Master Course Personalized Healthy
27th of March 2025

Towards personalized treatment strategies in neurological disorders - neurotechnology -

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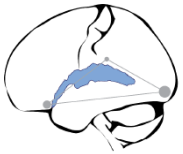
HUG Hôpitaux Universitaires Genève

Clinique romande de réadaptation

defitech fondation

Outline



- Intro Personalized Health
- Clinical oriented examples
- Research oriented examples

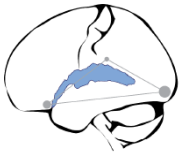
Why do we need personalized health for neurological disorders

…?

https://www.nytimes.com/2019/05/22/opinion/letters/drug-safety.html

https://www.slideshare.net/rsmehta/total-hip-replacement-35158107

Why do we need personalized health for neurological disorders



- **Non-satisfying treatment effects**
  - Interindividual large variance of treatment response and side effects
  - Responders, non-responders
  - No large scale clinical evidence (RCT)

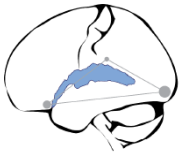
- **Heterogenous disorders**
  - Acute disorders, acute stage of the disorder
  - Towards chronic
  - Relapsing, remittent disorders (e.g. multiple sclerosis)
  - Overall significant changes over the course of the disorder (intraindividual changes)
  - Interindividual changes (se examples)

- **So far largely 'one-suits-all' treatments**

- **High cost of non-personalized medicine (cost-effectiveness, NNT)?**

- **Evidence based medicine and its disadvantages**

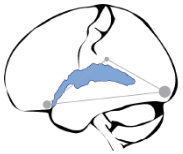
Why do we need personalized health for neurological disorders



- **Evidence-based Medicine (EBM)**
  - The **insistence** on **explicit** evaluation of **evidence** of **effectiveness** when issuing clinical practice guidelines and other population-level policies. The second is the introduction of **epidemiological methods** into medical education and individual patient-level decision-making
  - The **judicious use** of the **best** current available scientific research in **making decisions** about the care of patients. Evidence-based medicine (EBM) is intended to **integrate clinical expertise** with the **research evidence** and **patient values**.
  - Large randomized clinical trials (**RCT**) necessary for **strong** clinical evidence

- **Example**
  - Aspirin and Secondary Stroke Prevention
    - 18% relative risk reduction of recurrent stroke, 4% absolute risk reduction
    - NNT = 18

Why do we need personalized health for neurological disorders



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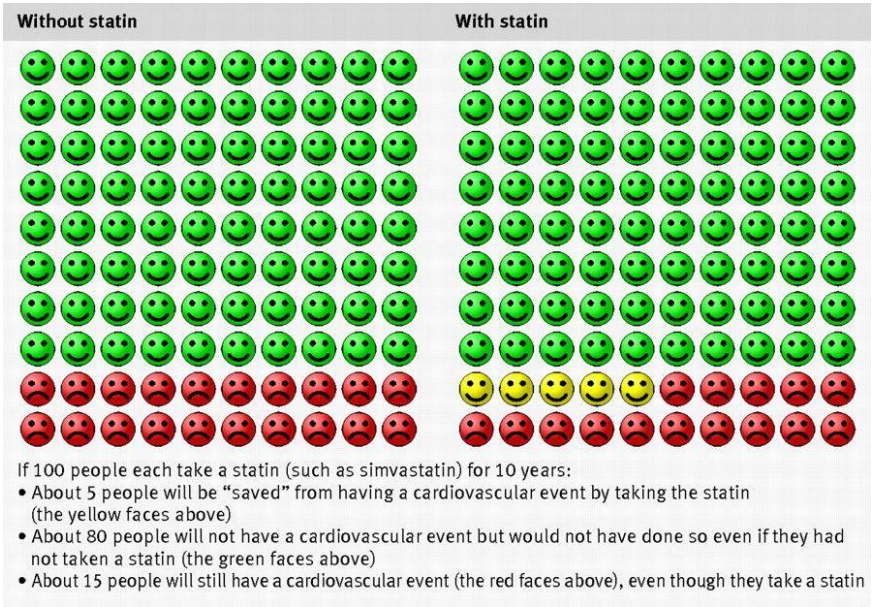
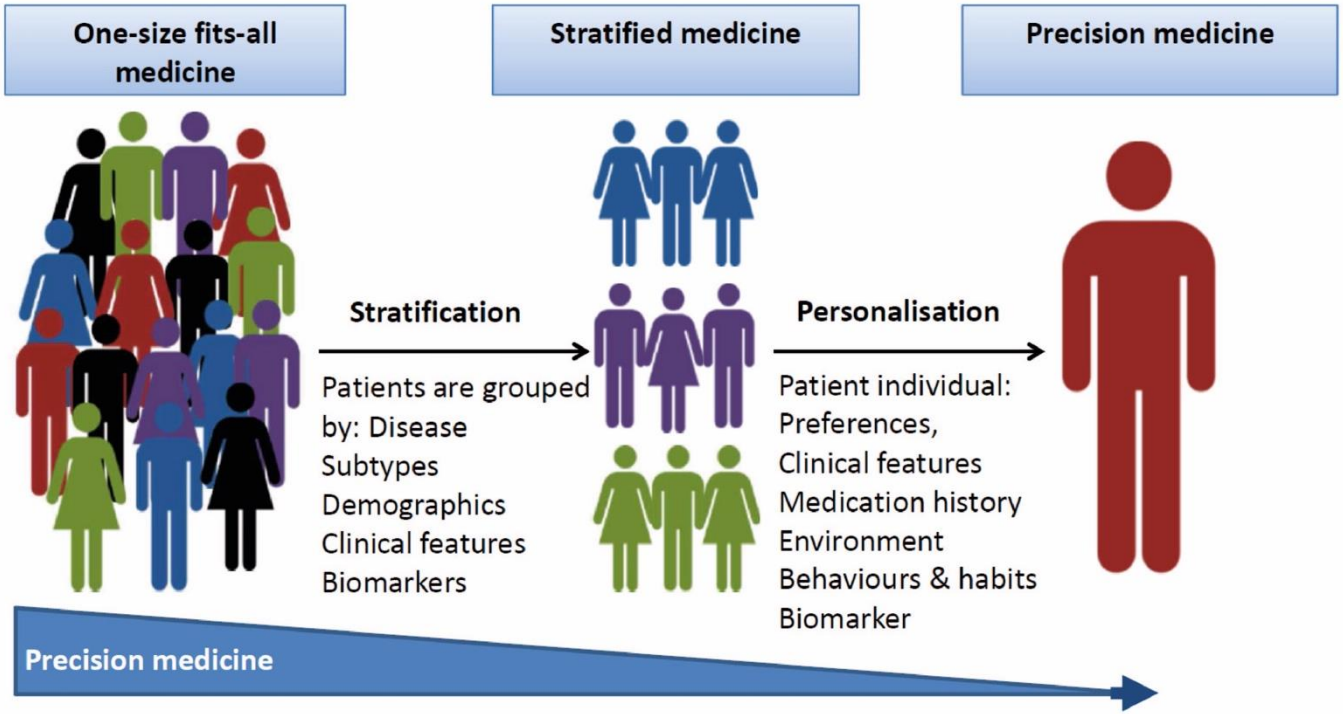
- **Example**
  - Aspirin and Secondary Stroke Prevention
    - 18% relative risk reduction of recurrent stroke, 4% absolute risk reduction
    - NNT = 18
- **Number Needed to treat**
  - The Number Needed to Treat (**NNT**) is the **number of patients** you **need** to treat to prevent **one** additional bad outcome (death, stroke, etc.). For example, if a drug has an **NNT of 18**, it means you **have to treat 18** people with the drug to prevent one additional bad outcome.

Why do we need personalized health for neurological disorders

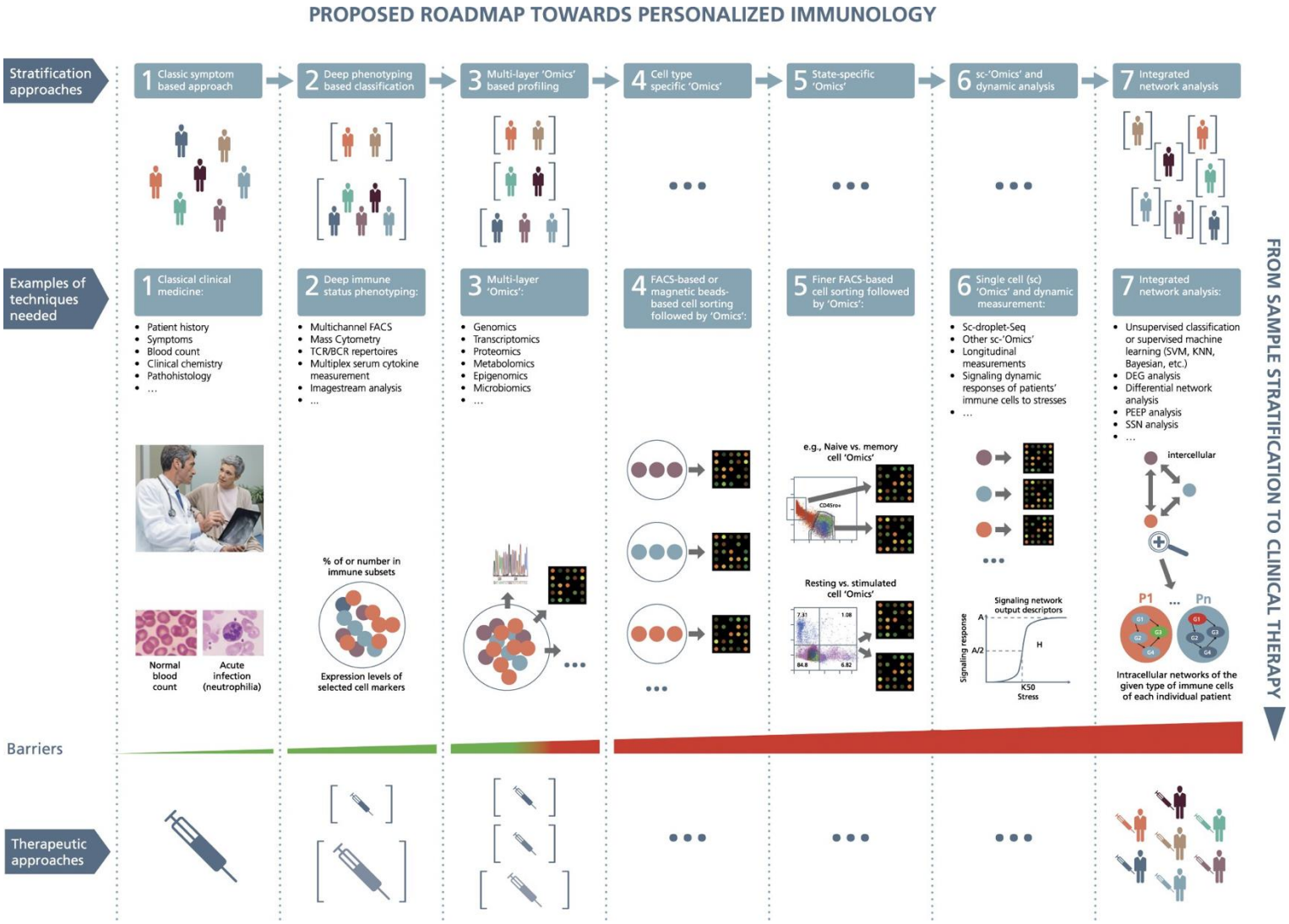
- **Ideal Case Scenario Precision Medicine**
  - Good prediction of outcome
  - Good prediction of course of the disorder
  - Good prediction of treatment response
  - Tailored Treatment for the individual patient
  - Ideally NNT = 1



The goal

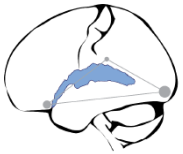

One-size fits-all medicine
Stratified medicine
Precision medicine
Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers
Personalisation
Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker
Precision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

The goal



Delhalle *et al.* 2018

Why do we need personalized health for neurological disorders



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  - Good prediction of outcome
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  - 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

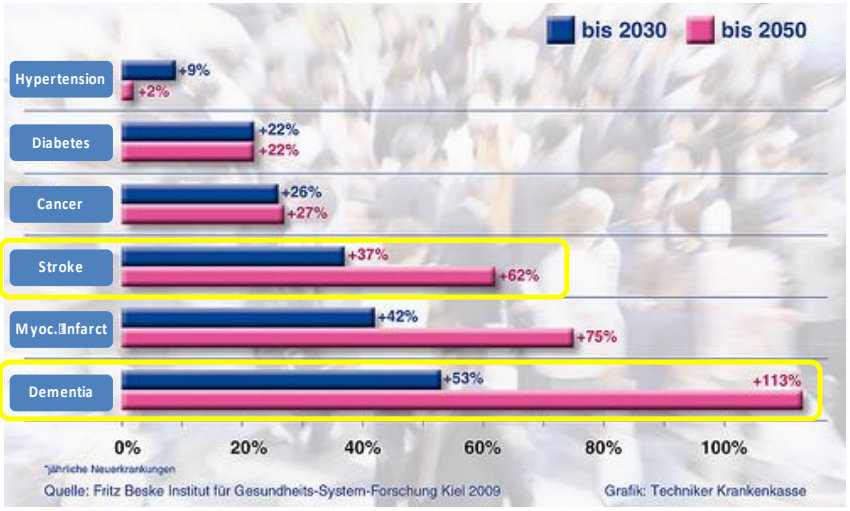
Examples of how different neurotechnology can drive personalized precision medicine

- Stroke -

Challenges of the 21st century

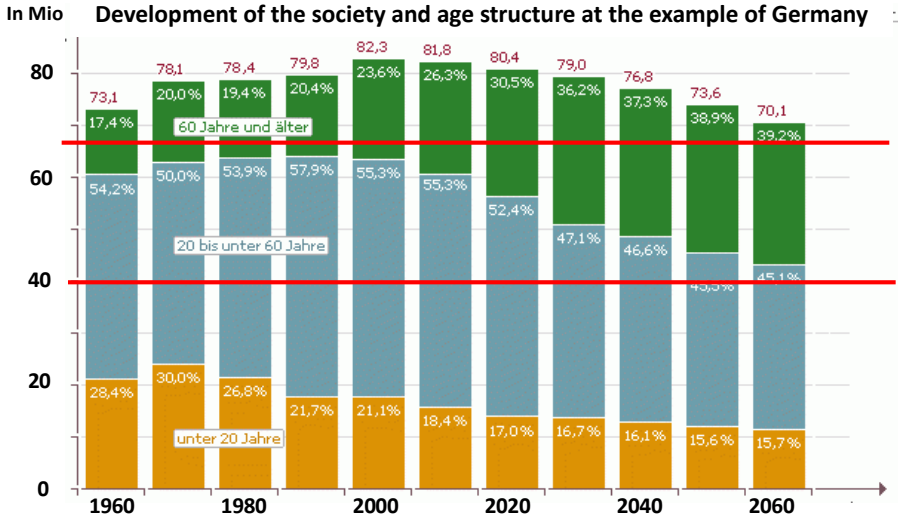
Aging society

- Cognitive Decline
- Neurodegenerative disorders (Alzheimer, Parkinson…)
- **Cerebrovascular disorders (e.g. Stroke, 2 Mio new strokes/year in EU)**
- Major work force
- Significant economic impact (currently **10-15 Milliards** CHF/year cost of Brain disorders in CH)



Diseases of civilisation

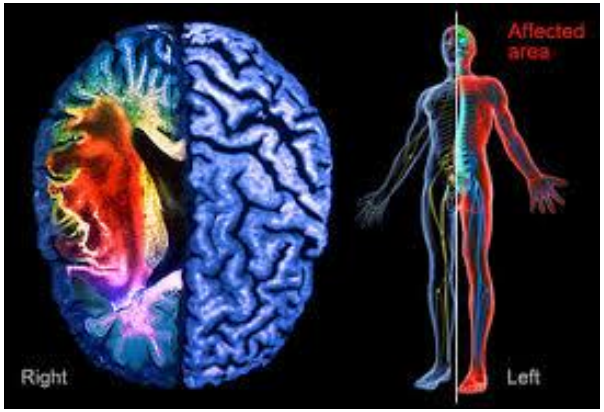
Prognosticated increase compared to 2007 in percent

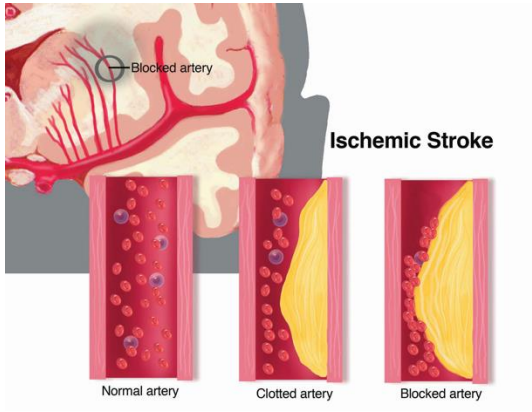


Main work force of the society

People, >50 a

Example Stroke



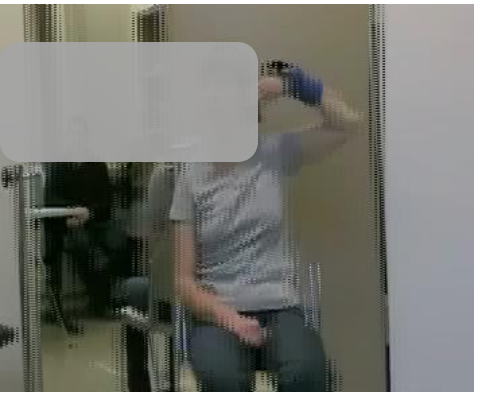


http://www.compelvisuals.com

Only 15-20% fully recover!

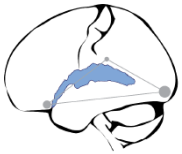
Stroke

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

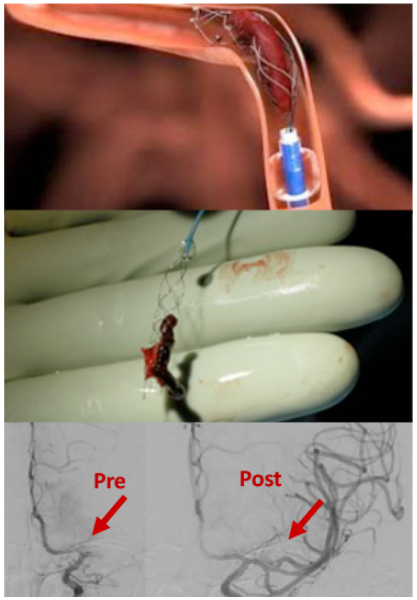


- **Impact on daily life**

Two main treatment areas:
acute vs recovery treatment

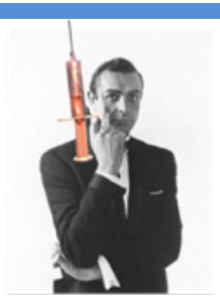


ACUTE



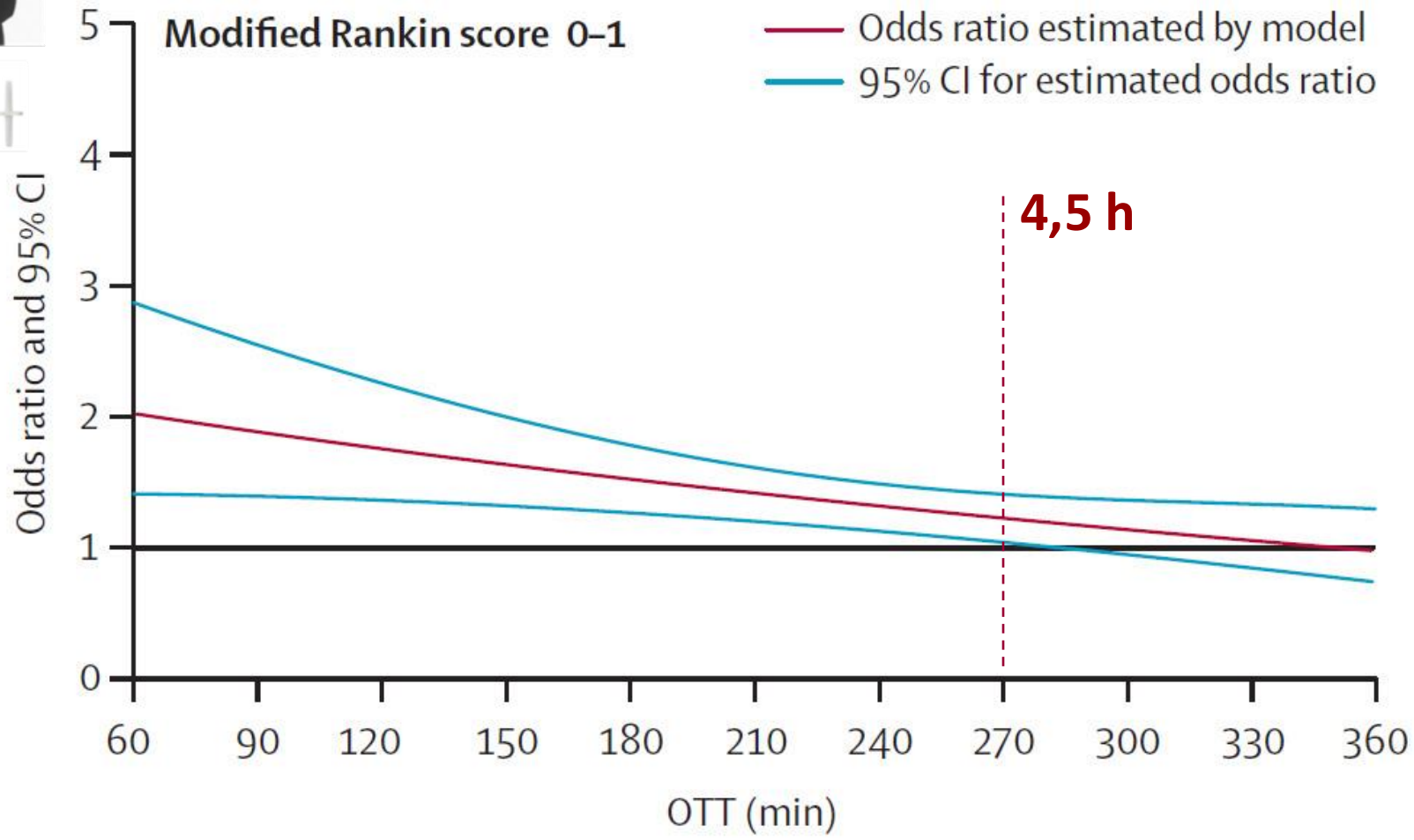
CHRONIC

Raffin & Hummel (2018) *Neuroscientist*



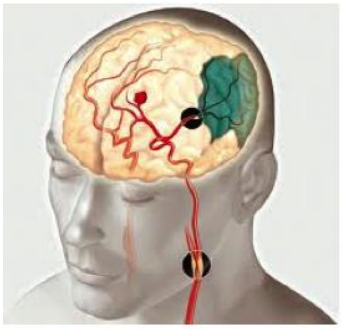
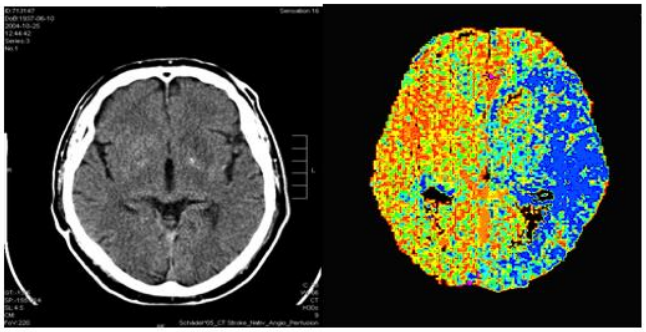
The relevance of time for the success of thrombolysis?

Towards personalized prediction of outcome



Lees et al. Lancet 2010

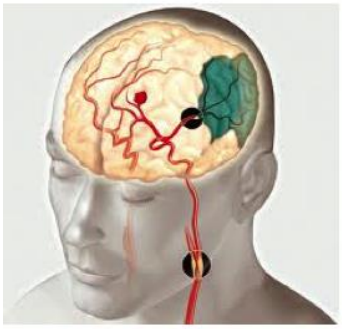
Problem

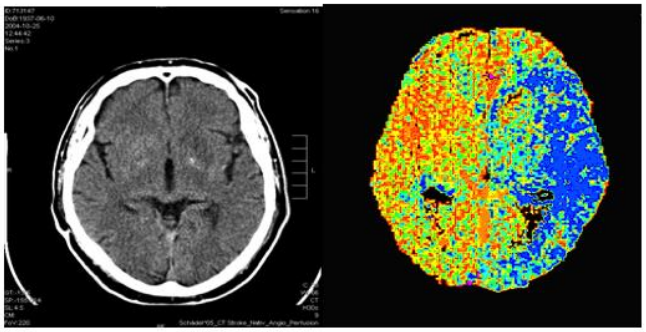




- The **personalization** of treatment here is **based** on the (**subjective**) information when the **symptoms started**
- **Problem**: start of the symptoms is often **not** clear (e.g. stroke during sleep (20%), patient cannot communicate or did not him/herself realize the symptoms)

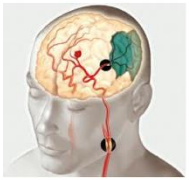
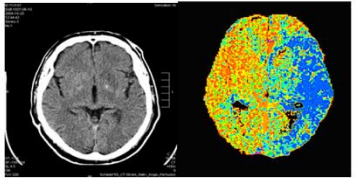
==> **no** treatment for these patients (thrombolysis)?

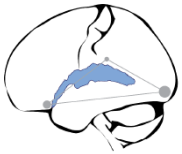
Acute trials:
example wake-up stroke



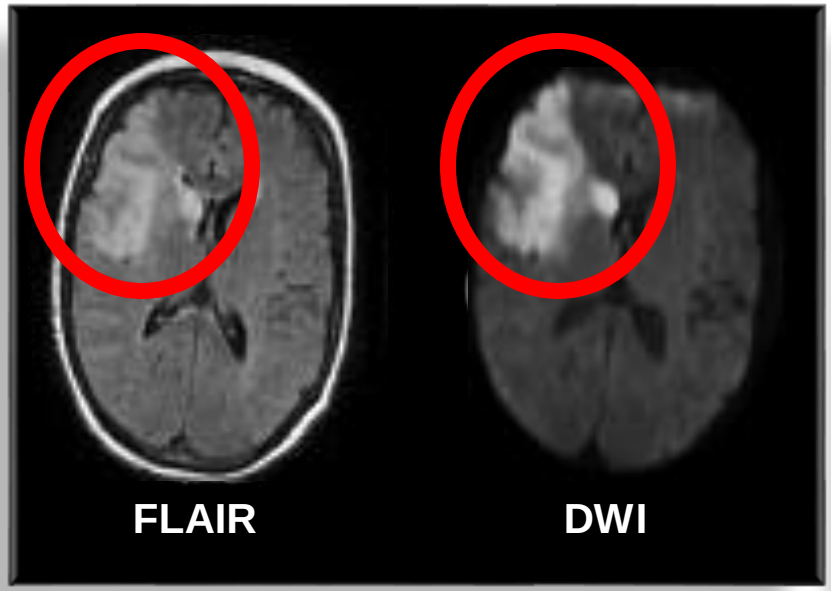


Can this problem be solved by applying technology?



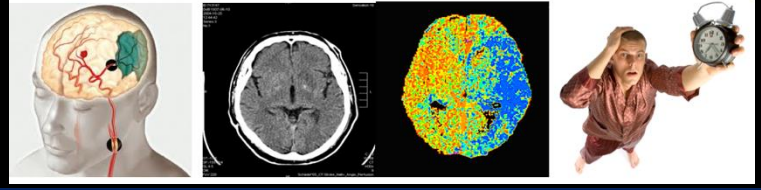
- FLAIR persistent damage, DWI probable reversive damage

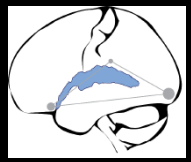


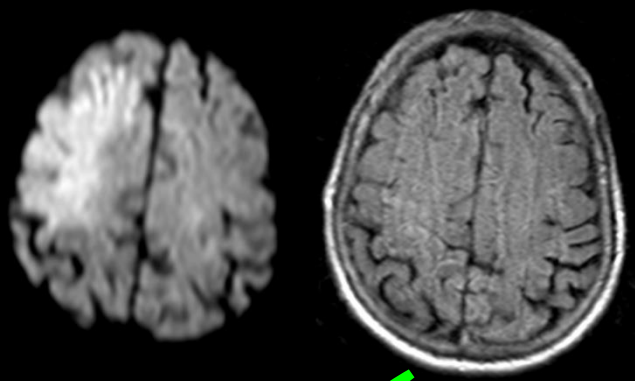
- DWI-FLAIR-Mismatch = patients might be within a time window for thrombolysis (<4.5h)?

Tissue clock?

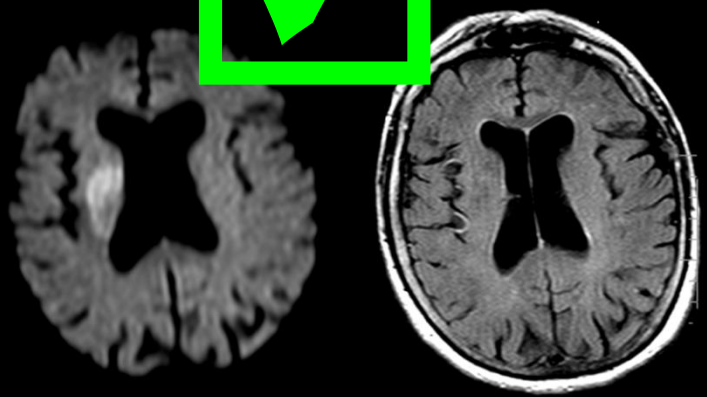
EPFL







DW FLAIR



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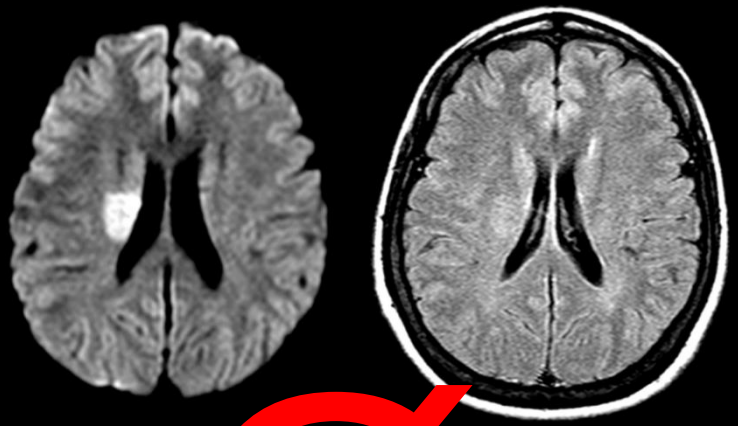

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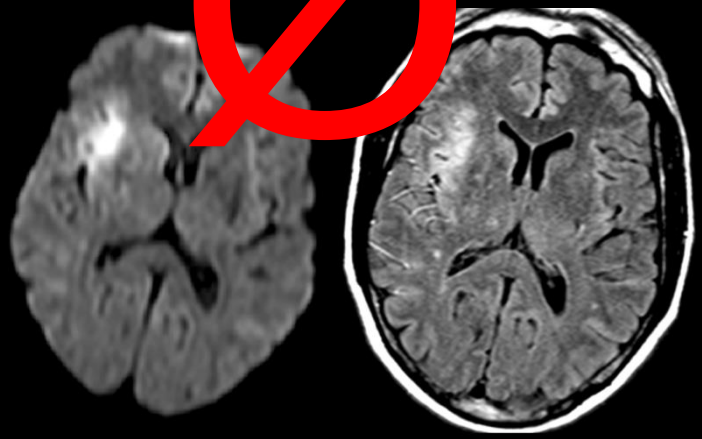

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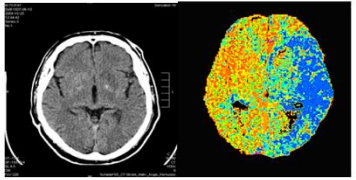
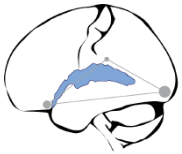
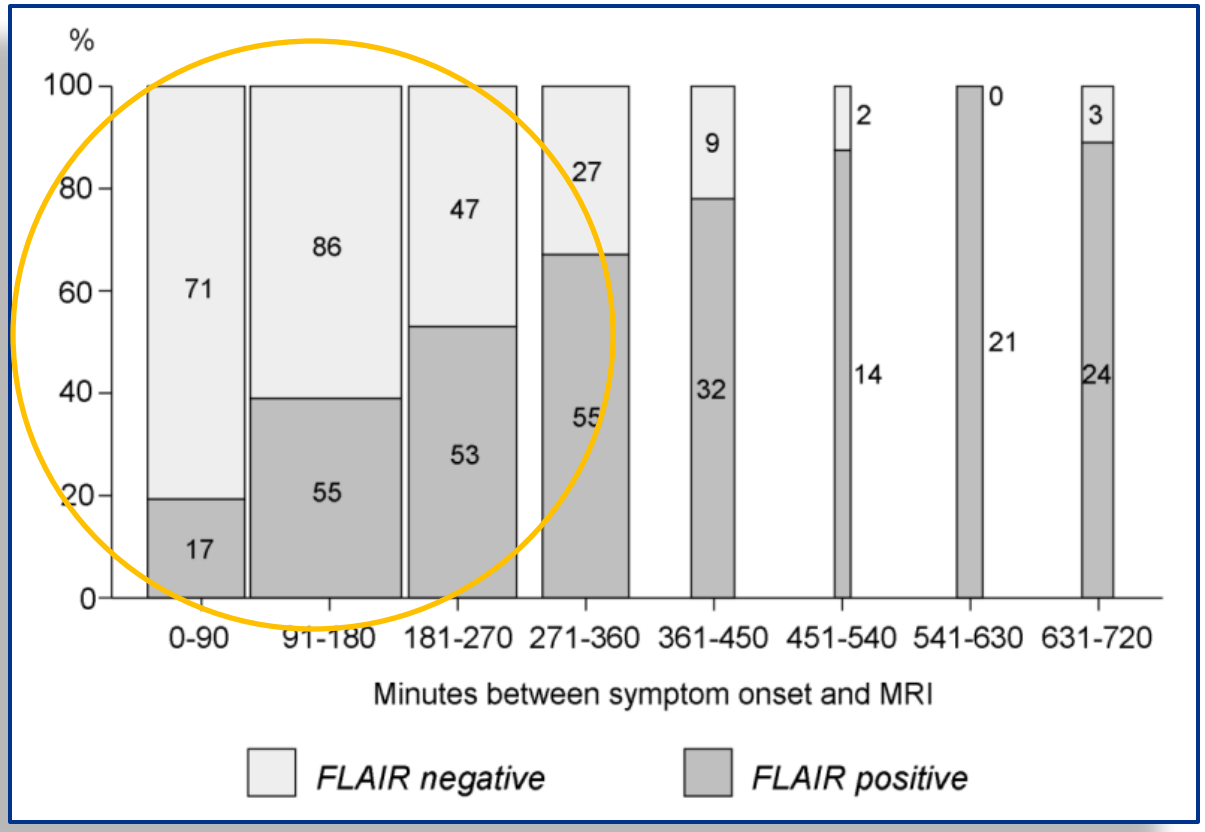


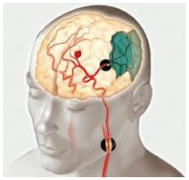
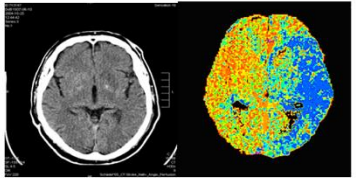


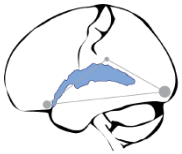
Existing big regular clinical data sets (n=543)

- search for a tissue clock -

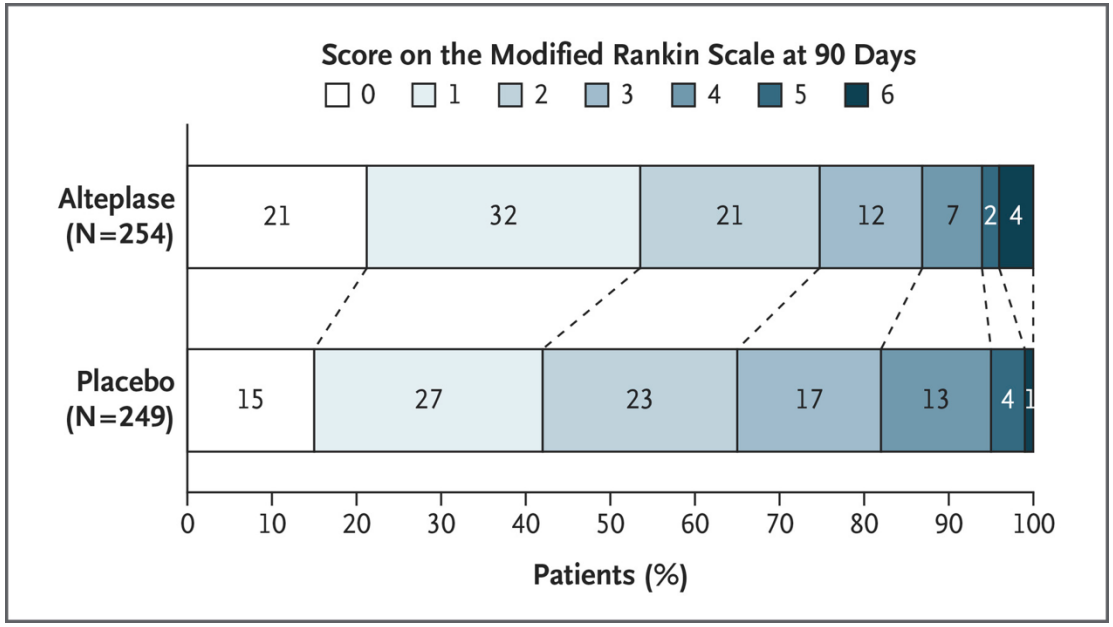


Thomalla *et al.* Lancet Neurol 2011



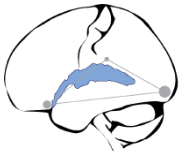
Translation into a large clinical treatment trial: Wake-Up trial



Thomalla et al. (2018) *NEJM*

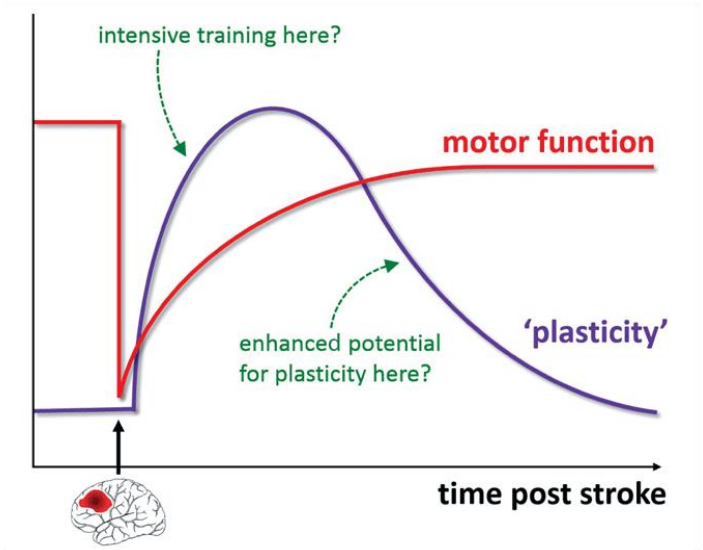
Successful extension of thrombolysis based on a tissue clock (MRI)

Personalized Treatment in Acute Stroke



- 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

Treatment area:
chronic treatment



Raffin&Hummel 2018

Recovery phase

(1) Prediction of outcome (phenotyping)

(2) Best treatment for individual patients (precision medicine)

Can we do this by **standard** clinical CT/MR imaging data **alone** (lesion location, size…)?

Recovery phase

(1) Prediction of outcome (phenotyping)

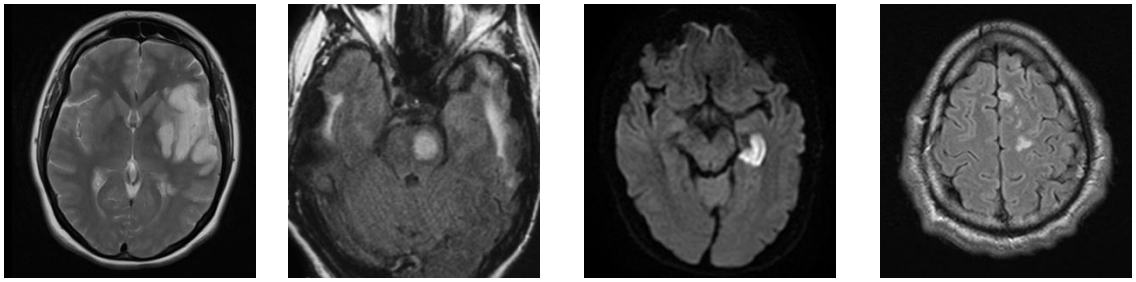
(2) Best treatment for individual patients (precision medicine)

Can we do this by **standard** clinical CT/MR imaging data **alone** (lesion location, size…)?

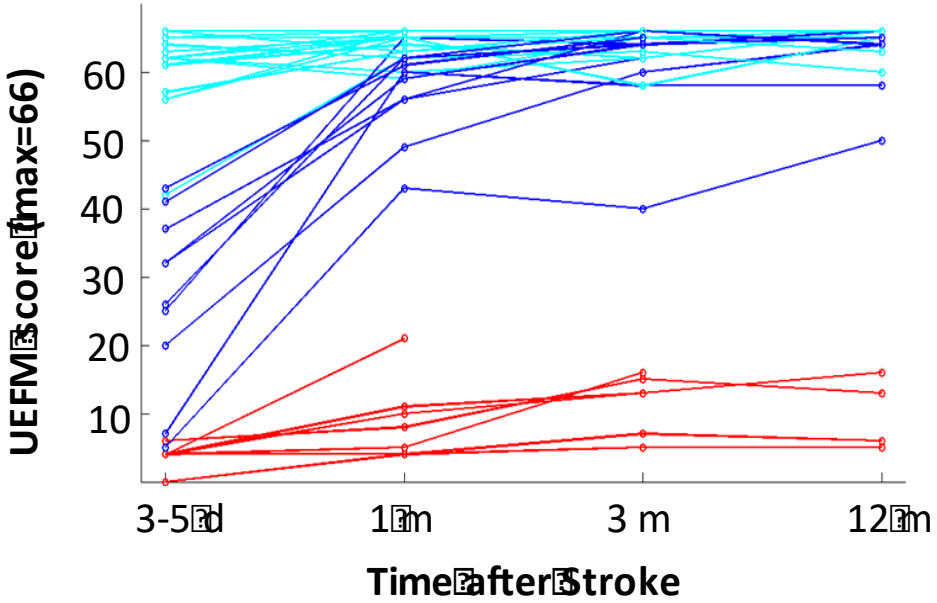
NO!

Recovery phase

Heterogeneity in lesion location



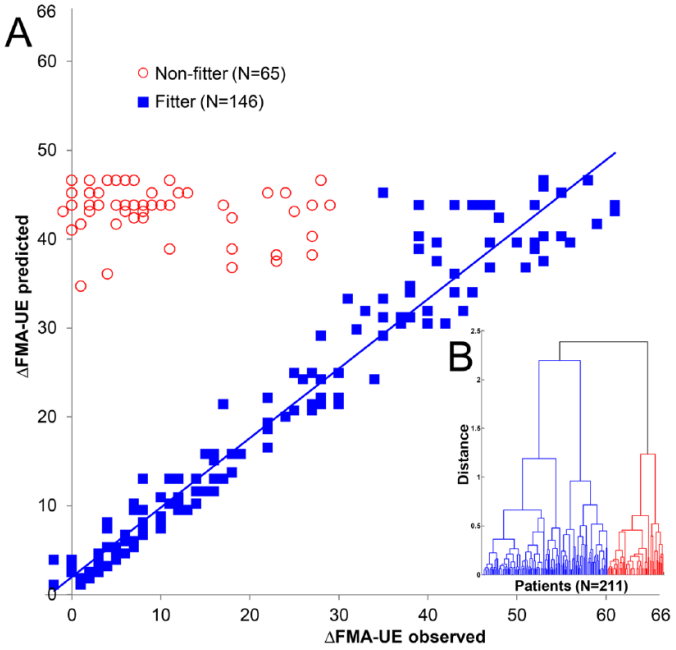
Heterogeneity in recovery



Recovery phase - heterogenity

Natural recovery vs. no natural recovery

Natural recovery
(fitters and non-fitters)

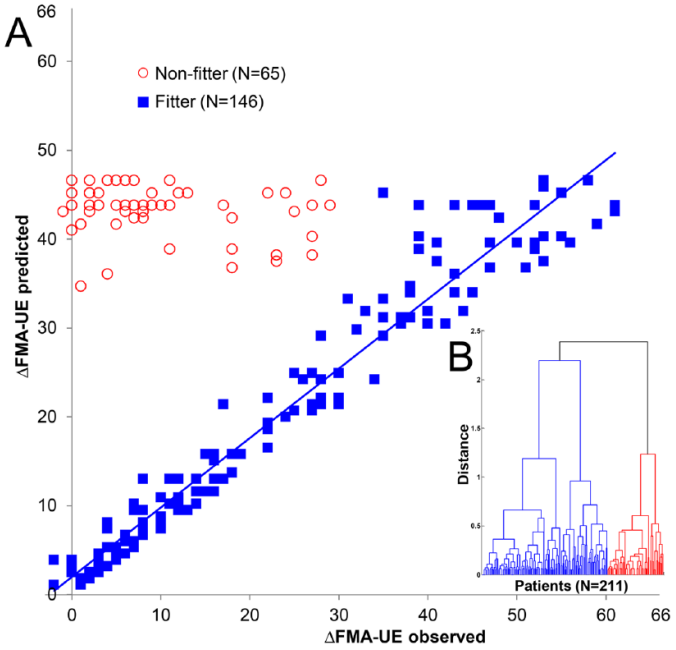


Winter et al. 2014

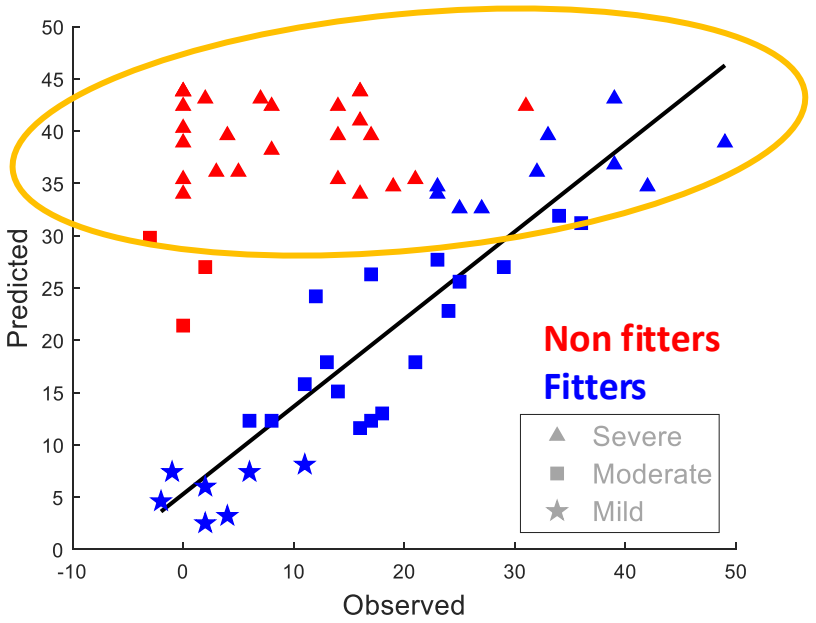
Natural recovery yes or no?

Natural recovery
(fitters and non-fitters)

Strong need for an early prediction
especially for severe patients
(treatment stratification)



Winter et al. 2014



Koch *et al.* 2021

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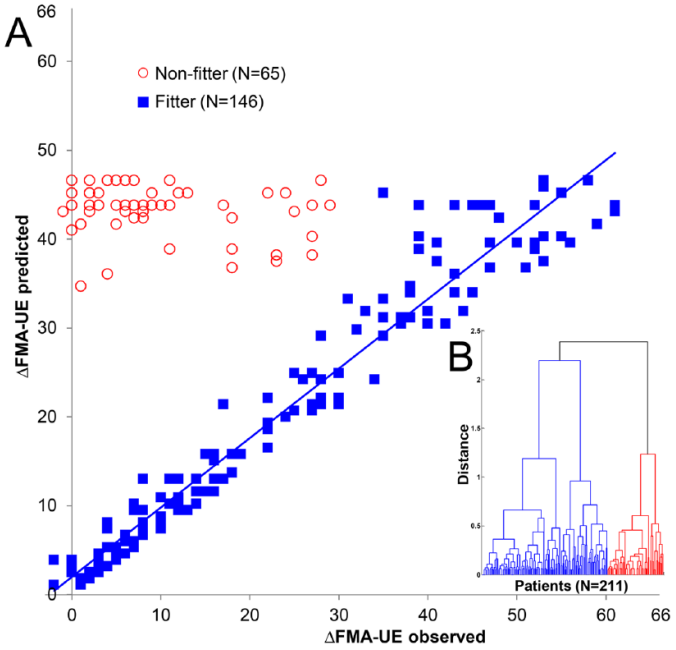
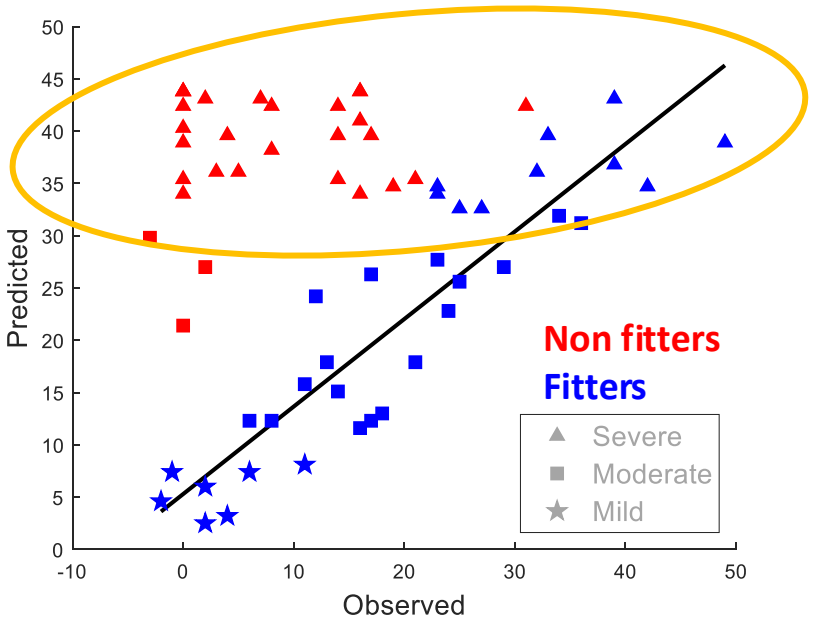
especially for severe patients
(treatment stratification)



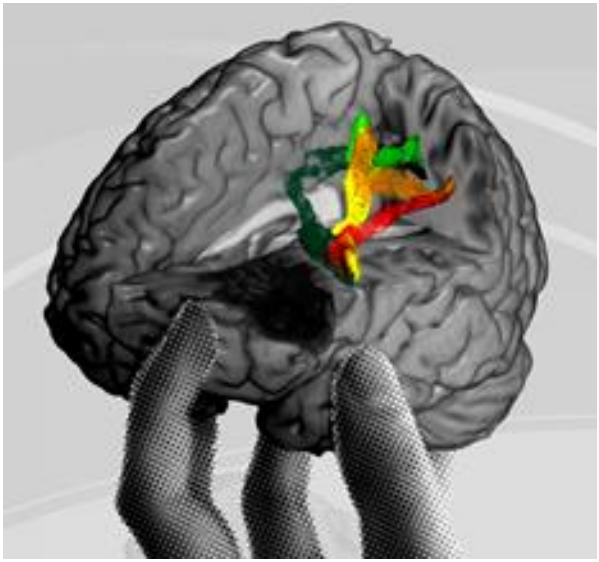
Winter et al. 2014



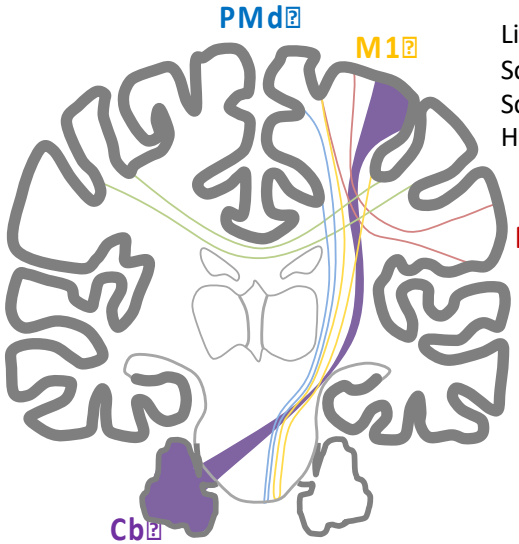
Koch *et al.* 2021

Can advanced neuroimaging and computational approaches help to address this problem ?

Stroke:
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**

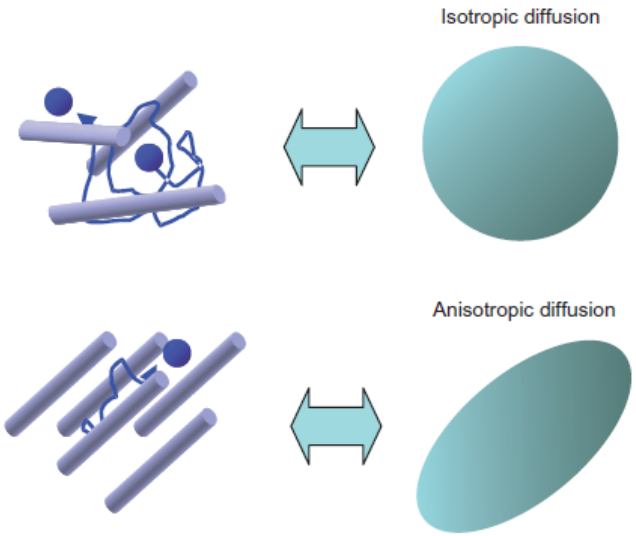
Schulz *et al.* 2015 **NeuroImage Clin**
Schulz *et al.* 2017 **Cerebral Cortex**

- **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**

For review Raffin & Hummel (2018) *The Neuroscientist,* Koch & *Hummel (2017) Current Opinion in Neurology*

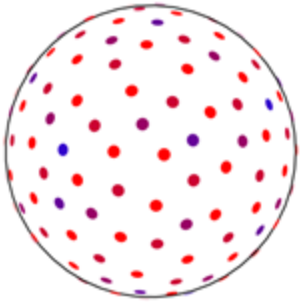
Structural MR imaging

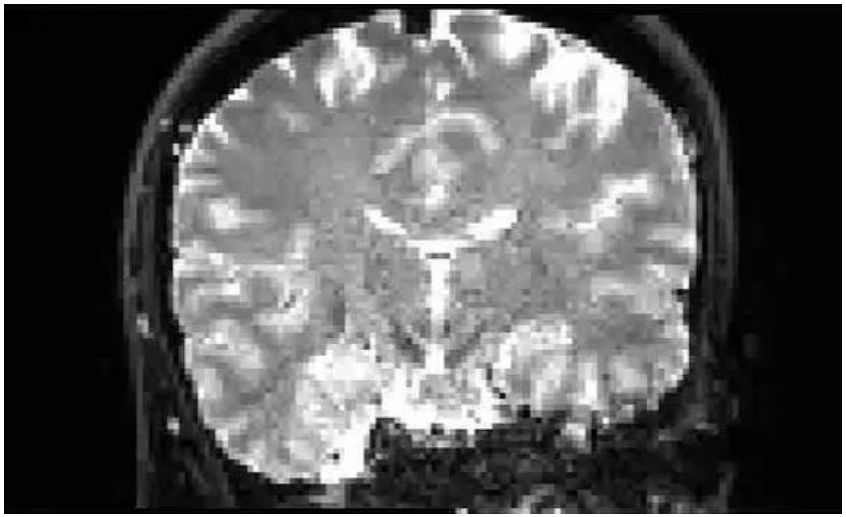
Diffusion weighted imaging (DWI)



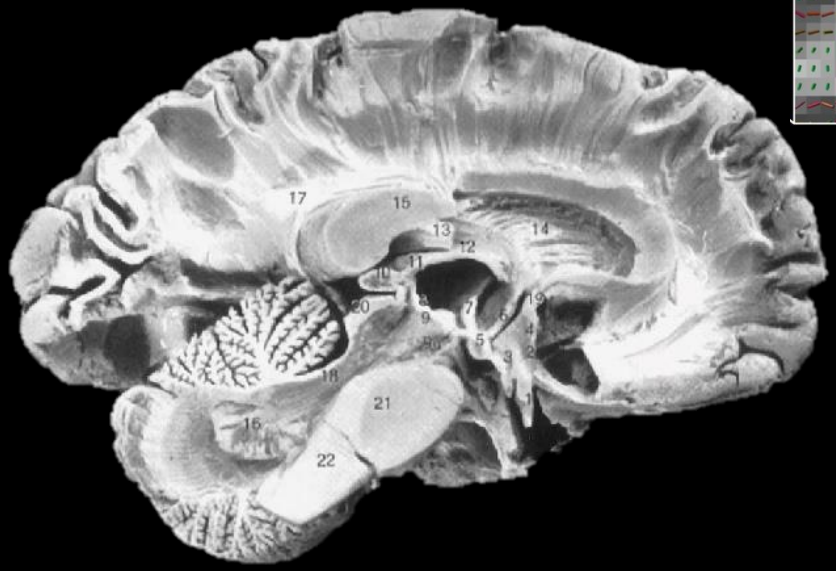
Mori 2014

Diffusion vector scheme

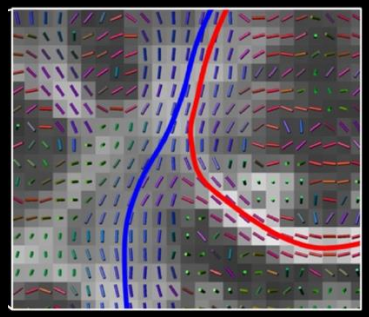




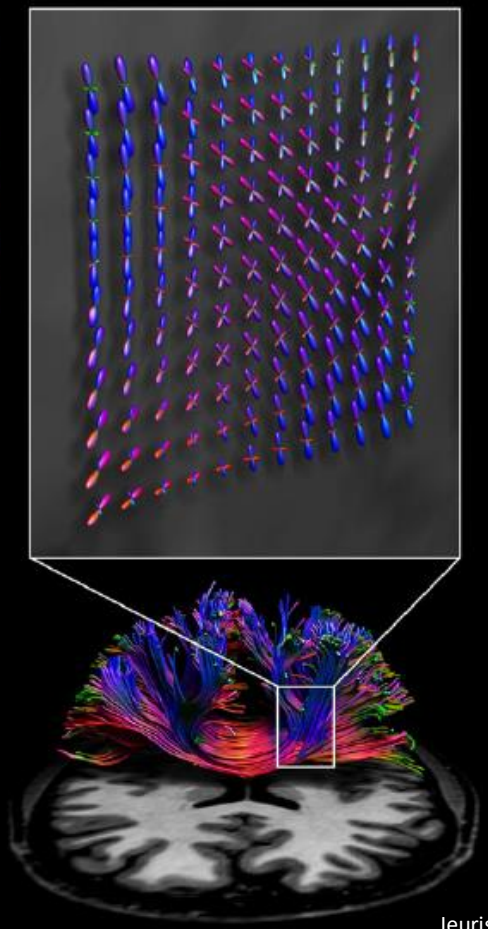
1. Tractography



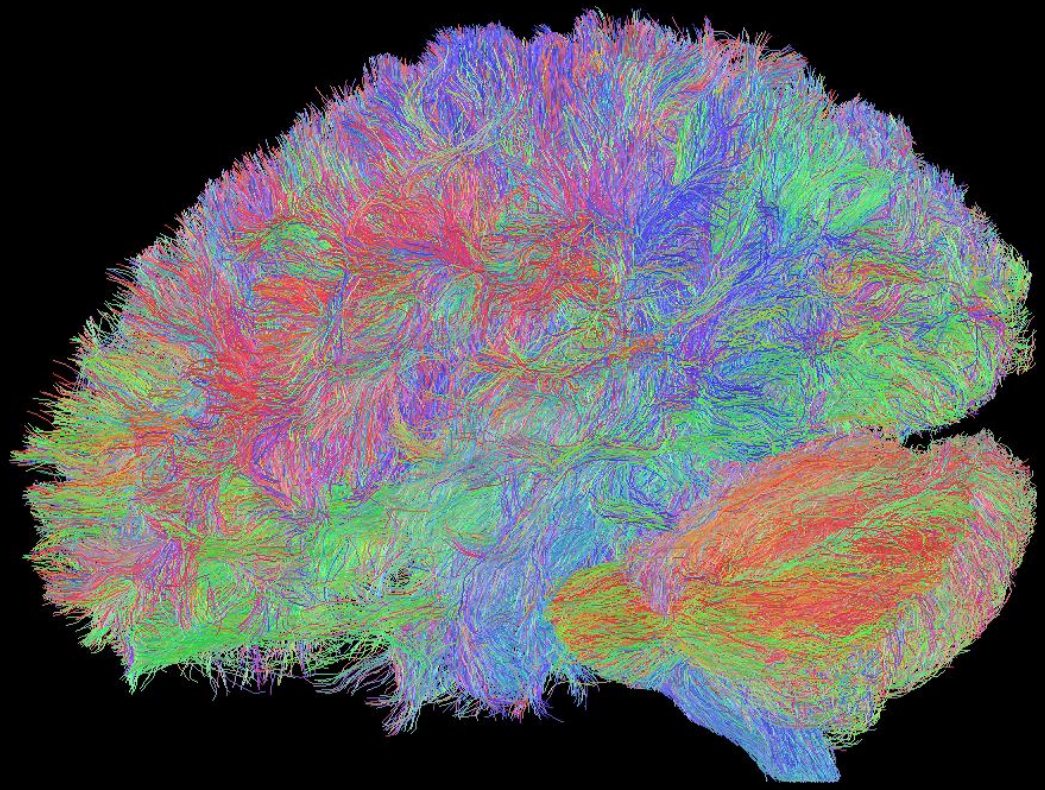
Huber 1971



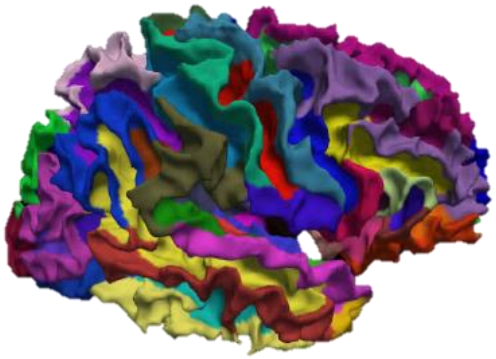
Non invasive



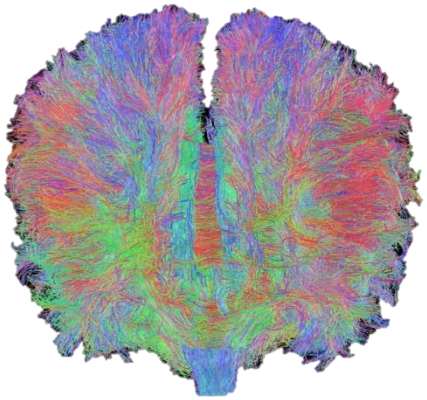
Jeurissen et al. 2019



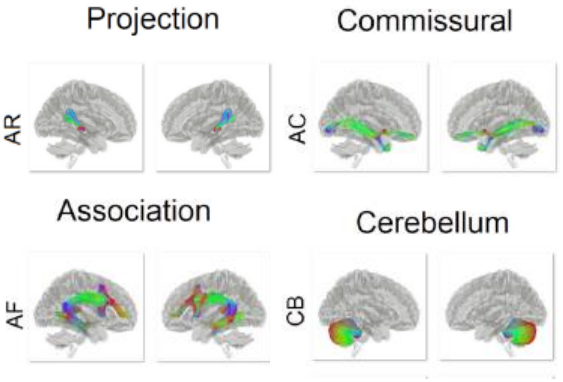
Structural MR imaging



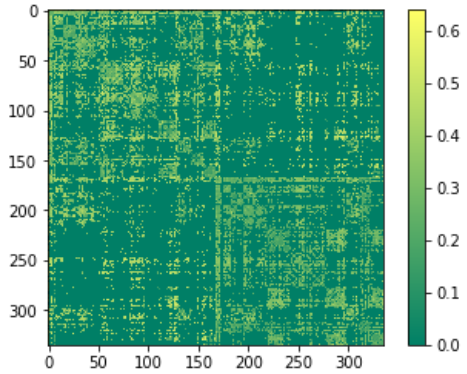
Brain parcellation



Tractography



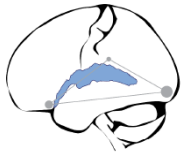
WM Fascicles Yeh et al 2018

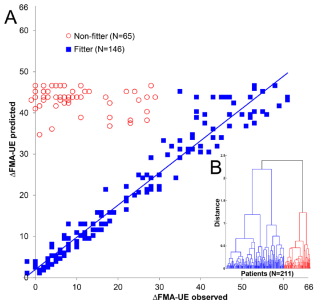


Connectome

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

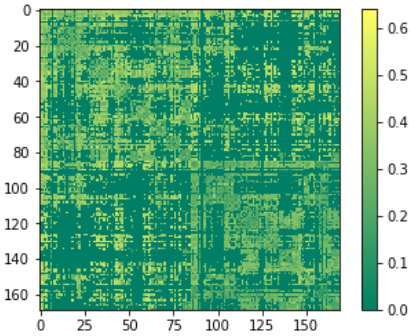
Classification of patients





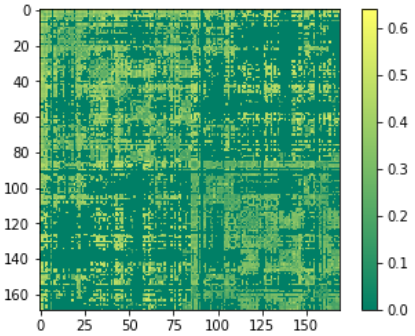
Can we predict Fitter and non Fitter using the connectome?

Initial Connectome 3 weeks



Residual/ Prerequisit

Change in Connectome 3months – 3 weeks



Degeneration/ Reorganizatio n

SVM - Classifier

Non fitters

vs.

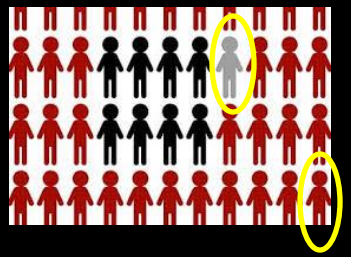
Fitters

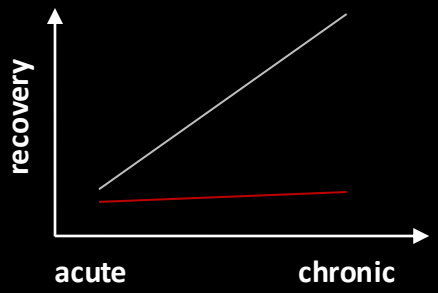
Koch *et al.* **Brain** (2021)

Phenotyping:
First results

Connectivity analyses

Prediction?



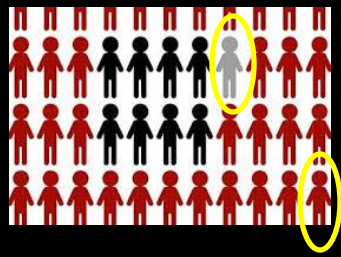


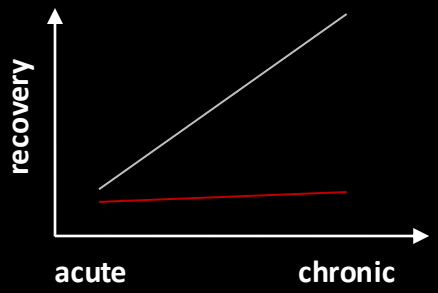
Koch *et al.* **Brain** (2021)

Phenotyping:
First results

Connectivity analyses

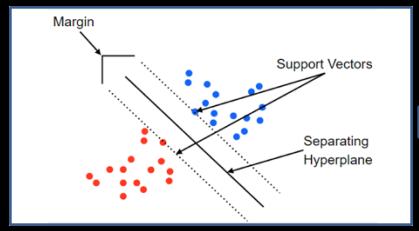
Prediction?



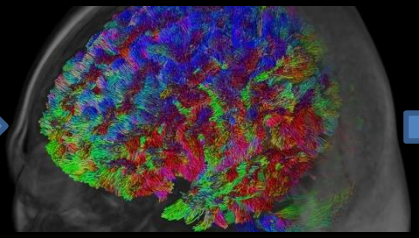


Prédiction ✓: combination of whole brain connectivity analyses and machine learning allowed to predict the degree of recovery already after 2 weeks!

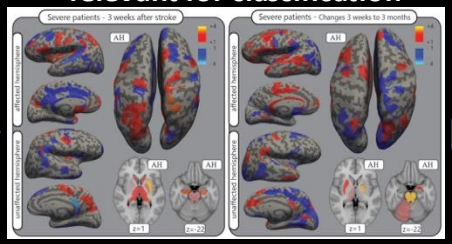
Support Vector Machine (SVM) classifiers



Whole brain tractography



Connectome relevant for classification



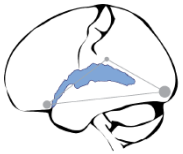
Classification/Prediction

Subgroup	Accuracy	Precision
Severely impaired patients	0.92	0.93
2 weeks after stroke		

Subgroup	Accuracy	Precision
Severely impaired patients	0.92	0.93
2 weeks to 3 months		

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

Classification of patients



- Modern MRI imaging and computational approaches allow to **classify** and **phenotype** patients
- Adds to **prediction** of outcome
- Will **guide personalized** treatments

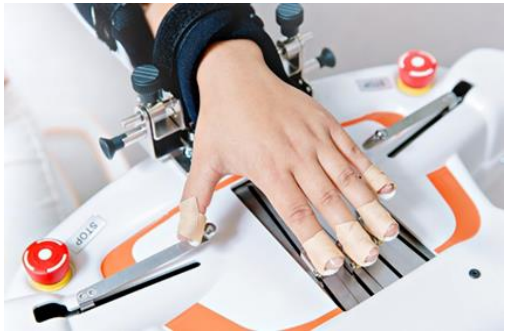
Summary

- **Large scale** clinical imaging strongly adds to **improve** stroke care (acute treatment)
- Supports acute **decision** making

- To develop **biomarkers** for patient **'phenotyping'** to **predict** outcome, course of recovery, treatment response classical clinical data might not be sufficient, even when on large scale available
- To achieve this, **specific, 'rich'** data sets are needed
- **Population-based**, easy **accessible**
- **Academic** and **non-academic** clinical environments

- **Standardizing** methods (clinical, imaging, electrophysiological, analytical)
- **Feasibility** for daily clinical life

Interventional strategies to enhance recovery

Raffin & Hummel (2018) *Neuroscientist*

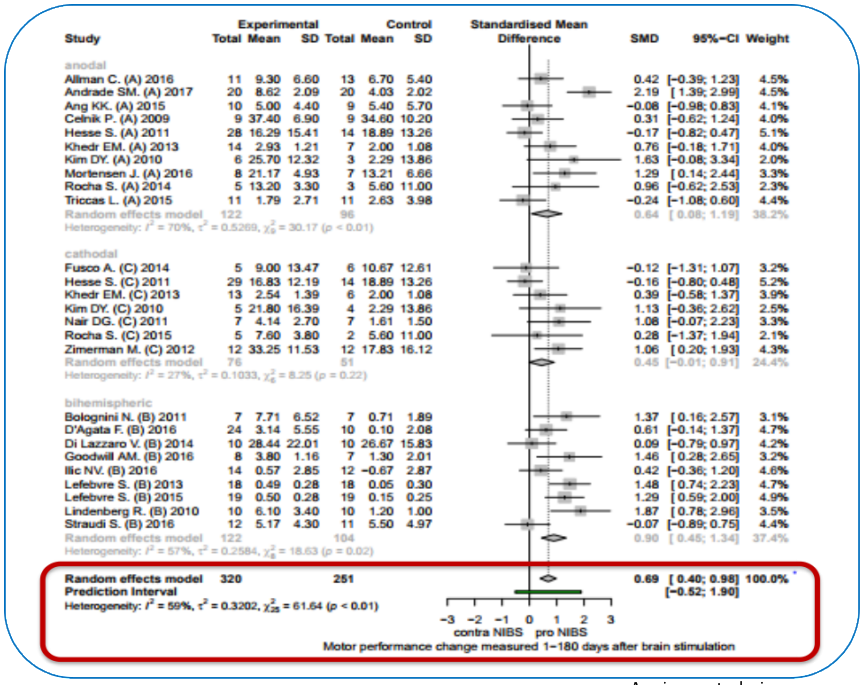
Non-invasive brain stimulation (NIBS) in Rehabilitation

- based on animal (e.g., Nudo et al. 1996) and human work (e.g., Murase et al. 2004) good evidence for the M1 as 1st target
- Up to know: 'one suits all strategy'
- promising results, but…

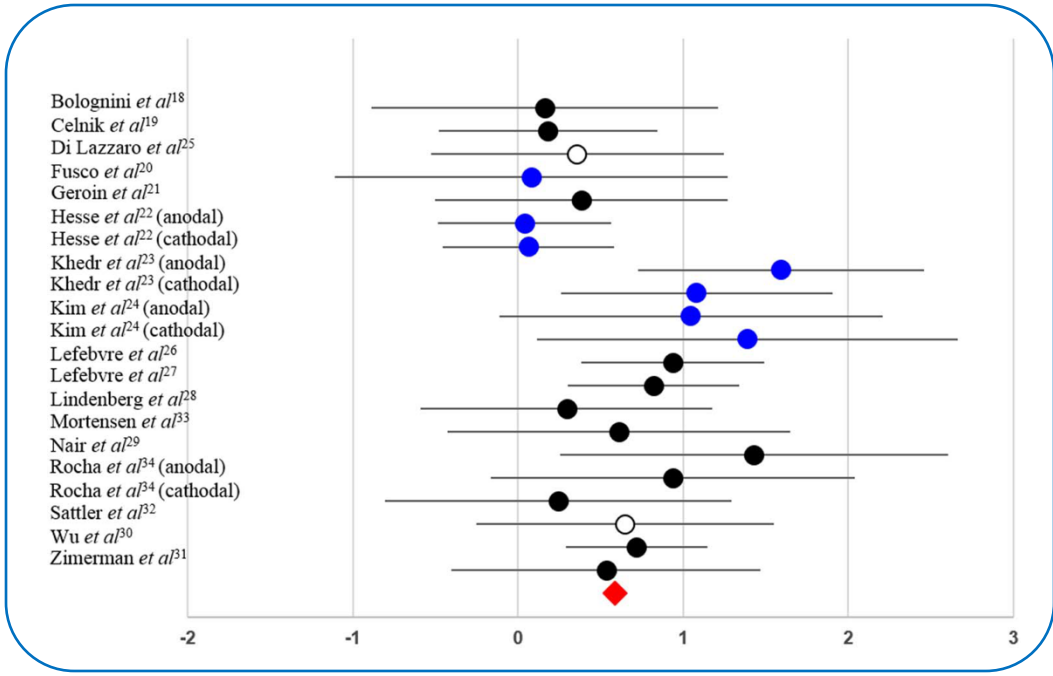
e.g., Hummel & Cohen (2006), Wessel et al (2015)

Response to Neurotechnology: -limited-

Example non-invasive brain stimulation



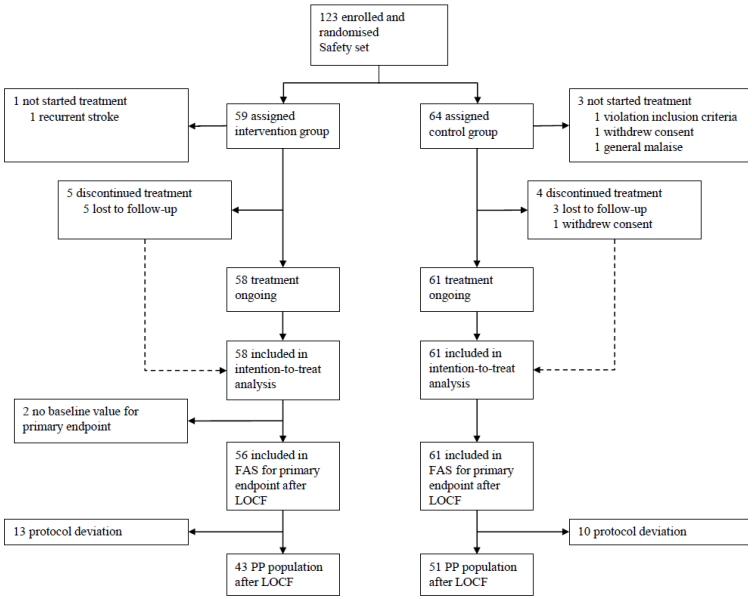
Anziano et al., in press

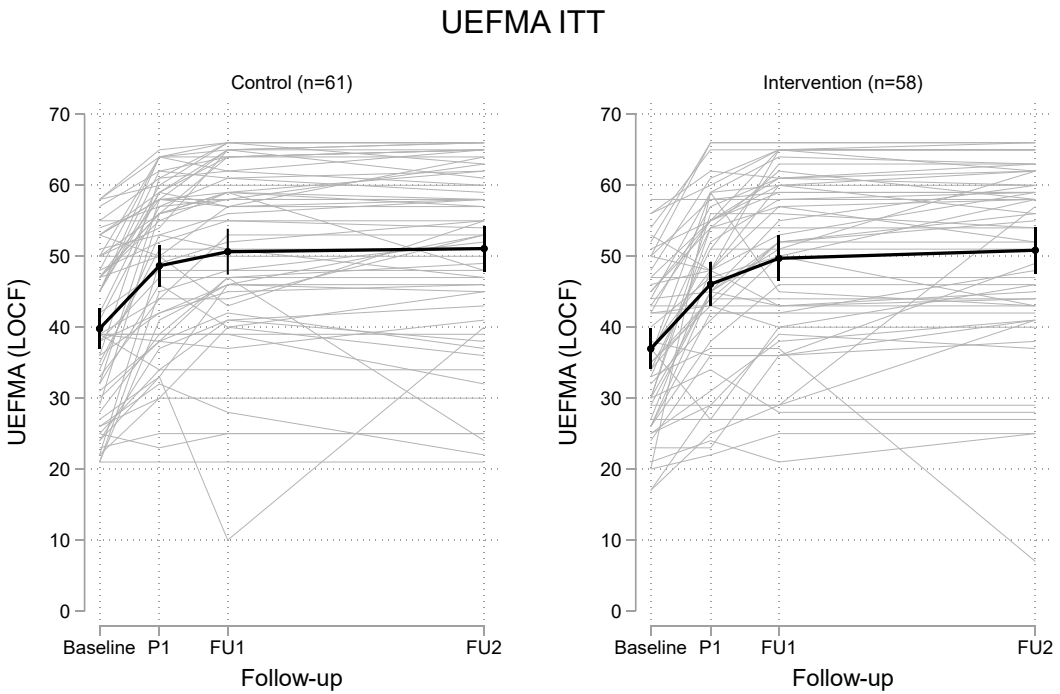


Kang et al., 2015

- Non-satisfying treatment responses
- Heterogeneous treatment responses
- Responders, non-responders

Dilemma: Imprecision Medicine

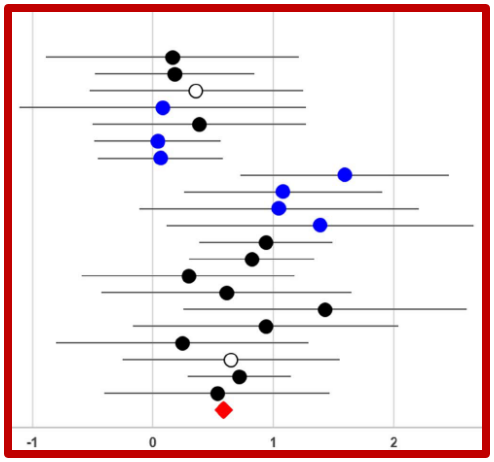




Gerloff et al The Lancet Regional Health – Europe 2024

Dilemma: Imprecision Medicine

Heterogenous Patient Population

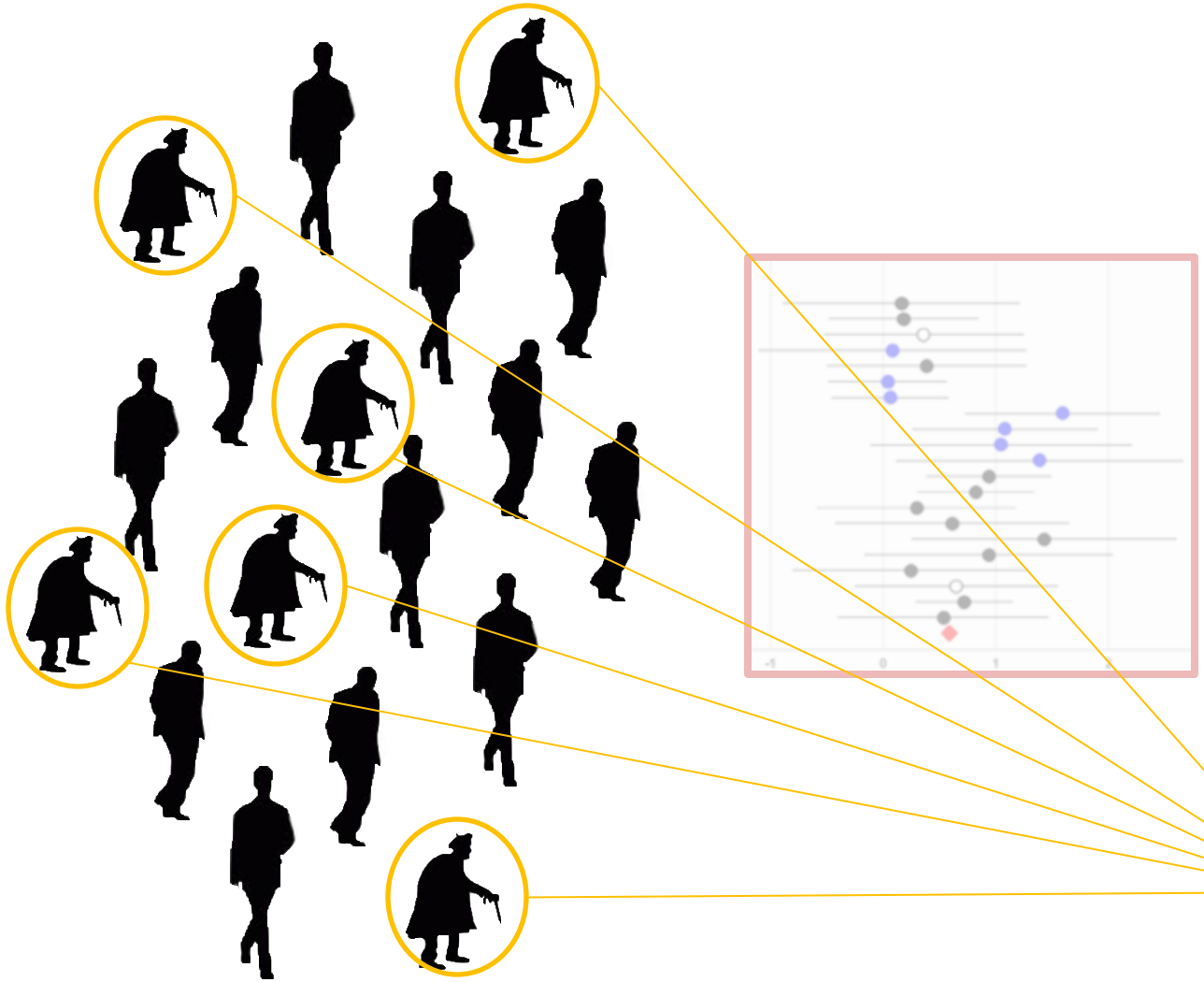


‘One suits all’ treatment

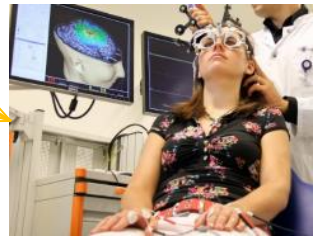
Different Treatment Opportunities

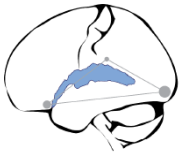
Personalized Precision Medicine

Heterogenous Patient Population



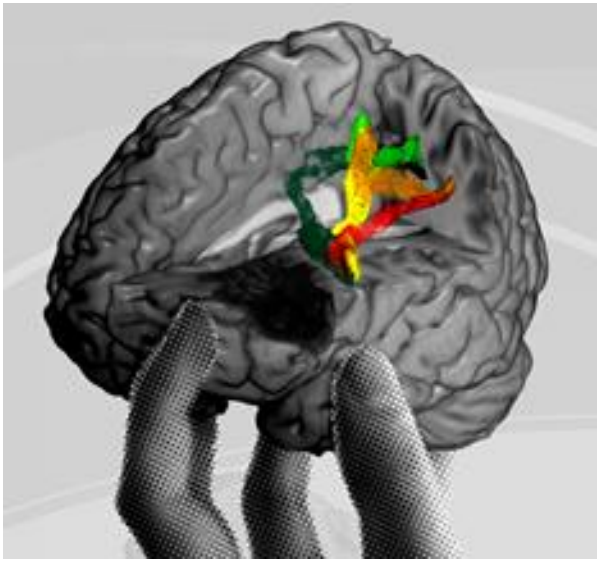
Different Treatment Opportunities





The basis for precision medicine are biomarkers for phenotyping of stroke patients allowing to stratify them for treatment

Stroke:
network disorder



Boenstrup *et al.* 2015 **RNN**
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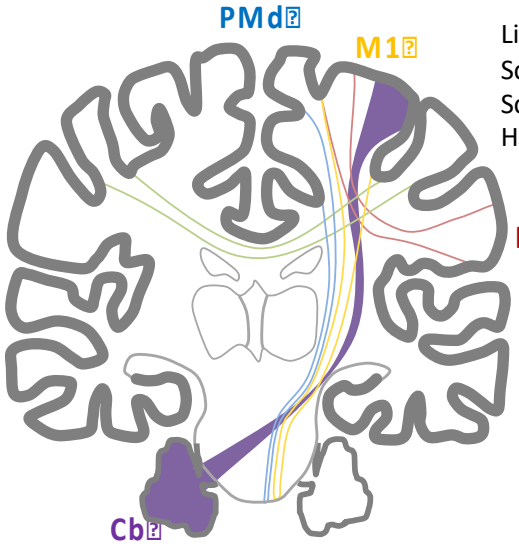

Liuzzi *et al.* 2014 **Neurology**
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Schulz *et al.* 2017 **Cerebral Cortex**

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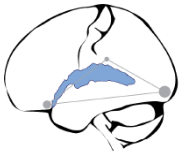
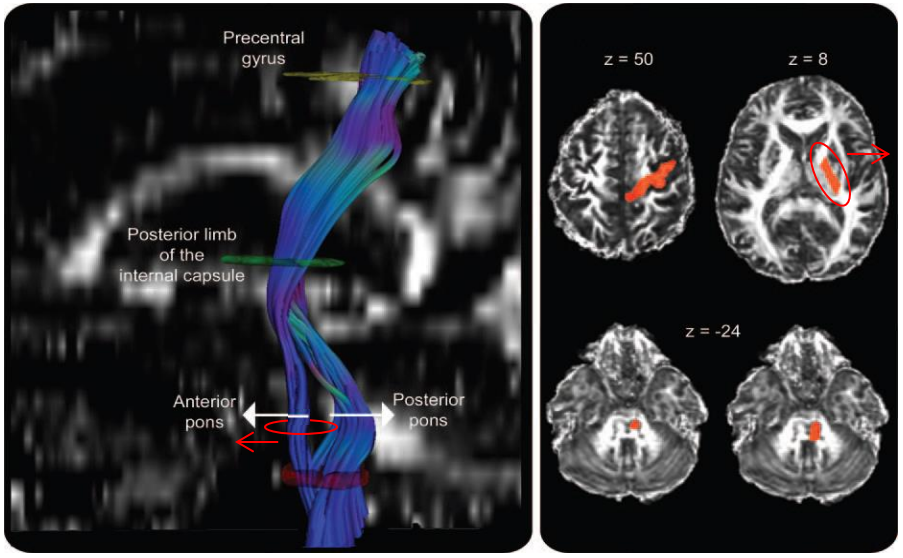
- **Stroke is a network disease** (Schulz *et al.* 2012, 2015, 2017, for review Koch & Hummel 2017; Grefkes & Fink 2014)
- **Massive changes and reorganization during the course of recovery**

For review Raffin & Hummel (2018) *The Neuroscientist,* Koch & *Hummel (2017) Current Opinion in Neurology*

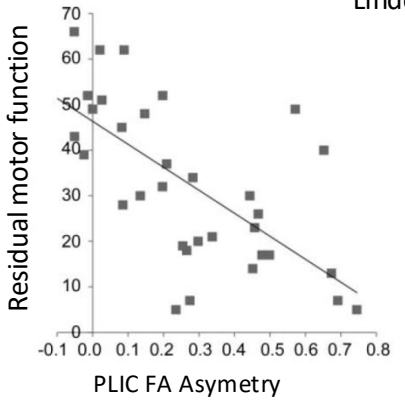
Prediction of residual motor function:
CST damage



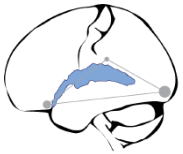
In vivo structural MR-based Imaging (DTI)



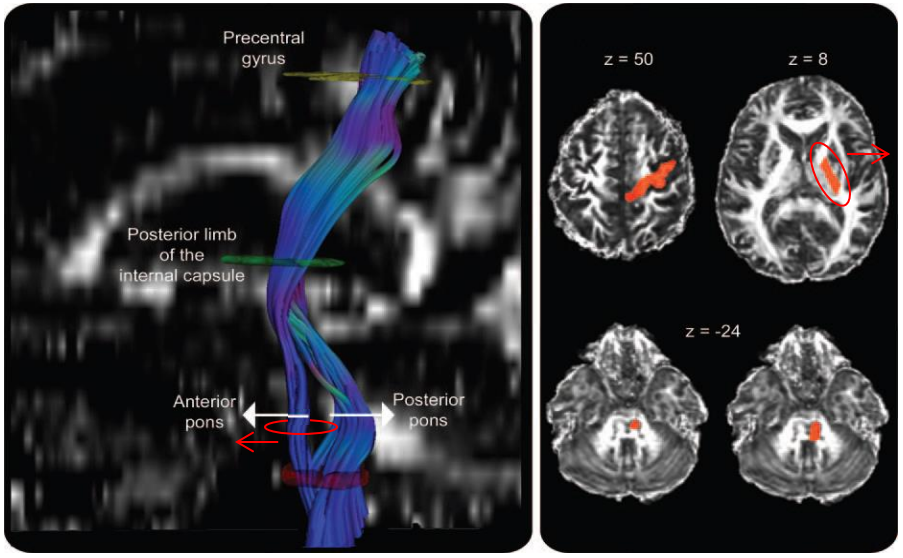
Lindenberg et al. (2010)



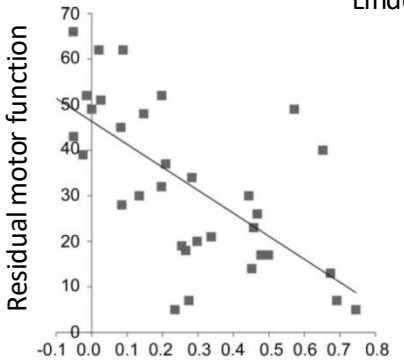
Prediction of treatment response: brain stimulation M1



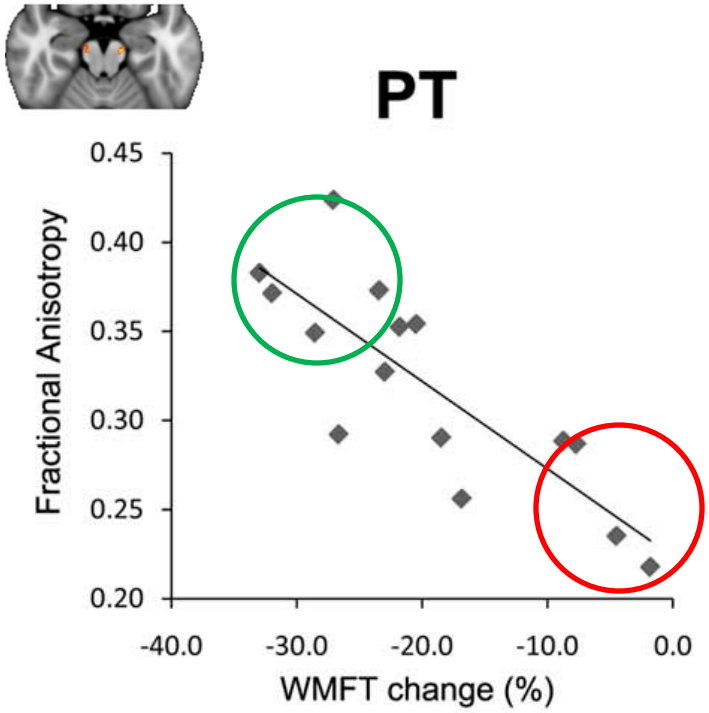
In vivo structural MR-based Imaging (DTI)



Lindenberg et al. (2010)



5 days of bihemispheric tDCS + PT/OT

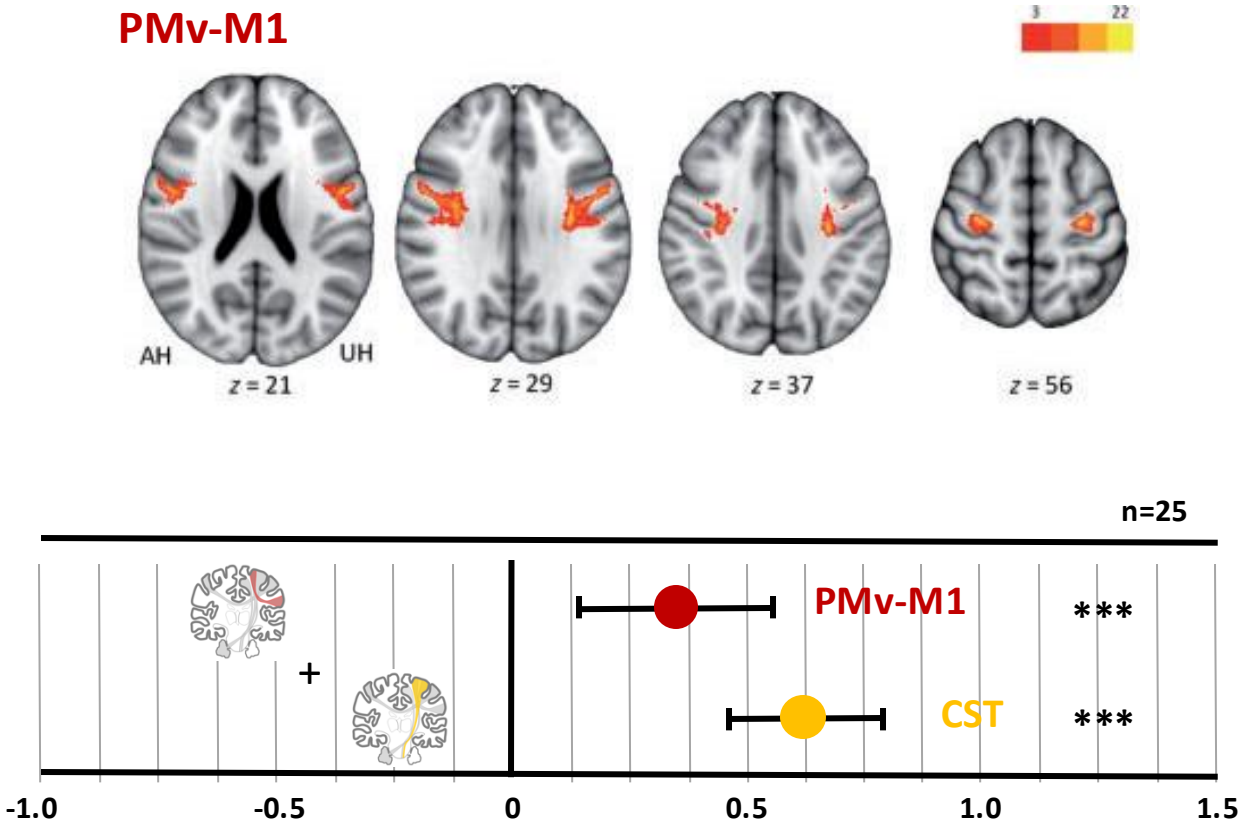


Lindenberg et al. (2012)

CST damage matters for brain stimulation **effectivity**!

For review Koch *et al.* (2016) *Annals of Translational and Clinical Neurology*

Interregional network changes:
cortico-cortical



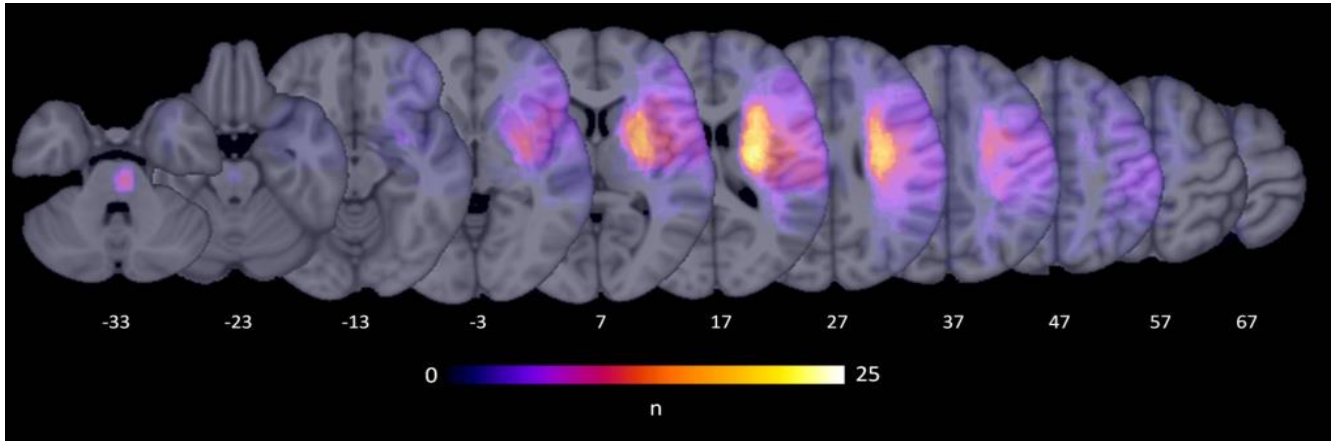
Structural integrity between PMv and M1 is associated with the degree of recovered function, additional to structural integrity of the CST!

Adapted from Schulz, Koch *et al.* (2015) *Brain*

Interregional network changes:
Interaction of structural connections

In cooperation with Prof. Yun-Hee Kim, Seoul

- n=53 stroke patients, 3 months after stroke
- heterogenous lesions and function (UEFM 40.8±19.1, range 4-66)
- DTI-based structural imaging
- Defined network: M1-PMv-PPC
- Patients **stratified** due to the **degree** of CST integrity (damage)

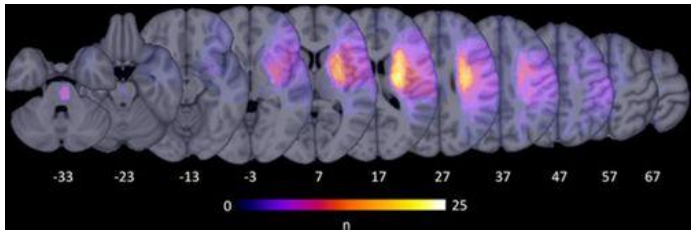


Schulz *et al.* (2017) *Stroke*

Interregional network changes:
Interaction of structural connections

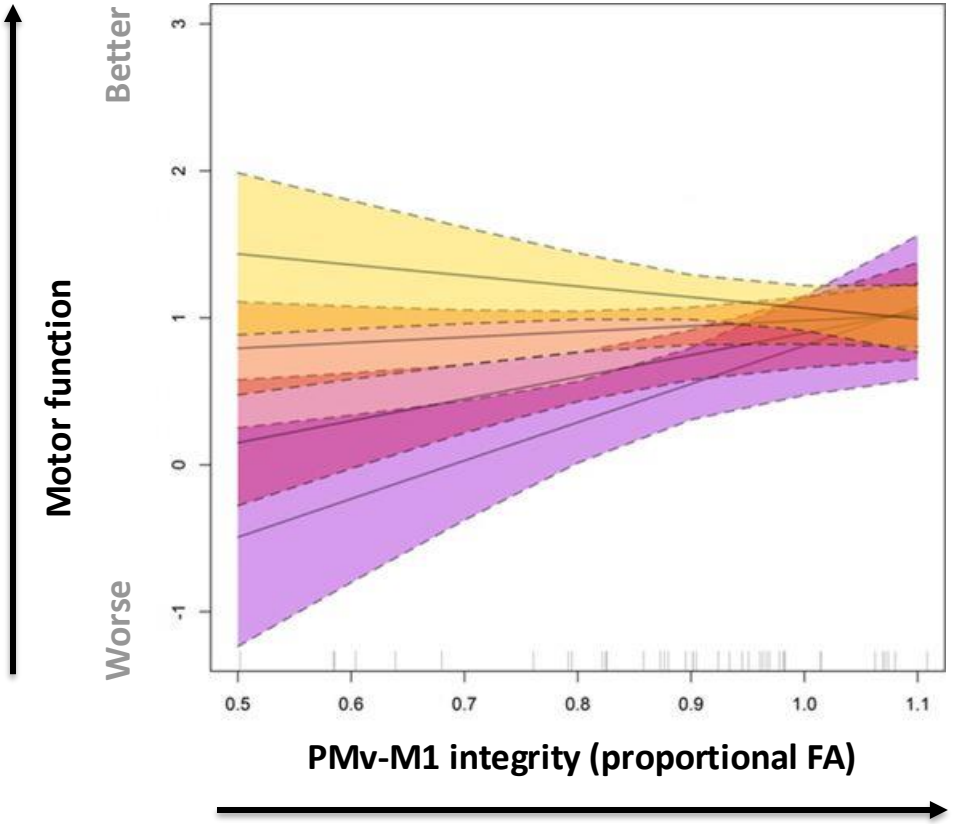
Degree of damage in one brain area determines the functional role of another one

N = 53 subacute brain stimulation



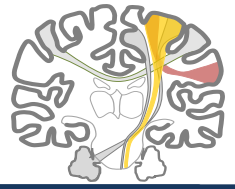
CST Integrity
(proportional FA)

0.6 0.7 0.8 0.9



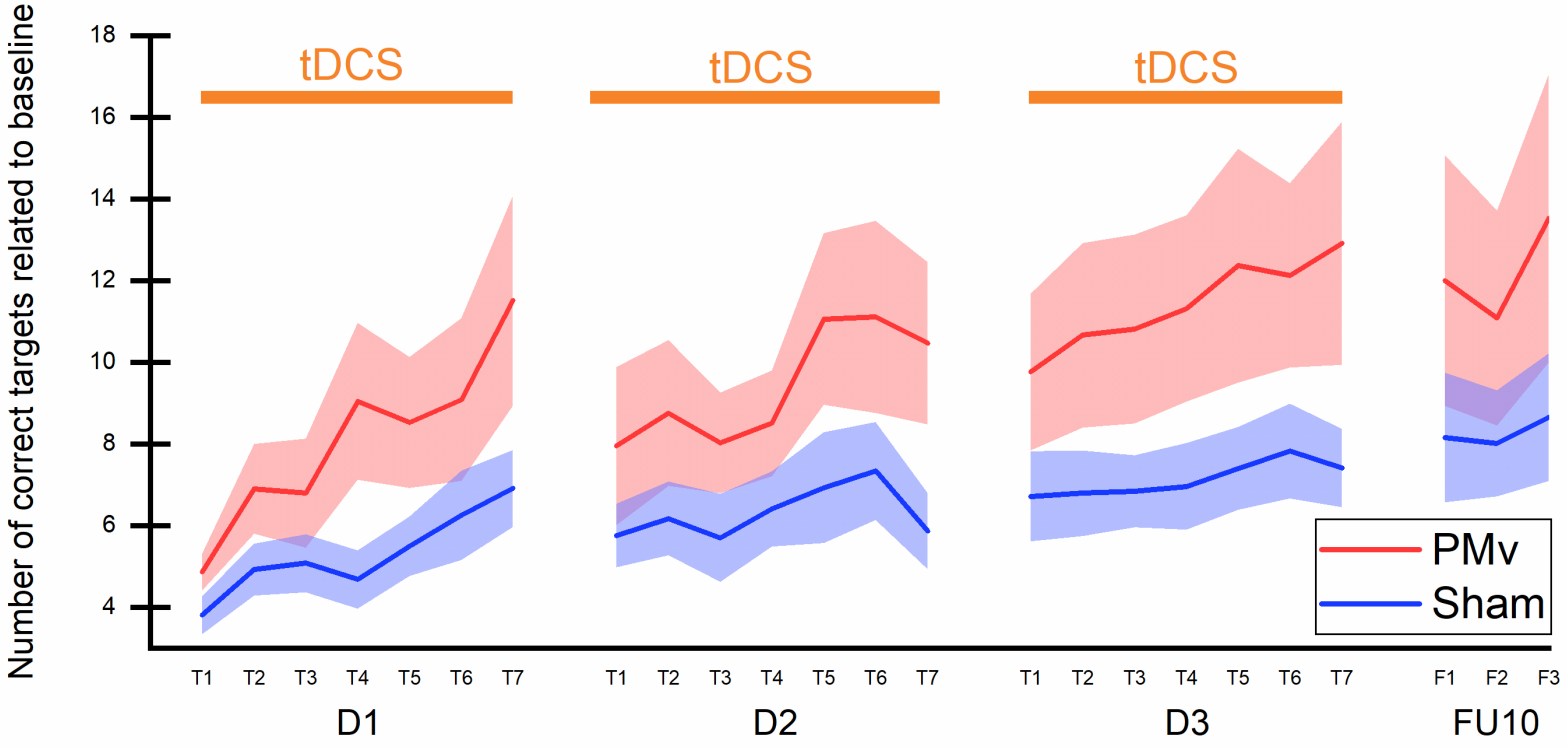
Schulz *et al.* (2017) *Stroke*

Interregional network changes:
Interaction of structural connections



Brain Stimulation to the vPM

N = 20 chronic stroke patients
Double-blind, sham-controlled, parallel design, sequential grip force modulation task



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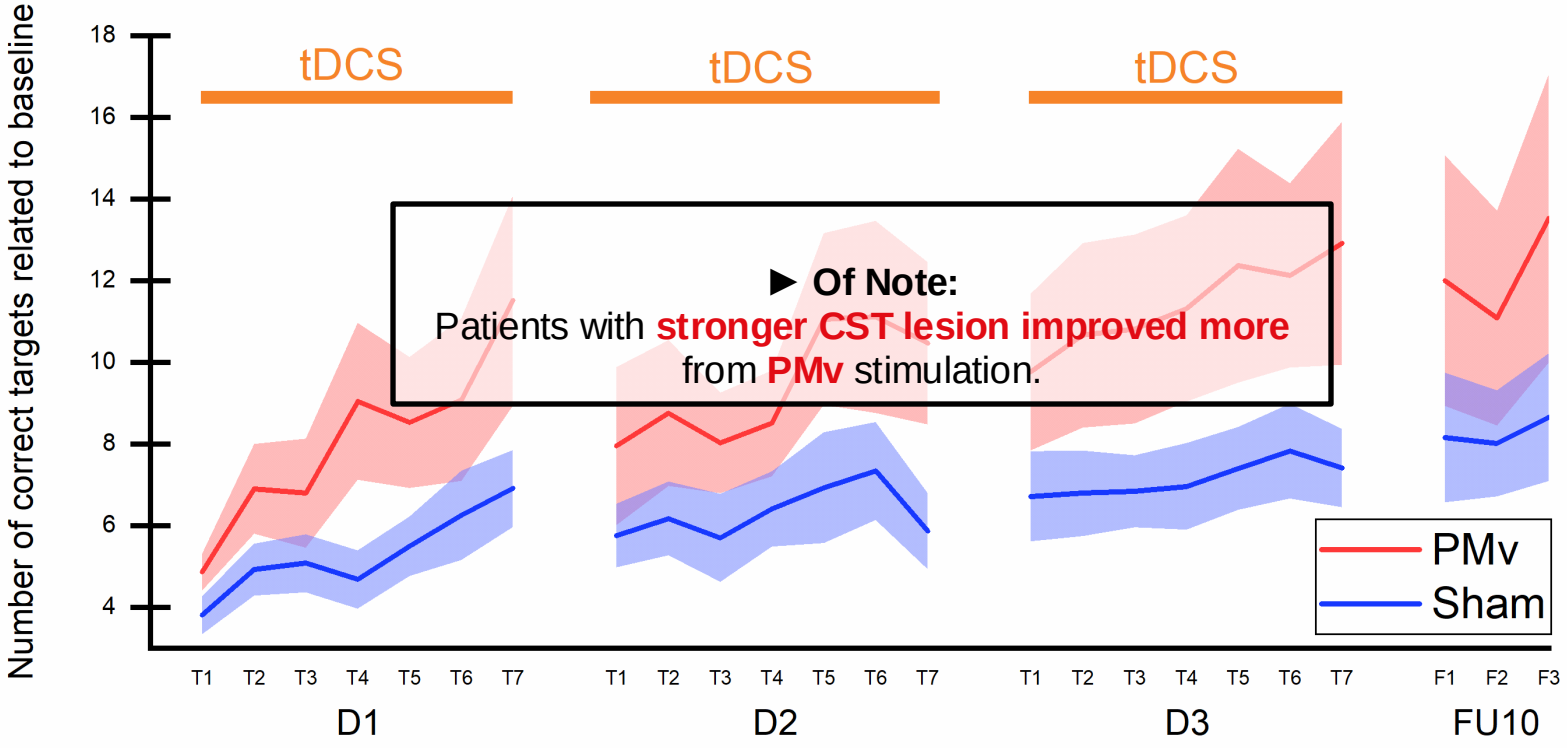
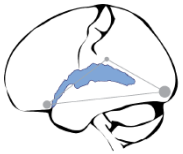
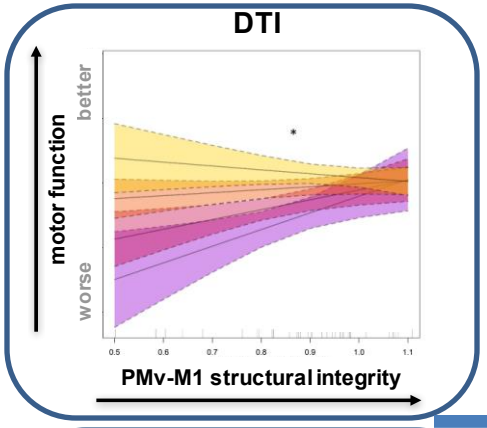
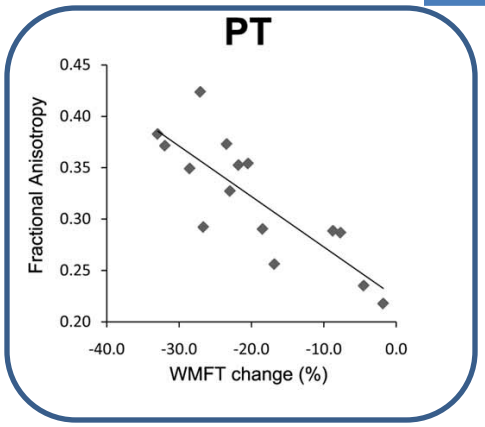


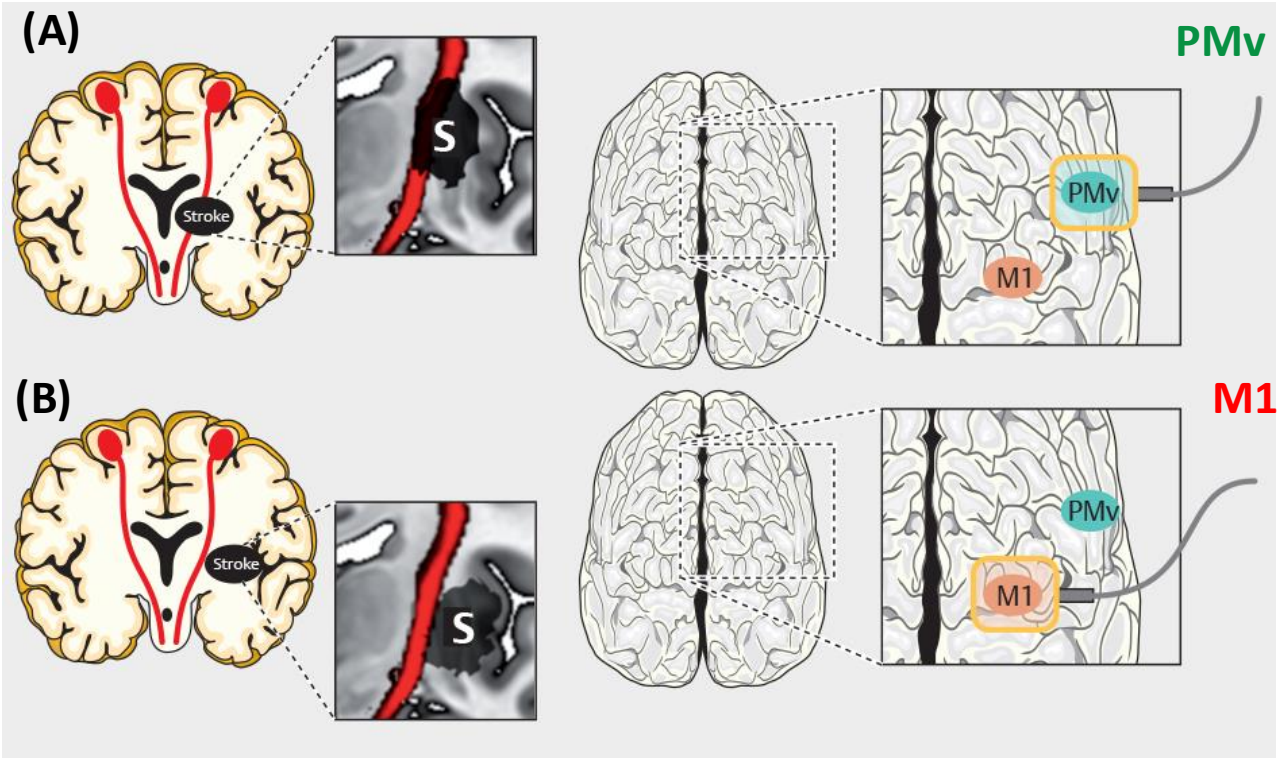
Towards biomarkers of phenotyping: treatment stratification







Phenotype **Personalized intervention**



(A) CST **significantly** lesioned	(B) CST **mildly** lesioned
Limited answer to M1 NIBS Strong answer to PMv NIBS	Strong answer to M1 NIBS Limited answer to PMv NIBS

Koch & Hummel (2017) *Current Opinion in Neurology,* Morishita & Hummel (2017) *Current Behavioral Neuroscience Reports*

Summary

- (Neuro-) Technologies are **promising** towards personalized health (neuropsychiatric disorders, neuroenhancement)
- Need to develop **patient-tailored**, **precision medicine**-based treatments
- **Computational approaches** (data access, machine/deep learning) will **facilitate** these processes in a cost-effective way
- **Computational approaches** (data access, machine/deep learning) will **provide** access

- Strong need of **understanding**, **biomarkers** based on this, novel **data acquisition tools** and **neuro-technology** based treatments

- **Change** in study design (from RCTs to patient-tailored trials)

Questions?

Coffee break