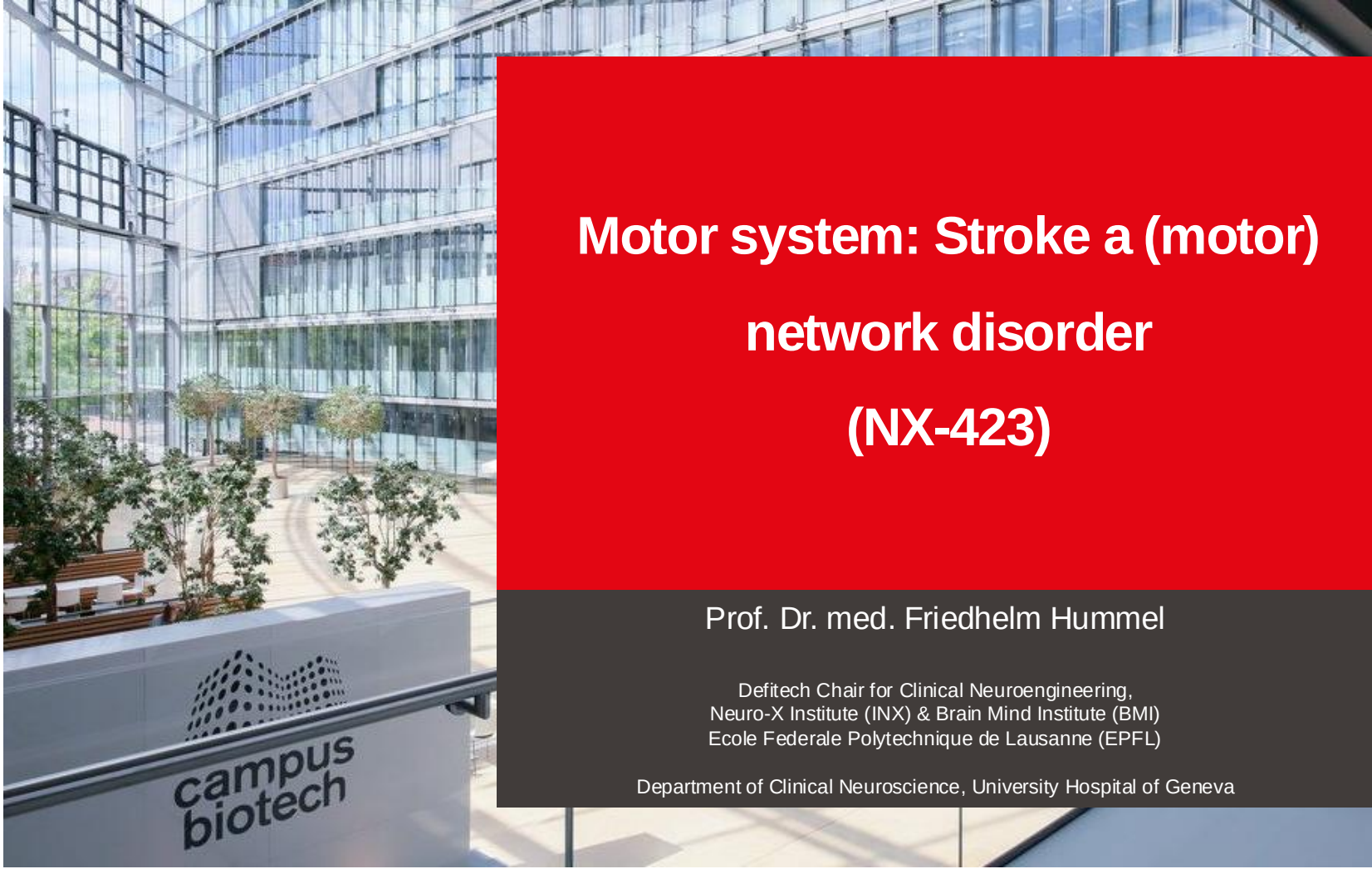
EPFL

Neuro X Institute

HUG Hôpitaux Universitaires Genève

Clinique romande de réadaptation



Motor system: Stroke a (motor) network disorder (NX-423)

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Neuro-X Master:

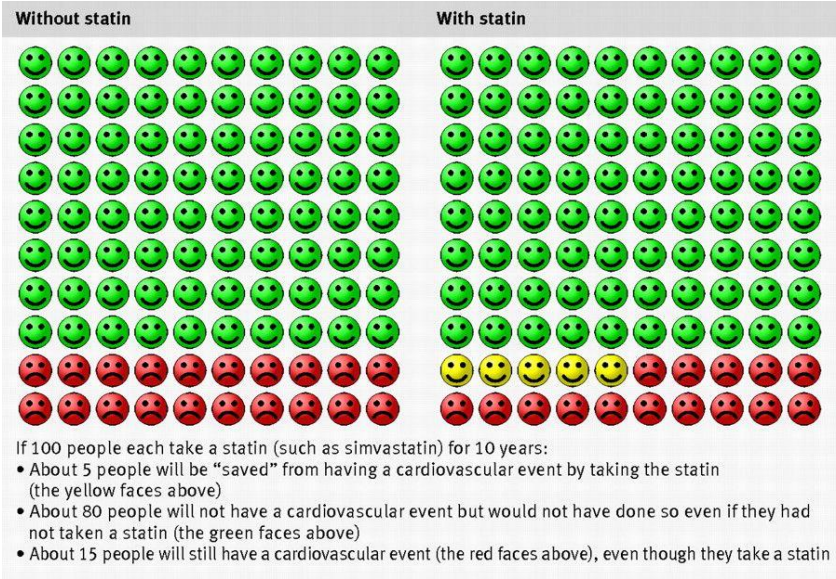
NX-423
Translational neuroengineering

Stroke

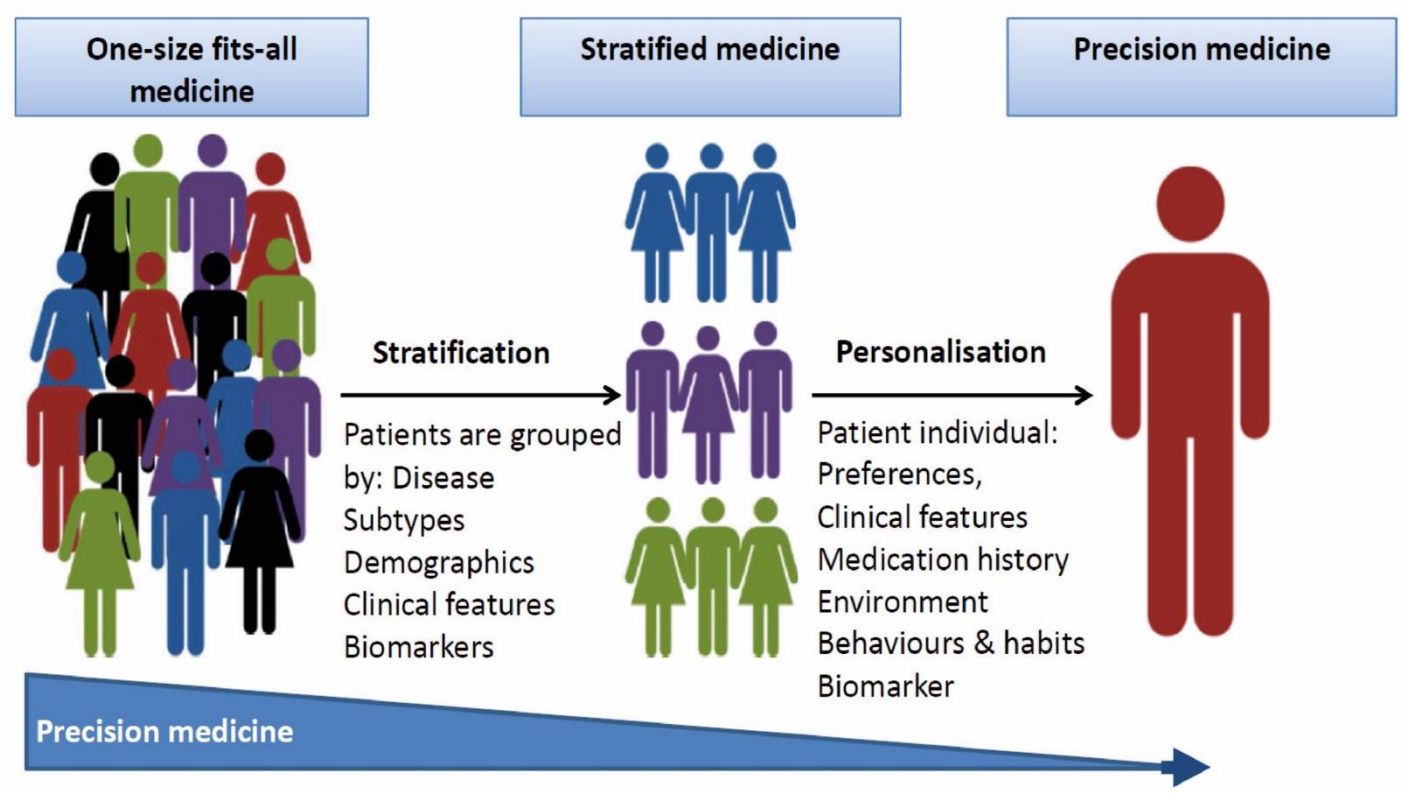
- Epidemiology
- Relevance of personalization
- Acute personalized stroke treatment, example wake-up stroke
- Prediction of stroke recovery trajectory by means of brain connectomics
- Underlying model for target treatment for neurorehabilitation (interhemispheric competition model)
- Different approaches to enhance neurorehabilitation (e.g. BCI, NIBS)
- Means of evaluating behavior/deficits of patients (e.g., SMART Kitchen)

Why do we need personalized health for neurological disorders

- **Ideal Case Scenario Precision Medicine**
  - Good prediction of outcome
  - Good prediction of course of the disorder
  - Good prediction of treatment response
  - Tailored Treatment for the individual patient
  - Ideally NNT = 1



The goal


One-size fits-all medicine
Stratified medicine
Precision medicine
Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers
Personalisation
Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker
Precision medicine

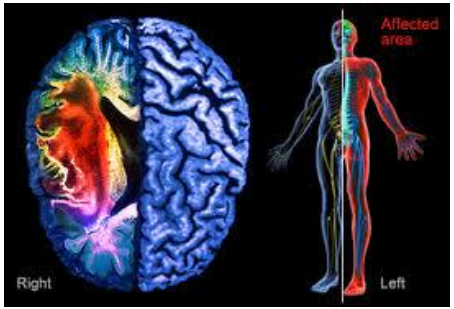
Why do we need personalized health for neurological disorders

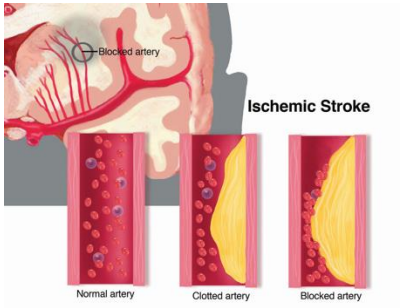
- **Ideal Case Scenario Precision Medicine**
  - Good prediction of outcome
  - Good prediction of course of the disorder
  - Good prediction of treatment response
  - Tailored Treatment for the individual patient
  - Ideally NNT = 1

- **What is needed for this**
  - Excellent understanding of the disorder (mechanisms, course of disorder)
  - Biomarkers to provide prediction
  - Patient-tailored treatment strategies
  - Health technologies
  - Respective health care system for this
  - Ethical framework

Examples of how different neurotechnology can drive personalized precision medicine

- Stroke -





Brain Disorders: ‚Epidemic of the 21st century'

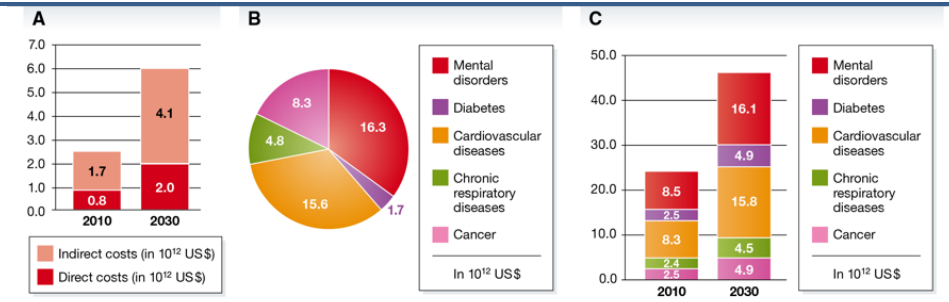


Figure 2. Economic costs of mental disorders in trillion US$ using three different approaches: direct and indirect costs (A), impact on economic growth (B), and value of statistical life (C).
Based on data from [6].

Trautmann *et al.* (2016) *EMBO reports*

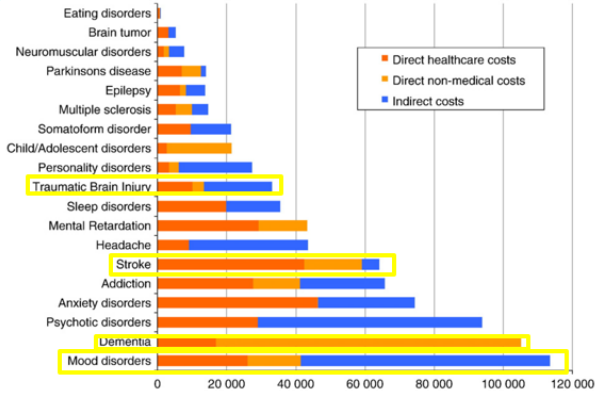


Figure 3 Total cost by disorder and type of cost (€PPP million, 2010), all disorders.

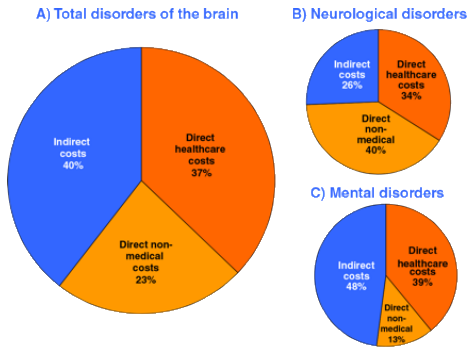
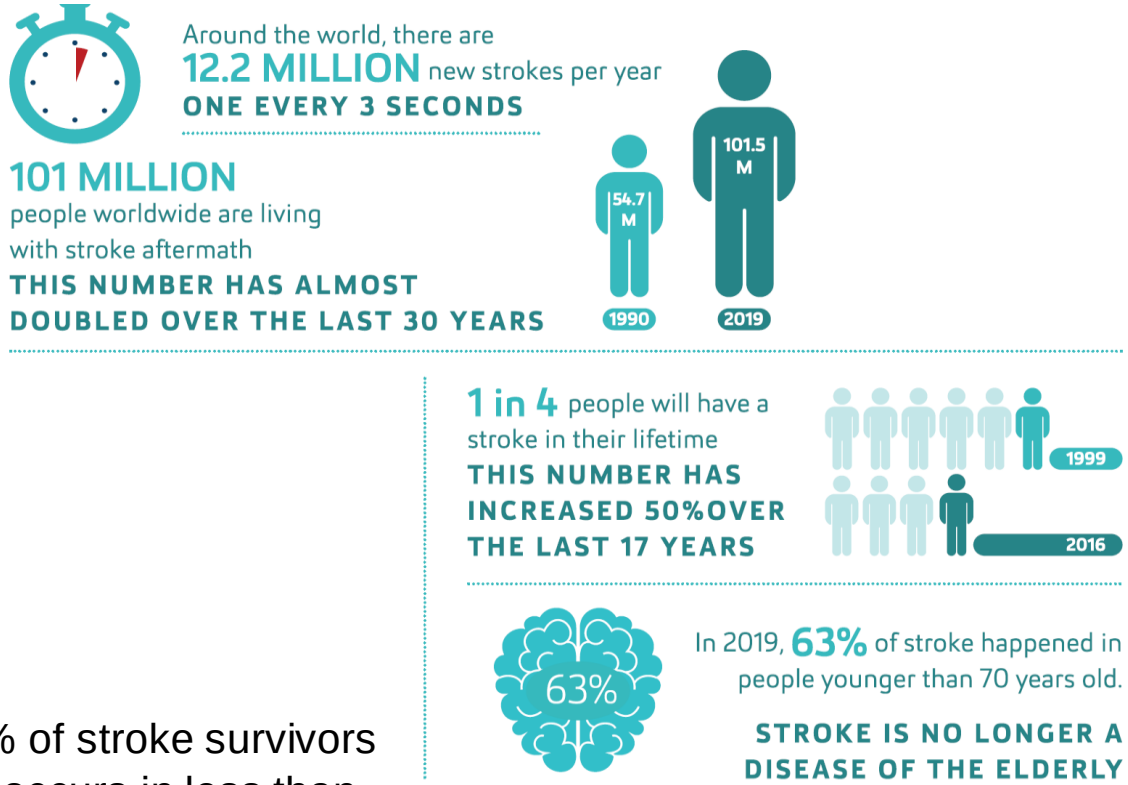


Figure 5 Distribution of costs.

Gustavsson *et al.* (2011) *European Neuropsychopharmacology*

Brain Disorders: **Stroke**

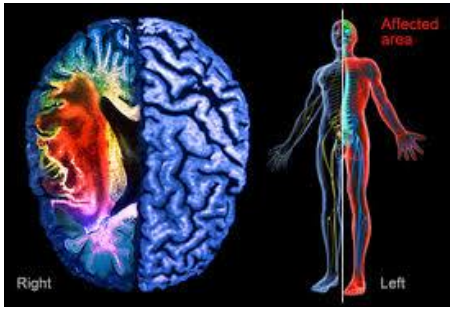


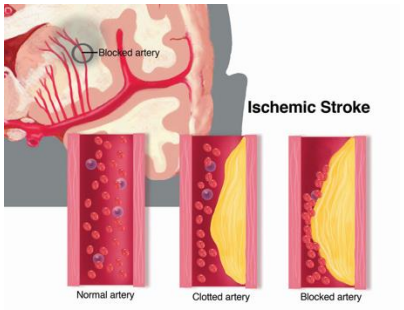
Motor impairment

- Occurs in 50 to 80% of stroke survivors
- Complete recovery occurs in less than 15% of the patients

Feigin *et al.* 2022, Int J Stroke

Example Stroke



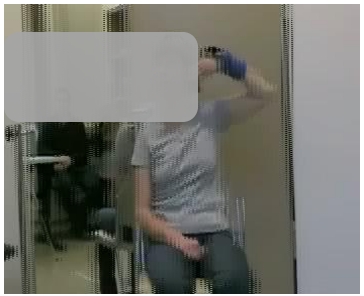


http://www.compelvisuals.com

Only 15-20% fully recover!

Stroke

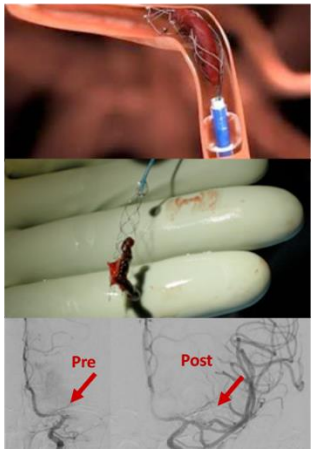
- **85%** with **persisting** symptoms
- only **15%** fully recover
- >**20%** of patients age <**55a!**



- **Impact on daily life**

Two main treatment areas: acute vs recovery treatment

ACUTE

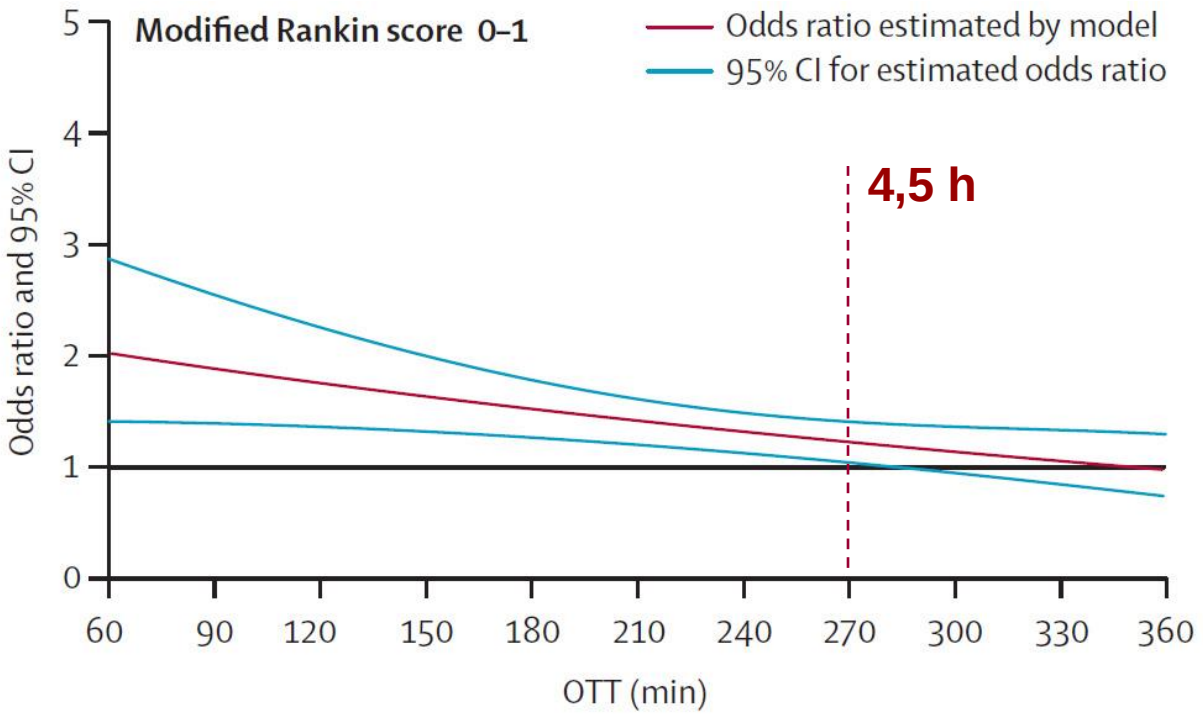


CHRONIC

Raffin & Hummel (2018) *Neuroscientist*

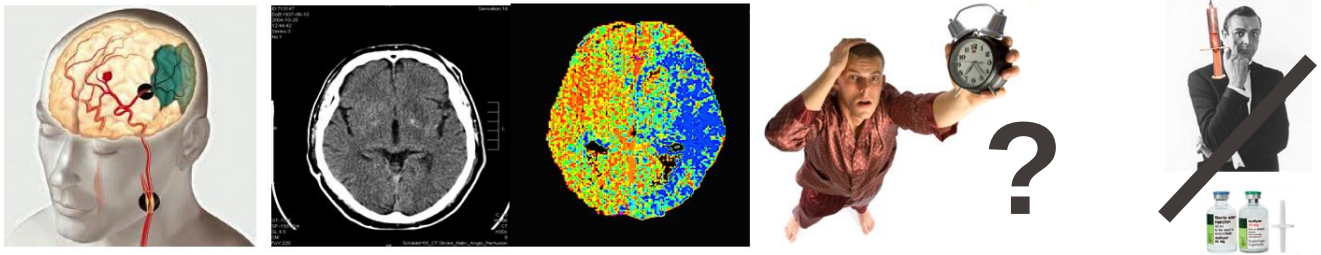
The relevance of time for the success of thrombolysis?

Towards personalized prediction of outcome



Lees et al. Lancet 2010

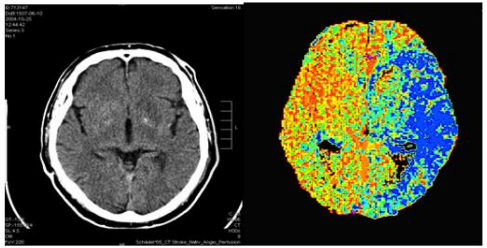
Problem



- The **personalization** of treatment here is **based** on the (**subjective**) information when the **symptoms started**
- **Problem**: start of the symptoms is often **not** clear (e.g. stroke during sleep (20%), patient cannot communicate or did not him/herself realize the symptoms)

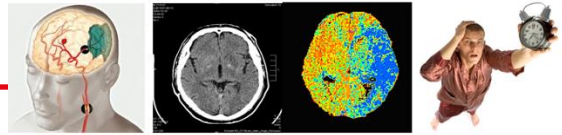
==> **no** treatment for these patients (thrombolysis)?

Acute trials: example wake-up stroke

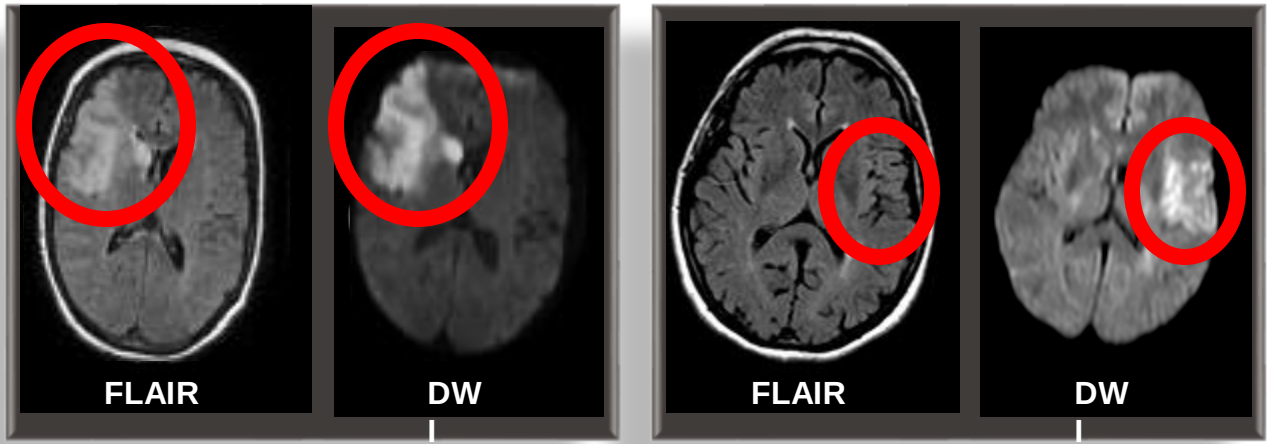



?


Can this problem be solved by applying technology?

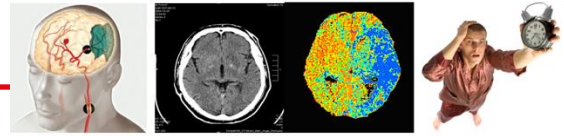


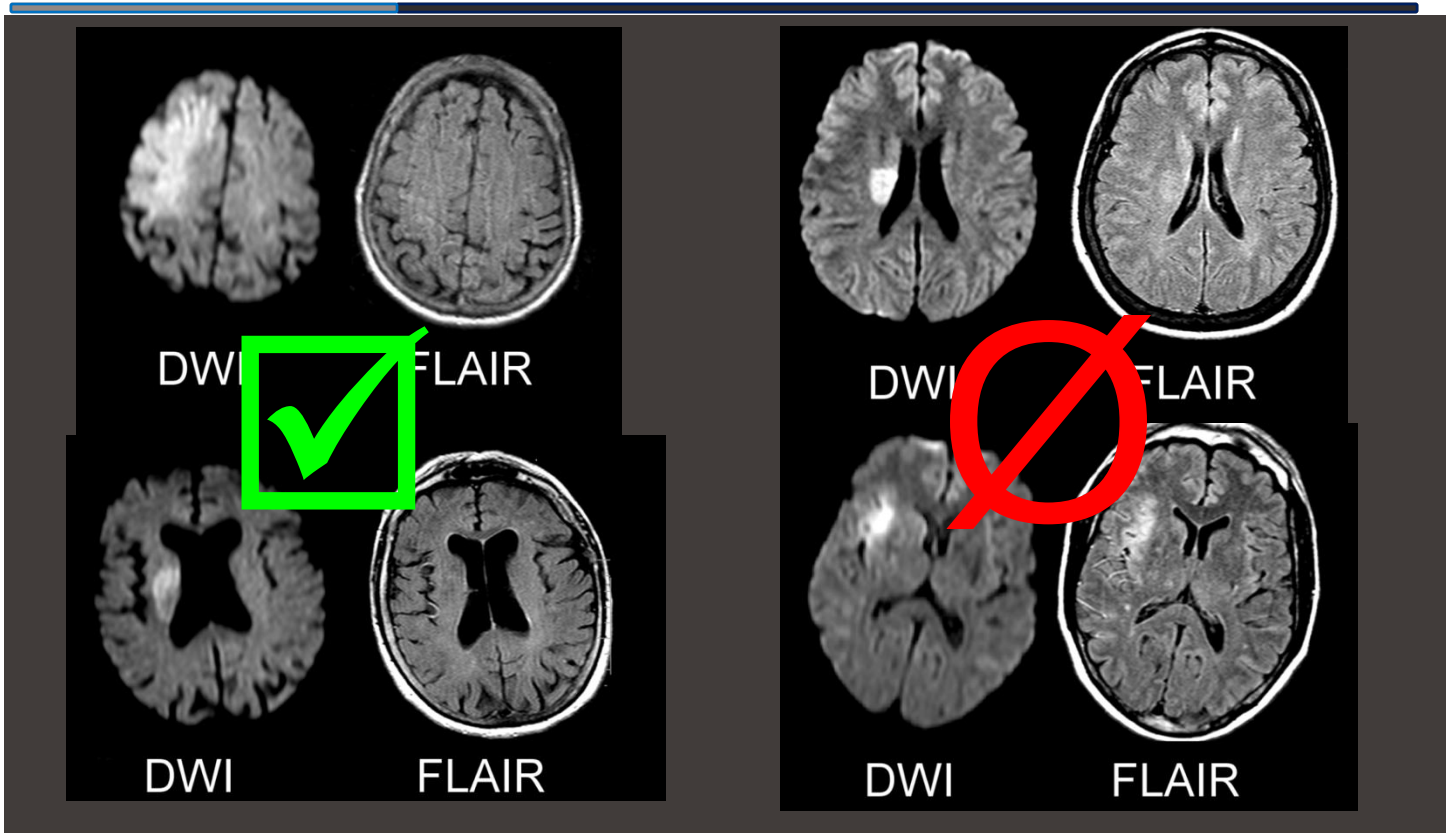
- FLAIR persistent damage, DWI probable reversive damage



- DWI-FLAIR-Mismatch = patients might be within a time window for thrombolysis (<4.5h)?

Tissue clock?




DWI
FLAIR
DWI
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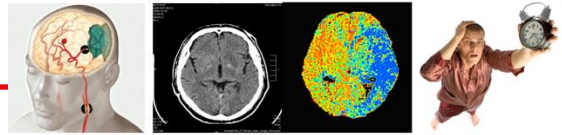
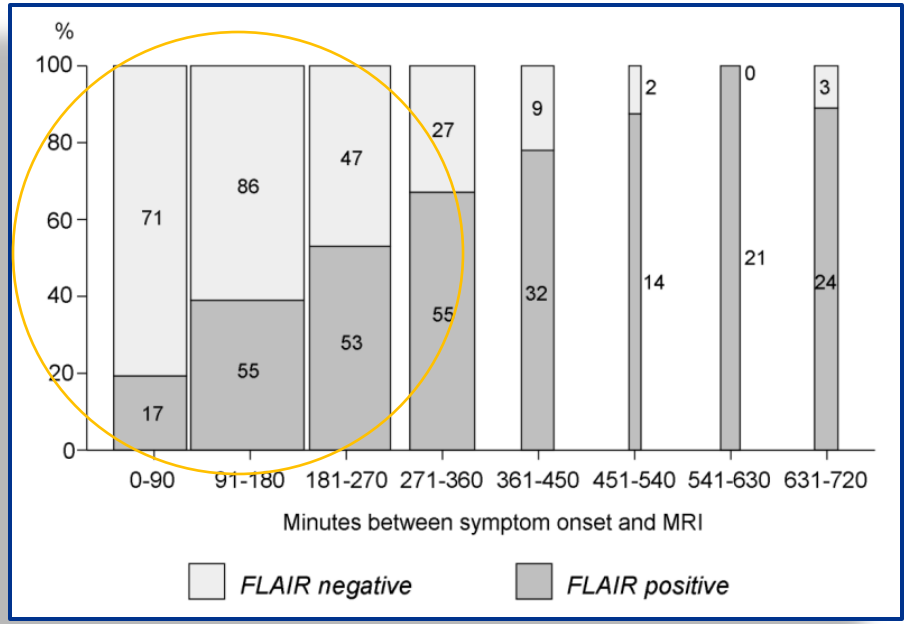
DWI
FLAIR
DWI
FLAIR

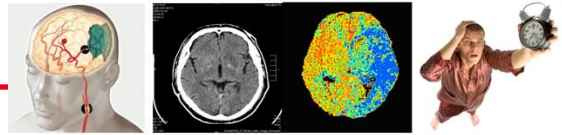


Existing big regular clinical data sets (n=543)

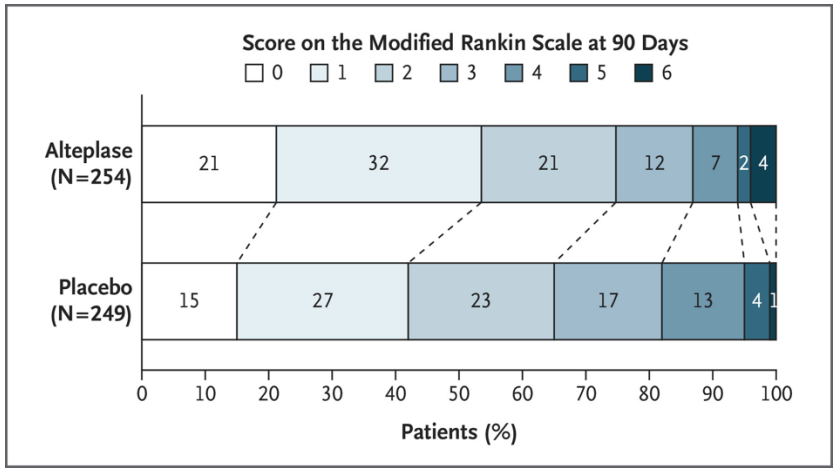
- search for a tissue clock -



Thomalla *et al.* Lancet Neurol 2011



Translation into a large clinical treatment trial: Wake-Up trial

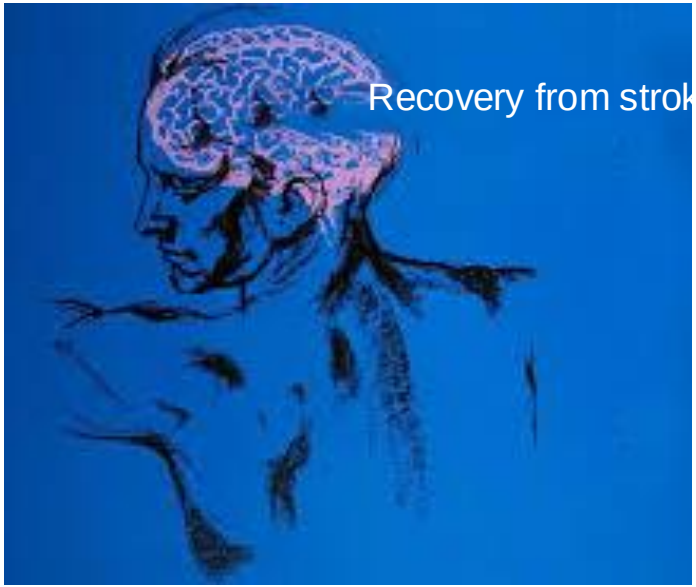


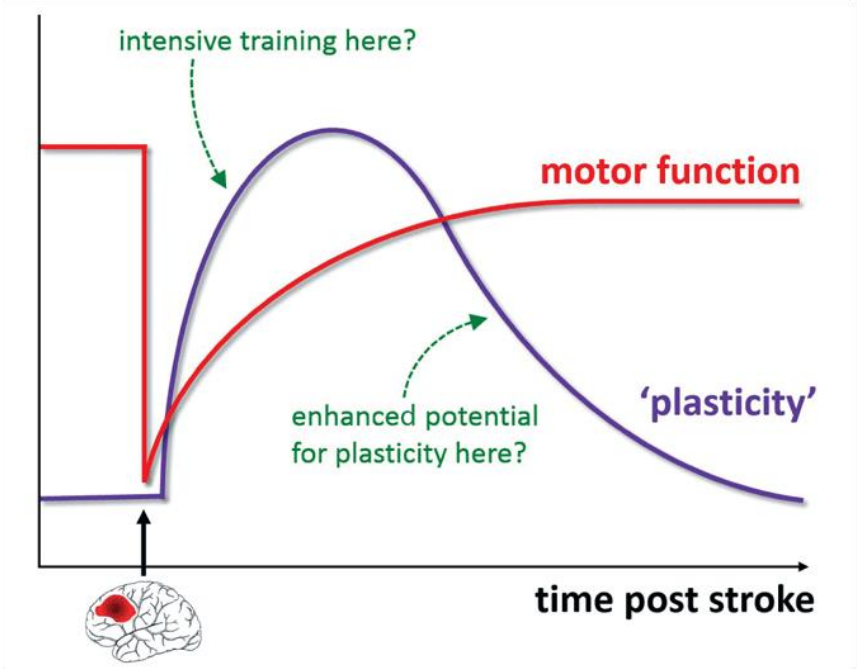
Thomalla et al. (2018) *NEJM*

Successful extension of thrombolysis based on a tissue clock (MRI)

- Using (neuro-) technology, here advanced MRI imaging, allows to provide a '**tissue clock**' to achieve **patient specific** information about the stroke
- This allows **patient-tailored** treatment
- Enhances the **individual** access to an approved treatment in a **safe** and **effective** way

Time course of natural recovery

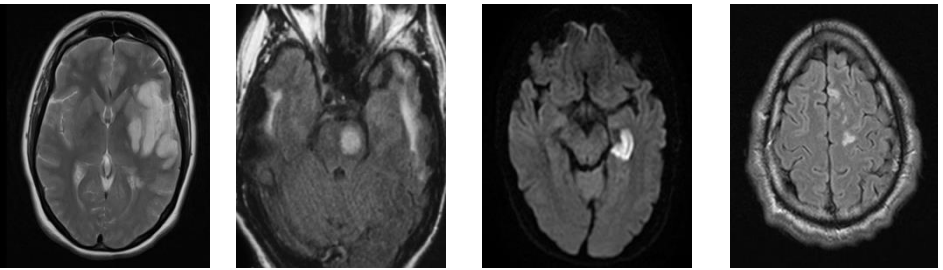




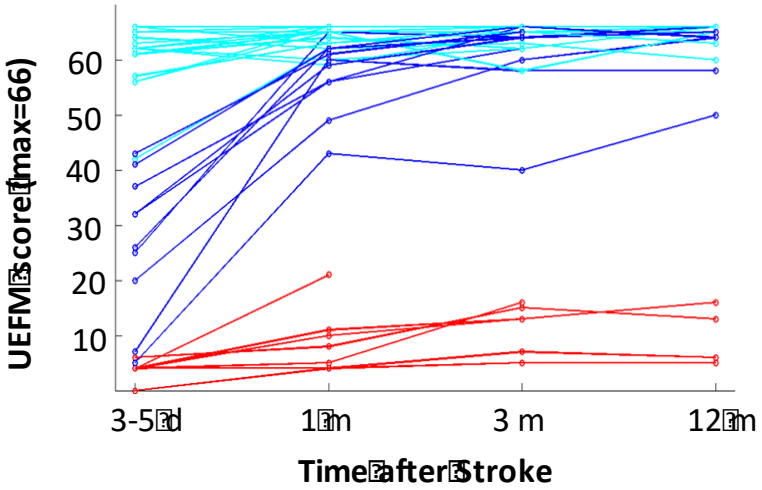
Raffin&Hummel 2018

Time course of natural recovery

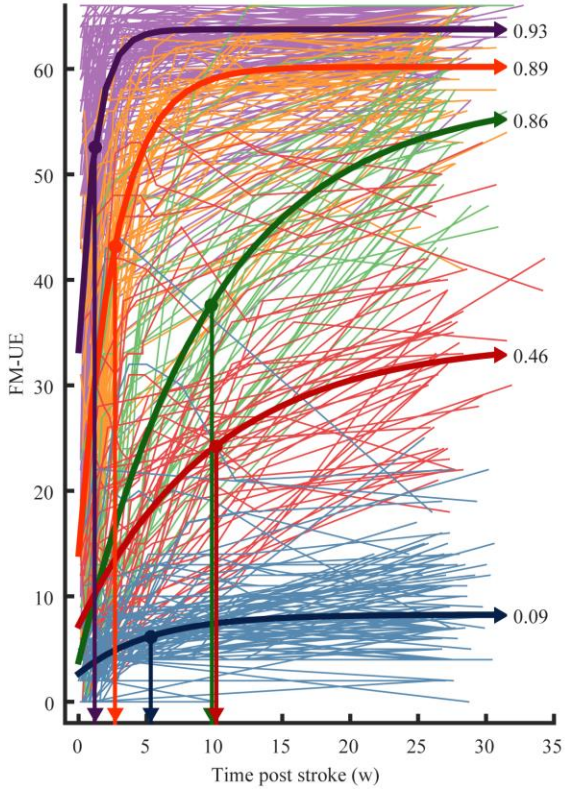
Heterogeneity in lesion location



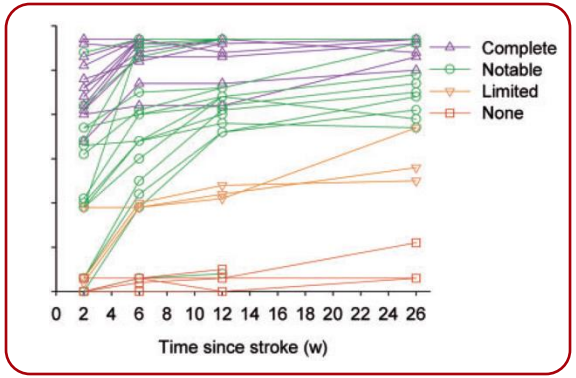
Heterogeneity in recovery



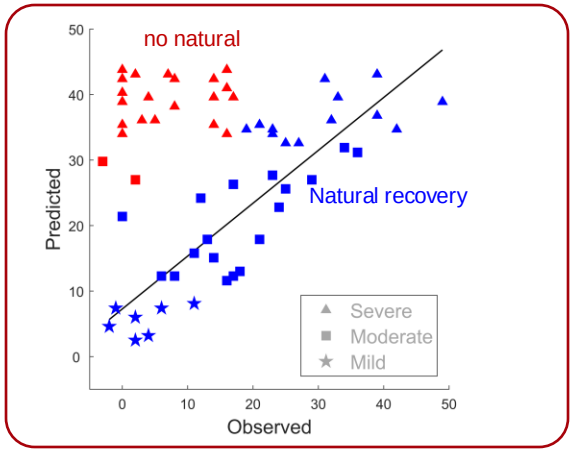
Natural recovery is heterogenous – can we predict it?



Van der Vliet *et al.* (2020) Ann Neurol

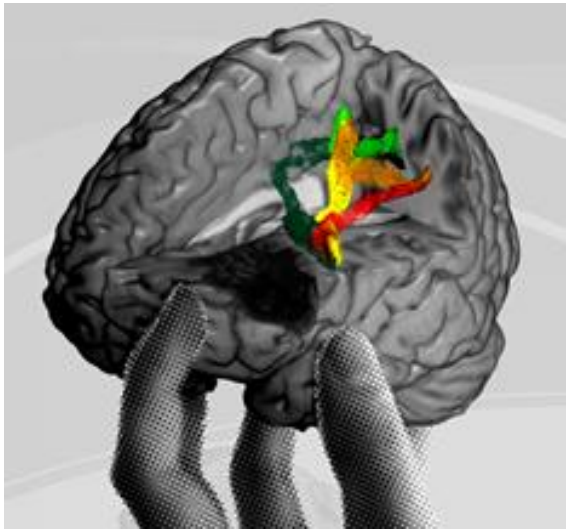


Stinear *et al. (*2011) Lancet Neurol

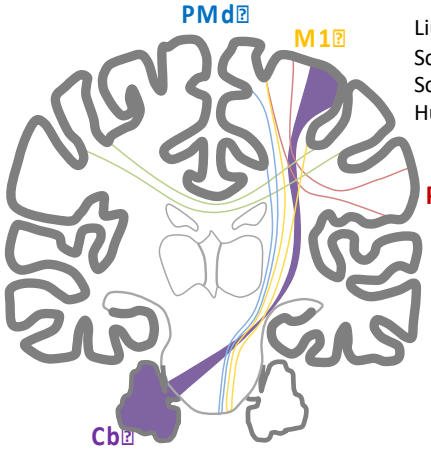


Koch *et al. (*2021) Brain

Stroke – a network disorder



Boenstrup *et al.* 2015 **RNN**
Cheng *et al.* 2012 **J Cereb Blood Flow Metab**



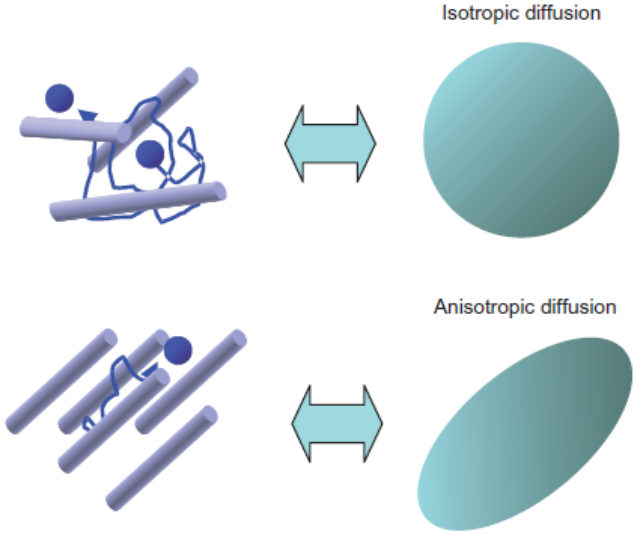
Liuzzi *et al.* 2014 **Neurology**
Schulz *et al.* 2014 **NeuroImage Clin**
Schulz *et al.* 2012 **Stroke**
Hummel *et al.* 2009 **Neurology**

Schulz *et al.* 2015 **Brain**
Schulz *et al.* 2016 **Stroke**
Schulz *et al.* 2017 **Stroke**

Schulz *et al.* 2015 **NeuroImage Clin**
Schulz *et al.* 2017 **Cerebral Cortex**

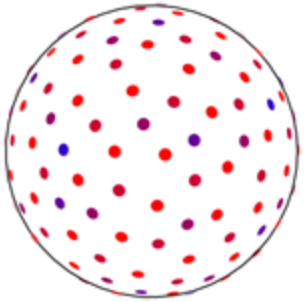
- **Brain: a network with well orchestrated hubs and interactions for optimal functioning**
- **Stroke is a network disease** (Schulz *et al.* 2012, 2015, 2017, for review Koch & Hummel 2017; Grefkes & Fink 2014)
- **Massive changes and reorganization during the course of recovery**

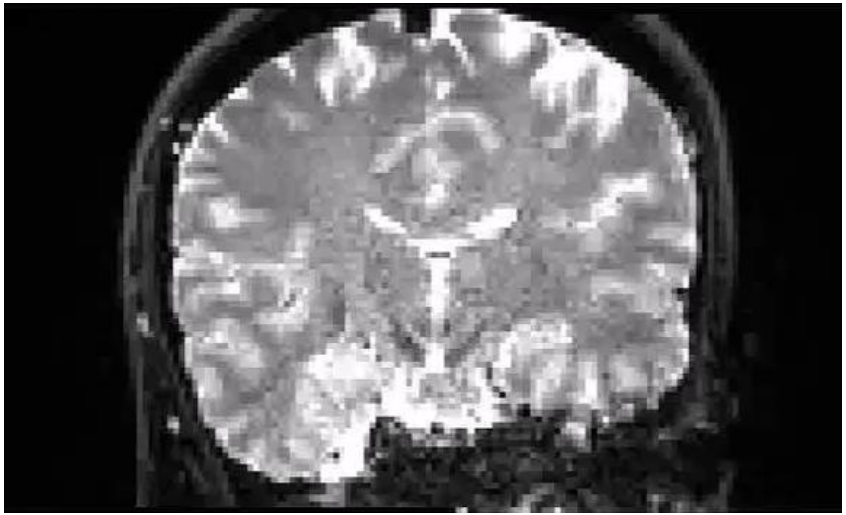
Diffusion weighted imaging (DWI)



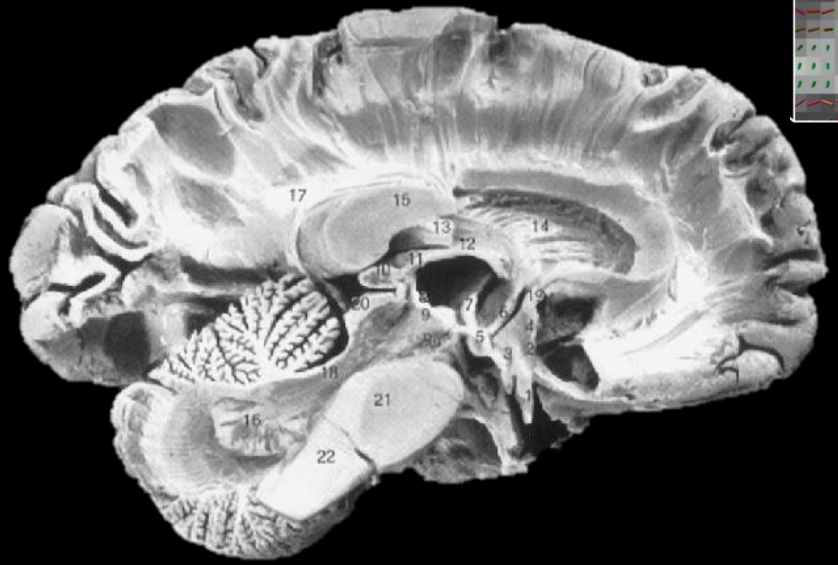
Mori 2014

Diffusion vector scheme

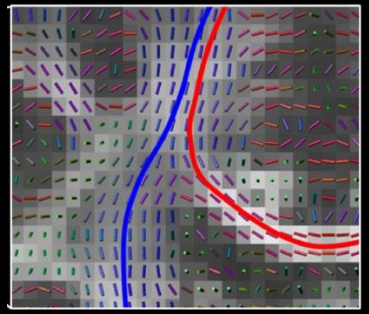


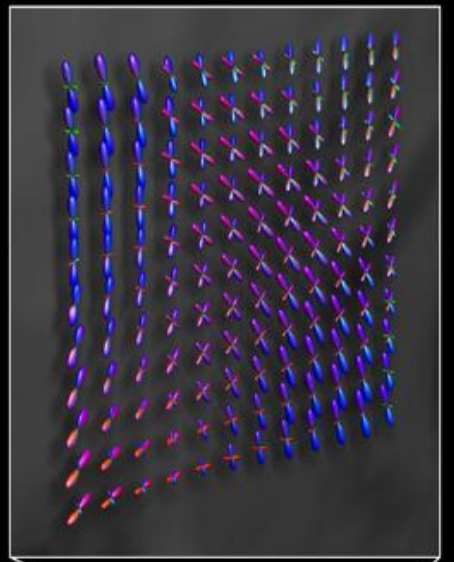


1. Tractography

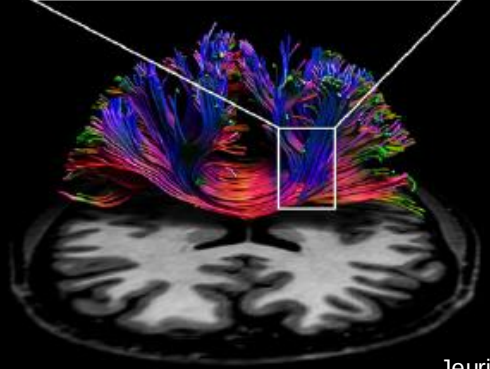


Huber 1971



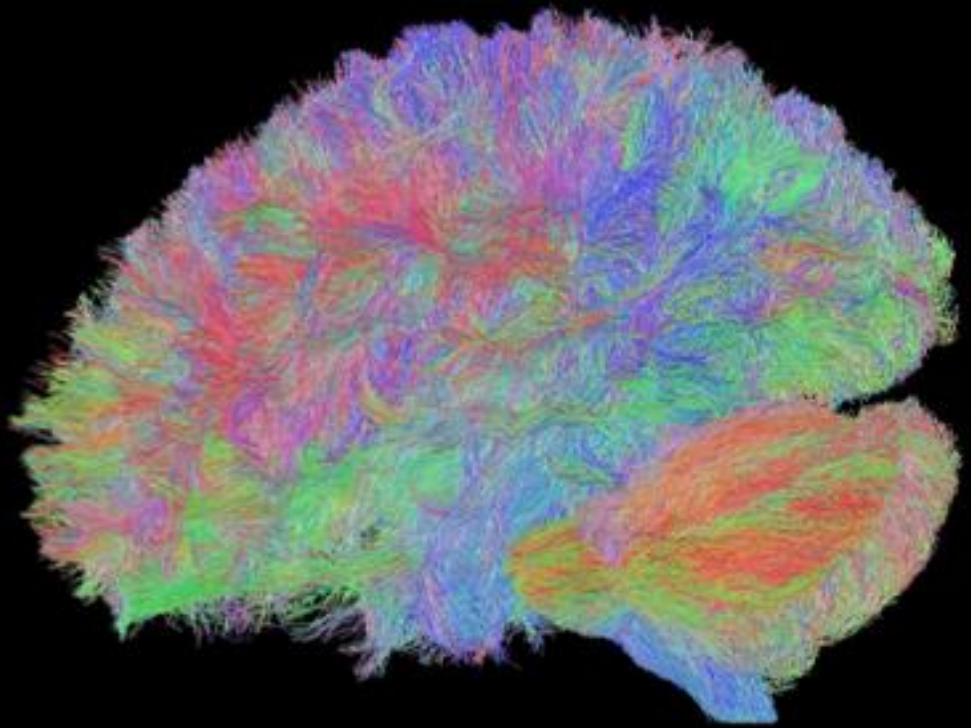


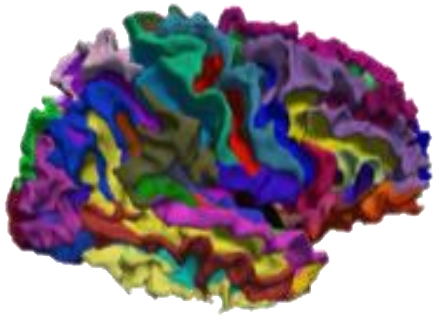
Non invasive



Jeurissen et al. 2019

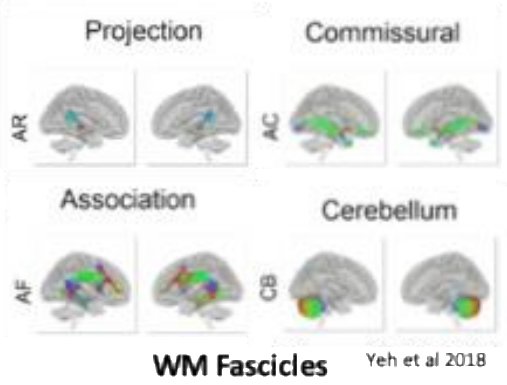
Structural Imaging - connectomics





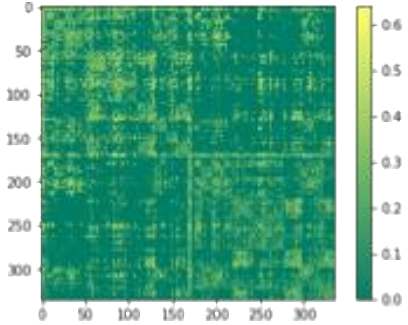
Brain parcellation

Tractography



WM Fascicles

Yeh et al 2018

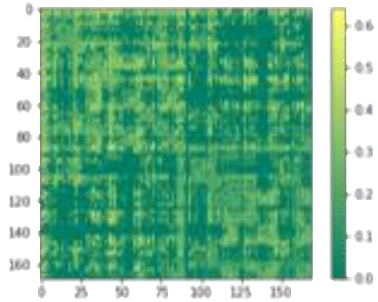


Connectome

Koch *et al.* **Brain** (2021)

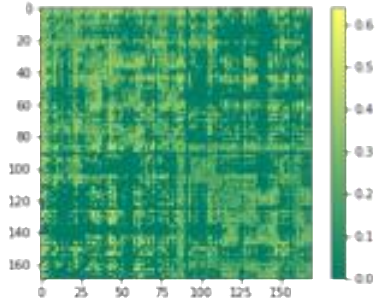
Can we predict Fitter and non Fitter using the connectome?

Initial Connectome 3 weeks



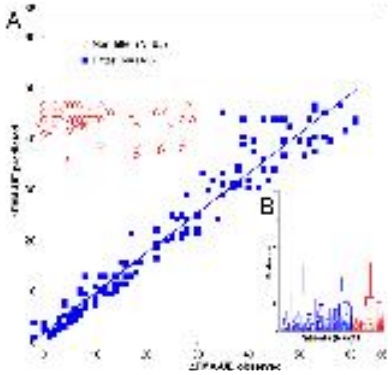
Residual/ Prerequisit

Change in Connectome 3months – 3 weeks



Degeneration/ Reorganization

SVM - Classifier

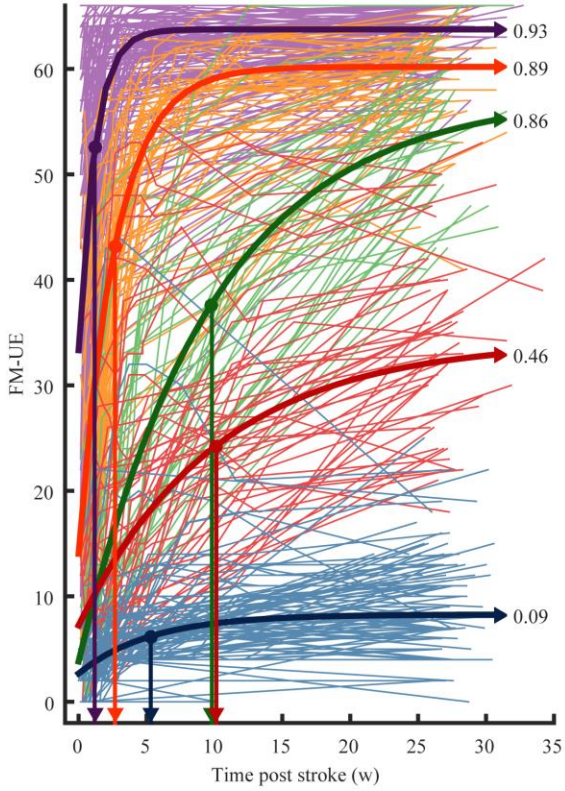


Non fitters

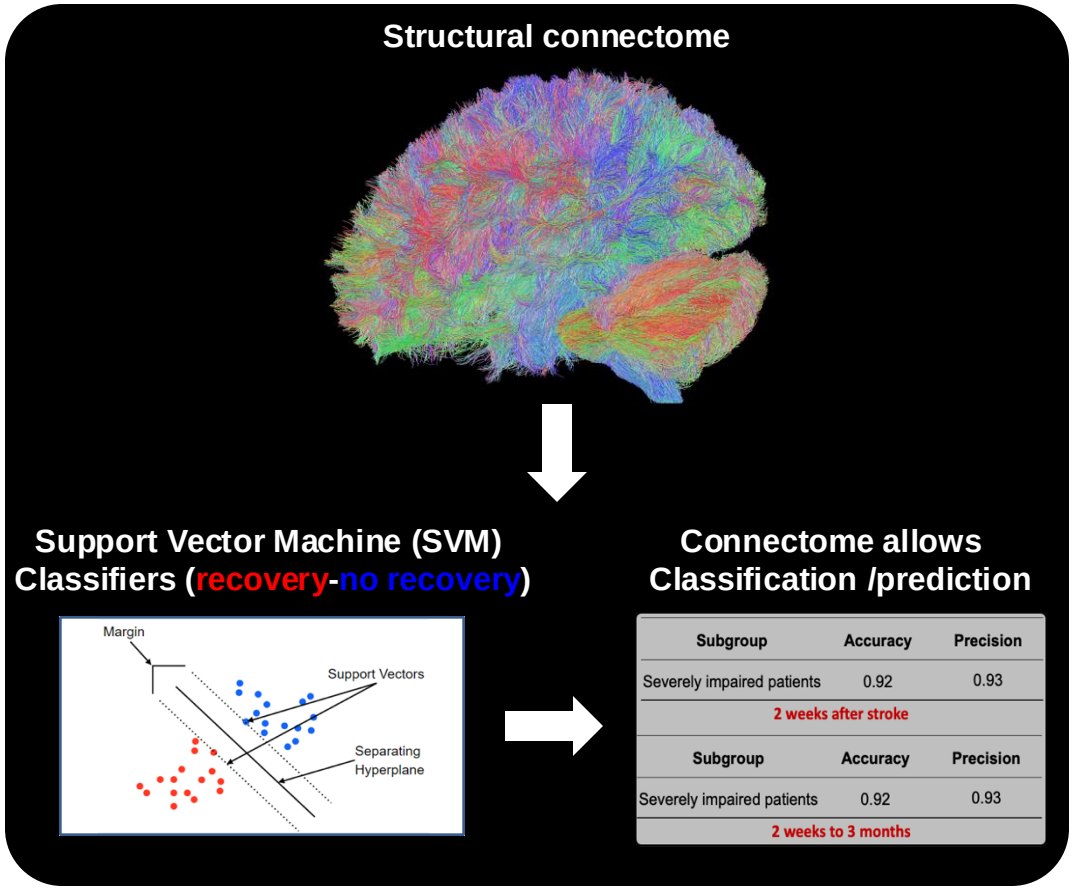
vs.

Fitters

Natural recovery - prediction



Van der Vliet *et al.* (2020) Ann Neurol



Koch *et al.* (2021) Brain

Personalized technology to support Neurorehabilitation/Recovery

Multifocal stimulation
(Wessel *et al.* 2023; Salamanca *et al.* 2021; Raffin *et al.* 2020)

Stimulation of deep brain structures
Striatum (Wessel, Beanato *et al*. 2023 Nat Neuroscience)

Spinal cord stimulation (Cervical)
(Powell *et al.* Nat Med 2023)

https://healthinfo.healthengine.com.au

Intensive rehabilitative training

+

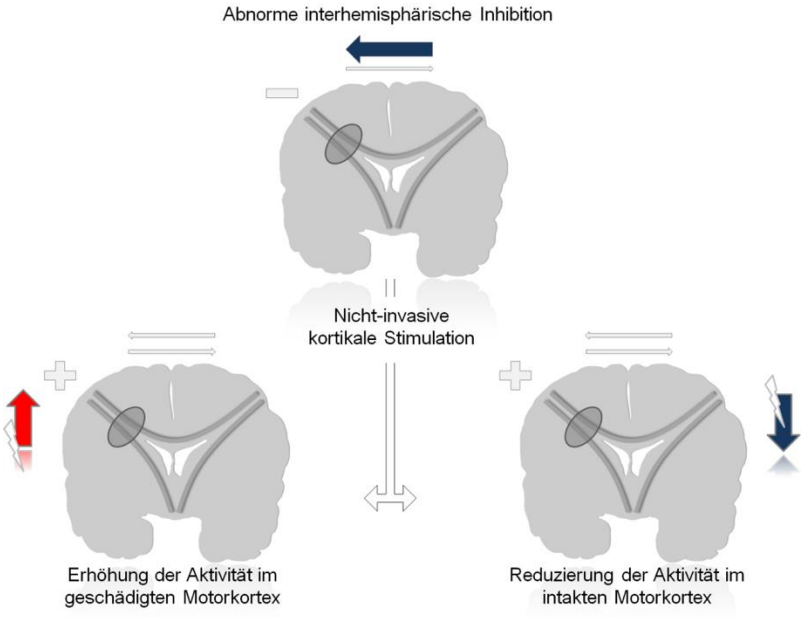
Gamifaction (Ozgur *et al.* 2022)

+

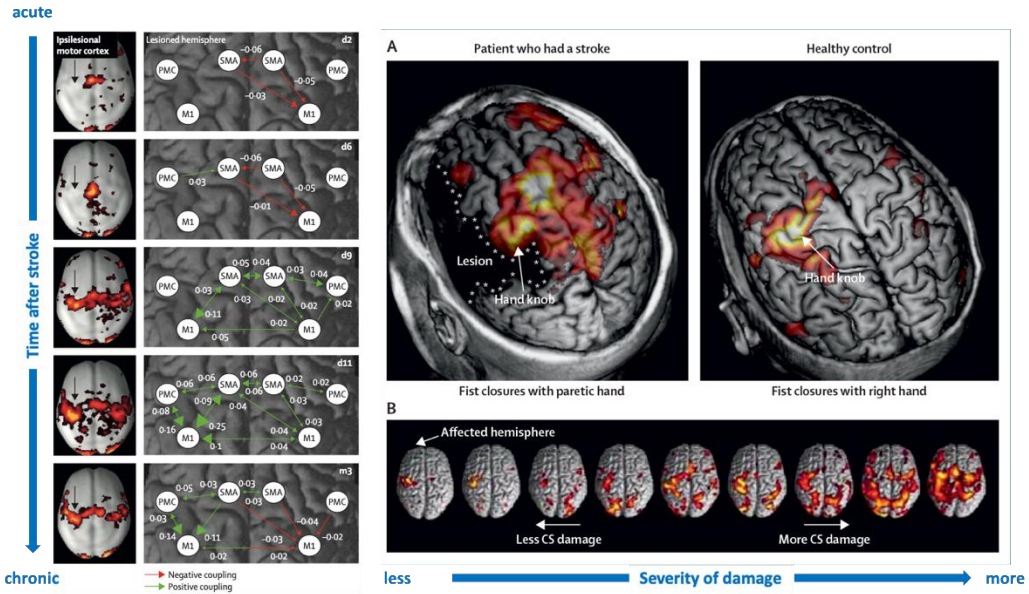
Combination with neurotechnology
(Bigoni *et al.* 2022 Front Neurol; Bigoni *et al.* 2023 Med)

Micera *et al.* (2020) Neuron; Coscia *et al.* (2019) Brain

Motor Recovery – interhemispheric competition model

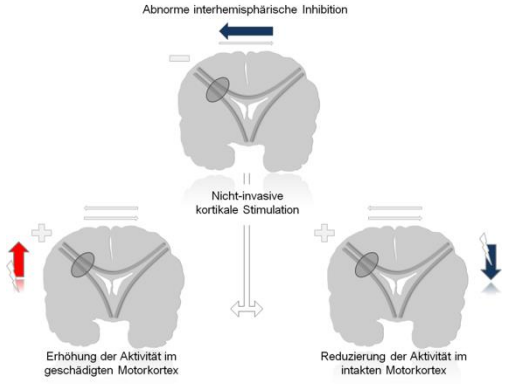


For review Di Pino *et al.* (2014); Hummel & Cohen (2006)



For review Guggisberg *et al.* (2019); Koch *et al.* (2017); Grefkes & Fink (2014)

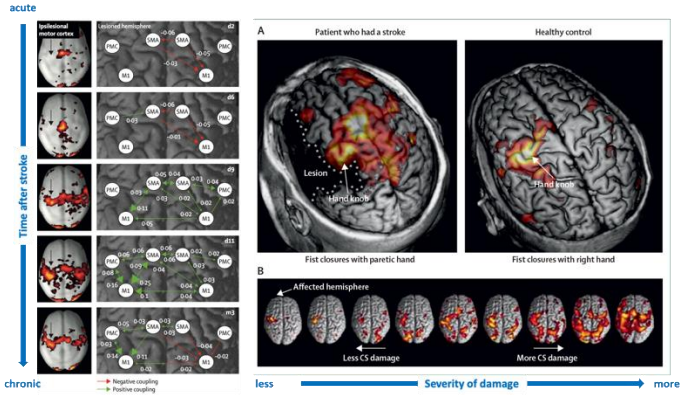
Motor Recovery – interhemispheric competition model



For review Di Pino *et al.* (2014); Hummel & Cohen (2006)

Intact hemisphere **impairs** residual function/recovery
- maladaptive changes
- enhanced inhibitory impact on the lesioned hemisphere

Intact hemisphere **supports** residual function/recovery
- by additional 'computational' power
- enhanced connectivity with the lesioned hemisphere
- by uncrossed projections



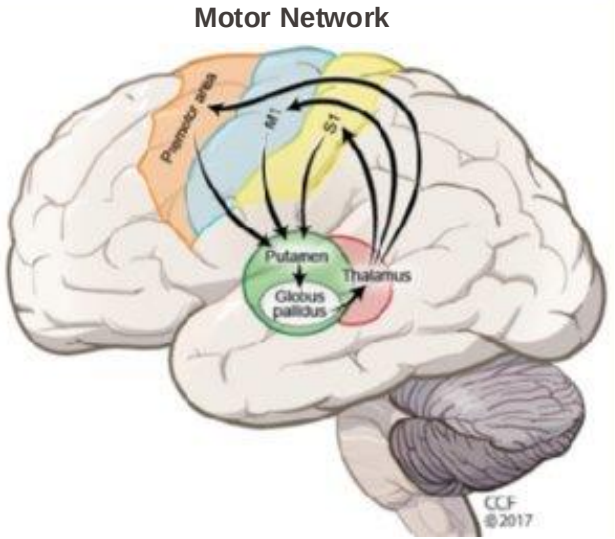
For review Guggisberg *et al.* (2019); Koch *et al.* (2017); Grefkes & Fink (2014)

Impacts massively on the **NIBS strategy** (inhibitory vs. facilitatory)

Knowledge of **individual** functional role will lead NIBS intervention, more homogenous and maximized effects of NIBS

For review Lefaucheur (2020); Hummel *et al.* (2008)

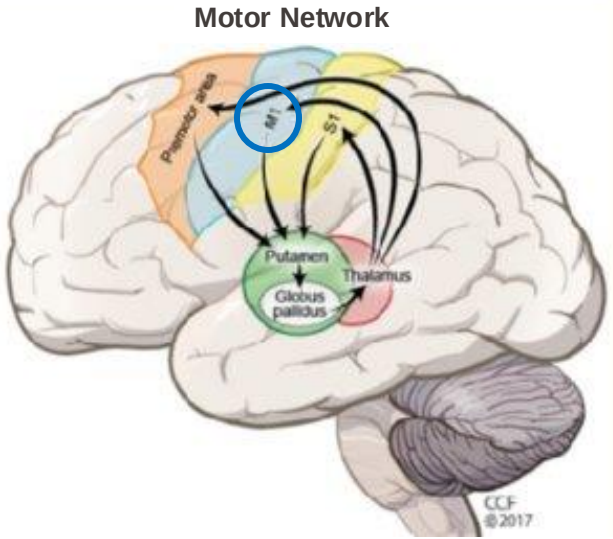
Motor, cognitive functions – cortico-subcortical processing



e.g., Maceira-Elvira *et al.* 2022 Sci Adv, Grover *et al.* 2022 Nat Nsc; Zimerman *et al.* 2013 Ann Neurol; Draaisma *et al.* 2022 BrainStimulation

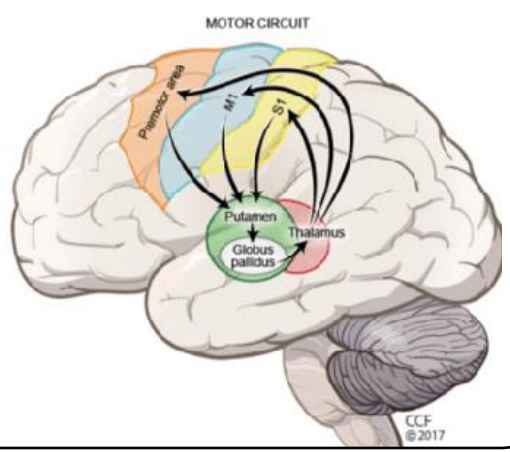
Motor, cognitive functions – cortico-subcortical processing

Non-invasive brain stimulation

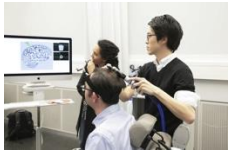


e.g., Maceira-Elvira *et al.* 2022 Sci Adv, Grover *et al.* 2022 Nat Nsc; Zimerman *et al.* 2013 Ann Neurol; Draaisma *et al.* 2022 BrainStimulation

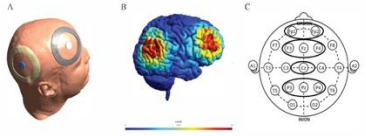
Motor functions – non-invasive brain stimulation (NIBS)



monofocal cortical NIBS

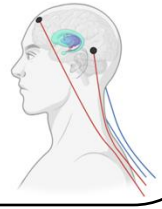


multifocal cortical NIBS



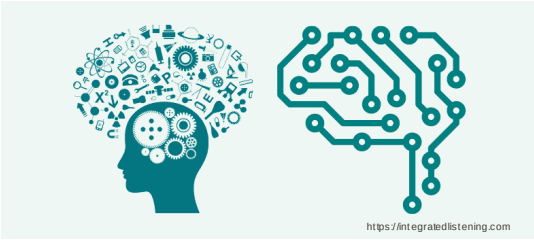
multidomain stimulation
(efferent-afferent)

non-invasive deep brain stimulation (nDBS)



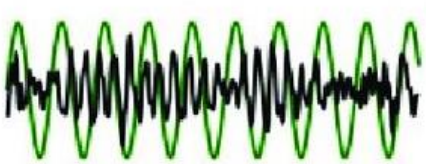
Motor, cognitive functions – non-invasive brain stimulation (NIBS)

Neuroplasticity



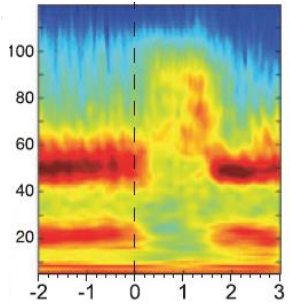
Bevilacqua *et al.* (2025) Brain
Beanato, Moon *et al. (2024)* Science Advances
Wessel, Beanato *et al.* (2023) Nature Neuroscience
Maceira-Elvira *et al.* (2022) Science Advances
Wessel *et al.* (2023) Cerebellum
Wessel *et al*. (2021) Sci Rep
Zimerman *et al*. (2014) Ann Neurol
Hummel *et al.* (2005) Brain

Neuronal entrainment



Raffin *et al.* under review
Bevilacqua *et al.* (2024) BrainStimulation
Draaisma *et al.* (2022) BrainStimulation
Salamanca *et al.* (2021) NeuroImage
Wessel *et al.* (2020) Sci Rep
Sauseng *et al.* (2009) Curr Biol
Plewnia *et al.* (2008) EJN

Interference

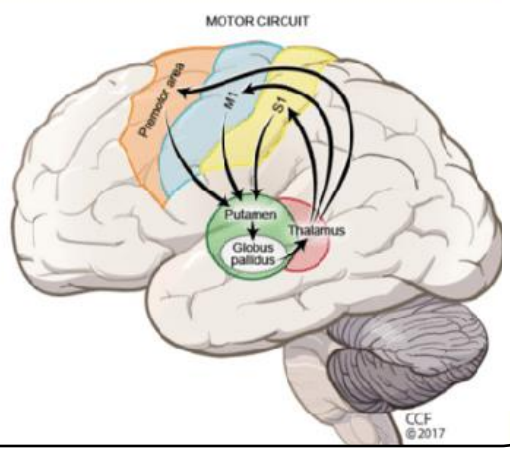


Vassiliadis *et al.* (2024) Nature Hum Beh
Renzi *et al.* (2013) J Cogn Neurosci
Liuzzi *et al*. (2010) Curr Biol
Fridman *et al.* (2004) Brain

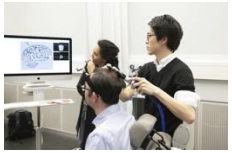
Multi-technology

Bigoni *et al.* (2023) MED
Bigoni *et al.* (2022) Front Neurol

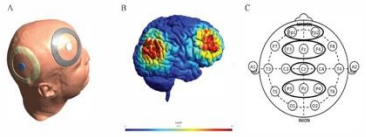
Motor functions – non-invasive brain stimulation (NIBS)



monofocal cortical NIBS



multifocal cortical NIBS



multidomain stimulation (efferent-afferent)

non-invasive deep brain stimulation (nDBS)

doi:10.1093/brain/awh369 *Brain* (2005), **128**, 490–499

Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke

Friedhelm Hummel,[1,2] Pablo Celnik,[1] Pascal Giraux,[1] Agnes Floel,[1] Wan-Hsun Wu,[1] Christian Gerloff[2] and Leonardo G. Cohen[1]

Rapid Review

Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?

Friedhelm C Hummel, Leonardo G Cohen

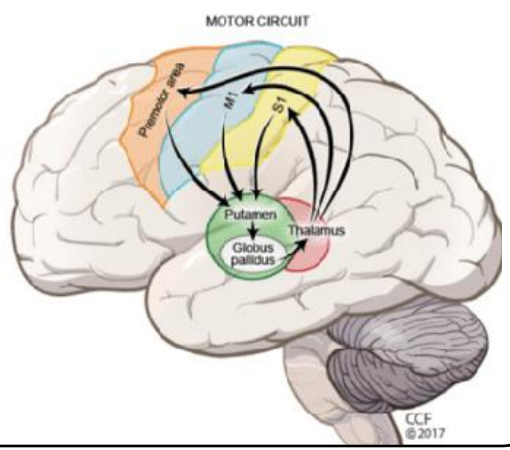
Lancet Neurol 2006; 5: 708–12

REVIEWS

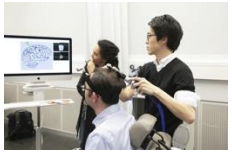
Modulation of brain plasticity in stroke: a novel model for neurorehabilitation

Giovanni Di Pino, Giovanni Pellegrino, Giovanni Assenza, Fioravante Capone, Florinda Ferreri, Domenico Formica, Federico Ranieri, Mario Tombini, Ulf Ziemann, John C. Rothwell and Vincenzo Di Lazzaro

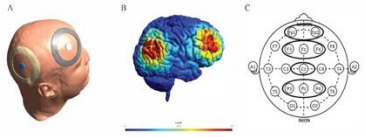
Motor functions – non-invasive brain stimulation (NIBS)



monofocal cortical NIBS



multifocal cortical NIBS



multidomain stimulation (efferent-afferent)

non-invasive deep brain stimulation (nDBS)

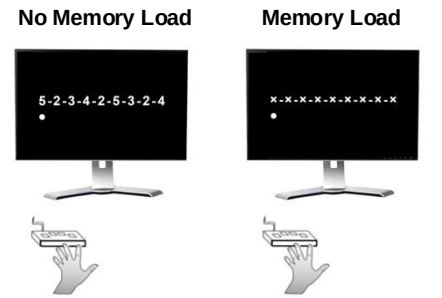
Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Targeting the frontoparietal network using bifocal transcranial alternating current stimulation during a motor sequence learning task in healthy older adults

L.R. Draaisma [a, b], M.J. Wessel [a, b, c], M. Moyne [a, d], T. Morishita [a, b], F.C. Hummel [a, b, d, *]



NeuroImage 240 (2021) 118299

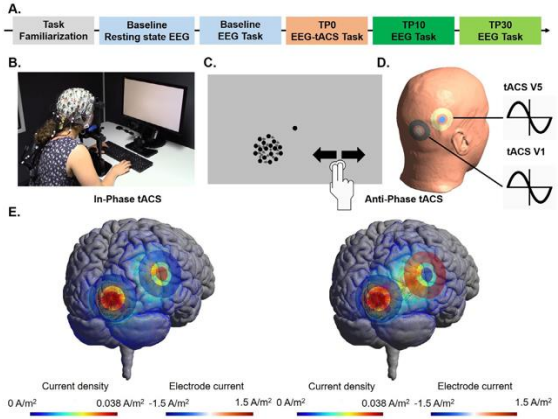
Contents lists available at ScienceDirect

NeuroImage

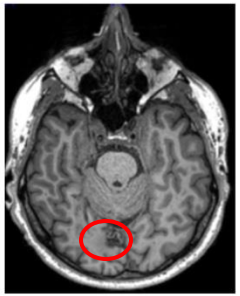
journal homepage: www.elsevier.com/locate/neuroimage

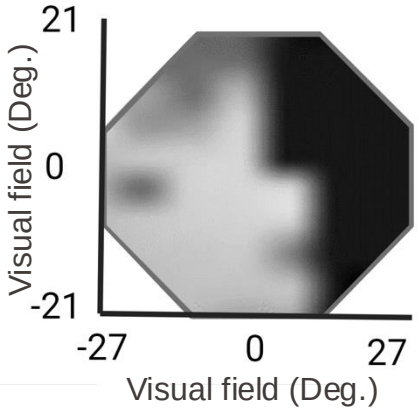
Enhancing visual motion discrimination by desynchronizing bifocal oscillatory activity

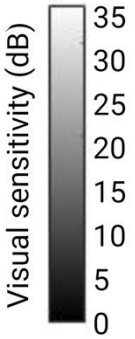
Roberto F. SALAMANCA-GIRON [a,b], Estelle RAFFIN [a,b], Sarah B. ZANDVLIET [a,b], Martin SEEBER [c], Christoph M. MICHEL [c,d], Paul SAUSENG [d], Krystel R. HUXLIN [e], Friedhelm C. HUMMEL [a,b,f,*]

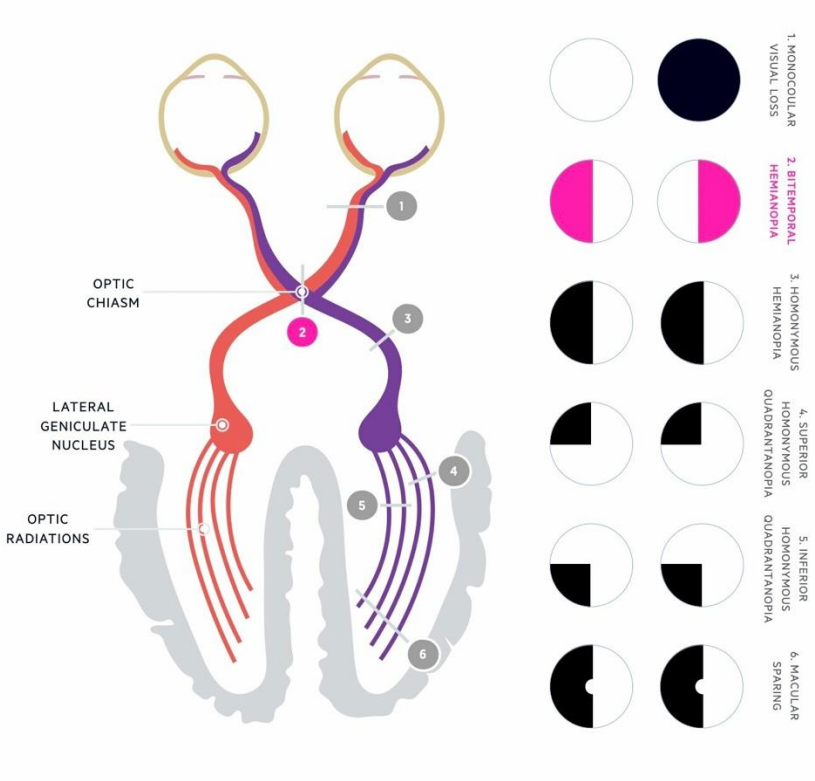


Target patients – Hemianopia

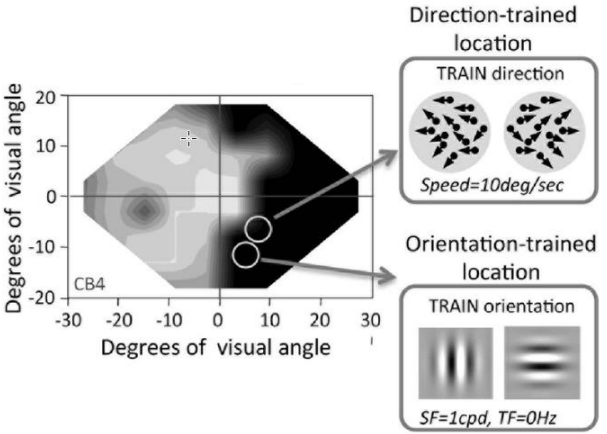


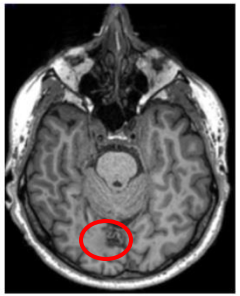


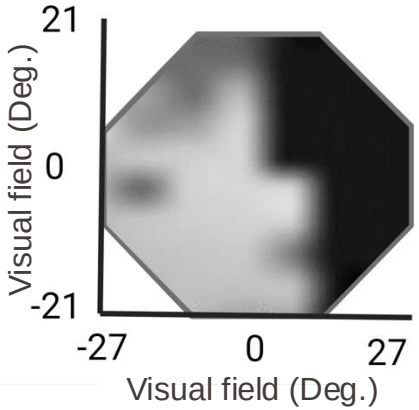


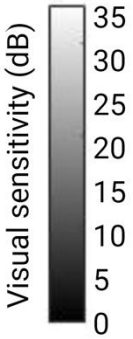


Target patients – Hemianopia

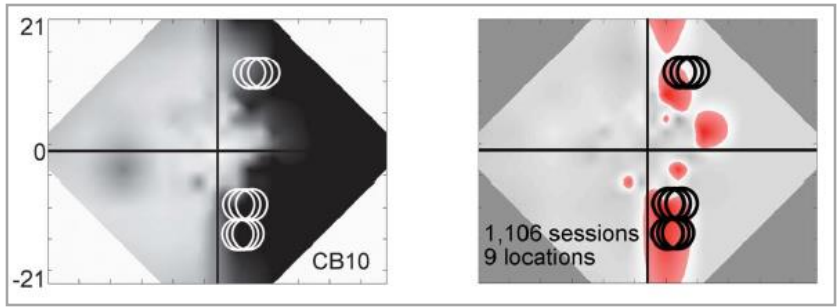








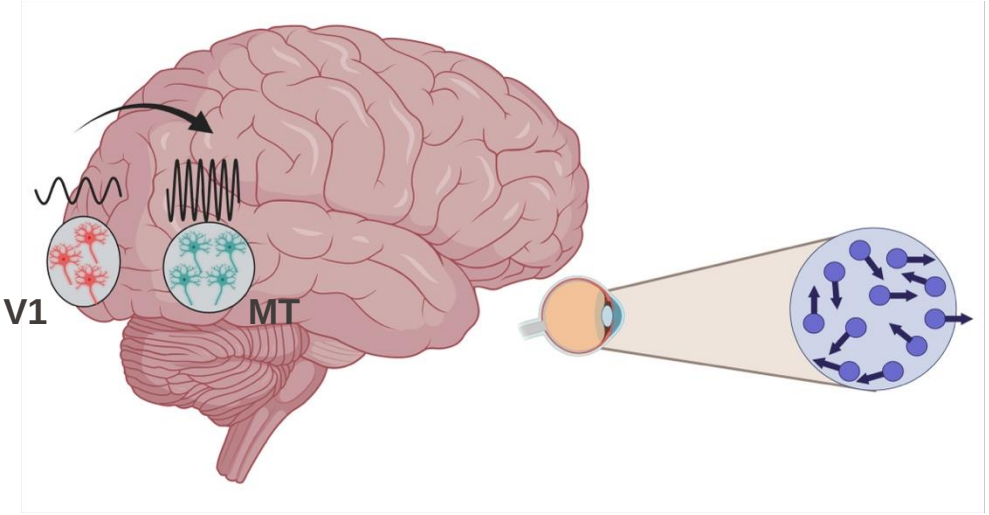
Extensive training over months



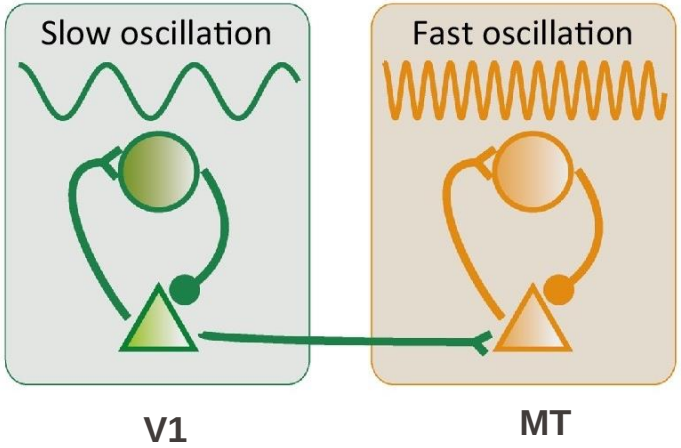
Cavaunaugh and Huxlin *et al., 2017*, Neurology

Orchestrated neuromodulation – physiology inspired

Motion processing

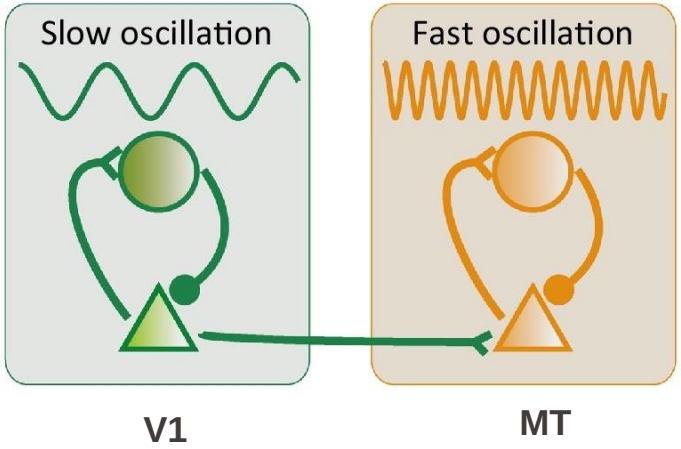


Cross-frequency inter-regional interactions

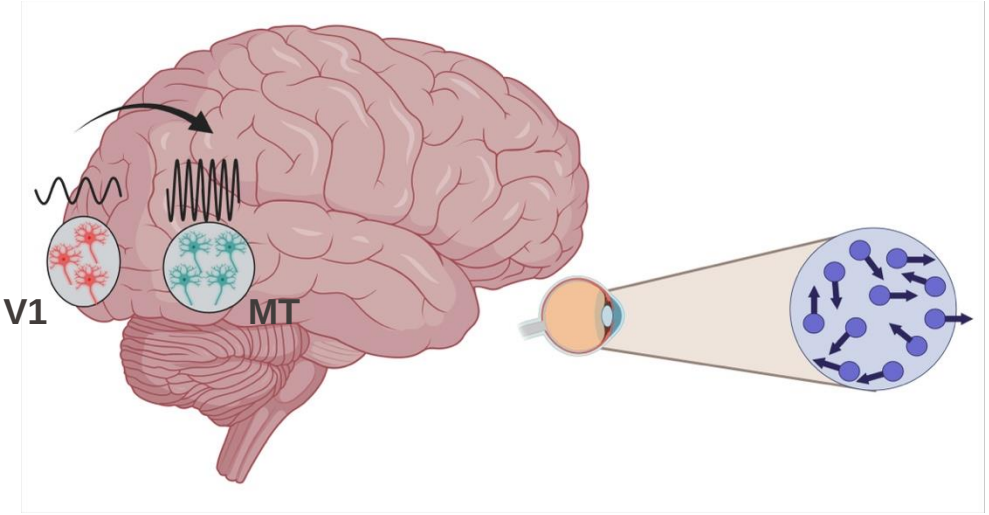


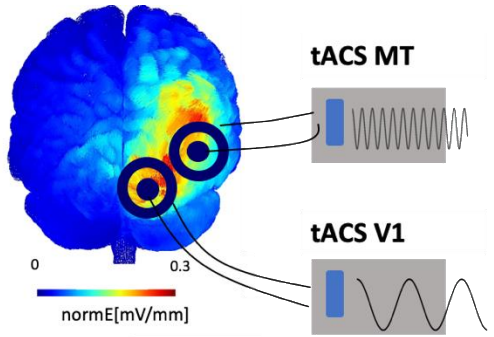
Orchestrated neuromodulation – physiology inspired

Cross-frequency inter-regional interactions



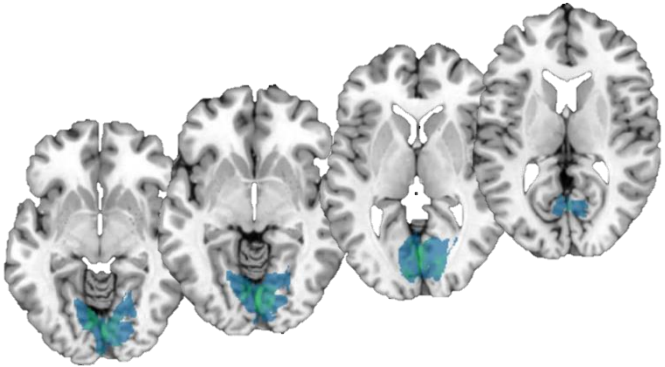
Motion processing

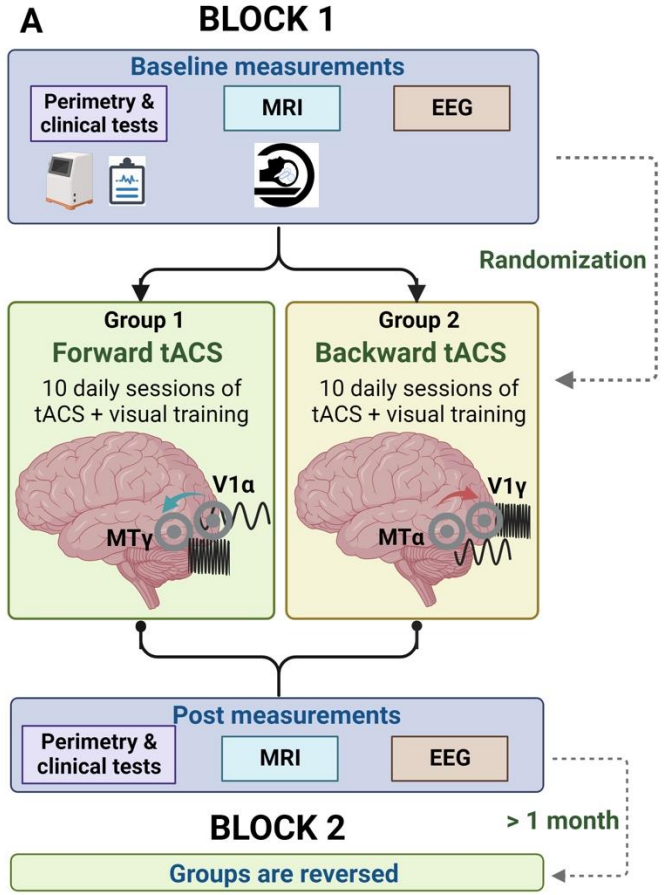




Physiology-inspired tACS

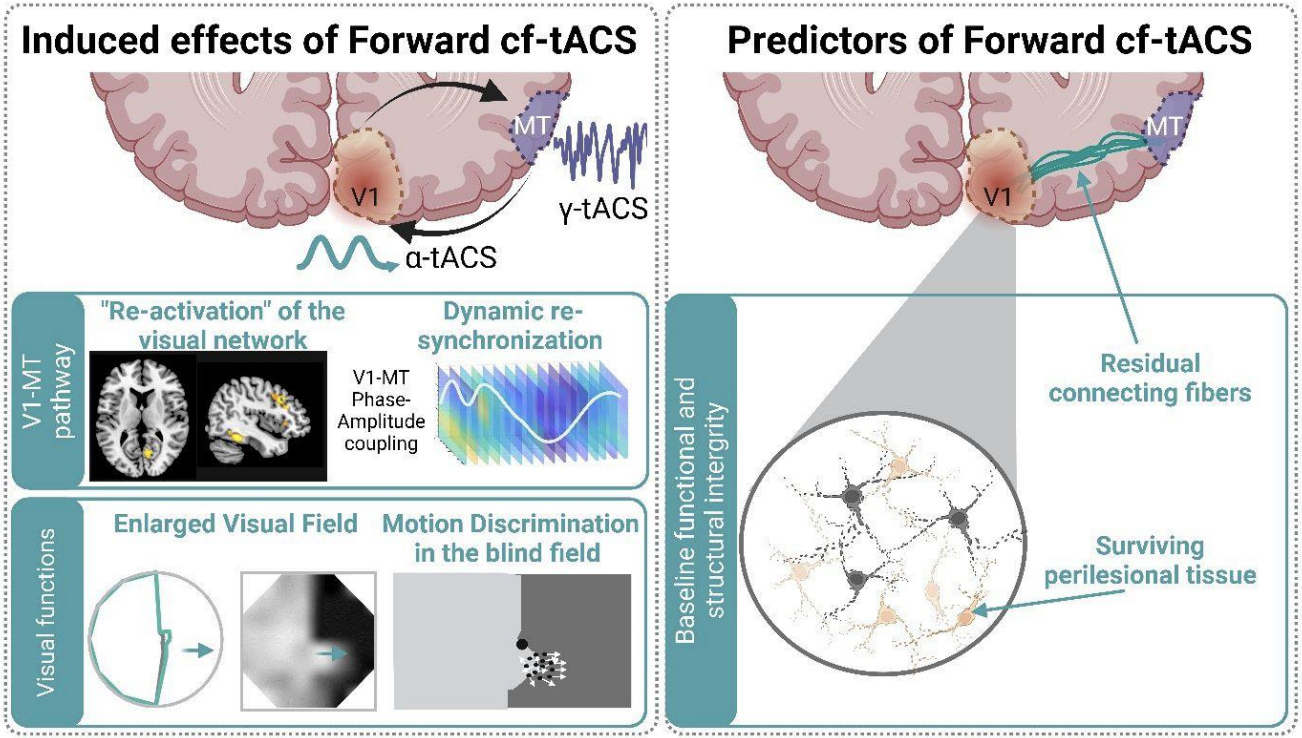
Re-Orchestrate 4 Vision Trial





Raffin *et al.*, (**under review**)

Re-Orchestrate 4 Vision Trial

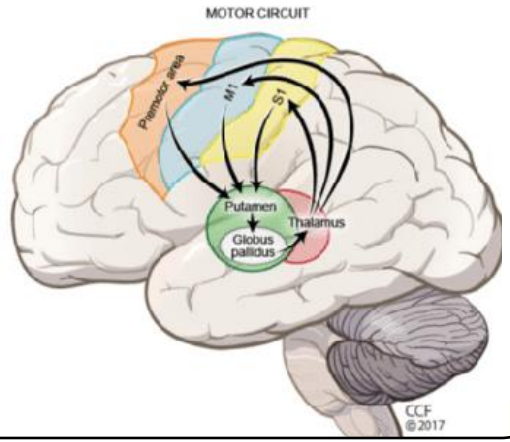


Orchestrated neuromodulation combined with visual **training** led to significant **reduction** of visual **deficits** in stroke patients

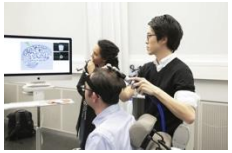
Treatment **effects** were achieved in **10 sessions** over 2 weeks whereas **without neuromodulation**, training of **several months** is required for comparable effects (Cavaunaugh *et al.*, 2017)

Raffin *et al.*, (**under review**)

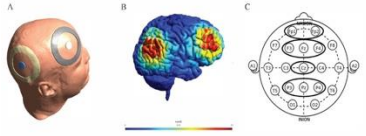
Motor functions – non-invasive brain stimulation (NIBS)



monofocal cortical NIBS

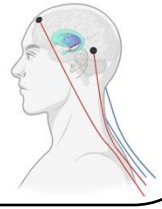


multifocal cortical NIBS

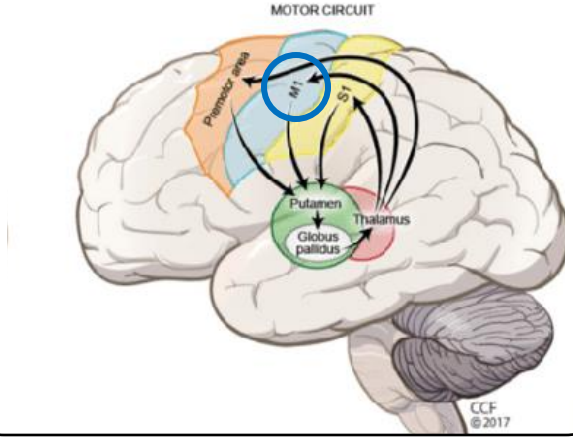


multidomain stimulation (efferent-afferent)

non-invasive deep brain stimulation (nDBS)



Motor, cognitive functions – cortico-subcortical processing



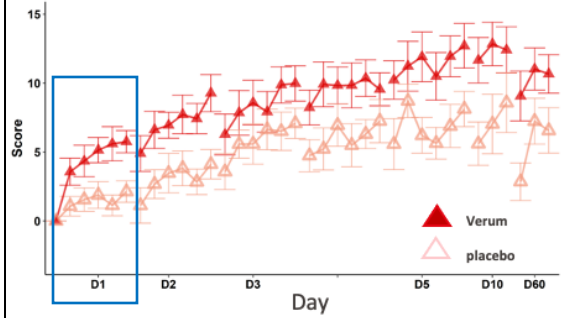
SCIENCE ADVANCES | RESEARCH ARTICLE 2022 Jul 22;8(29):eabo3505.

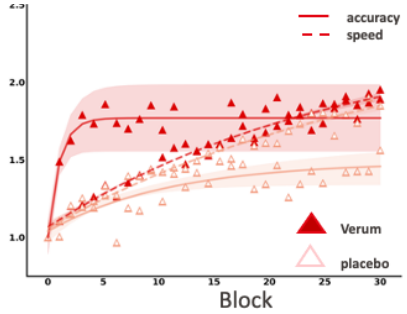
NEUROSCIENCE

Dissecting motor skill acquisition: Spatial coordinates take precedence

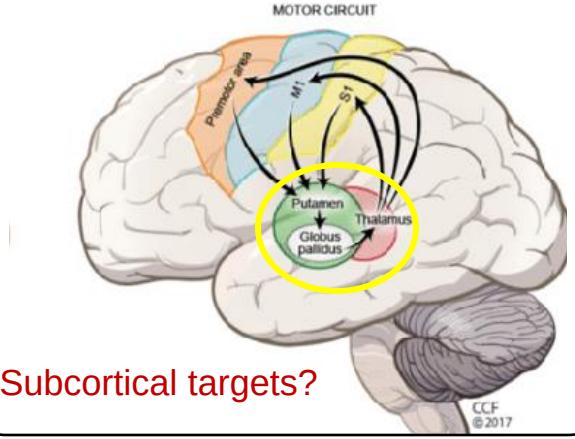
Pablo Maceira-Elvira[1,2]†, Jan E. Timmermann[3]†, Traian Popa[1,2]‡, Anne-Christine Schmid[1,2]‡, John W. Krakauer[4], Takuya Morishita[1,2], Maximilian J. Wessel[1,2,5], Friedhelm C. Hummel[1,2,6]*

Effect of M1 stimulation, limited to very early stage of skill acquisition





Motor, cognitive functions – cortico-subcortical processing



Subcortical targets?

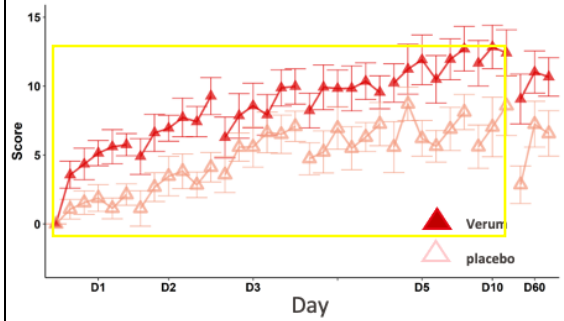
SCIENCE ADVANCES | RESEARCH ARTICLE 2022 Jul 22;8(29):eabo3505.

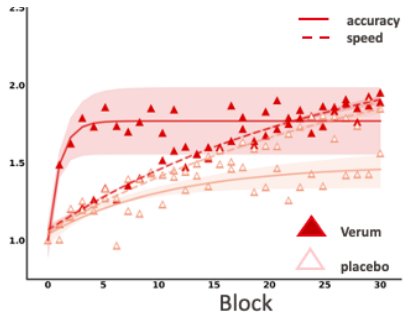
NEUROSCIENCE

Dissecting motor skill acquisition: Spatial coordinates take precedence

Pablo Maceira-Elvira[1,2]†, Jan E. Timmermann[3]†, Traian Popa[1,2]‡, Anne-Christine Schmid[1,2]‡, John W. Krakauer[4], Takuya Morishita[1,2], Maximilian J. Wessel[1,2,5], Friedhelm C. Hummel[1,2,6]*

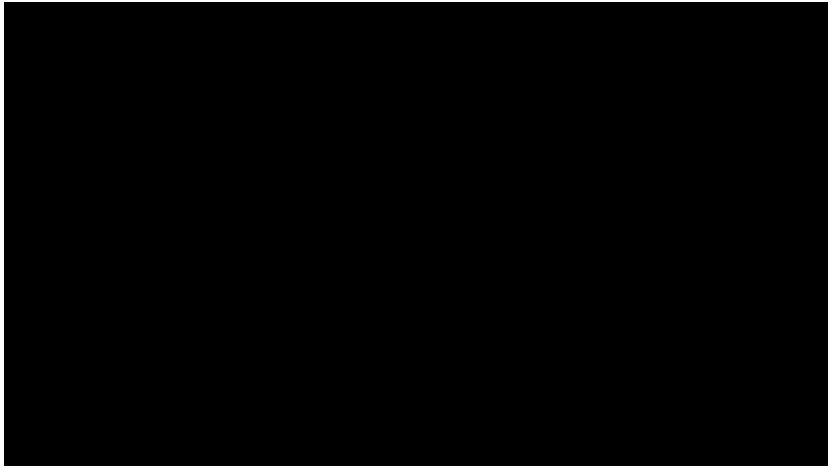
Impact on several stage of skill acquisition?

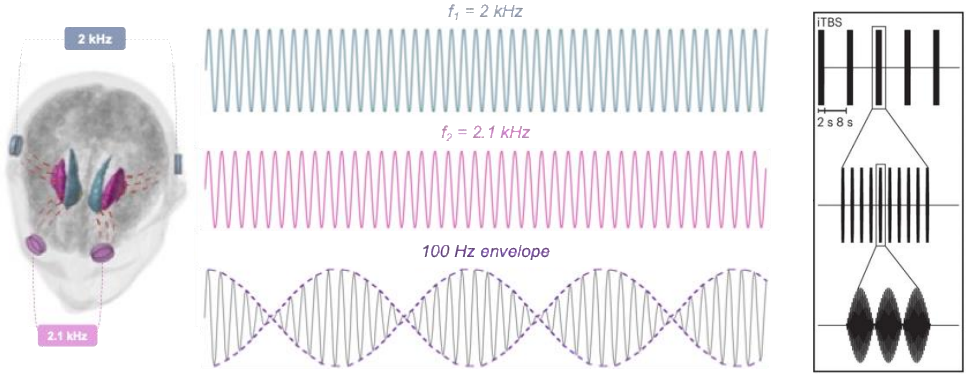




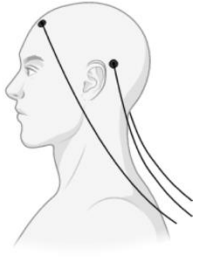
Neuroplasticity - Striatum

Can striatal tTIS modulate striatal activity and improve motor learning?





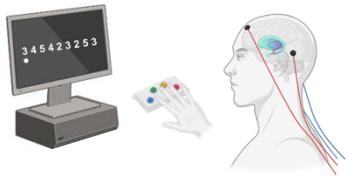
Intermittent theta bursts tTIS



Wessel, Beanato *et al.* 2023 Nature Neuroscience

Enhancing Learning in TBI Patients

15 TBI patients
3 female, 12 male
age: 52.67 ± 13.6
double-blind
Cross-over



Motor Learning
tTIS or Control

- Training
- Post - assessment
- Follow-up 1 (90 min)
- Follow-up 2 (24h)

Ploumitsakou*, Beanato* *et al.*, in preparation

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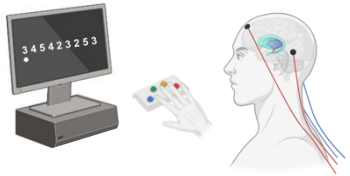

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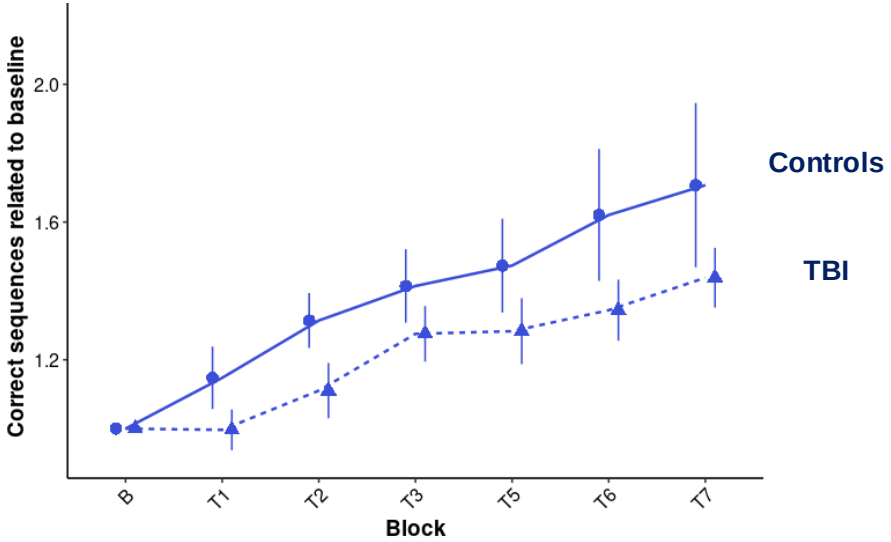
TBI vs Age-matched controls - behavior



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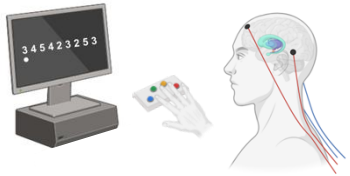

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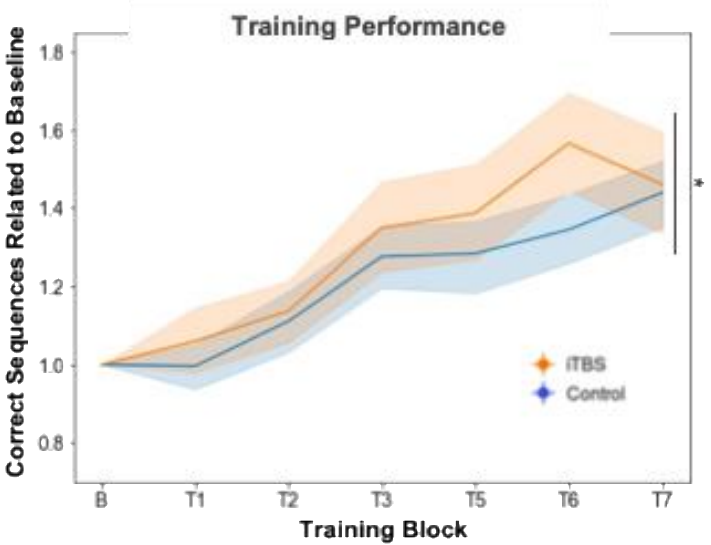
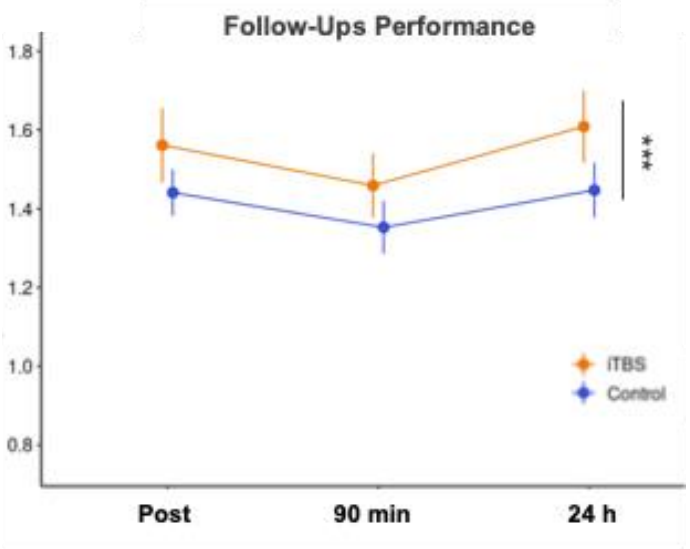
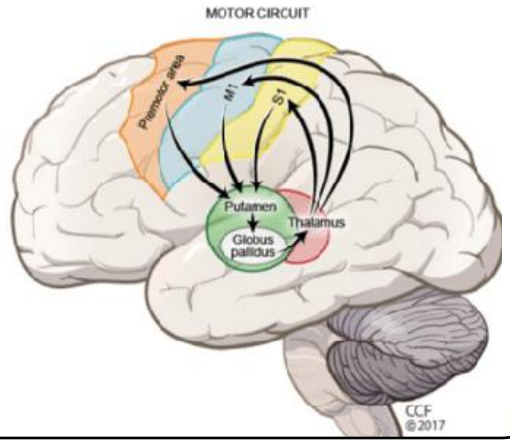


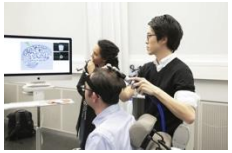


Ploumitsakou*, Beanato* *et al.*, in preparation

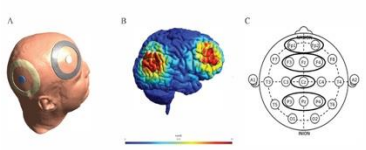
Motor functions – non-invasive brain stimulation (NIBS)



monofocal cortical NIBS



multifocal cortical NIBS

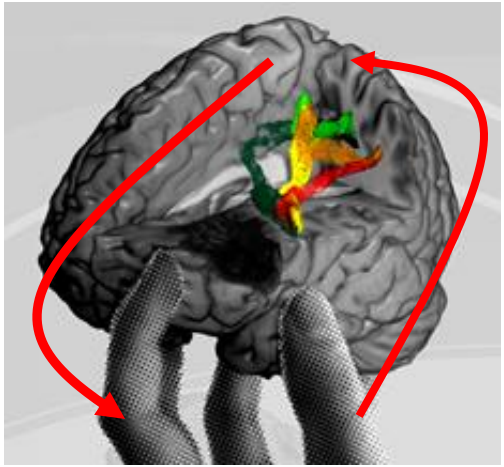


multidomain stimulation (efferent-afferent)

non-invasive deep brain stimulation (nDBS)

Reclosing the efferent-afferent loop

- **Severely impaired patients:** UEFME < 20/66, chronic stage



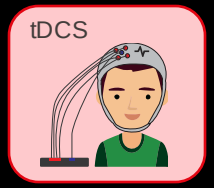
Main pillars

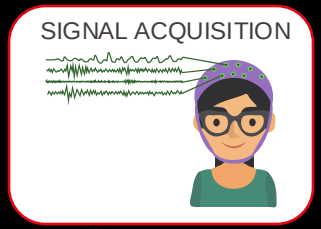
- **Combination of neurotechnologies** given in hierarchical manner:
  - brain-computer interface (BCI), hand exoskeleton, functional electrical stimulation (FES)
  - transcranial direct current stimulation (tDCS)
- **Personalized-therapy**:
  - Therapy duration
  - Single session – tailored exercises

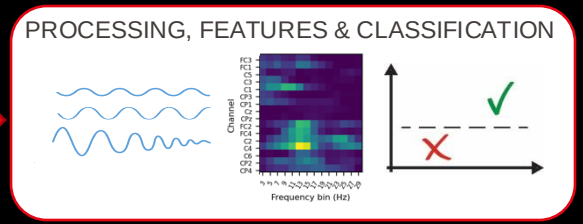
Crema *et al.* 2022 MED
Hummel & Cohen 2006 Lancet Neurol
Coscia *et al.* 2019 Brain
Micera *et al.* 2020 Neuron

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

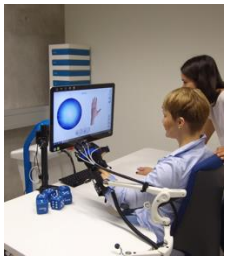






Hebbian learning – central and peripheral synchronisation

EXOSKELETON



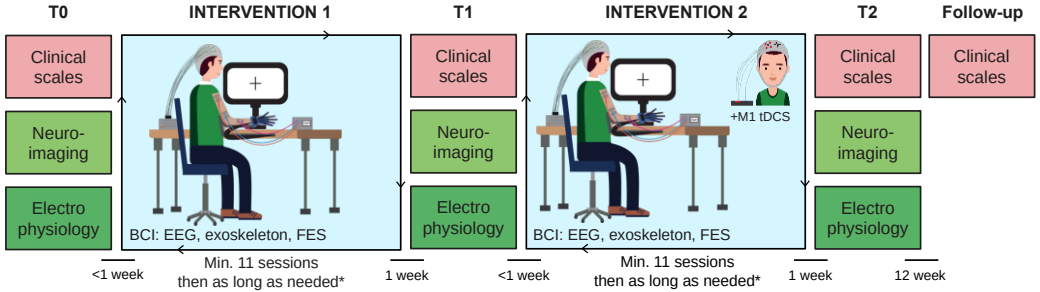
- Extend/flex each finger independently
- Anti-gravity support for the arm

FES

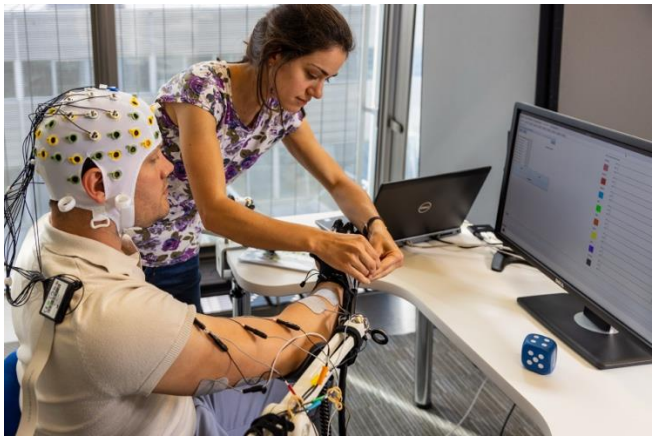
- Concurrent activation of 7 upper-limb muscles
- Active contraction

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

AVANCER clinical trial



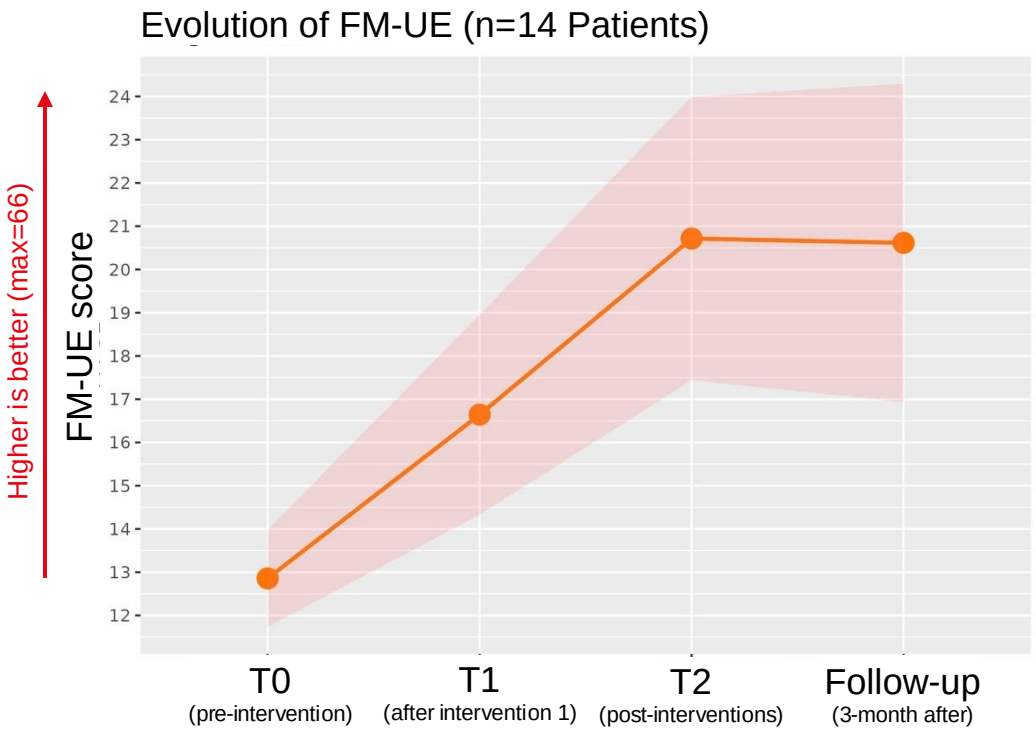
*According to motor improvement:
$FM\text{-}UE_{Si} \leq median(FM\text{-}UE_{Si\text{-}2}, FM\text{-}UE_{Si\text{-}4}, FM\text{-}UE_{Si\text{-}6})$
$Si=i^{th}$ (current) session



Severely impaired stroke patients: UEFME < 20/66, chronic stage

Bigoni *et al.*, (**2023**) MED; Bigoni et al. (**2022**) Frontiers

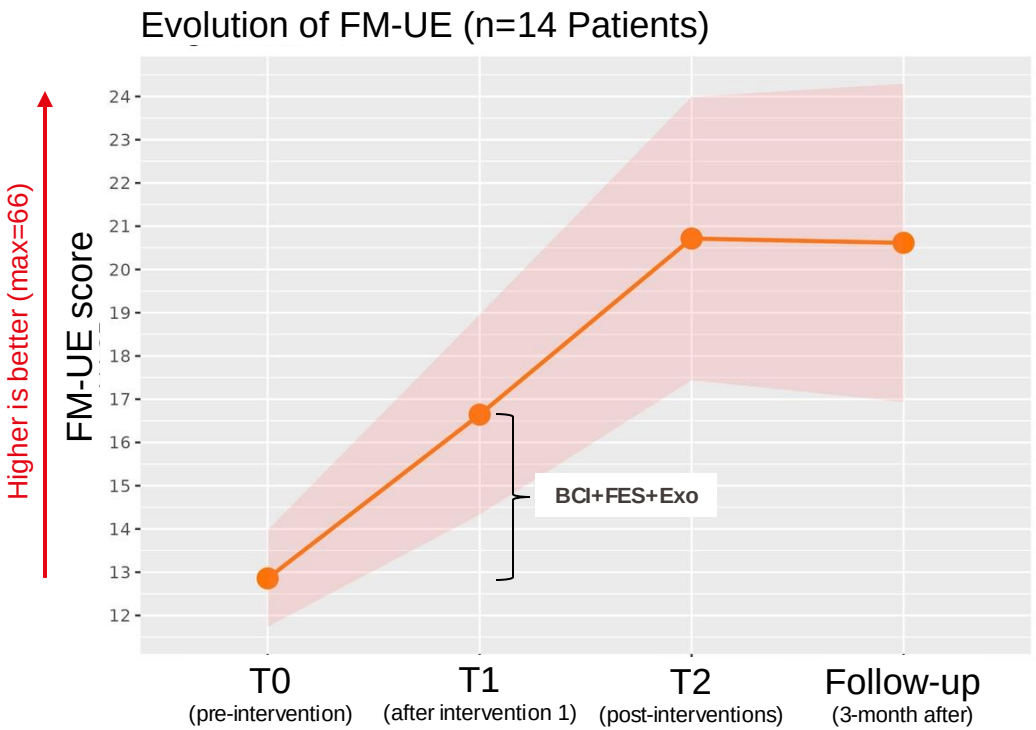
Primary outcome



- 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**

in prep

Primary outcome



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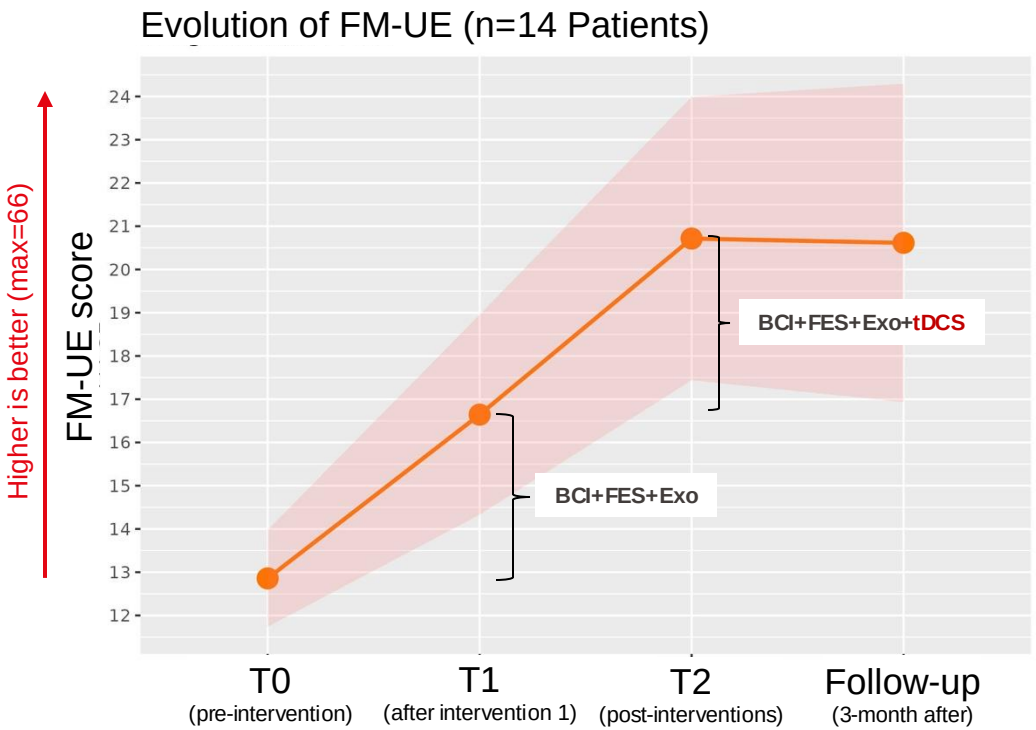

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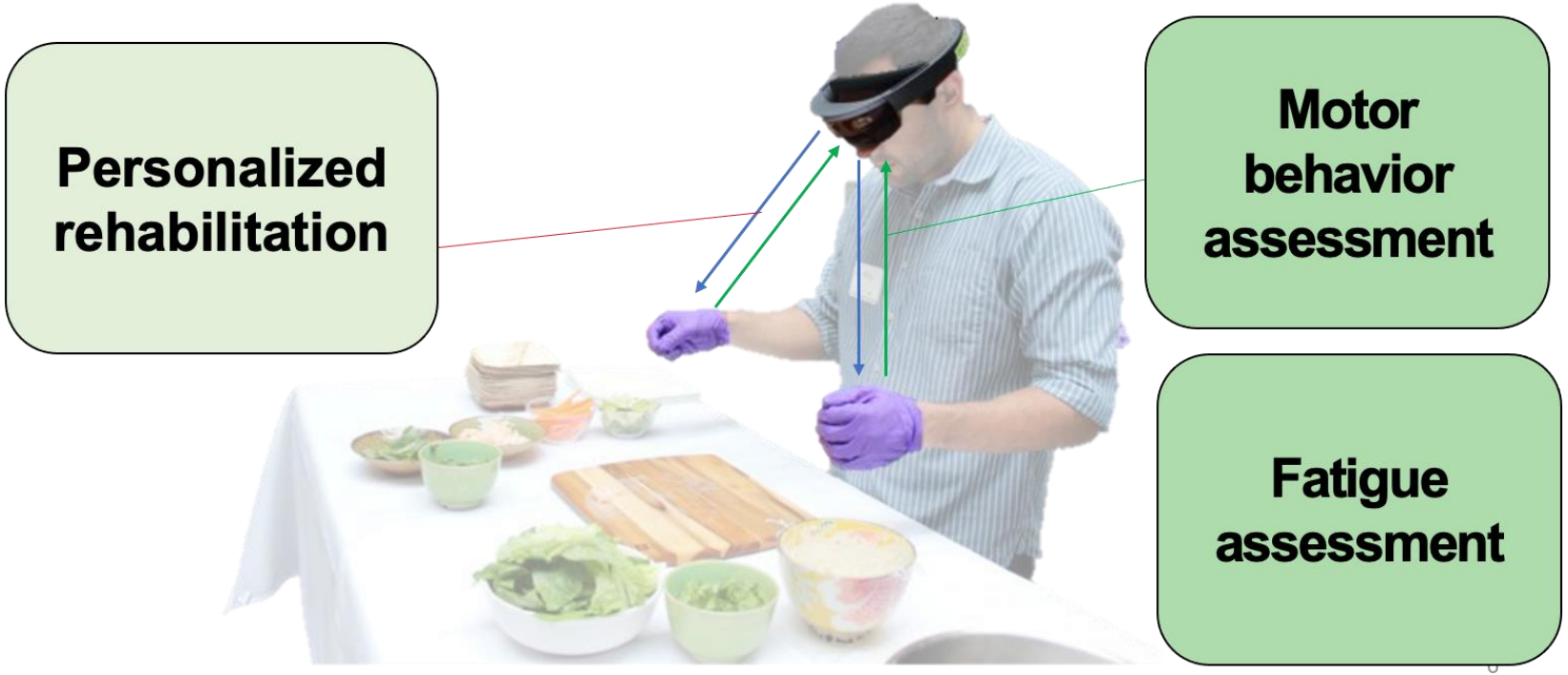
in prep

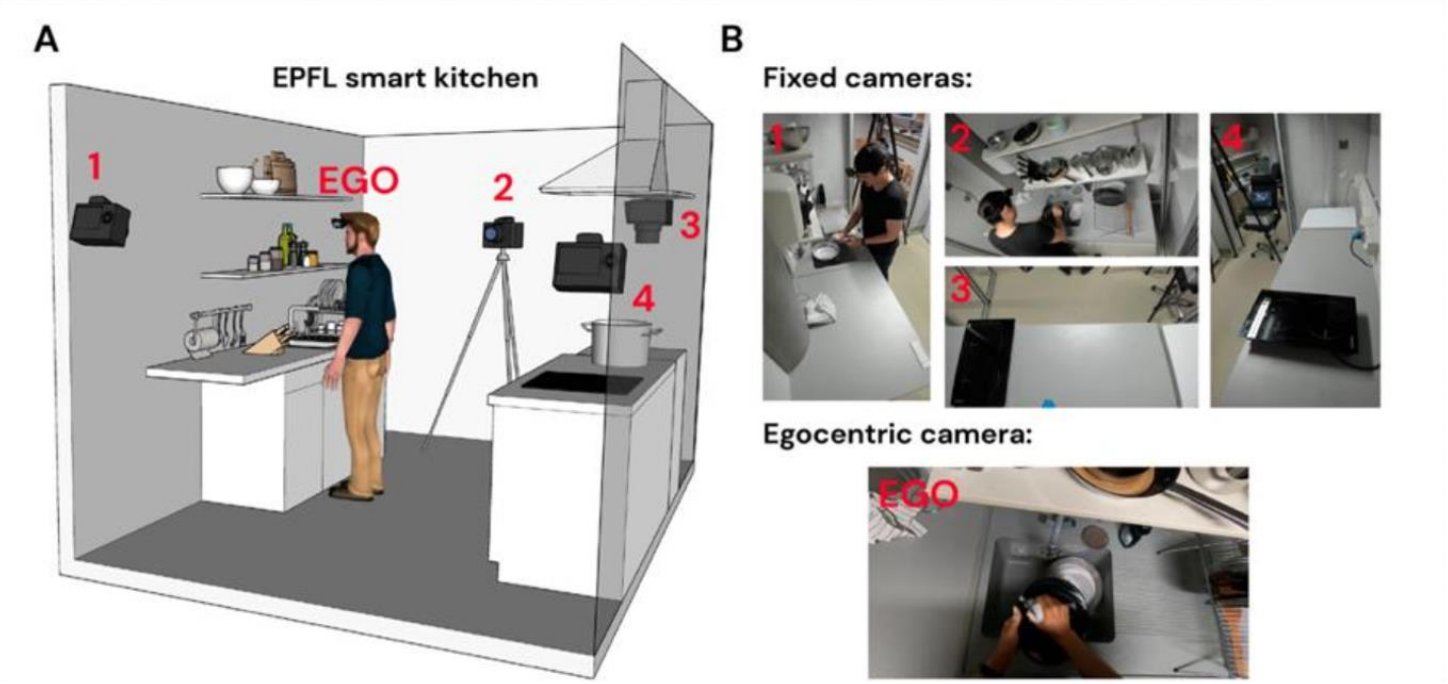
Feedback patients

in prep

Goal:
Functional assessment platform for daily life functions for neurological patients



Neurotechnology to better evaluate patients



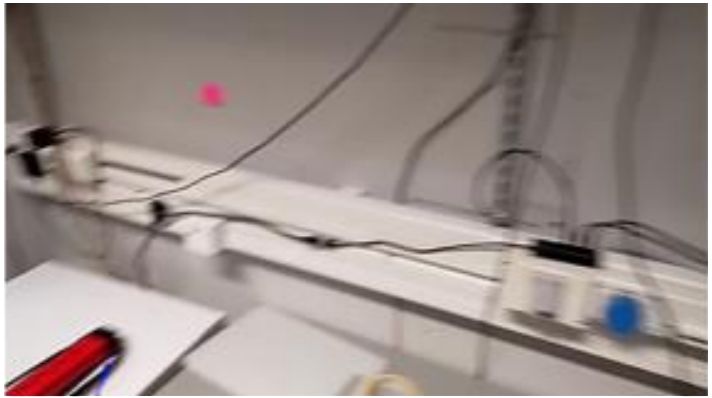
EPFL smart kitchen,

- Collect benchmarking data using multi-view RGBD cameras and sensors
  - 3D hand posture
  - 3D object pose for interactions
- **100 subjects** including patients
- **5 Hours** for each subject

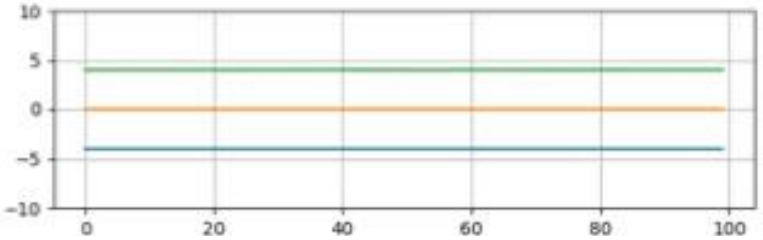
3D models of kitchen objects

Neurotechnology to better evaluate patients

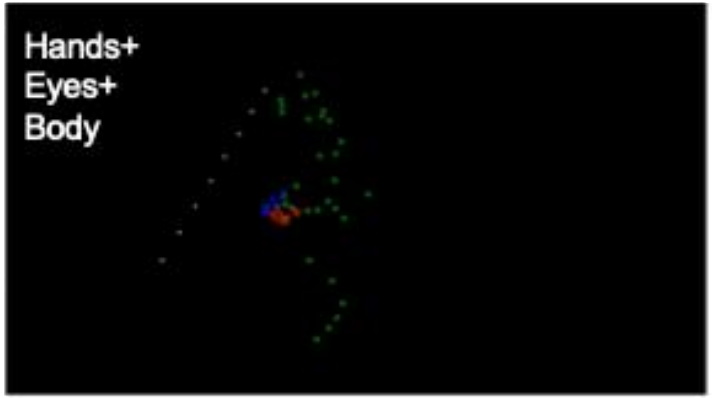
Hololens view

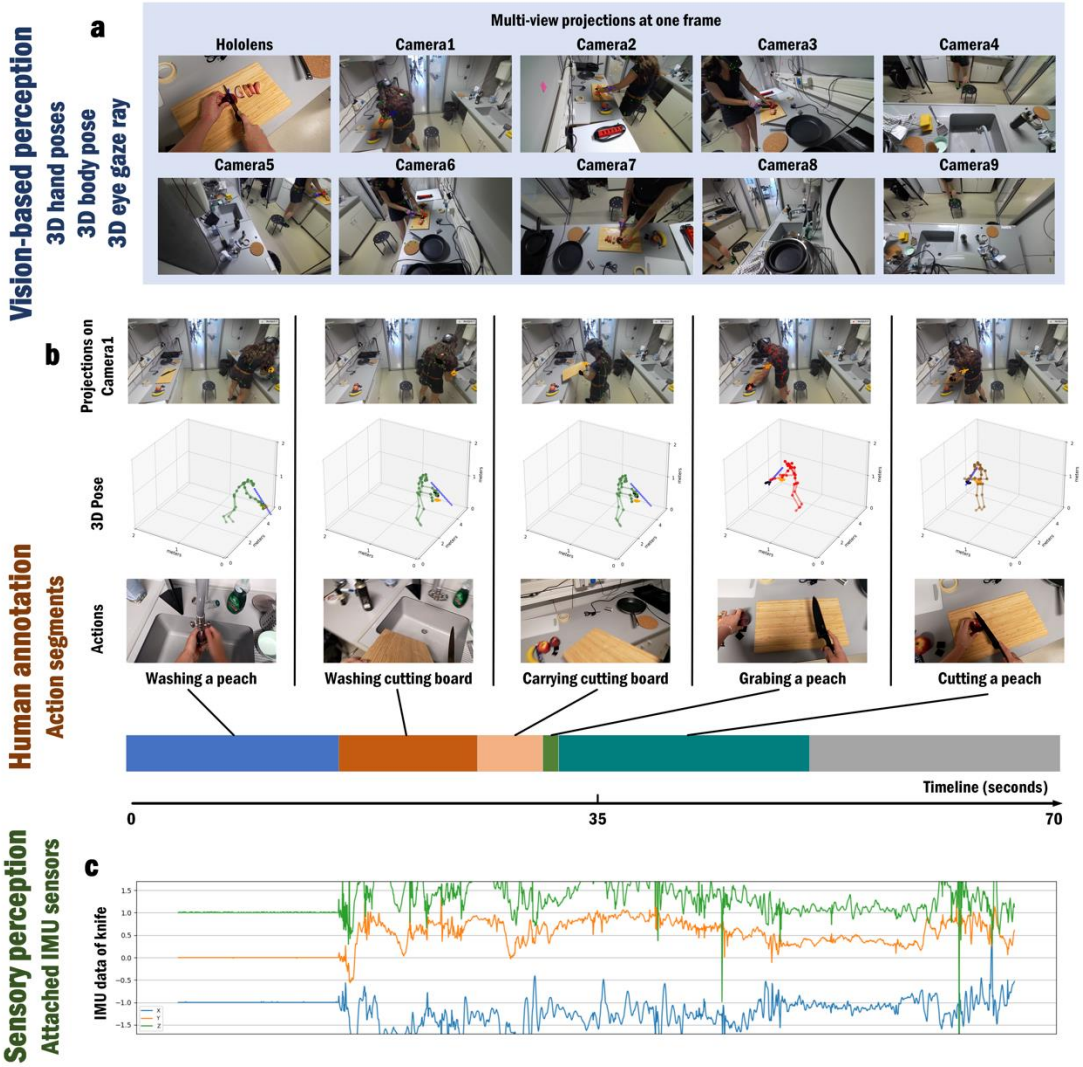


Kinect view



IMU data from knife




Vision-based perception
3D hand poses
3D body pose
3D eye gaze ray
a
Multi-view projections at one frame
Hololens
Camera1
Camera2
Camera3
Camera4
Camera5
Camera6
Camera7
Camera8
Camera9
Human annotation
Action segments
b
Projections on Camera1
3D Pose
Actions
Washing a peach
Washing cutting board
Carrying cutting board
Grabing a peach
Cutting a peach
Timeline (seconds)
0
35
70
Sensory perception
Attached IMU sensors
c
IMU data of knife

Take-home message

Stroke is

- Network disorder
- Personalized treatments in the acute and chronic stage are needed
- Structural connectomics for prediction of course of recovery
- Interhemispheric competition model as a basis for interventional startegies (but has limitations)
- Different interventional approaches
- Better evaluation of stroke deficits and treatment effects (SMART kitchen)

Questions?