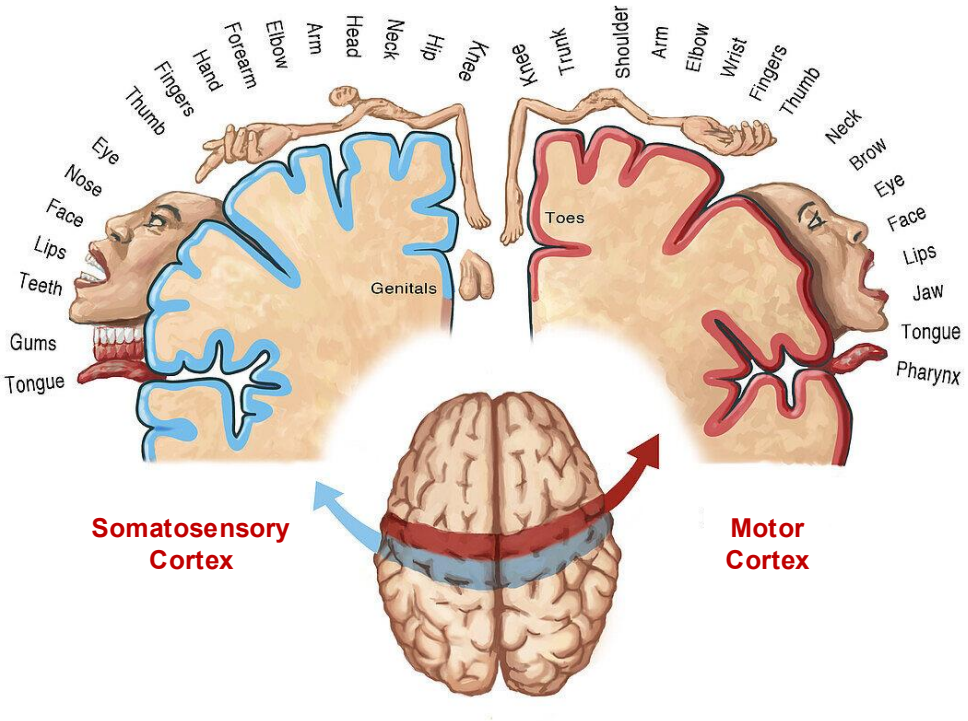


Anterior



Posterior

Somatotopic cortical arrangement



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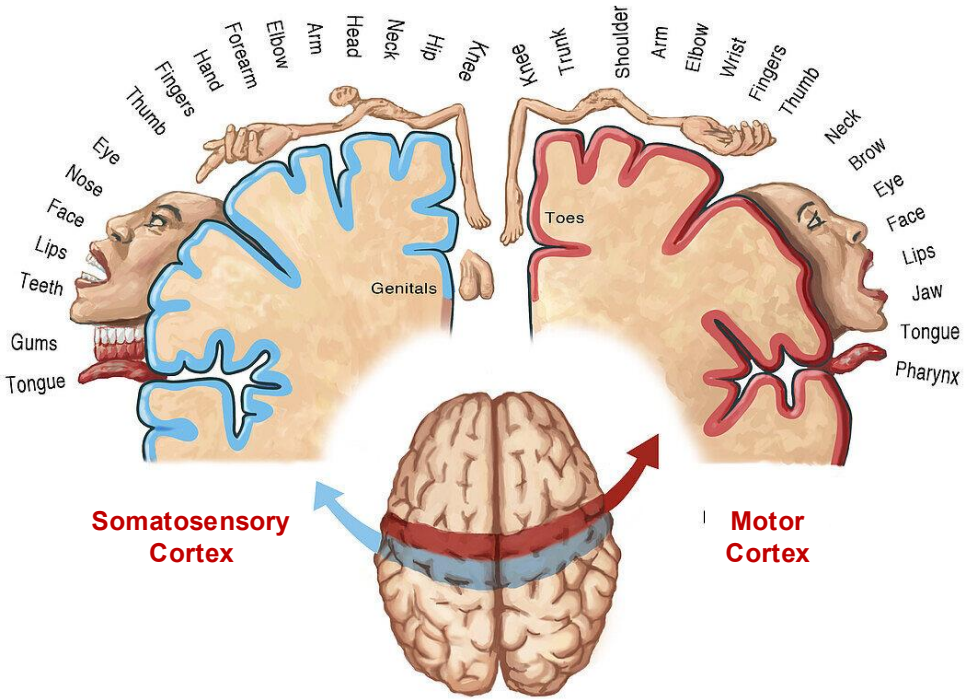

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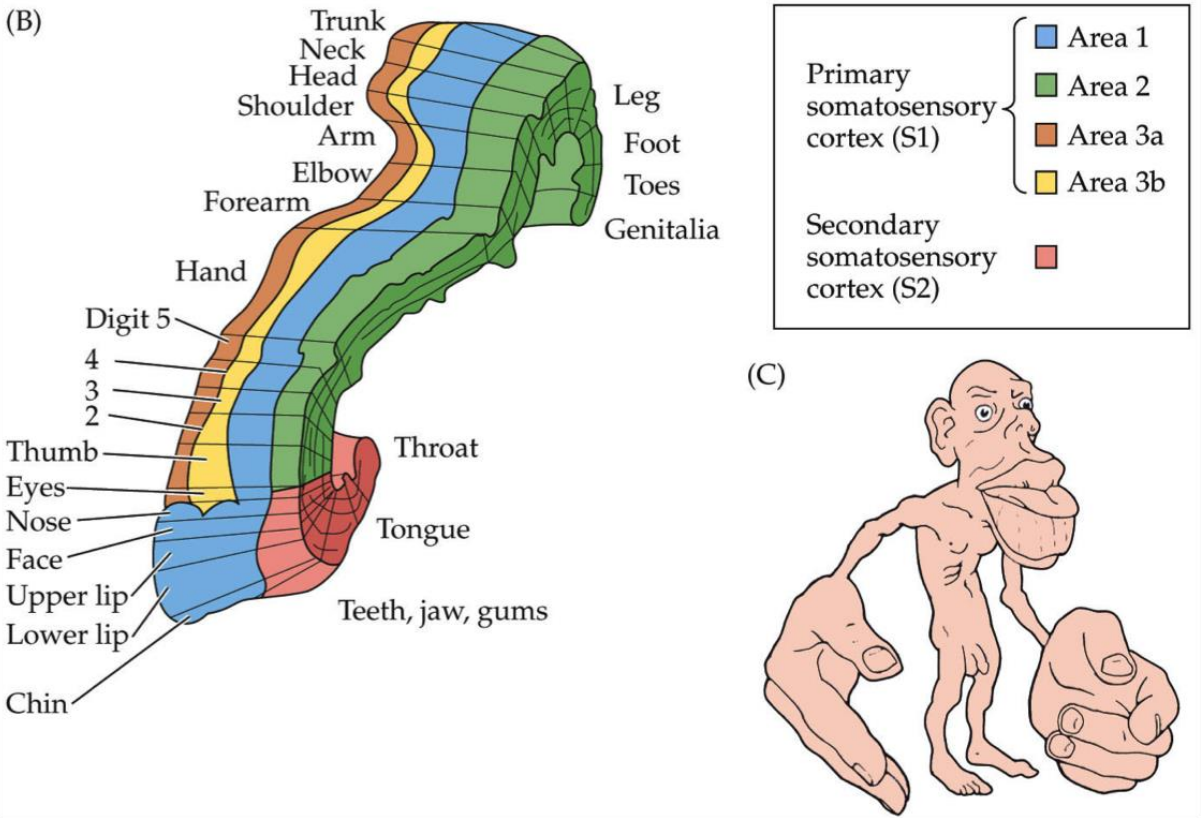
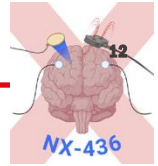
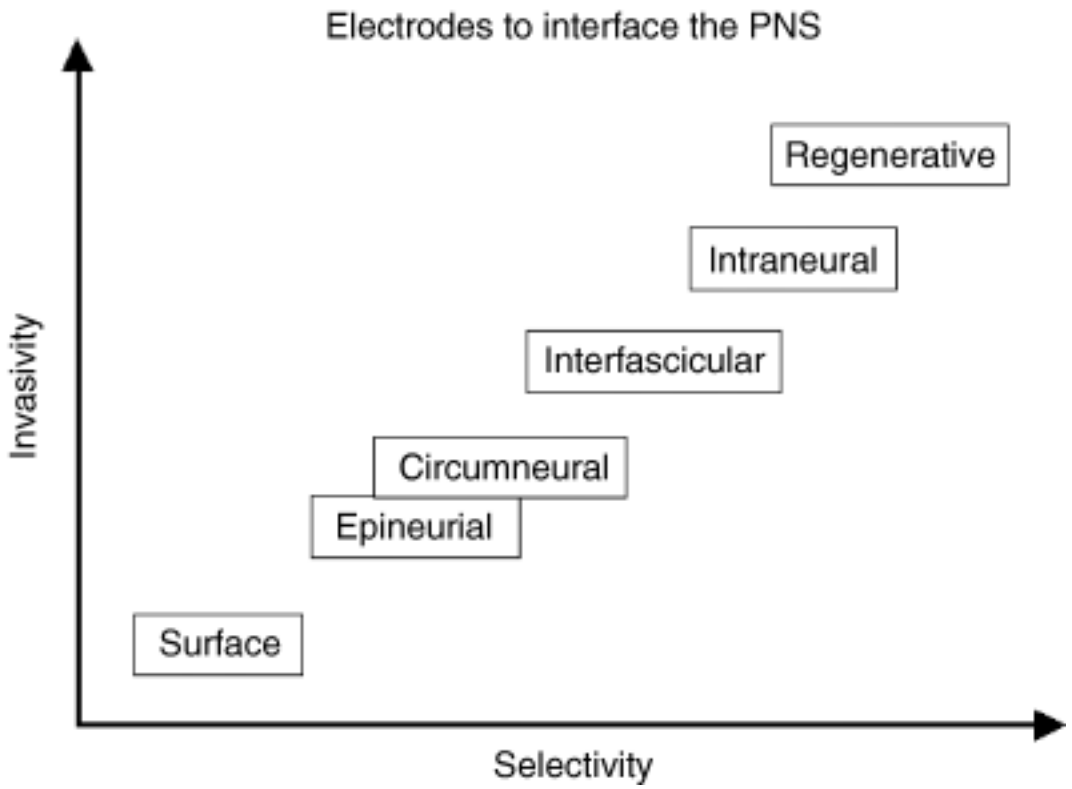


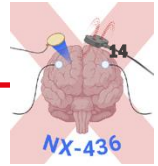


Neuromodulation?

Interfaces with the PNS

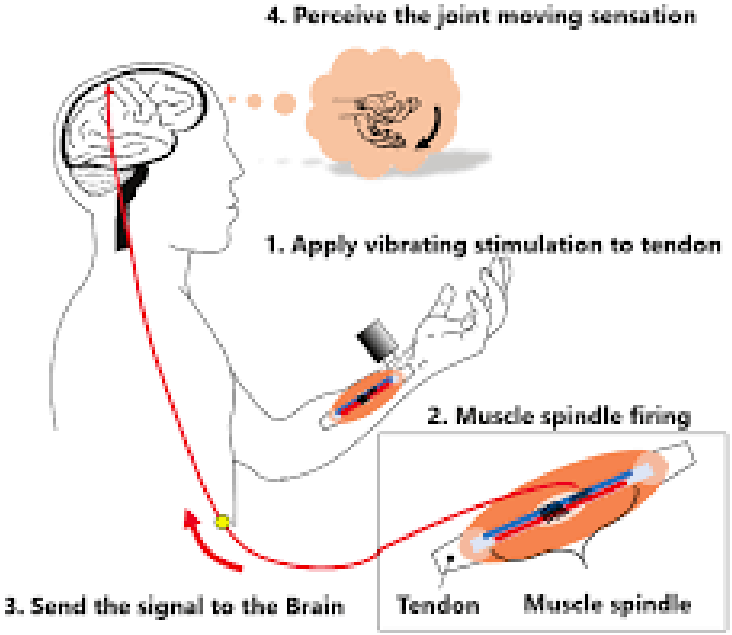


Navarro et al. 2005

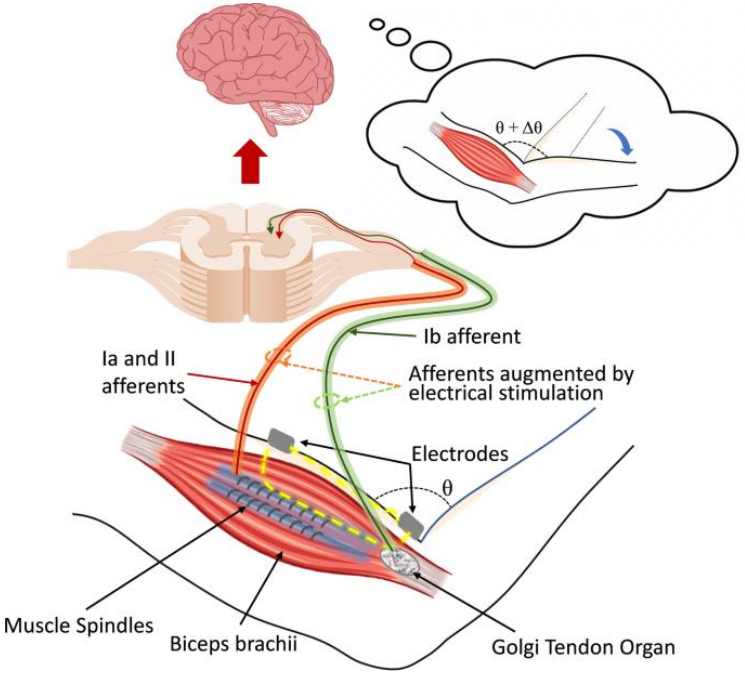


Mechanical Stimulation

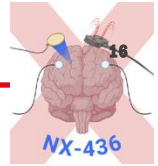
Surface - Kinesthetic illusion



Kimura et al. 2019

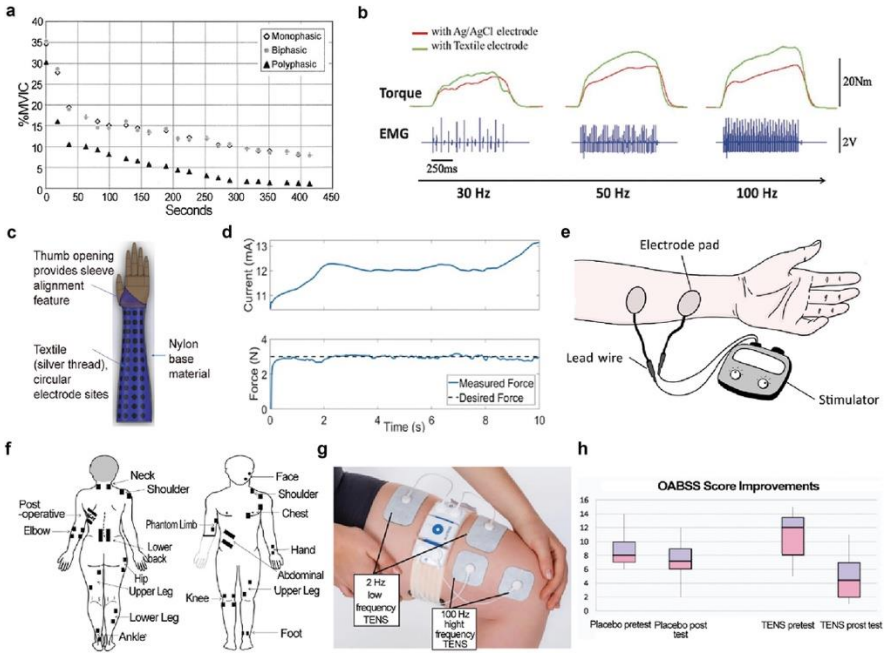


Rangwani et al. 2021



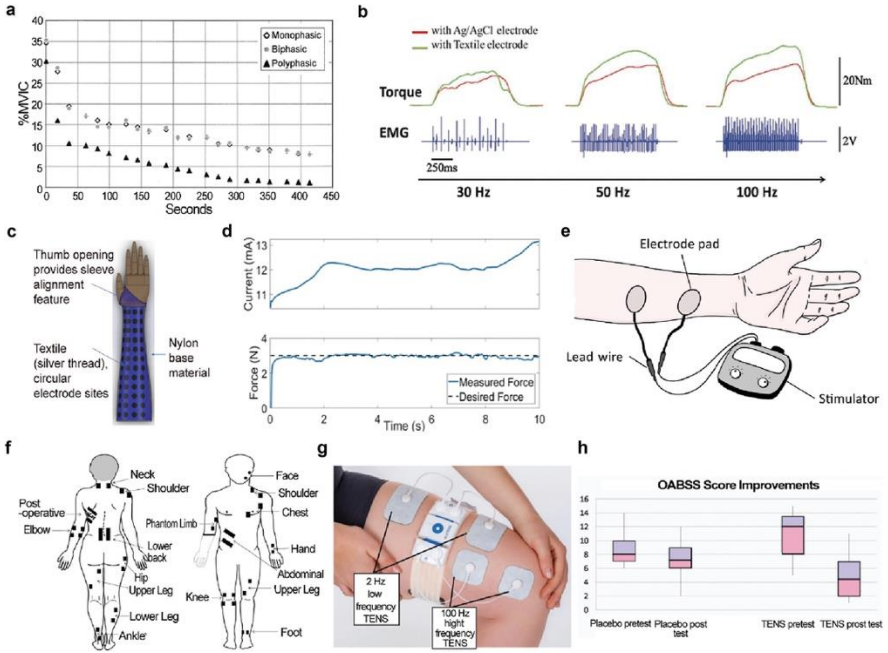
Peripheral nerve stimulation (PNS)

Electrical non-invasive Neuromodulation

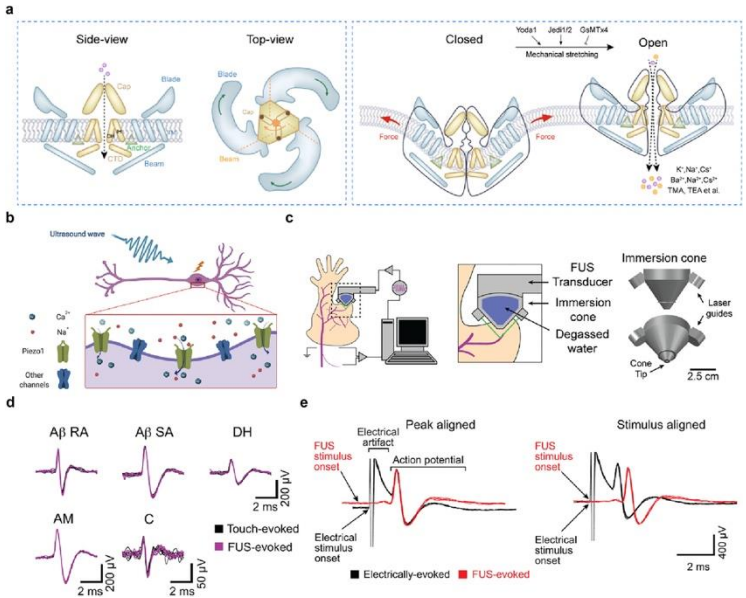


BMEMat, Volume: 2, Issue: 1, First published: 26 September 2023, DOI: (10.1002/bmm2.12048)

Electrical non-invasive Neuromodulation



Mechanical Neuromodulation



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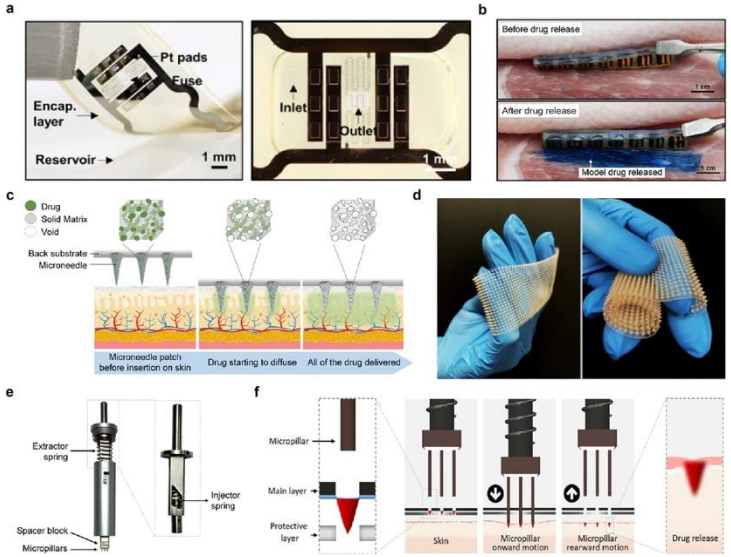
Chemical Neuromodulation



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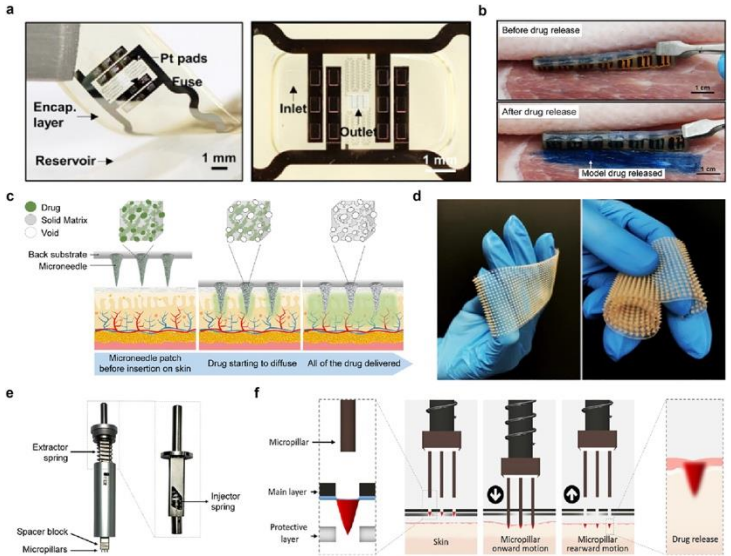
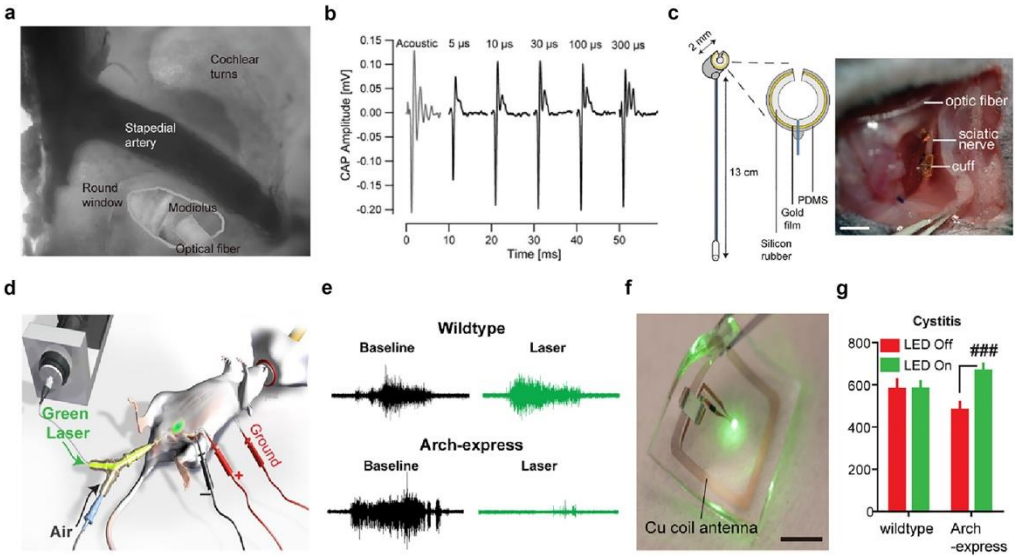
Peripheral nerve stimulation

Chemical Neuromodulation



Optical Neuromodulation



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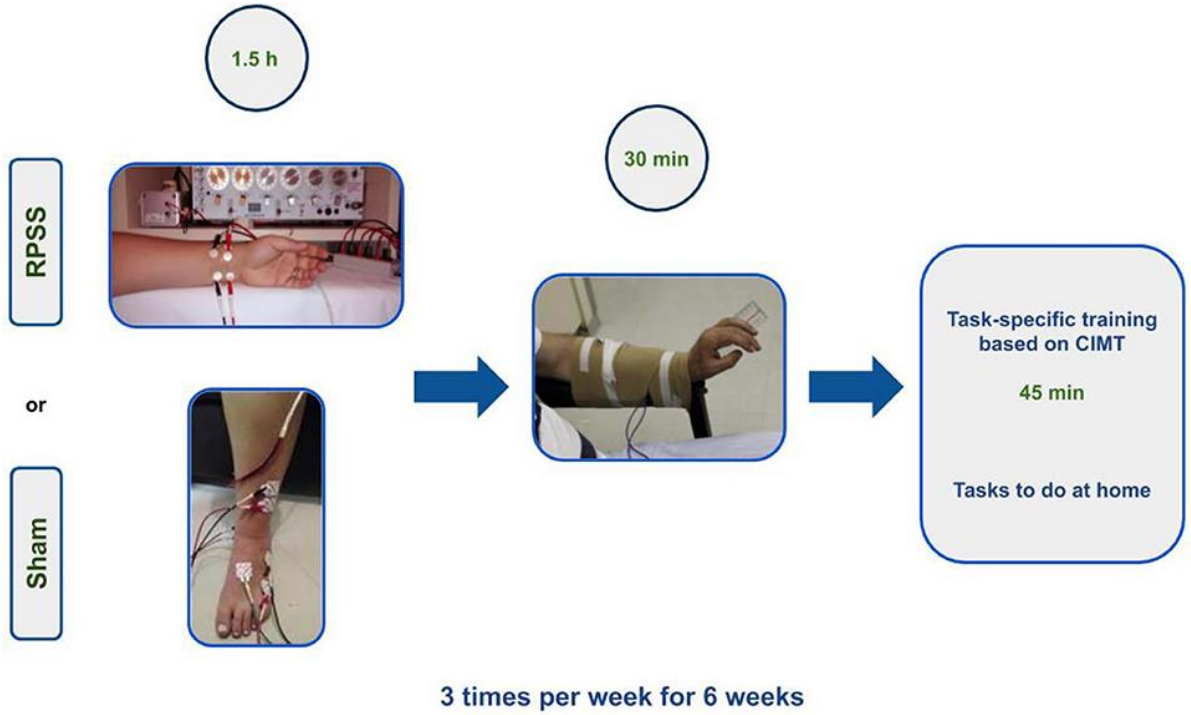
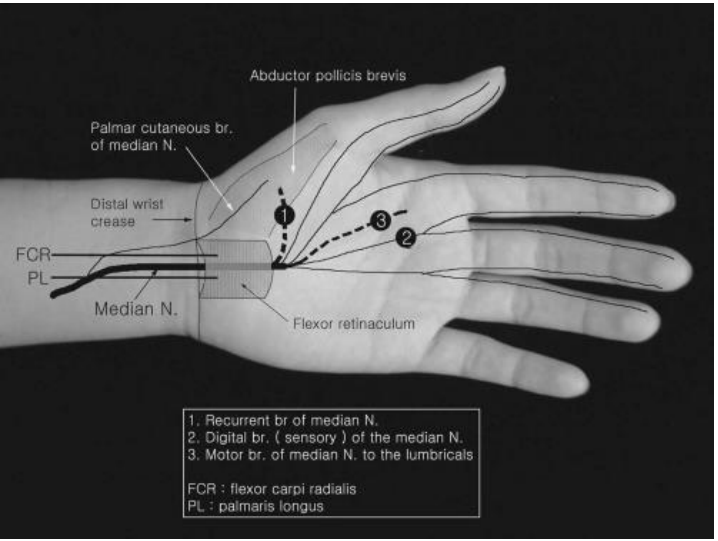
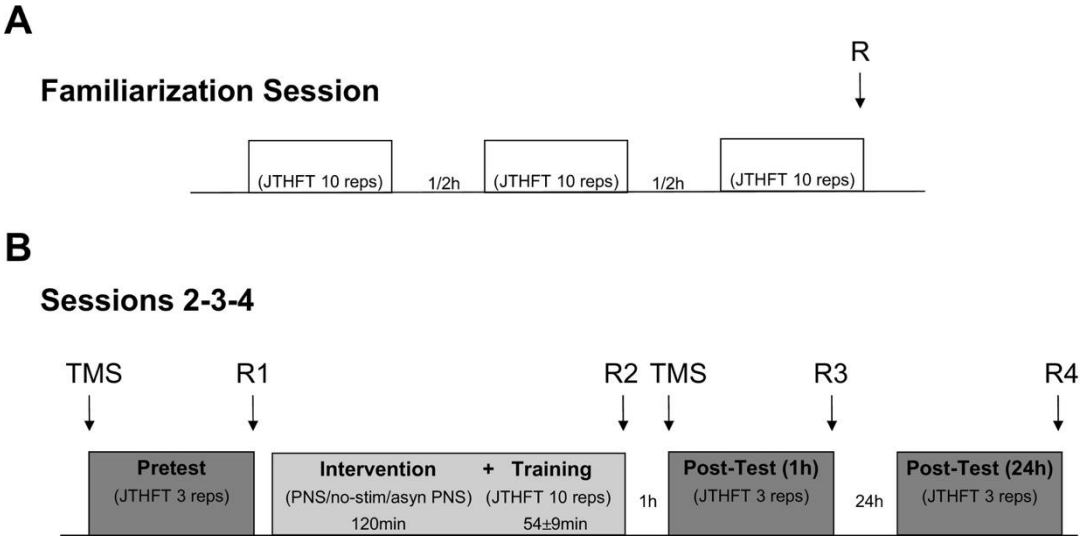
Peripheral nerve stimulation + Stroke recovery



Conforto et al. 2007

Peripheral nerve stimulation + Stroke recovery

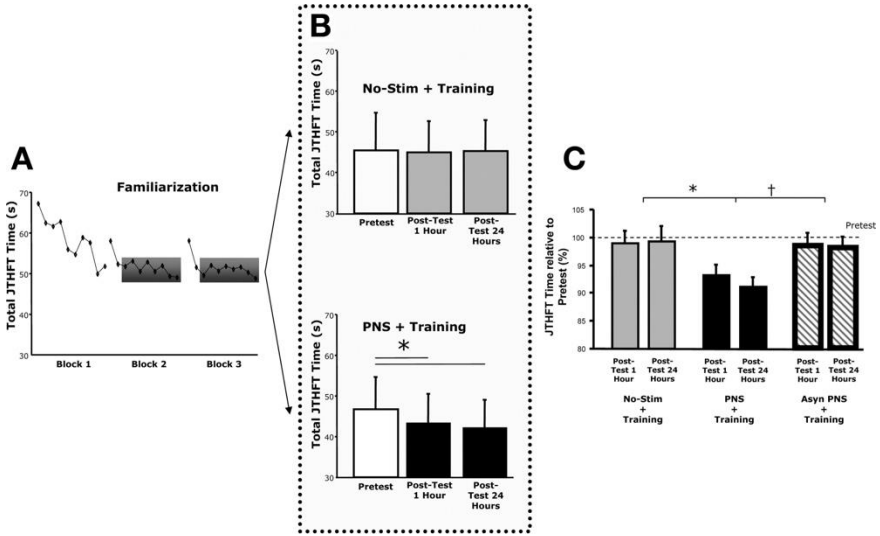


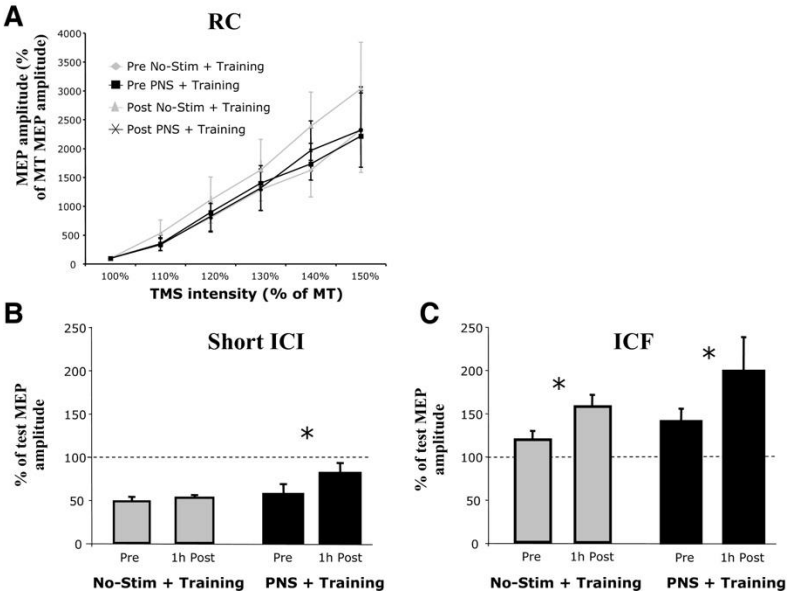


Celnik et al. 2007

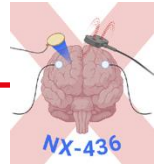
Peripheral nerve stimulation + Stroke recovery

Combination of PNS with motor training leads to an improvement in residual motor functions in stroke patients
This is associated with changes in motor-cortical excitability



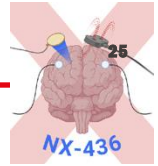


Celnik et al. 2007



- Peripheral nerve stimulation (PNS) allows to modulate cortical activity

- If combined with motor training it leads to an improvement of the effects of training, e.g. in stroke patients



Paired associative stimulation (PAS)

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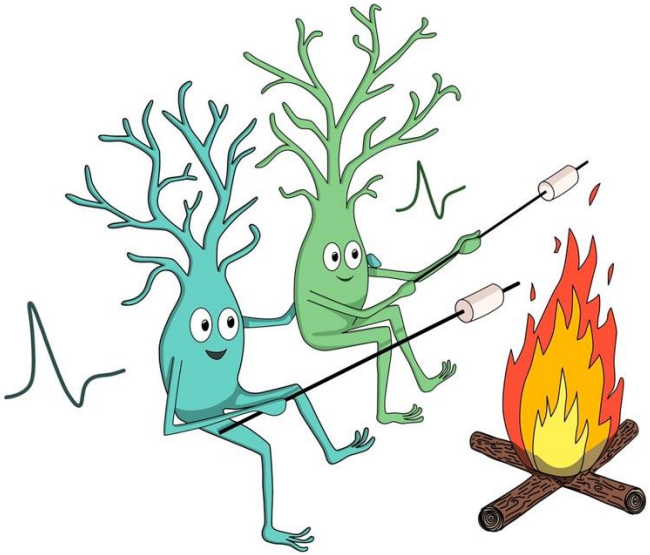
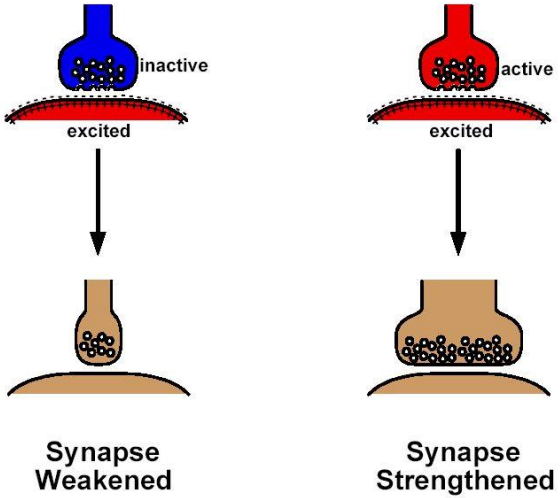


"Neurons that FIRE together, WIRE together"
- Donald Hebb

the NEURON family

https://twitter.com/theNeuronFamily/

A property of Hebbian synapse



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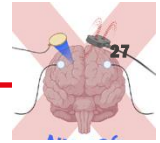
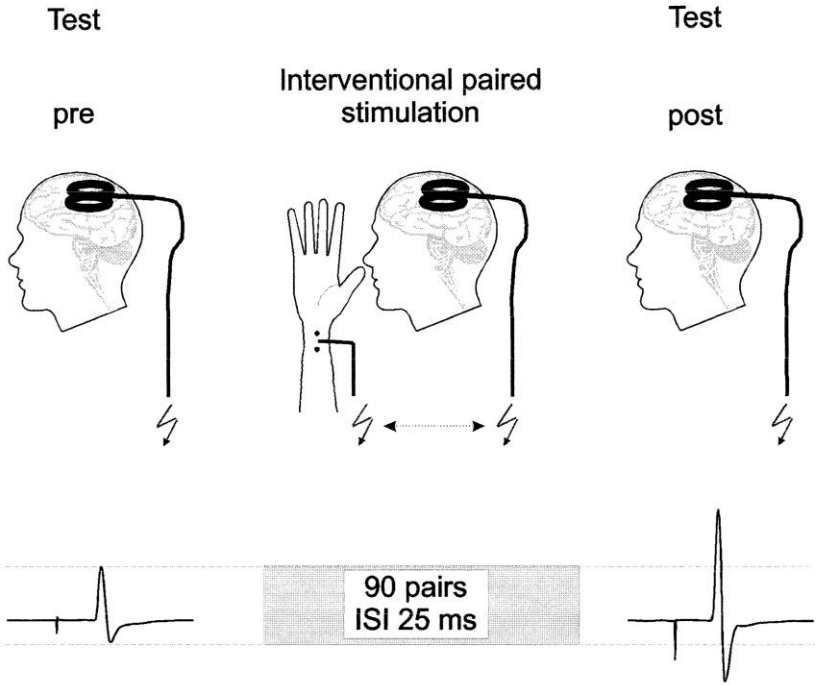
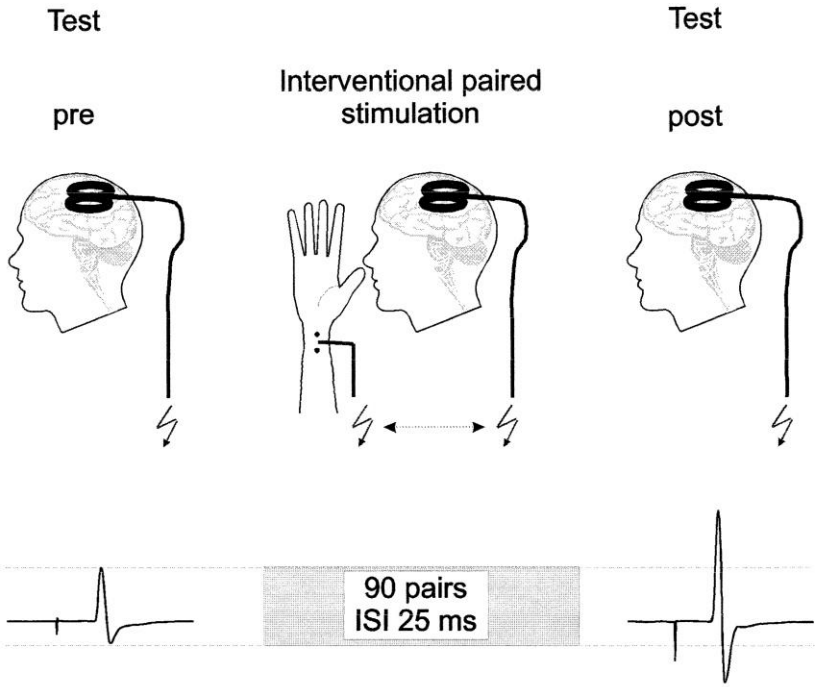


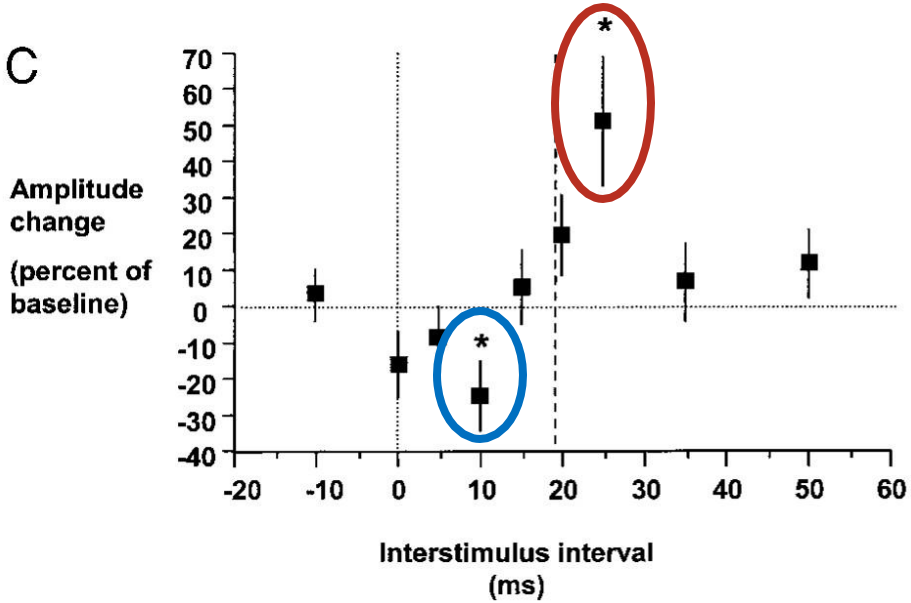


Standard protocol: 90 pairs at 10 or 25 ms ISI and at 0.05 Hz inter-pair interval with 1mV-MEP TMS intensity and 300% sensory threshold for median nerve stimulation

Stefan (2000) *Brain*; Wolters (2003) *JNeurophys*

Paired associative stimulation (PAS)





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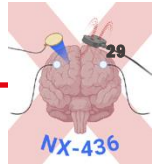

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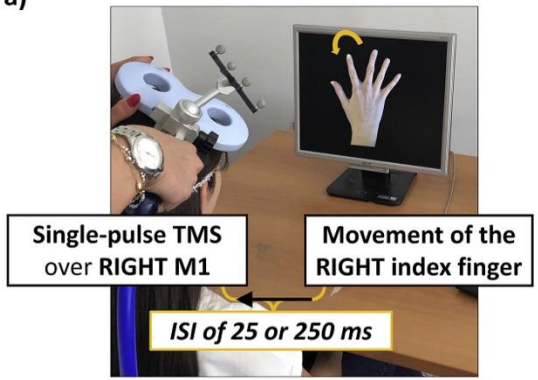

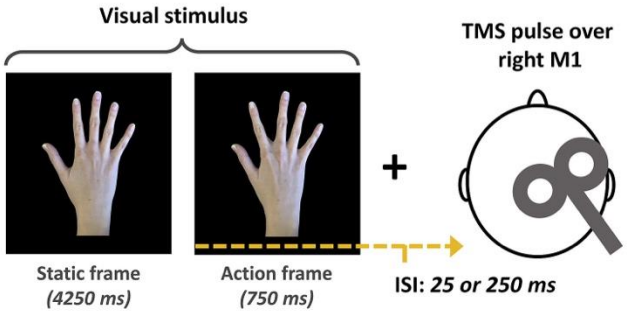

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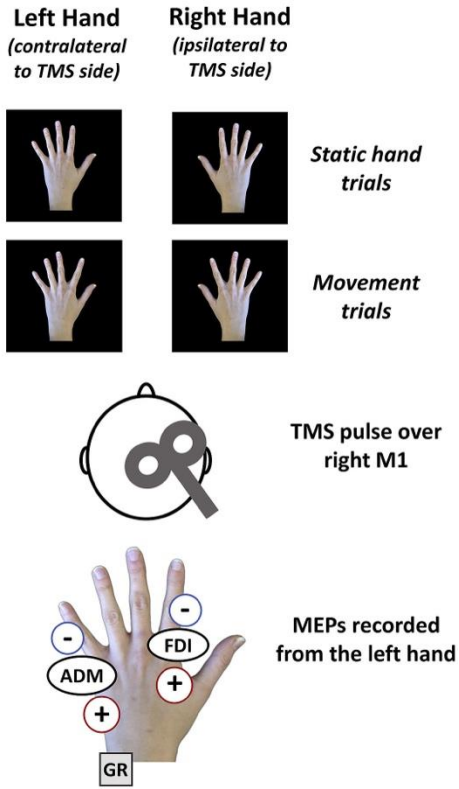
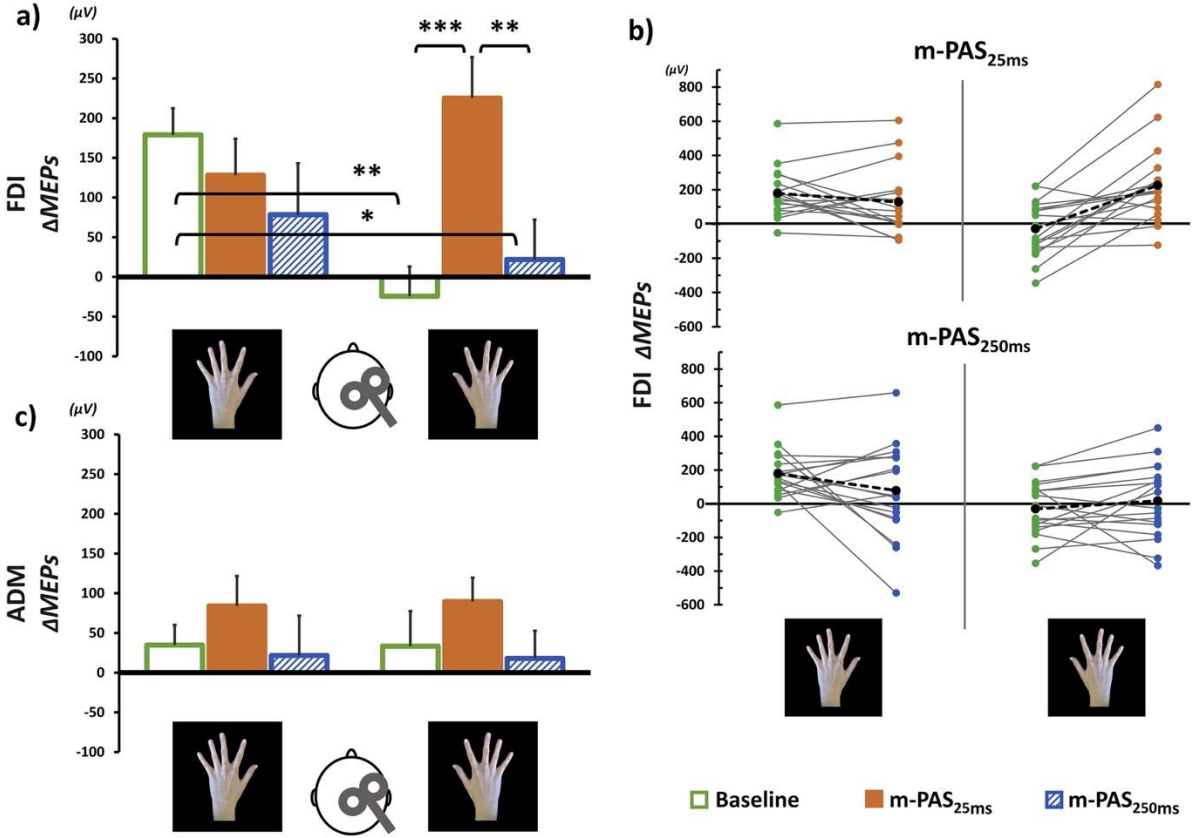


Guidali et al. 2020

Paired associative stimulation (PAS)



Guidali et al. 2020

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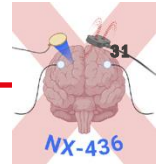

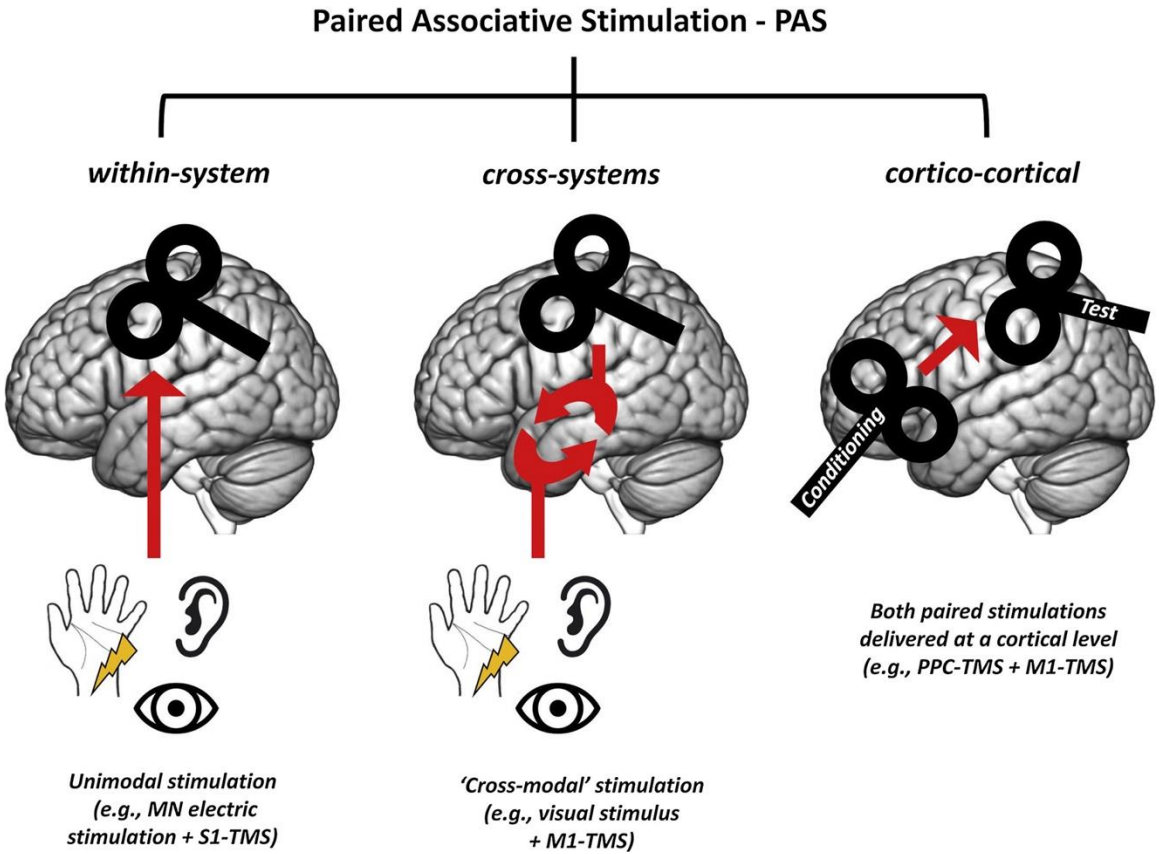

Guidali et al. 2021

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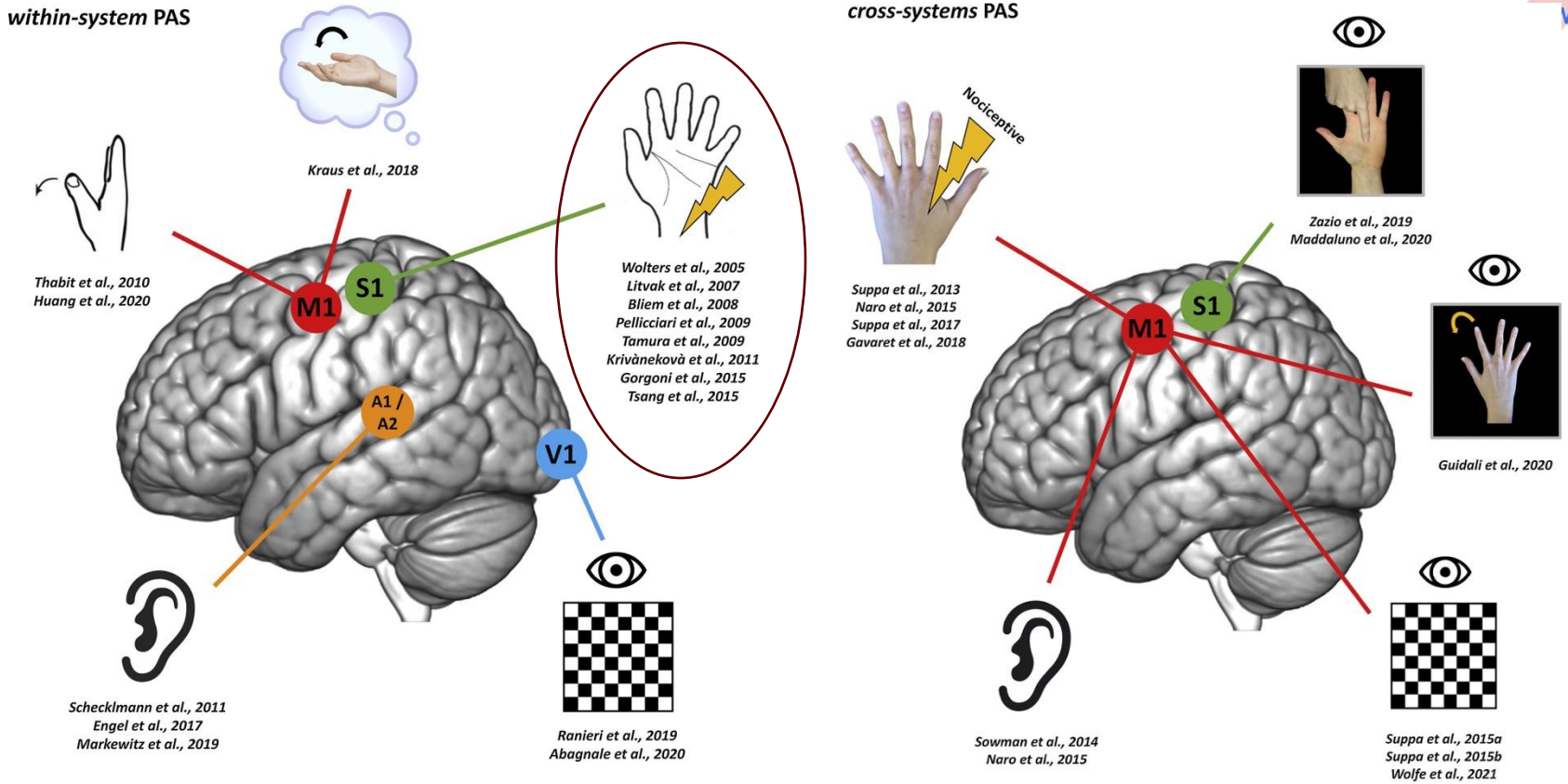
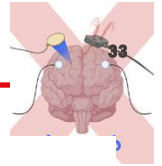
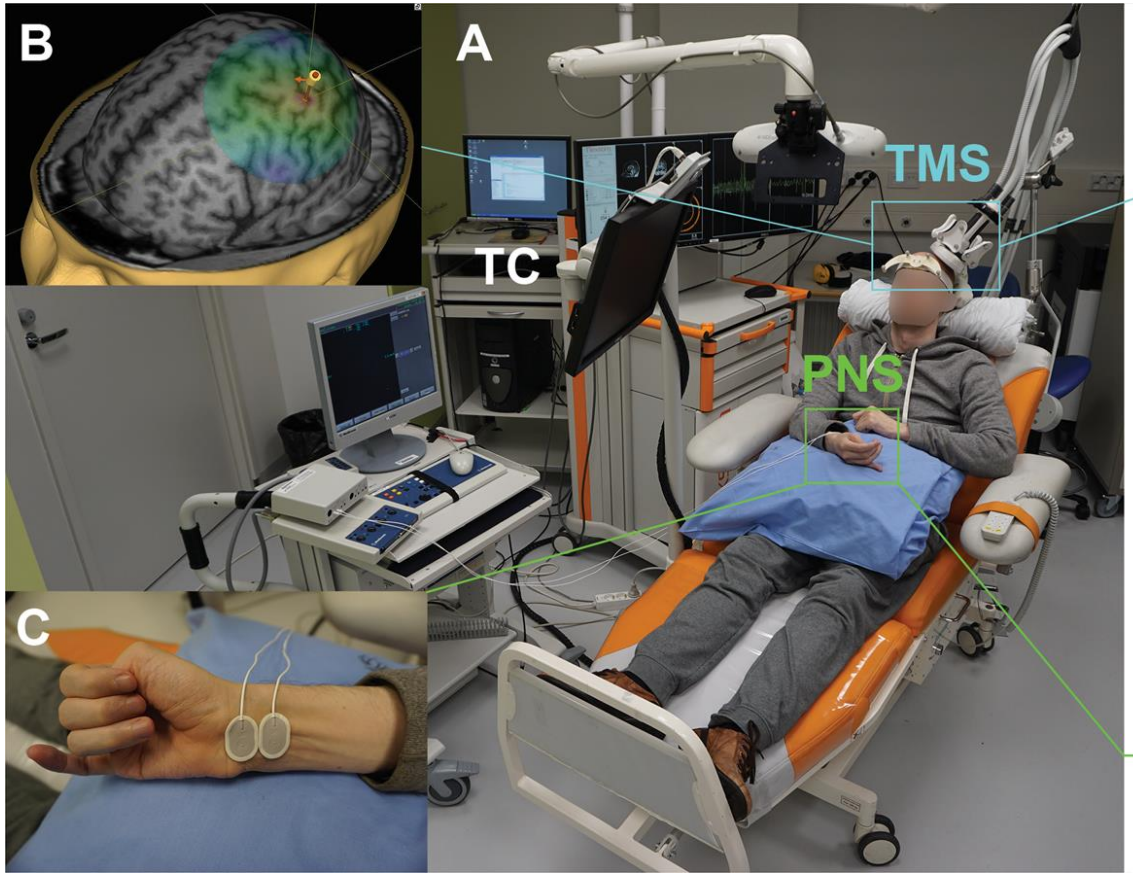
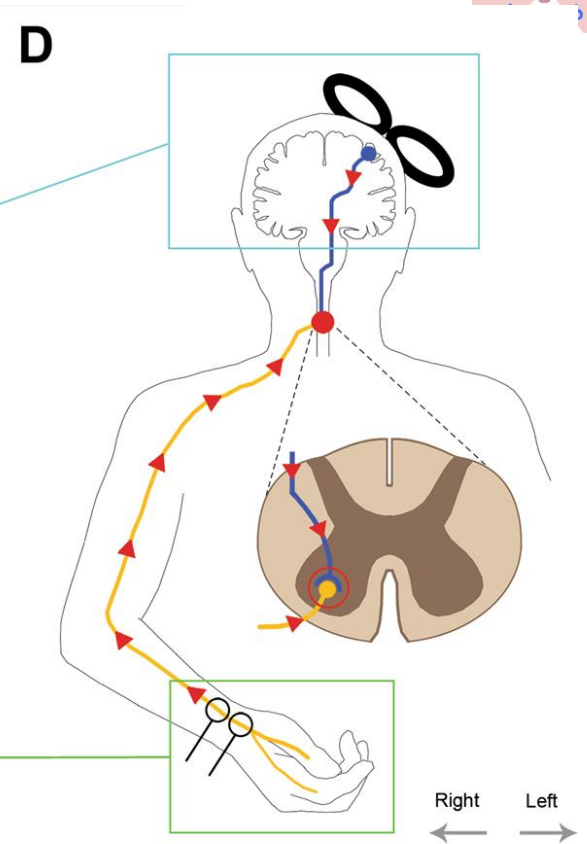


Guidali et al. 2021

Paired associative stimulation (PAS) + Tetraplegia

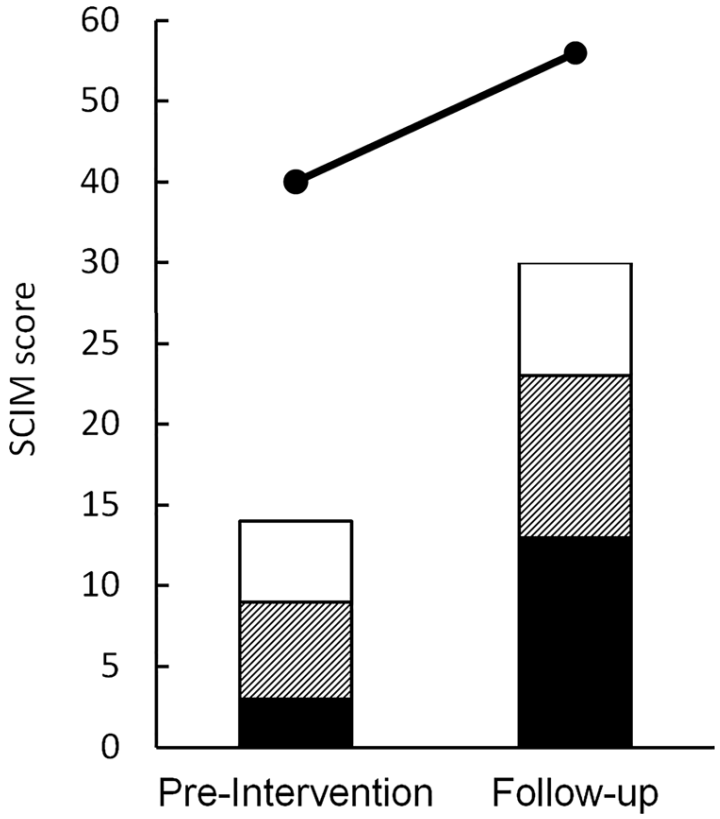


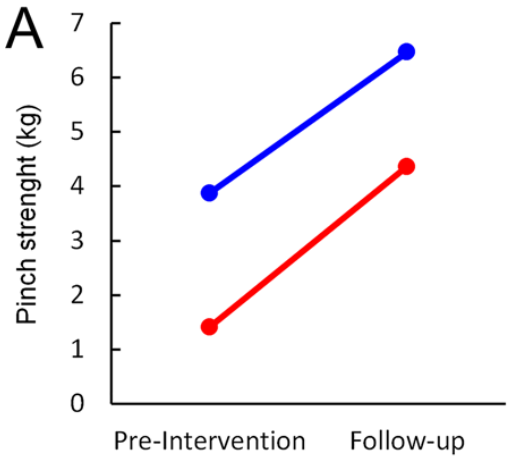


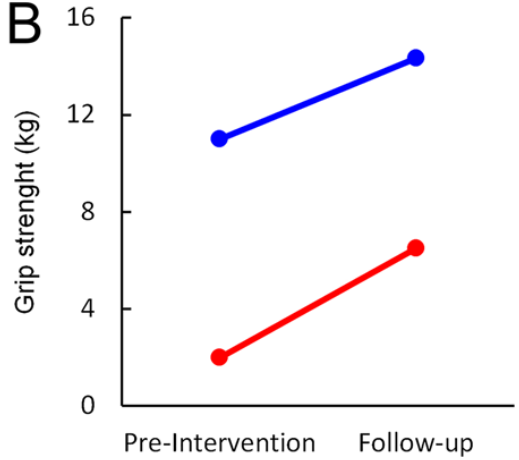


Guidali et al. 2021

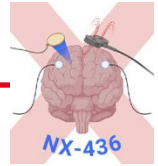
Paired associative stimulation (PAS) + Tetraplegia





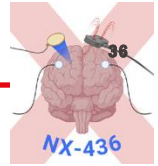


Guidali et al. 2021



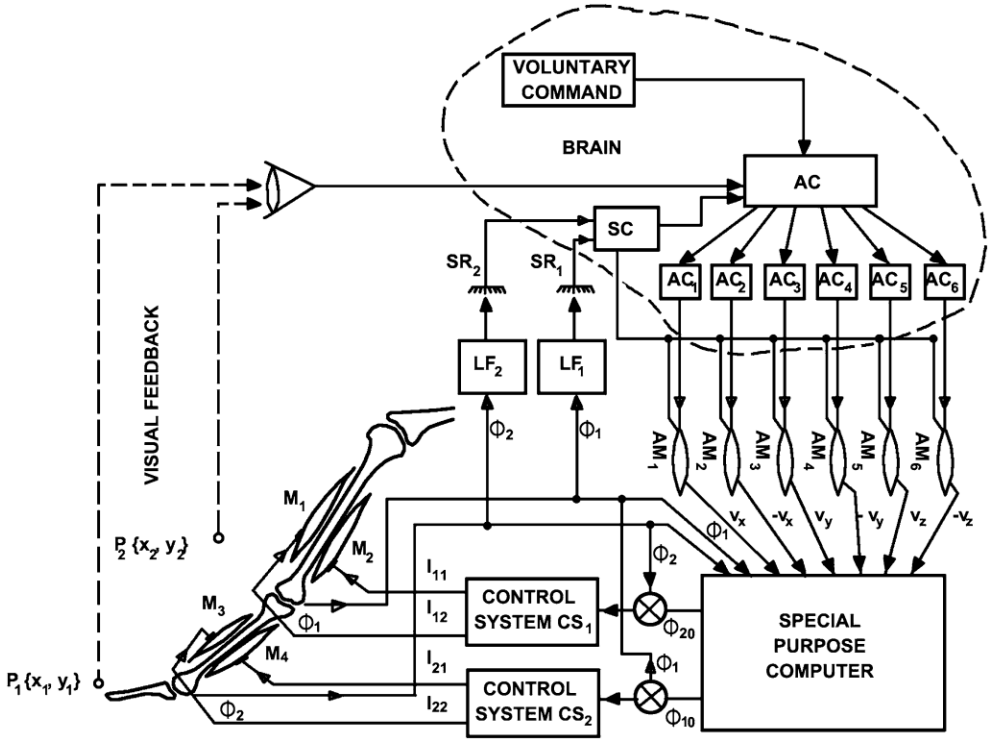
- Based on principles of Hebbian plasticity paired associative stimulation (PAS) allows to modulate cortical processing, plasticity and activity by peripheral stimulation

- Possible within and between domains

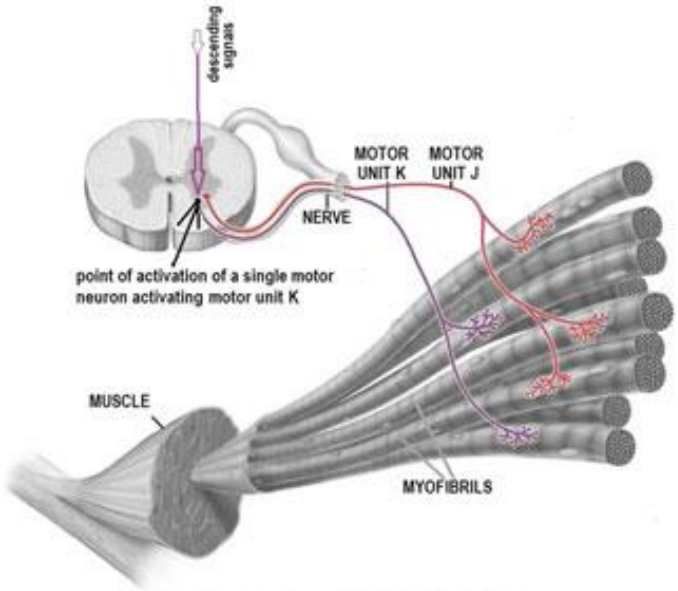


Functional Electrical Stimulation (FES)

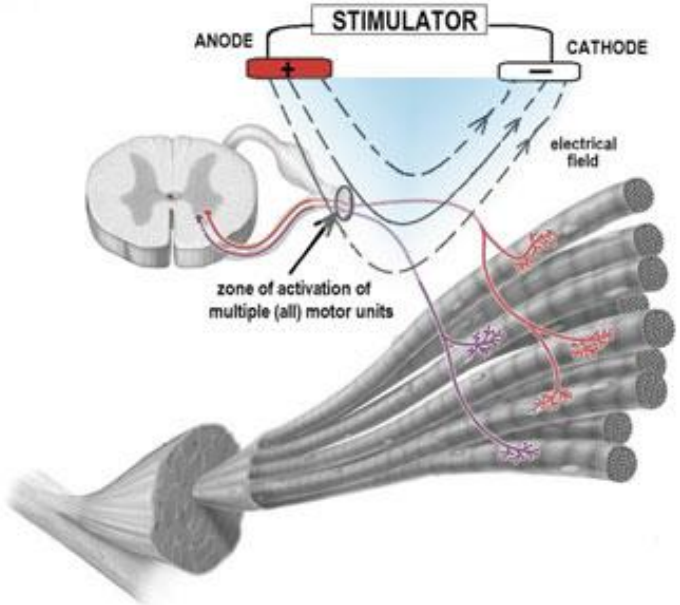
Functional electrical stimulation (FES)



Handbook of biomedical engineering Popovic 2020 modified from Reswick et al. 1967

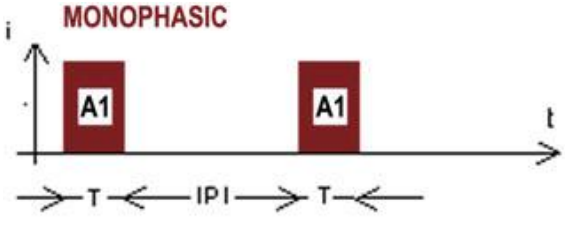


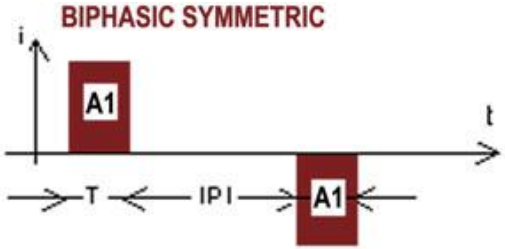
NATURAL ACTIVATION OF A MUSCLE

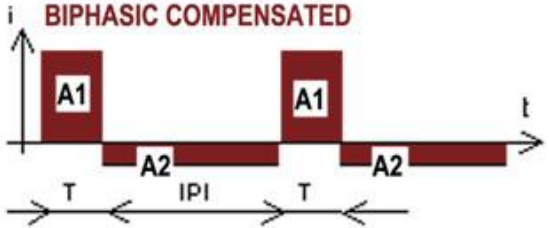


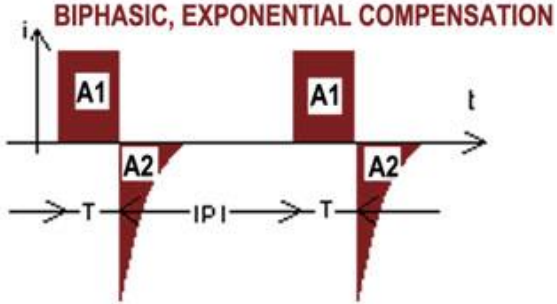
FES ACTIVATION OF A MUSCLE

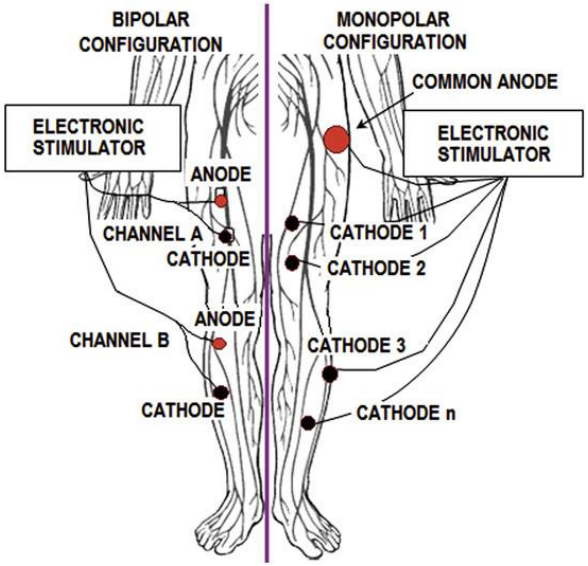
Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020







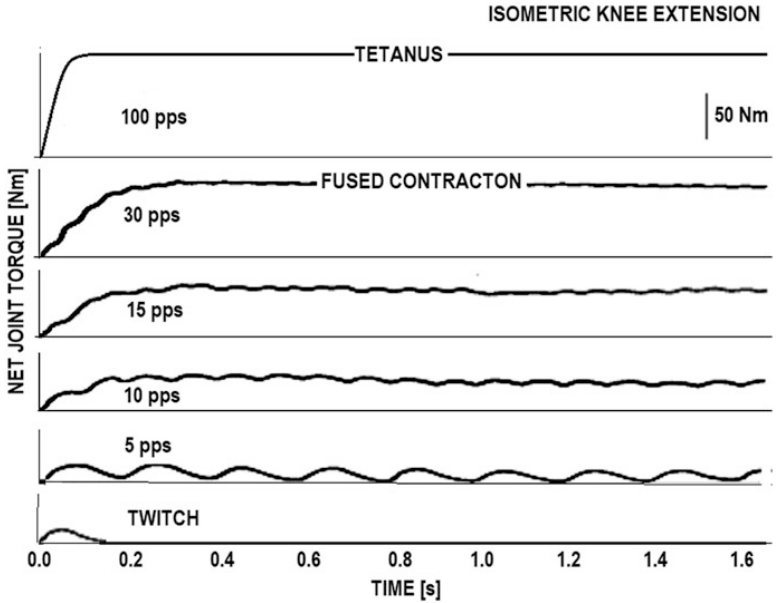


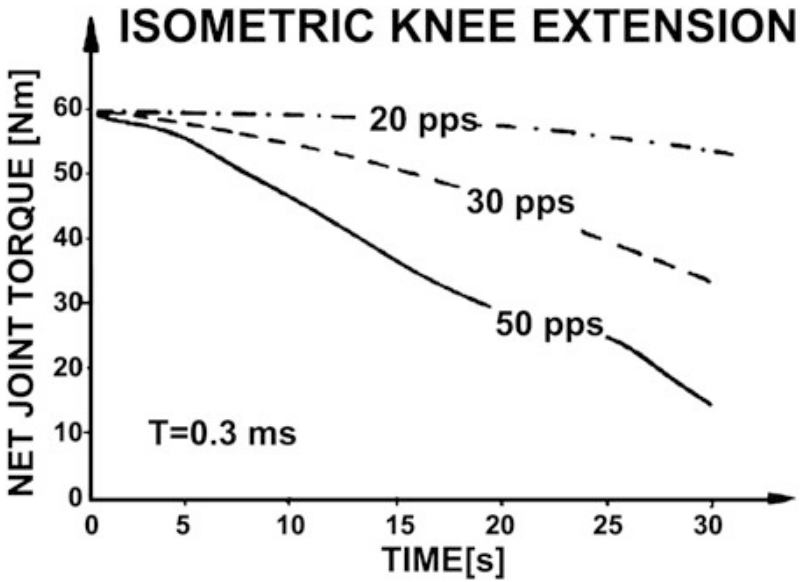


Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020

Functional electrical stimulation (FES)

The normalized force to the maximum isometric force at various FES frequencies

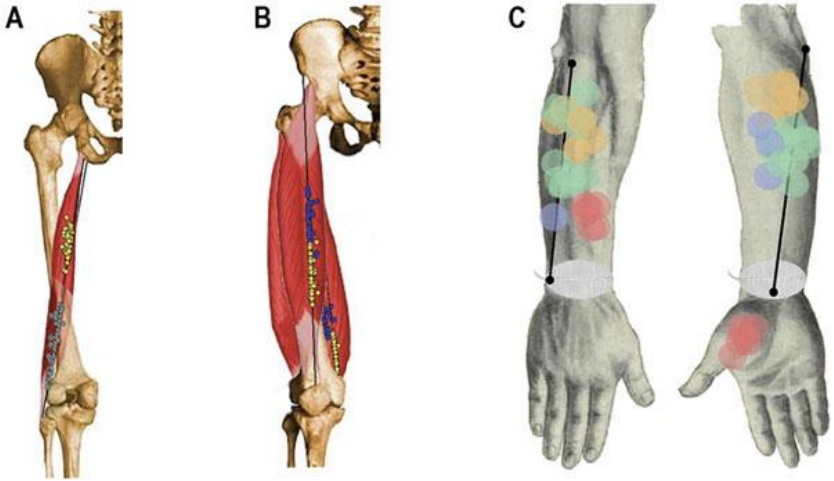


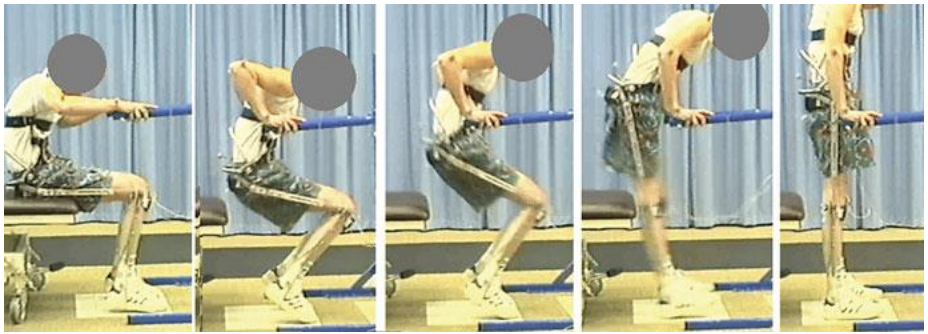


Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020

Functional electrical stimulation (FES)

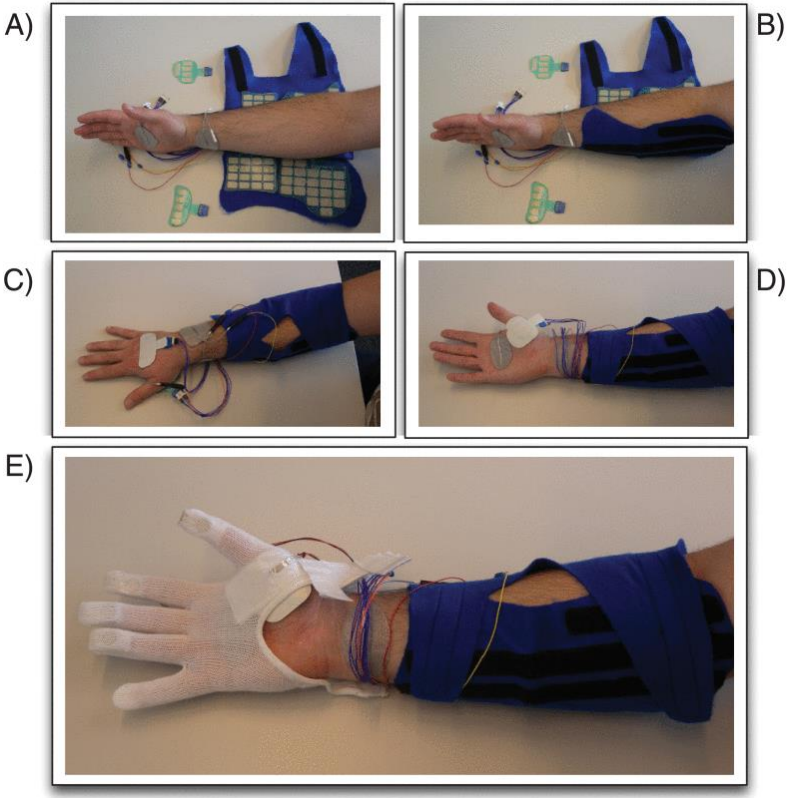
The normalized force to the maximum isometric force at various FES frequencies

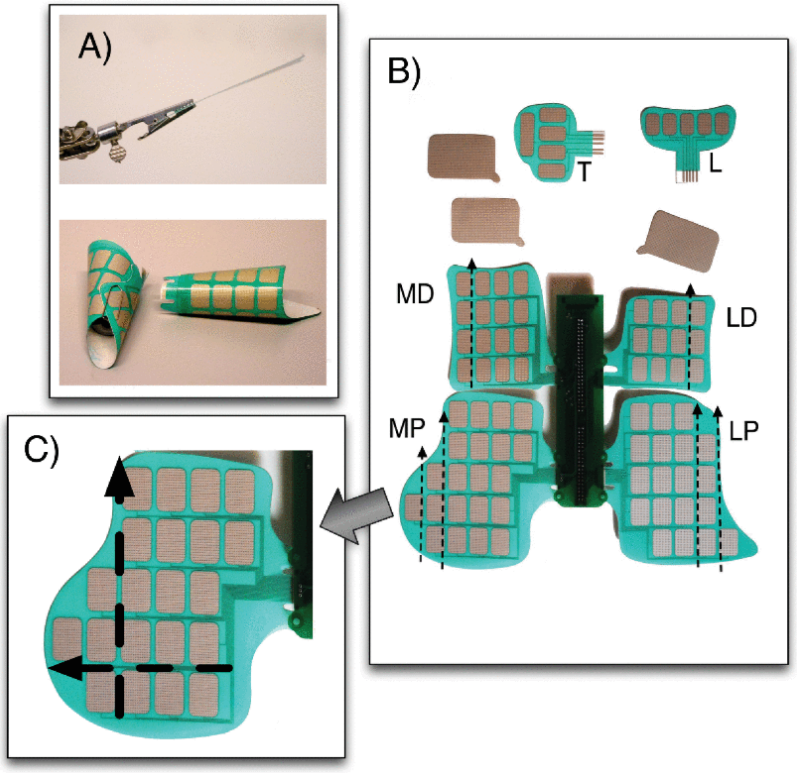




Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020

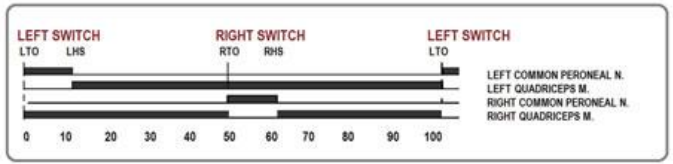
Functional electrical stimulation (FES)

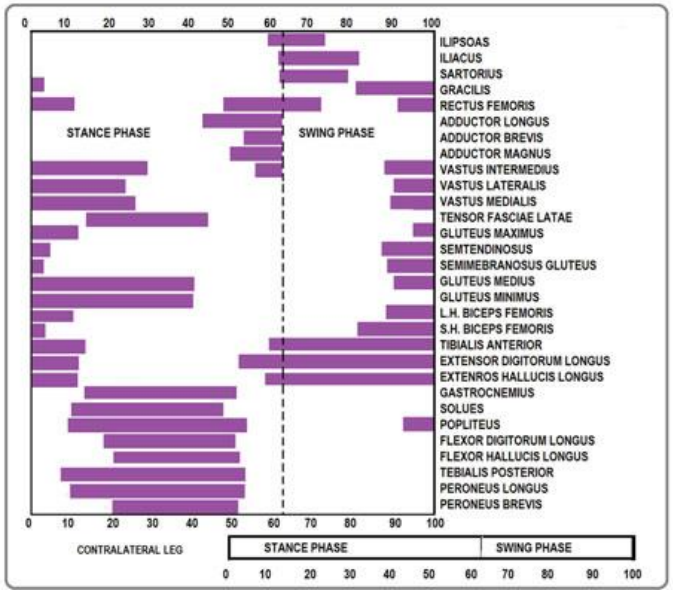




Crema et al. 2019

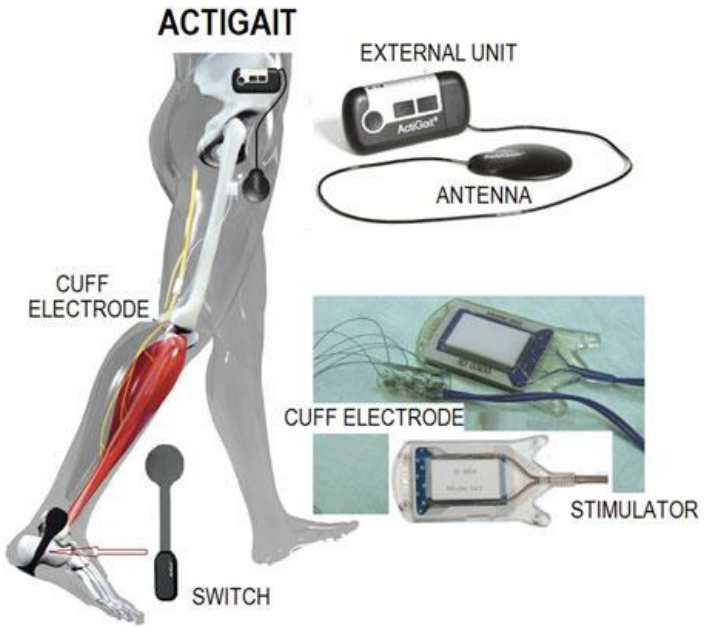
Functional electrical stimulation (FES)





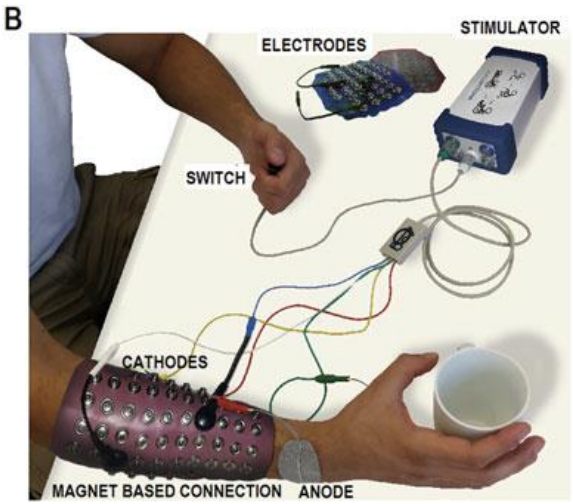
FOUR-CHANNEL FES (SURFACE ELECTRODES) ASSISTING THE STANCE AND THE SWING

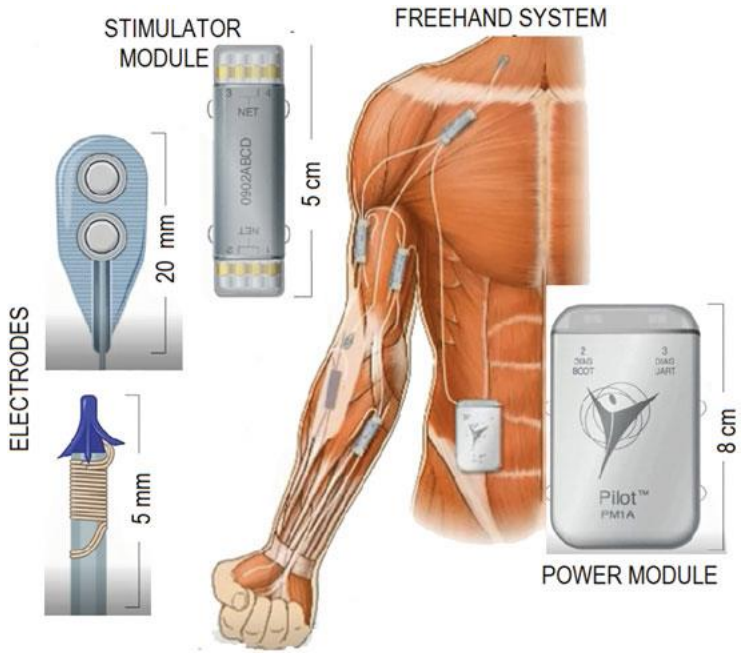
16-CHANNEL FES WITH 64 IMPLANTED ELECTRODES ASSISTING THE GAIT



Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020

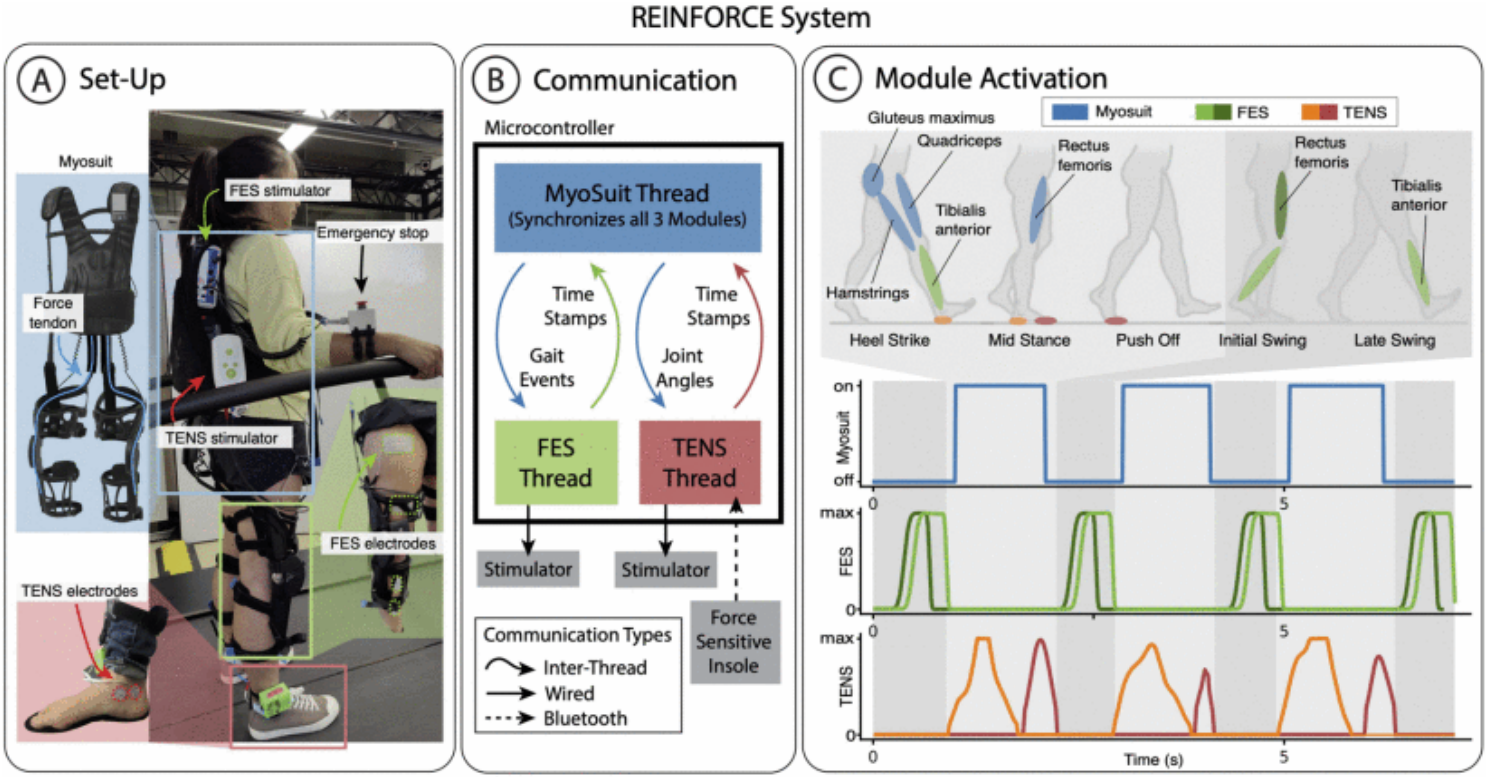
Functional electrical stimulation (FES)





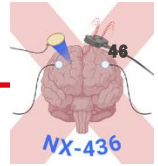
Handbook of biomedical engineering, Chapter FES Popovic & Popovic-Maneski 2020

Functional electrical stimulation (FES)

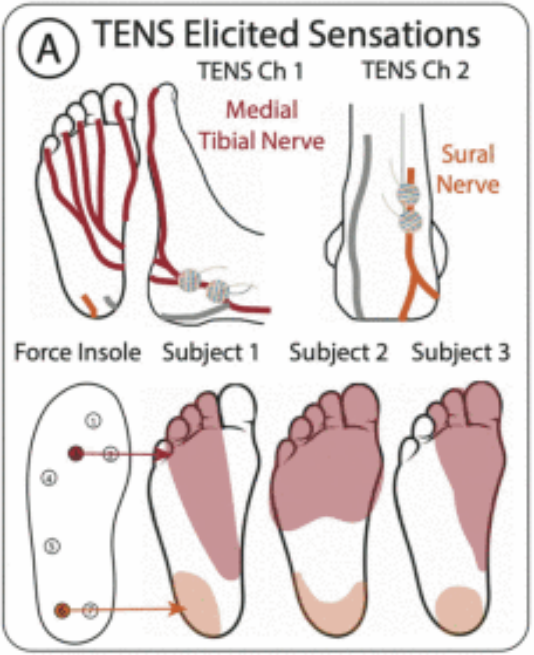


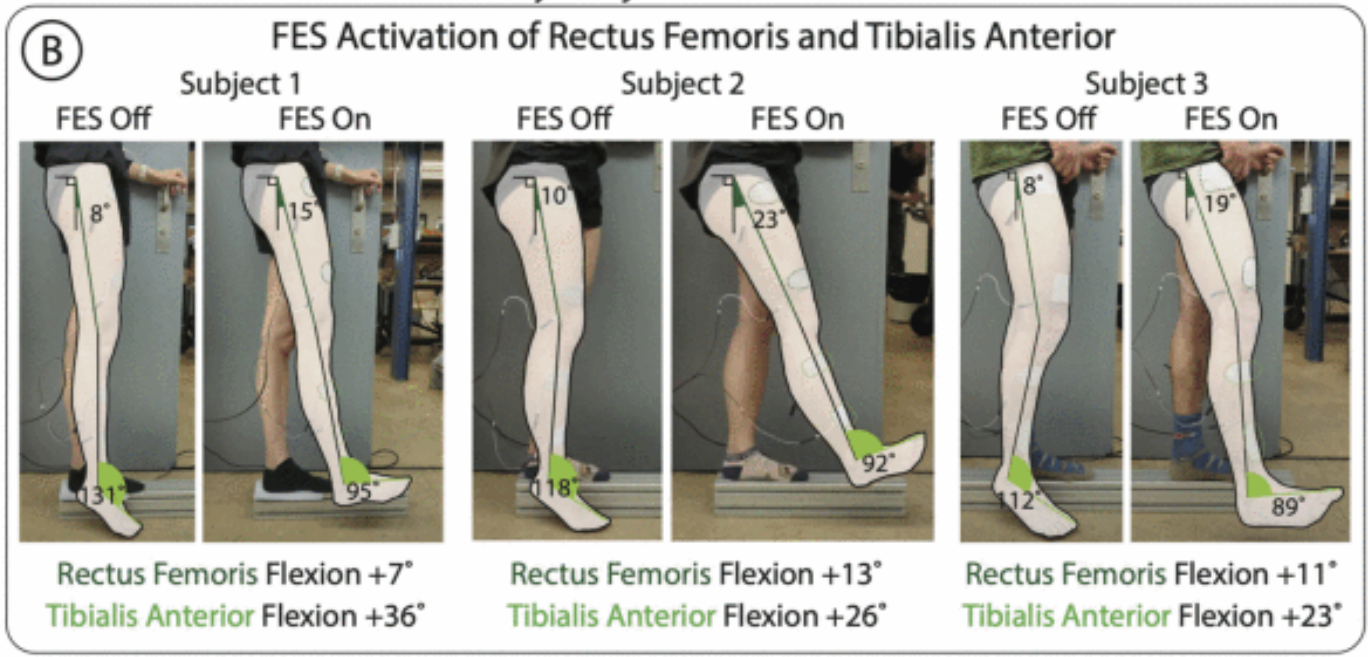
Crema et al. 2023

Functional electrical stimulation (FES)



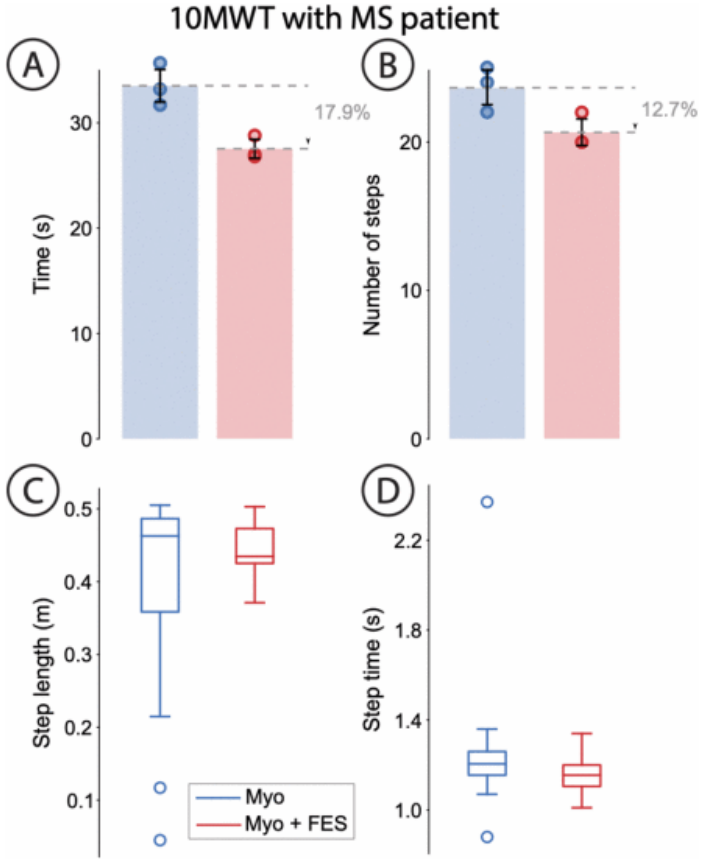
Module Tests in Healthy Subjects





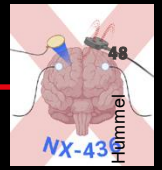
Crema et al. 2023

Functional electrical stimulation (FES)

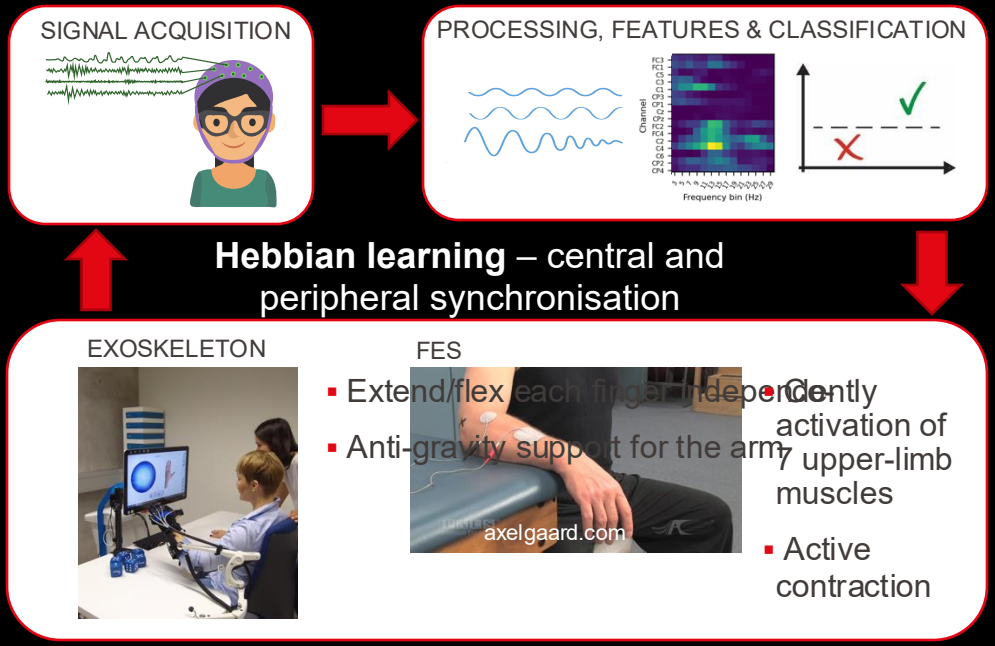


Crema et al. 2023

Multitechnology - personalized



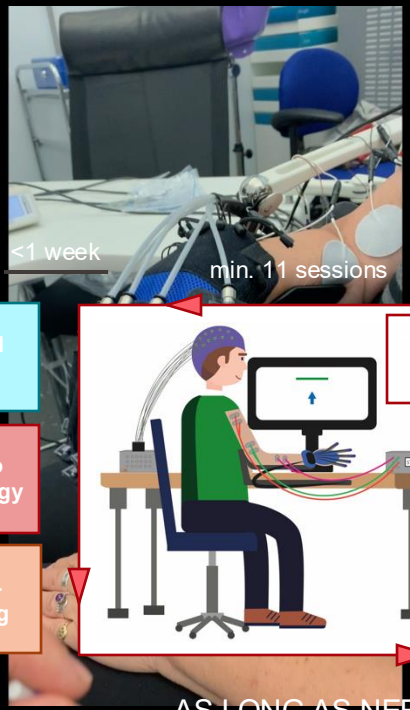
- **Combination of neurotechnologies** given in hierarchical manner:
  - hand exoskeleton, functional electrical stimulation (FES), brain-computer interface (BCI)
  - Anodal transcranial direct current stimulation (tDCS) to motor cortex lesioned hemisphere

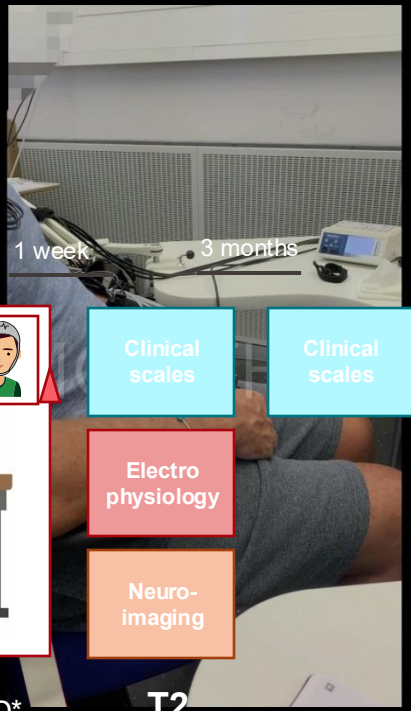


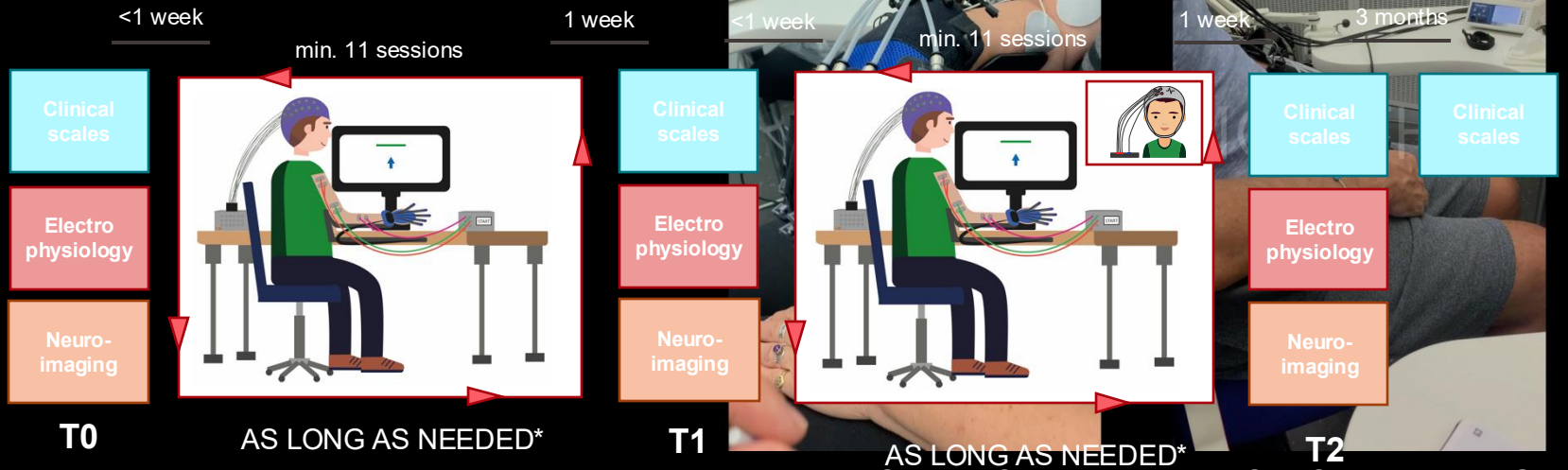
Bigoni *et al.*, Frontiers Neurology 2022; Bigoni *et al.*, 2023 Med

Multitechnology - personalized

- **Combination of neurotechnologies** given in hierarchical manner
- **Personalized-therapy**:
  - Single session – tailored exercises
  - Therapy duration



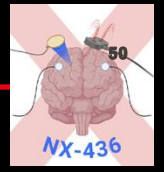




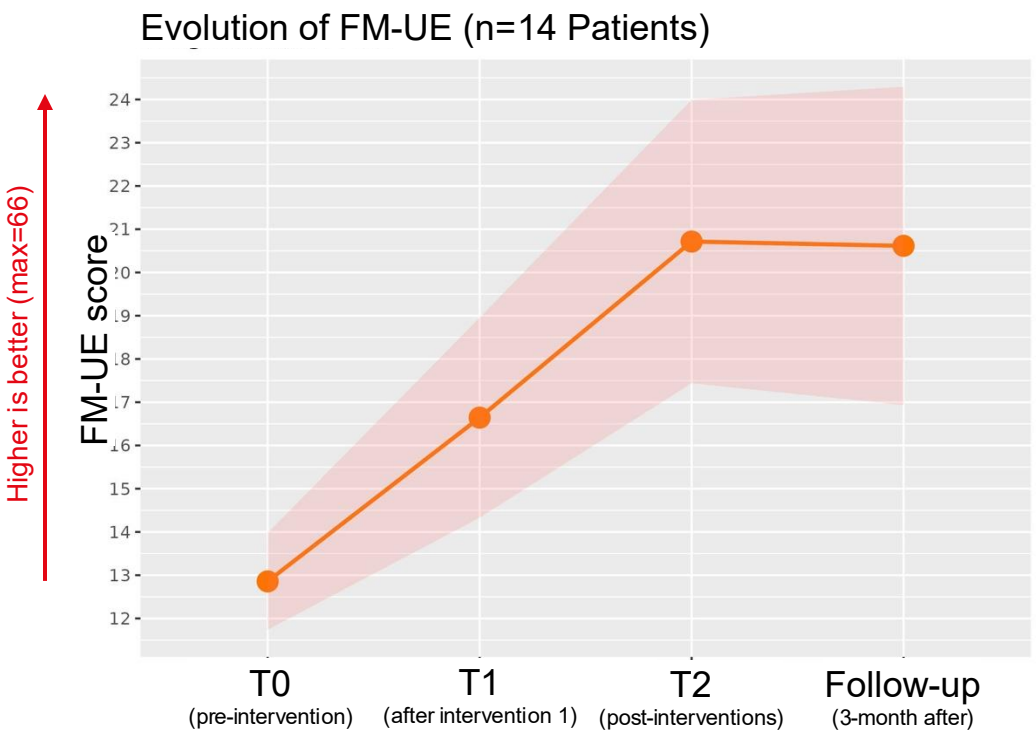
*Fugl-Meyer Assessment of upper extremity (FM-UE) measured every second session

Bigoni *et al.*, Frontiers Neurology 2022; Bigoni *et al.*, 2023 Med

Multitechnology - personalized



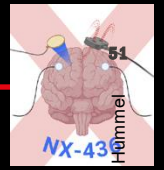
Primary outcome – reduction of motor impairement



- Primary outcome met
- Average increase of **7.8 points**
- Max increase = **30 points**
- **$FM\text{-}UE_{T2} > FM\text{-}UE_{T0}$**
- $FM\text{-}UE_{Follow\text{-}up} \sim FM\text{-}UE_{T2}$
  → **improvement retained**

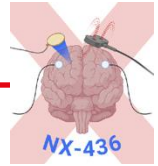
Bigoni *et al.*, Frontiers Neurology 2022; Bigoni *et al.*, 2023 Med

Multitechnology - personalized

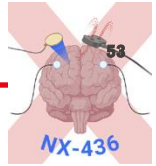


Primary outcome – reduction of motor impairement

Bigoni *et al.*, Frontiers Neurology 2022; Bigoni *et al.*, 2023 Med



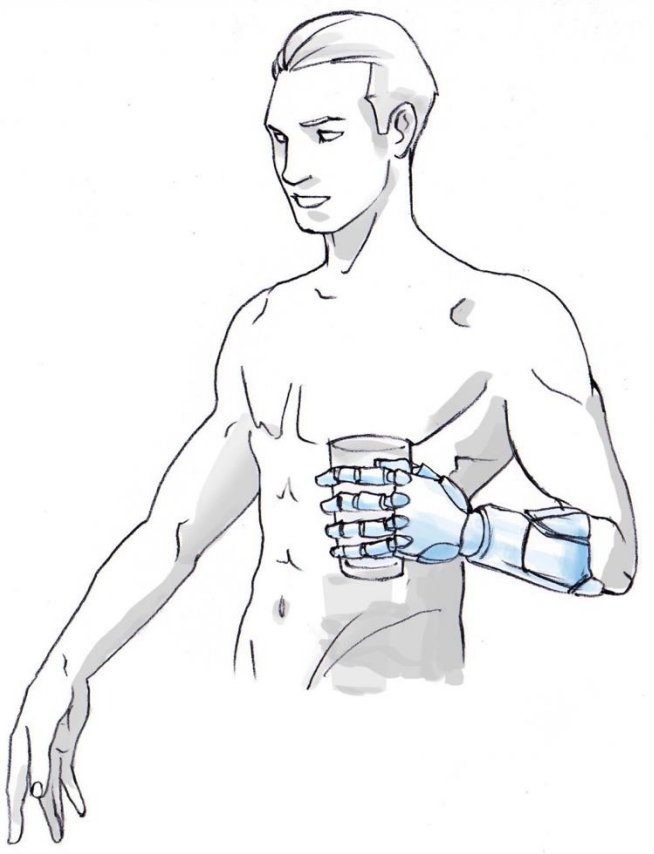
- FES allows to stimulate peripheral muscles to induce functional movements
- Applications range from single to multiple electrode arrays
- Applications in clinical conditions, e.g., to enhance stroke recovery
- Well-suited to be combined to other neurotechnologies, e.g. BCI



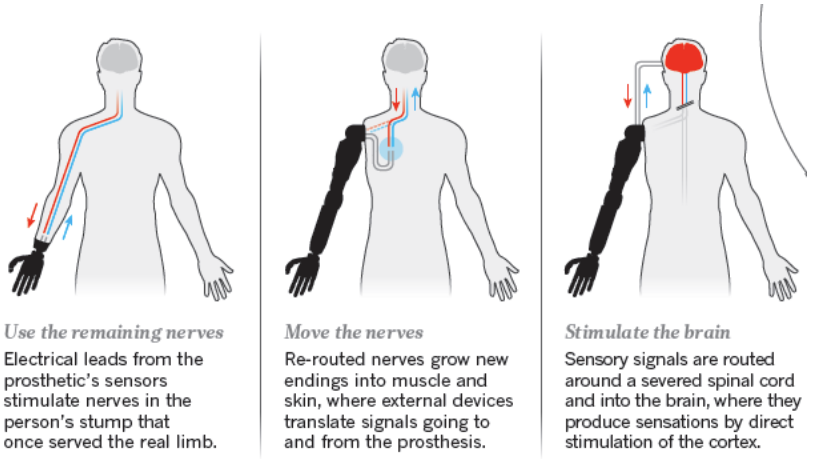
Restoration of homologous somatosensory sensations in upper limb amputees

Slides courtesy to Solaiman Shokur

Restoration of somatosensory functions

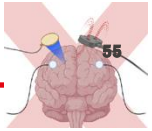


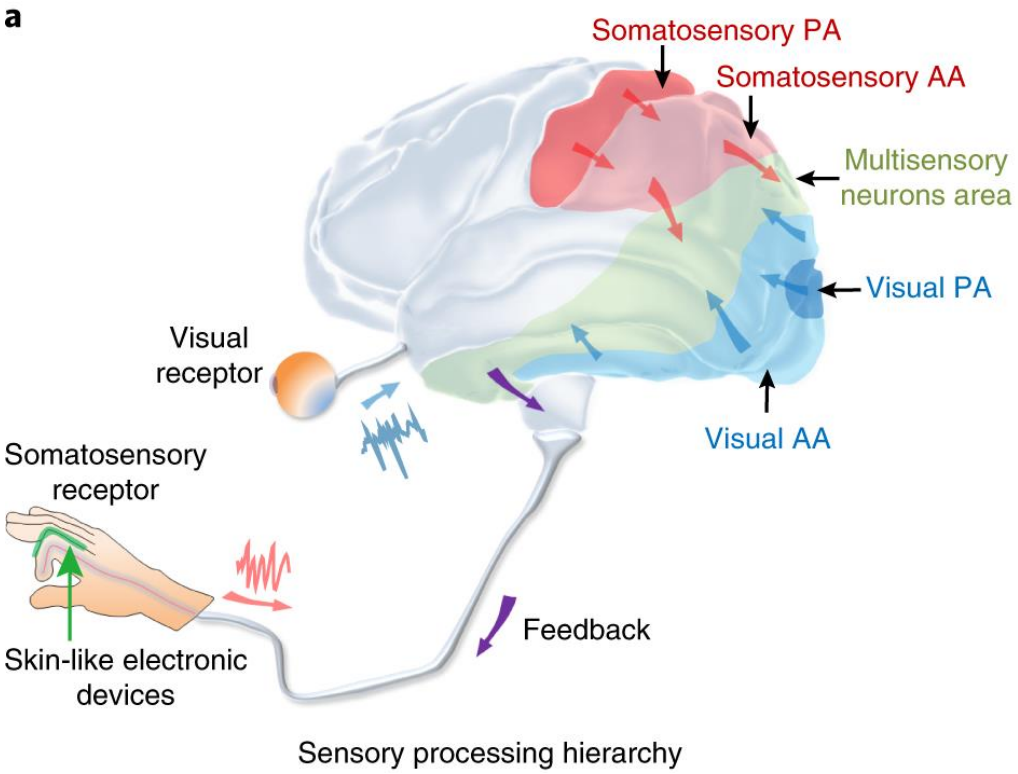
Real-time, and **natural** feedback **from** the **hand prosthesis** to the user is essential in order to enhance the control and functional impact of prosthetic hands in daily activities, prompting their full acceptance by the users



Kwok, Nature, 2013

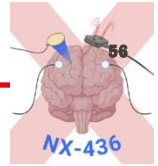
Restoration of somatosensory functions



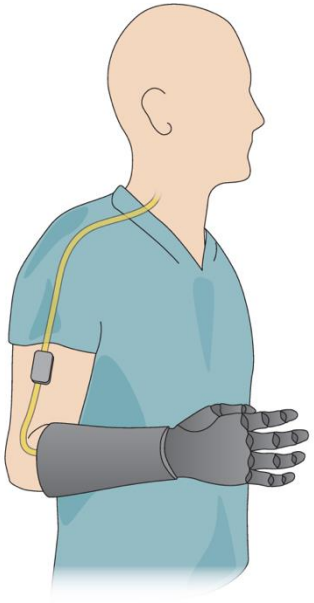


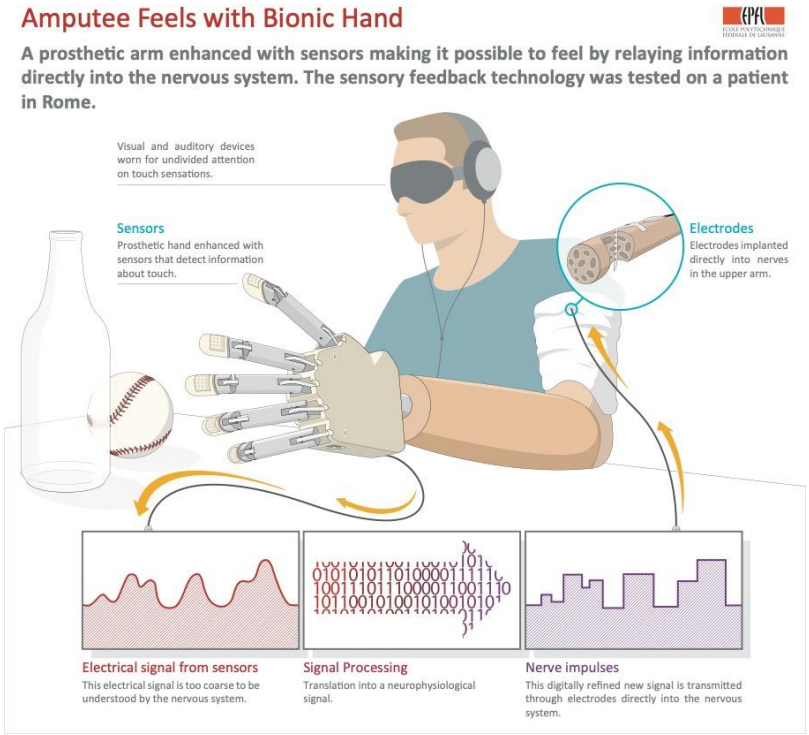
Wang et al 2020

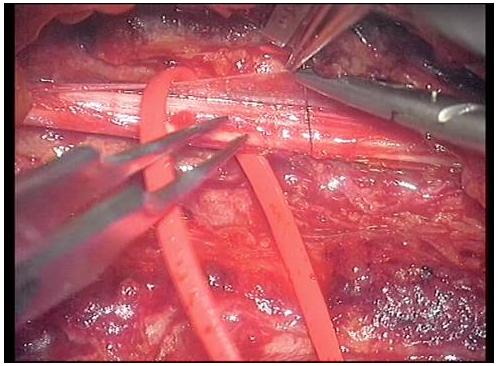
Restoration of somatosensory functions



Restoration of sensory feedback

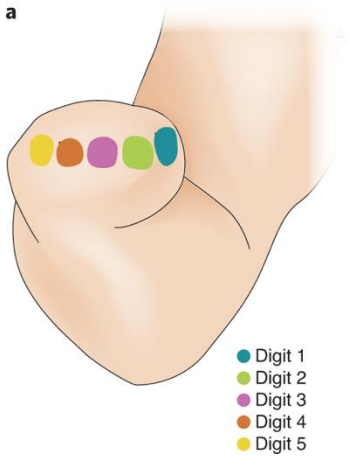






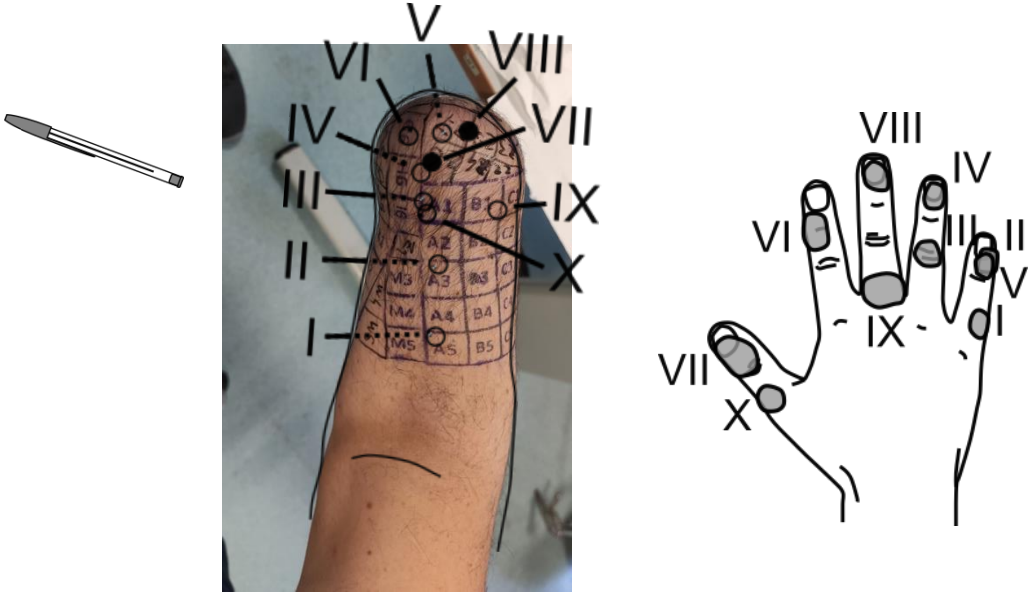
Raspopovic, S et al. (2014). Restoring natural sensory feedback in real-time bidirectional hand prostheses. Science translational medicine, 6(222), 222ra19-222ra19.

Can we provide phantom thermal sensations non-invasively?



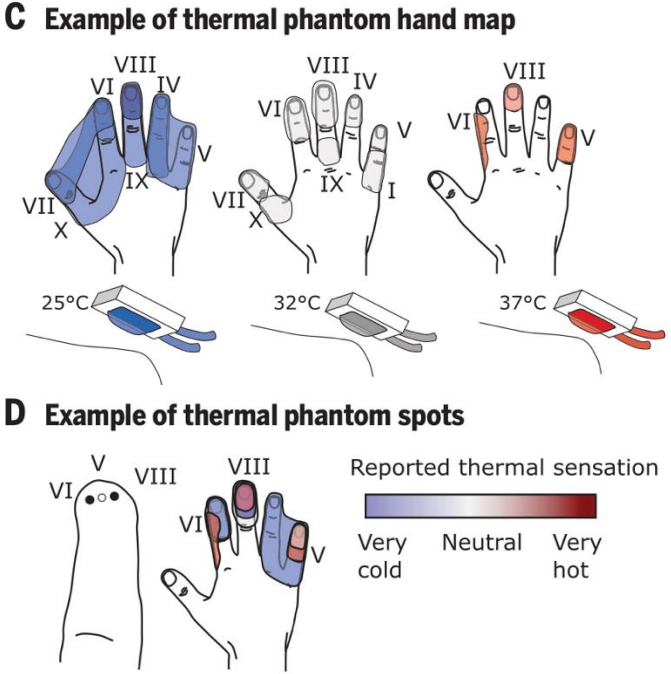
Bensmaia, S. J., et al. (2020). Restoration of sensory information via bionic hands. Nature Biomedical Engineering, 1-13.

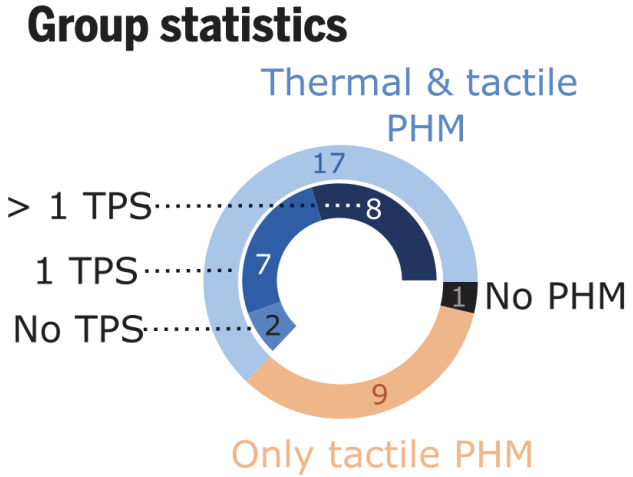
Presence of tactile phantom sensations in upper limb amputees



F. Iberite, et al. Restoration of natural thermal sensation in upper-limb amputees (2023). Science.

Presence of phantom thermal sensations in upper limb amputees



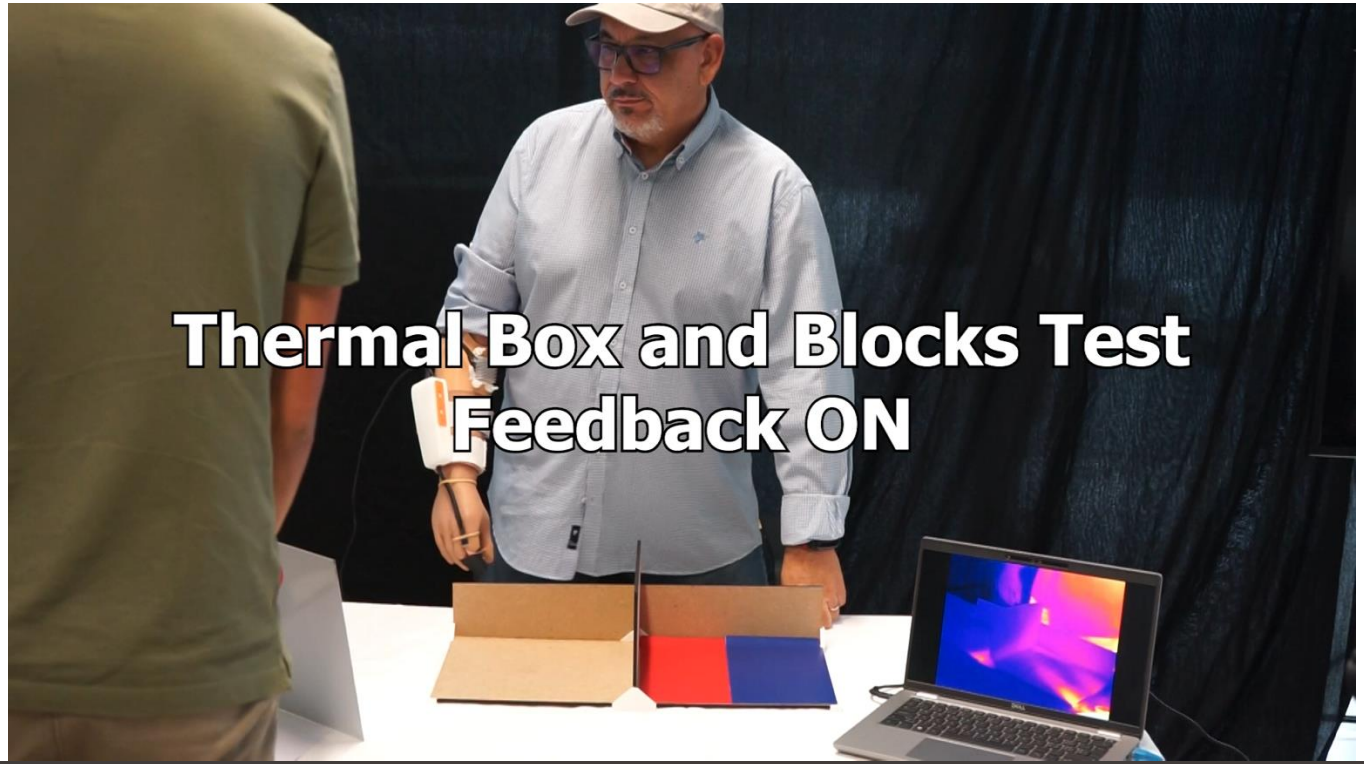


TPS: Thermal phantom spot

PHM: Phantom hand map

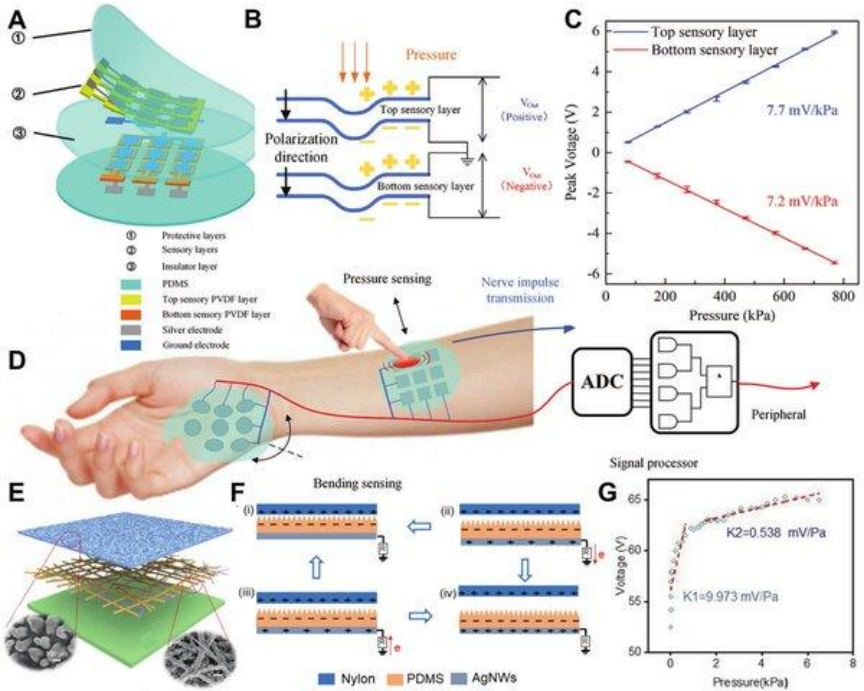
F. Iberite, J. Muheim, O. Akouissi, S. Gallo, G. Rognini, F. Morosato, A. Clerc, M. Kalff, E. Gruppioni, S. Micera*, S. Shokur*. Restoration of natural thermal sensation in upper-limb amputees (2023). Science.

Sensory motor tasks with real-time feedback

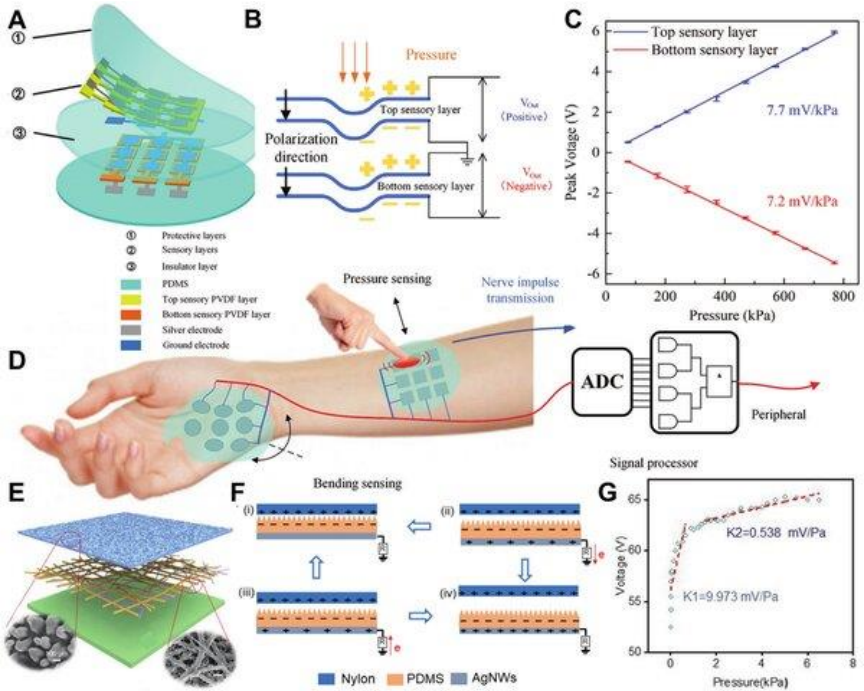


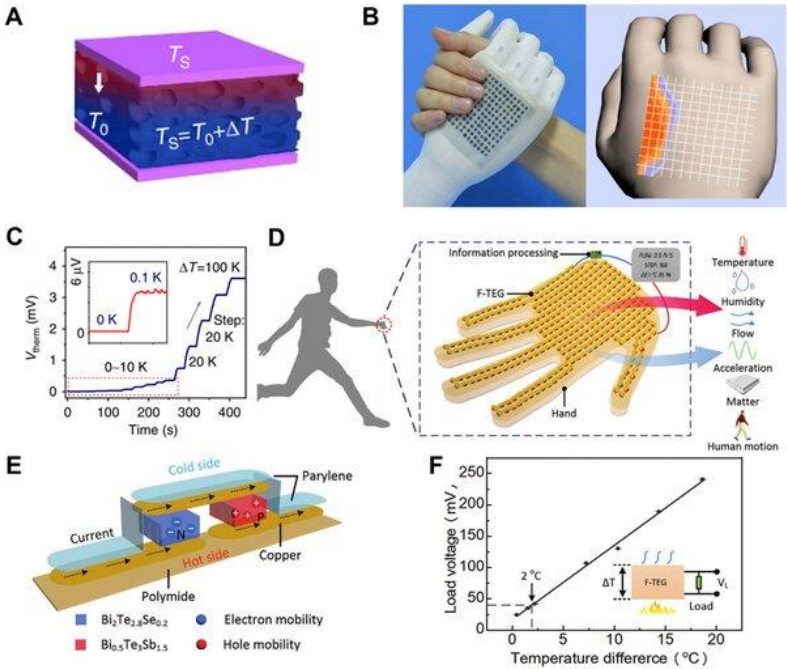
J. Muheim*, F. Iberite*, et al. . Validation of a sensory-motor prosthesis with integrated thermal feedback in a transradial amputee. In 2024. MED.

E-skin



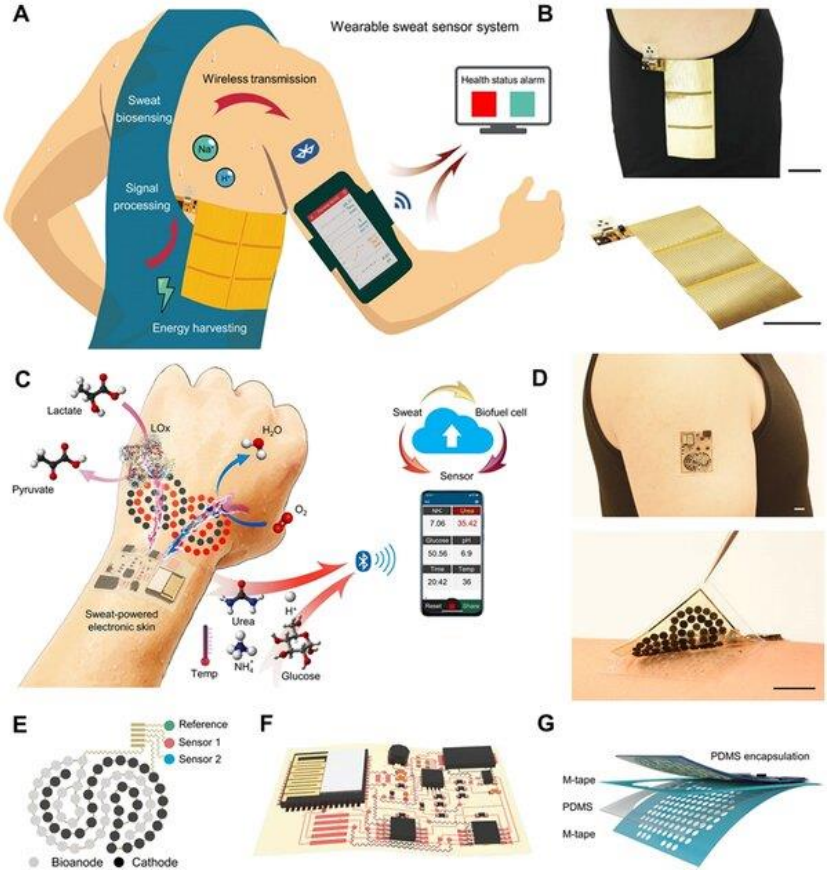
Chen *et al.* 2022 Exploration 2022;2:20210112. https://doi.org/10.1002/EXP.20210112





Chen *et al.* 2022 Exploration 2022;2:20210112. https://doi.org/10.1002/EXP.20210112

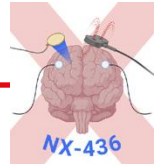
E-skin



Chen *et al.* 2022 Exploration 2022;2:20210112. https://doi.org/10.1002/EXP.20210112

- Peripheral nervous system represents important motor and somatosensory aspects that can be neuromodulated
  - PNS
  - PAS
  - FES

- These neurotechnologies can be applied in clinical conditions
  - e.g., to support functional recovery
  - to restore peripheral functions such as e.g. thermal sensations



Questions?