UNIVERSITY of WASHINGTON

Advances in Stroke Recovery:

A Physical Medicine and Rehabilitation Perspective

Nicole Mazwi, MD
Associate Professor
Director of Stroke Rehabilitation
Department of Rehabilitation Medicine


TOLEDO


MICHAEL E. DEBAKEY
HIGH SCHOOL FOR HEALTH PROFESSIONS

Outline

- When:
  - Acute care physiatry
- What:
  - Biomarkers
- How:
  - Treatments
    - Medications
    - Activity
    - Brain stimulation

A Paradigm Shift

Stucki et al, Disabil and Rehab, 2005
Rusk, Can Med Assoc J, 1949

Physiatry in Acute Care

Acute Management

Prognostication/ Goal-setting

Disposition

Acute Management

We have many arrows…

- Early mobility options and techniques
- Spasticity and contracture management
- Bracing prescription and application
- Use of electrical nerve and muscle stimulation in immobilized patients
- Delirium management
- Agitation management
- Sympathetic hyperactivity management
- Neurogenic bowel/bladder management
- Sleep-wake cycle regulation
- Appropriate use and timing of stimulant therapy
- Evaluation and management of patients with DoC
- Patient/family education
- Identifying barriers to rehabilitation candidacy
- Continuity of care for patients transitioning to the floor

etc….

ICU-acquired Impairments in Stroke

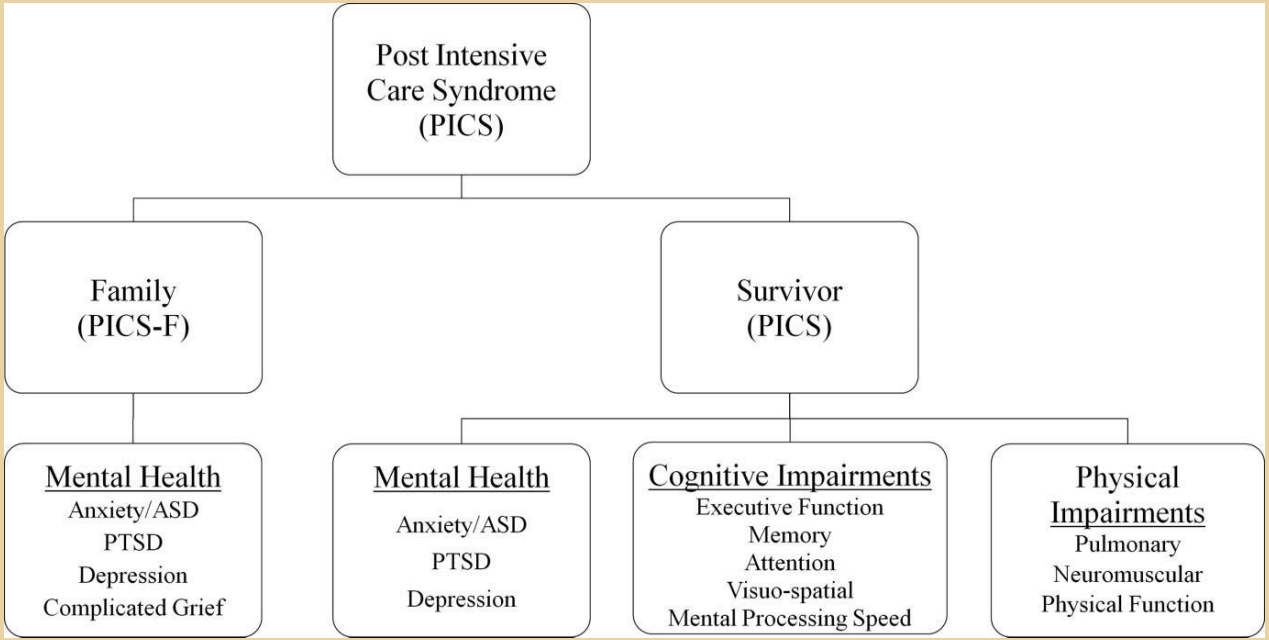
- ***ICU-acquired weakness:*** 25-60%
  - Muscle strength loss: Up to 5% per week of bedrest
  - Detectable weakness in up to 1/3 patients on MV for 7 days
- ***Delirium:*** 50-80% surgical, trauma, burn ICU
- ***Psychiatric symptoms:*** 28% (depression), 24% (anxiety), 22% (PTSD)

- Problems persist beyond acute care hospitalization
  - Loss of muscle bulk, proximal muscle weakness, fatigue evident at 1 yr follow-up

Herridge, et al., NEJM 2003
Banarjee et al, Curr Opin Anaesthesiol. 2011
Rawal, Yadav, & Kumar, 2017; Desai, Law, & Needham, 2011)

Post-Intensive Care Syndrome (PICS)

*New or worsening impairments in **physical**, **cognitive**, or **mental health status** arising after critical illness and persisting beyond acute care hospitalization.*



(Needham, et al, Crit Care Med, 2012)

Sleep-wake Cycle Disruption

- Up to 70% of neuro patients
- Poorer functional recovery, depression, cardiac and cerebrovascular morbidity
- In a recent study in hyperacute stroke, physiologic sleep cycles were universally absent
- Suspicion for OSA must be high

- Management Effort for Delirium and Insomnia in Patients with Acute Ischemic Stroke (MEDIAS) study:
  - #1: Sleep hygiene - Minimizing disruptions and turning lights on or off in the hospital room to mimic actual time of day are steps that can be easily implemented.
  - Pharmacotherapy: zolpidem improving sleep but also providing neuroprotection and improved functional recovery.
  - Melatonin well-tolerated, low potential for dependence - reinforce normal circadian rhythm

Agitation

- Up to 86% of neuro patients in the ICU
- DDx: central, constipation, pain, urinary retention, delirium, anxiety, seizure, new ICH, PTA, hypoxia, PSH

Management:

- Conservative: redirection, 1:1, net beds, restraints, delirium precautions, mobilization
- Dexmedtomidine – may lower risk of delirium compared to benzos and opioids
- Beta-blockers – reduction in Overt Agitation Scale
- AEDs – VPA (less sedation, cog impairment), CBZ (irritability, disinhibition)
- Antipsychotics/Neuroleptics – atypicals, Haldol?
- Benzodiazepines – midazolam, lorazepam (cog impairment, slow recovery)

Ganau et al. 2018

Hypoarousal

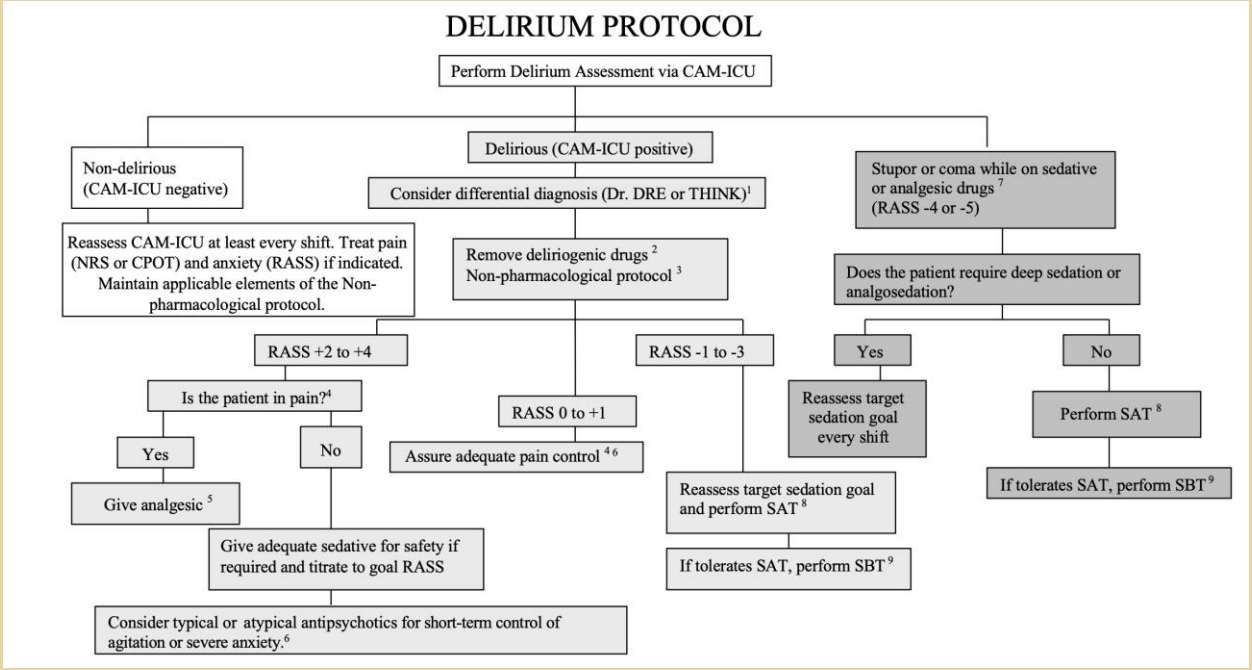
Barrier to participation in early rehab efforts and transitioning to the next level of care.

Modafinil, amantadine and methylphenidate prescribing patterns have recently been studied in the ICU setting with low rates of adverse events and improved GCS score in TBI and stroke patients.

Modafinil in Recovery after Stroke (MIRAS) study: early use of modafinil to treat fatigue and lethargy in patients with moderate to severe stroke was associated with improved discharge disposition without significant adverse events.

Mo et al. J Clin Pharm 2018
Barra et al. Neurorit Care 2020
Leclerc et al. Neurocrit Care 2020
Giacino et al. NEJM 2012

Delirium



icudelirium.org

Spasticity

- 5-40% of patients after UMN injury (higher in patient with initial UE impairment
- Hemorrhagic stroke > ischemic subtypes
- Severe paresis > minor paresis
- Rarely in acute stroke but important to identify early
- Impaired mobility, difficulty with ADLs, pain, increased caregiver burden.

- Treatment:
  - Non-pharmacologic: NMES, ROM (moderate quality evidence), splints, serial casting
  - Pharmacologic: Tizanidine, Dantrolene, Valium, Baclofen, Botox
    - Possibility of early motor recovery and fluctuations tone

Sunnerhagen et al. Annals PM&R 2019

Early Mobilization

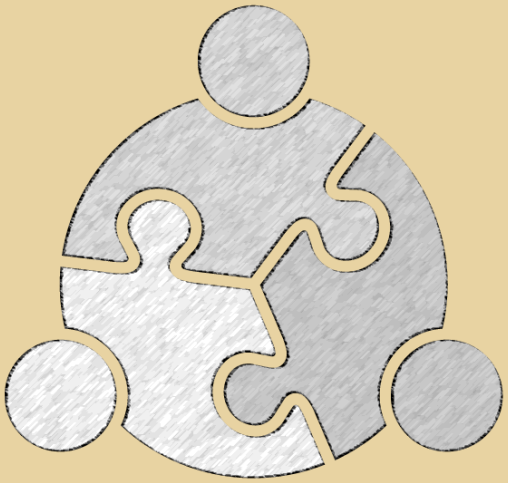
Application of physical activity within the first 2 to 5 days of critical illness or injury

(Cameron et al., 2015)

- ROM/Active-assisted exercises
- Bed mobility activities
- Cycle ergometer
- ADLs
- Transfer training
- Postural stability, static and dynamic balance
- Ambulation with or without mobility aids

(Morris et al., 2008; Needham et al, 2010; Goodson et al., 2017)

Biomarkers: Outcomes



Some basic principles:

PM&R has a *long* lens

Acute care teams tend to the nihilistic

Recognize multilaterality of goal-setting

- Huddle in advance
- Family expectations must be clear
- "Environmental" considerations are 2ndary

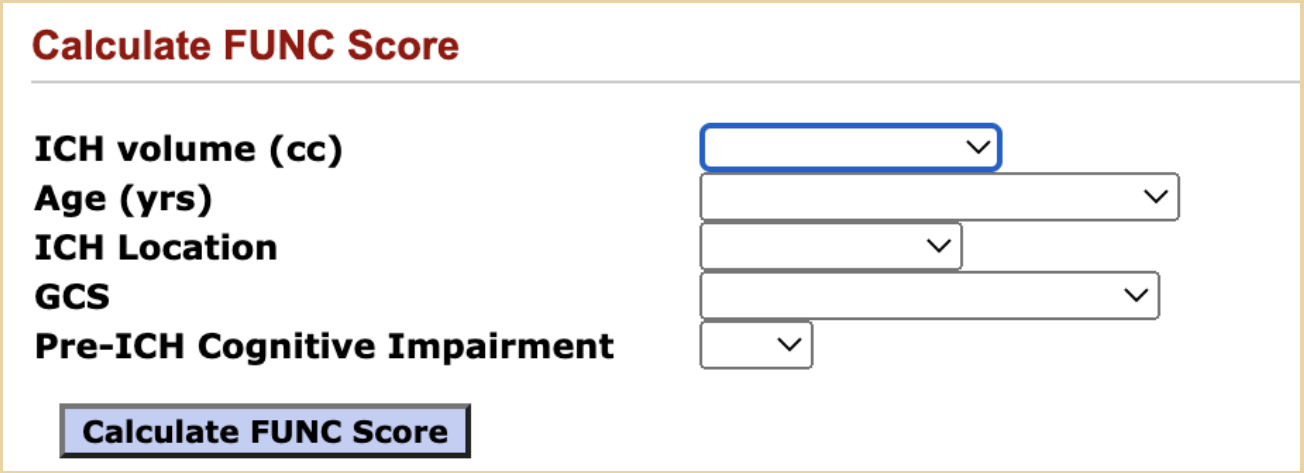
Data to guide prognostication is limited…humility is crucial

What is a Good Outcome?

- modified Rankin Scale [mRS] ≤2
- Fugl-Meyer Motor >75
- ARAT 39-57
- 6 Minute Walk Test >400m
- Timed Up and Go <10s
- Barthel Index >91
- Functional Independence Measure (FIM) 100

Biomarker: Clinical Scores

- FUNC
- ICH score
- THRIVE-c



Bioma Recovery

Proportional recovery

Limited recovery

Lin et al. Stroke 2019
Krakauer et al. 2015

Biomarkers: Imaging/Neurophysiologic

Proportional recovery after stroke depends on corticomotor integrity

Annals of NEUROLOGY

Winston D. Byblow PhD, Cathy M. Stinear PhD, P. Alan Barber MBChB, PhD, Matthew A. Petoe PhD, Suzanne J. Ackerley BPhty, PhD

CLINICAL NEUROPHYSIOLOGY

OFFICIAL JOURNAL OF THE INTERNATIONAL FEDERATION OF CLINICAL NEUROPHYSIOLOGY

Are early measured resting-state EEG parameters predictive for upper limb motor impairment six months poststroke?

Mique Saes [a], Carel G.M. Meskers [a, b], Andreas Daffertshofer [c], Erwin E.H. van Wegen [a], Gert Kwakkel [a, b, d], on behalf of the 4D-EEG consortium

Resting-State Functional Connectivity Magnetic Resonance Imaging and Outcome After Acute Stroke

Stroke

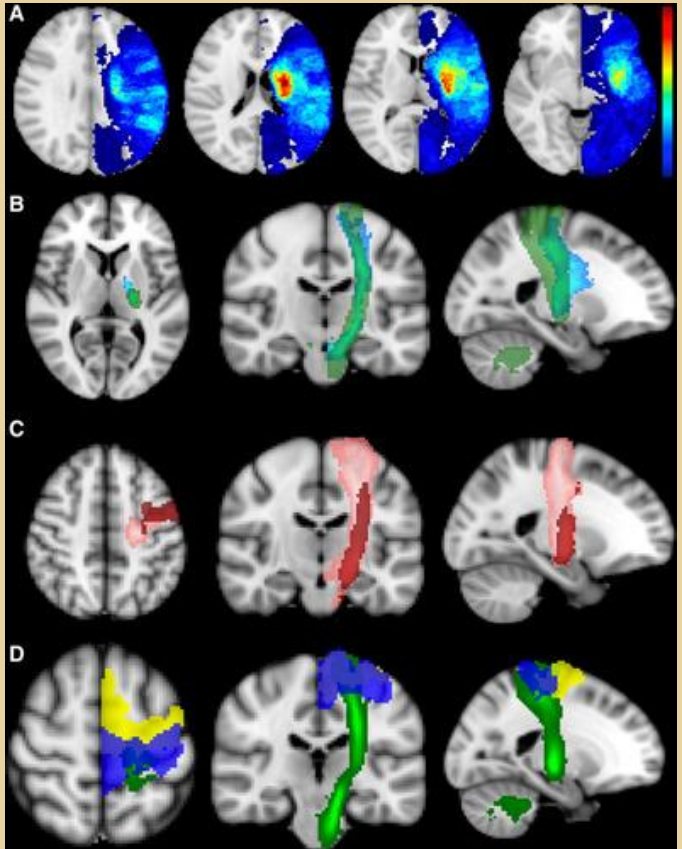
Josep Puig, Gerard Blasco, Angel Alberich-Bayarri, Gottfried Schlaug, Gustavo Deco, Carles Biarnes, Marian Navas-Martí, Mireia Rivero, Jordi Gich, Jaume Figueras, Cristina Torres, Pepus Daunis-i-Estadella, Celia L Oramas-Requejo, Joaquín Serena, Cathy M Stinear, Amy Kuceyeski, Carles Soriano-Mas, Götz Thomalla, Marco Essig, Chase R. Figley, Bijoy Menon, Andrew Demchuk,

BRAIN
A JOURNAL OF NEUROLOGY

Functional potential in chronic stroke patients depends on corticospinal tract integrity FREE

Cathy M. Stinear, P. Alan Barber, Peter R. Smale, James P. Coxon, Melanie K. Fleming, Winston D. Byblow

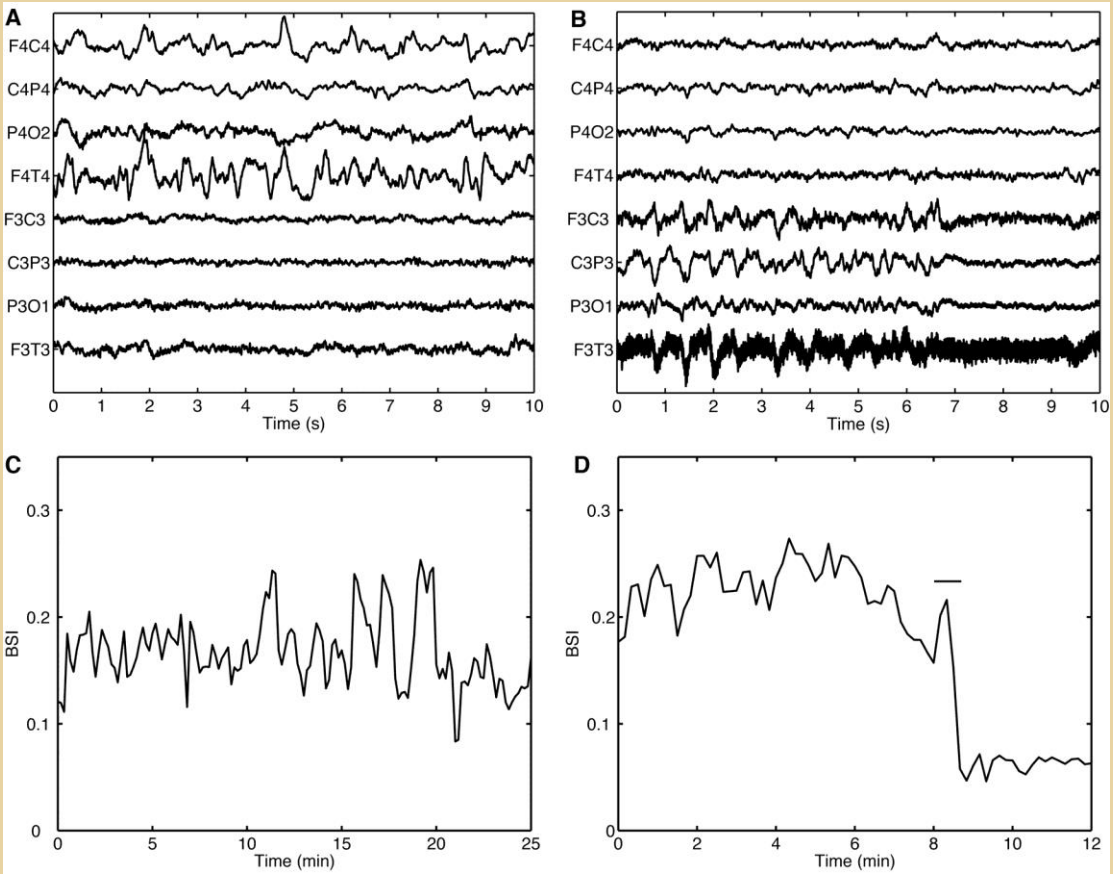
Biomarker: Acute CST Integrity



Explains ≈20% of the variance in magnitude of UE recovery, even after controlling for the severity of initial impairment.

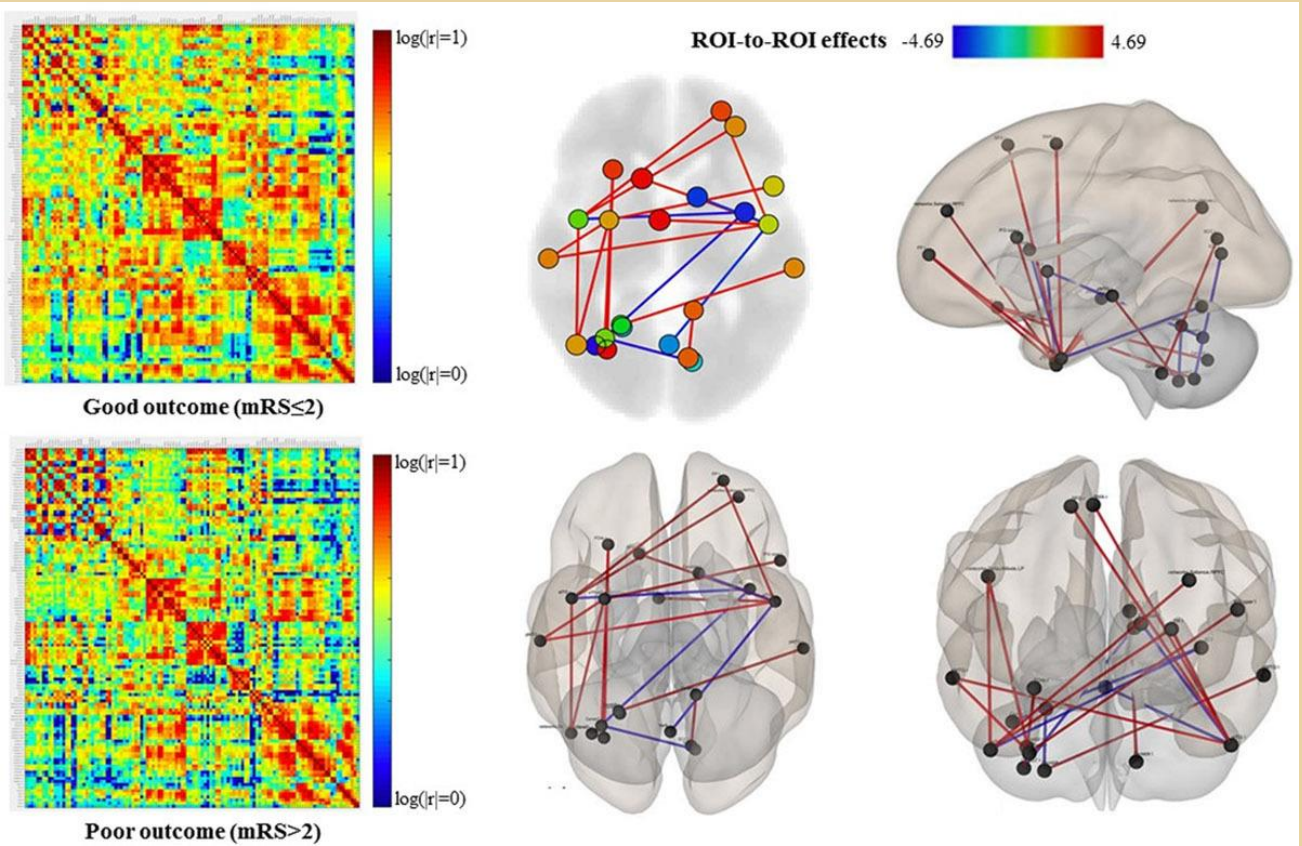
Lin et al. Stroke 2019

Biomarker: EEG



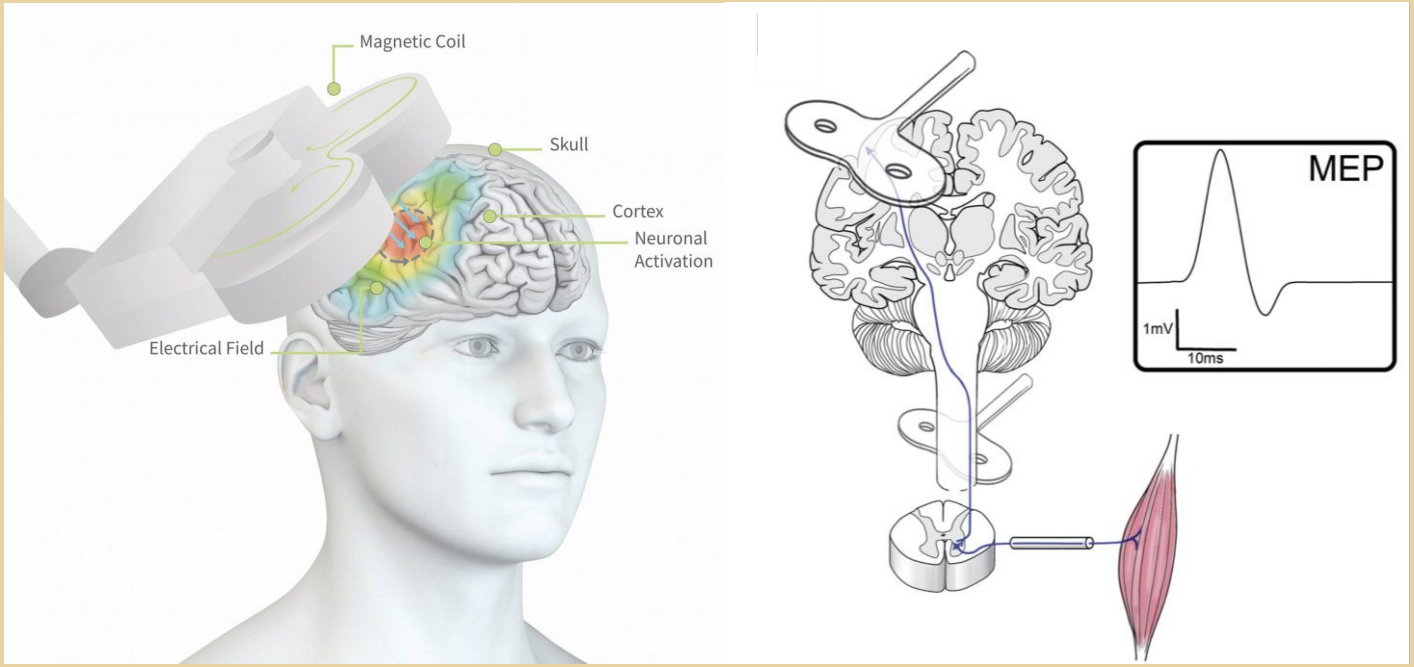
Saes et al. Clin Neurophys 2021
van Puten et al. Stroke 2004

Biomarker: Resting-State Functional Connectivity



Puig et al. Stroke 2020

Biomarker: MEPs using TMS

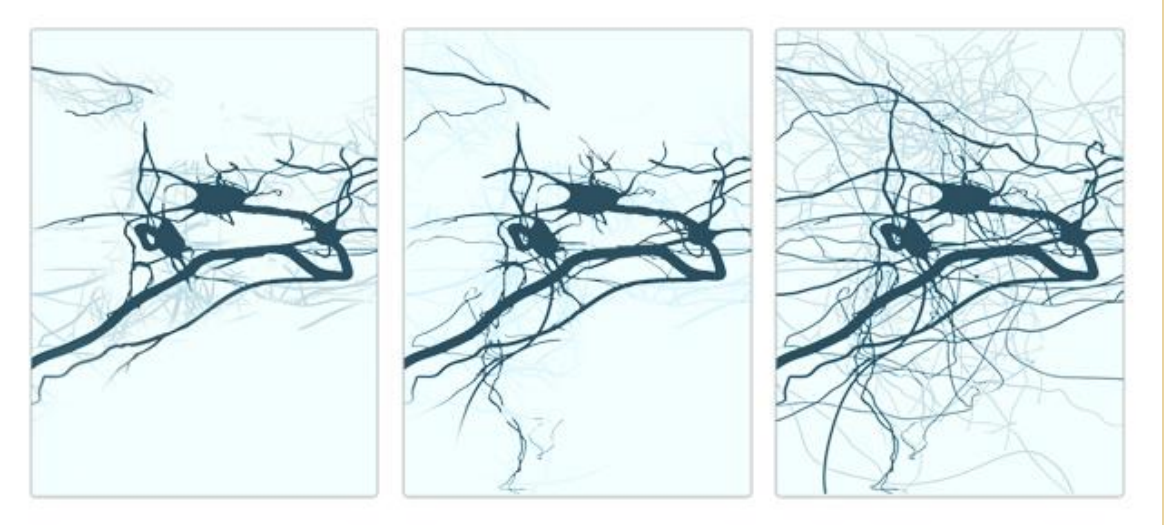


+MEP has PPV of 86-93%, as predictor of good 90-day UE motor outcome

Kimberley T, et al. Arch PM&R 2022
De Gruyter online 2017
Vora et al. 2022
Wang et al. 2020

Neural Repair

- Experience-dependent Brain Plasticity → Improved behavioral outcomes
- Goal:
  - 1. Increase function in surviving tissue
  - 2. Promote clinically favorable brain plasticity



Neural Repair

Targets in Biological Post-stroke Pathways

Mechanisms

- Gene expression
- Growth inhibitors
- Capillary outgrowth
- Axonal sprouting
- Synaptogenesis
- Glial activation

Brain changes

- activity
- network
- structure

Result

Behavioral recovery

Neural Repair: Medication

FLAME

Chollet et al. Lancet Neurol 2011
FOCUS Collab. Lancet 2019

FOCUS

Neural Repair: Medication

Sinemet vs. Placebo *prior* to therapy

Two trials: 53 and 593 patients

+ Arm and leg motor function
+ Ability to walk independently

Ford et al. 2015
Scheidtmann et a. Lancet 2001

Neural Repair: Activity

Constraint-Induced Movement Therapy (CIMT)

EXCITE, VECTORS

Neural Repair: Activity

LEAPS Trial: BWSTT

- Early vs. Late vs. Home
- Outcome: Improved gait speed

Positive for ALL groups – 52% of patients with improved gait speed

Duncan et al. NEJM 2011

Neural Repair: Robotics

- Traditional stroke rehabilitation: repetitive exercise → facilitate motor learning and build strength
  - Acute: PROM → AAROM

- Robotic devices:
  - simple, repetitive tasks with consistency
  - guide patient through specific motions; maintaining a prescribed level of support and restrict undesired movements
  - “stand-in” for the skilled clinician AND collect objective quantitative data
  - software: compelling games and physical challenges → increased pati engagement

End-organ Robotics

ReoGo

Amadeo

MIT-Manus Shoulder-Elbow

Rogers et al. Lancet 2019

Exoskeleton Workstations

Armeo

Lokomat

Wearable Technology

Myomo

Ekso GT

Evidence limited, growing:

+ Fugl-Meyer
+ Strength
? ADLs

+ Functional Ambulation Scale
+ 10m and 6m Walk Test
+ Trunk Control Test

Molteni et al. 2017
Meeker et. al. Intl Conf on Rehab 2017
Peters et al. Arch PMR 2016
Mehrholz et al. Cochrane 2017

Robotics: Data

- **InMotion**
  - Decrease motor impairment, improve function, enduring change
  - Robot provided similar, but not superior benefit for motor performance
- **Armeo**
  - Acute Rx: 30 sessions x 60min + SOC. Nonsuperior but "enjoyable and efficient"
  - Treatment group (chronic): higher Fugl-Meyer scores compared to dose-matched conventional therapy, but not clinically meaningful
- **Lokomat**
  - Mixed in acute and chronic phase; nonsuperior vs slightly better functional and motor outcomes

Klamroth-Marganska et al. 2014
Krakauer et al. Neurorehabil Neural Repair 2021
Lo et al. NEJM 2010
Volpe et al. 1999

Robotics: Limitations

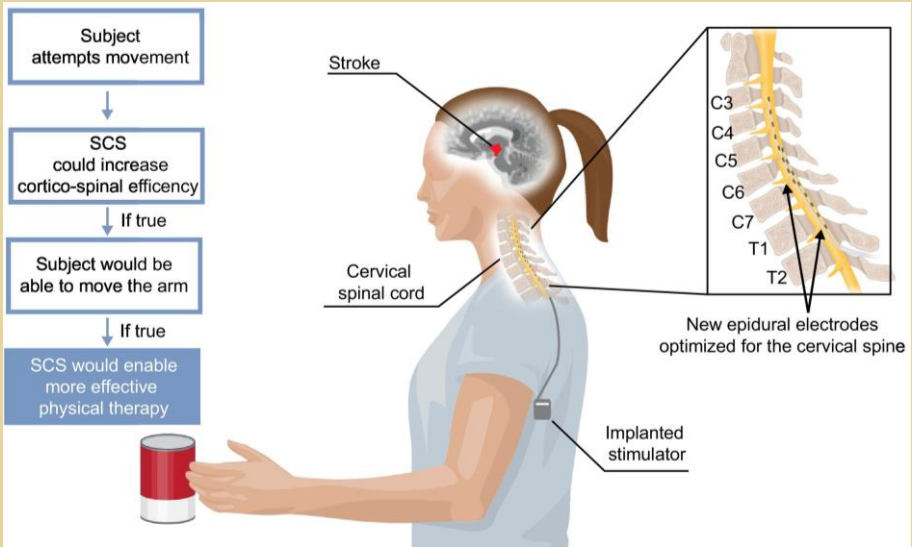
- "Experimental" → Cost-prohibitive
- Low bar for FDA approval
- Size
- Human oversight during use

Neural Repair: Brain Stimulation

> Transcranial Magnetic Stimulation (TMS)

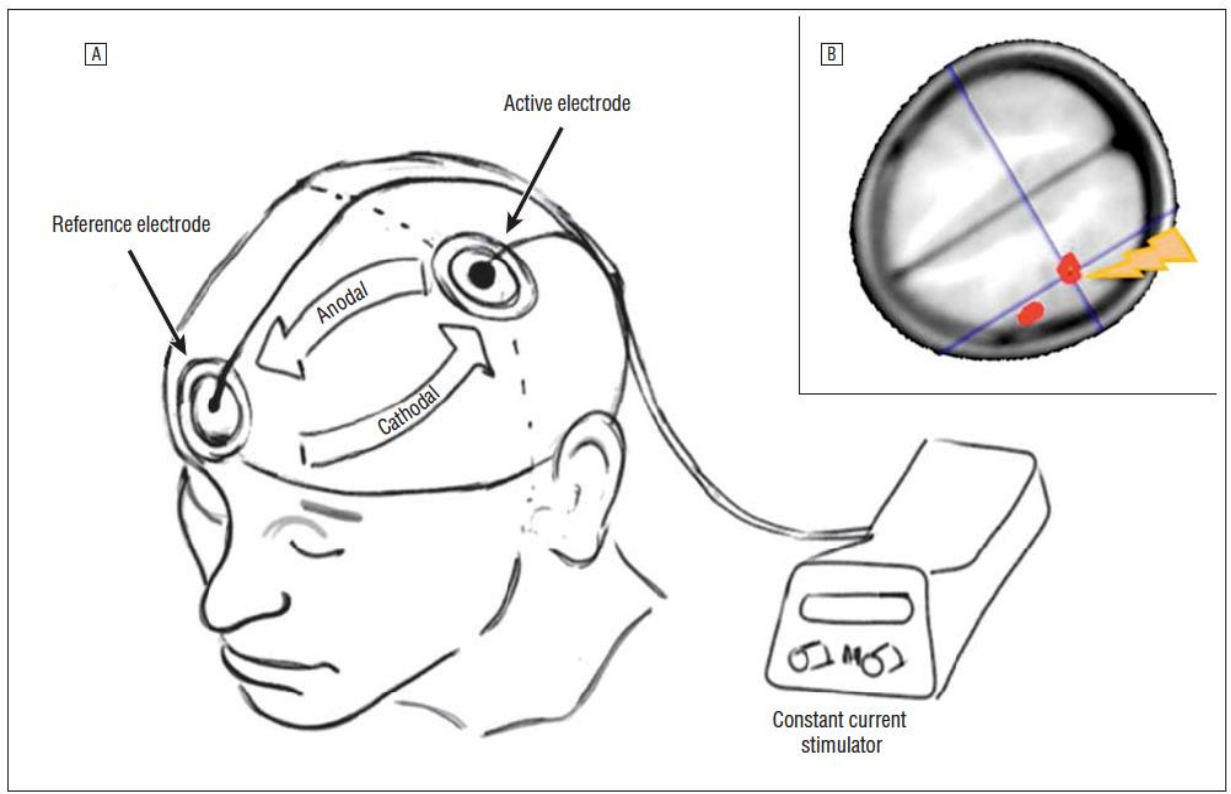
> Transcranial Direct Current Stimulation

> Epidural Stimulation of Cortex



Pirondini et al. Trend Neurosci 2022

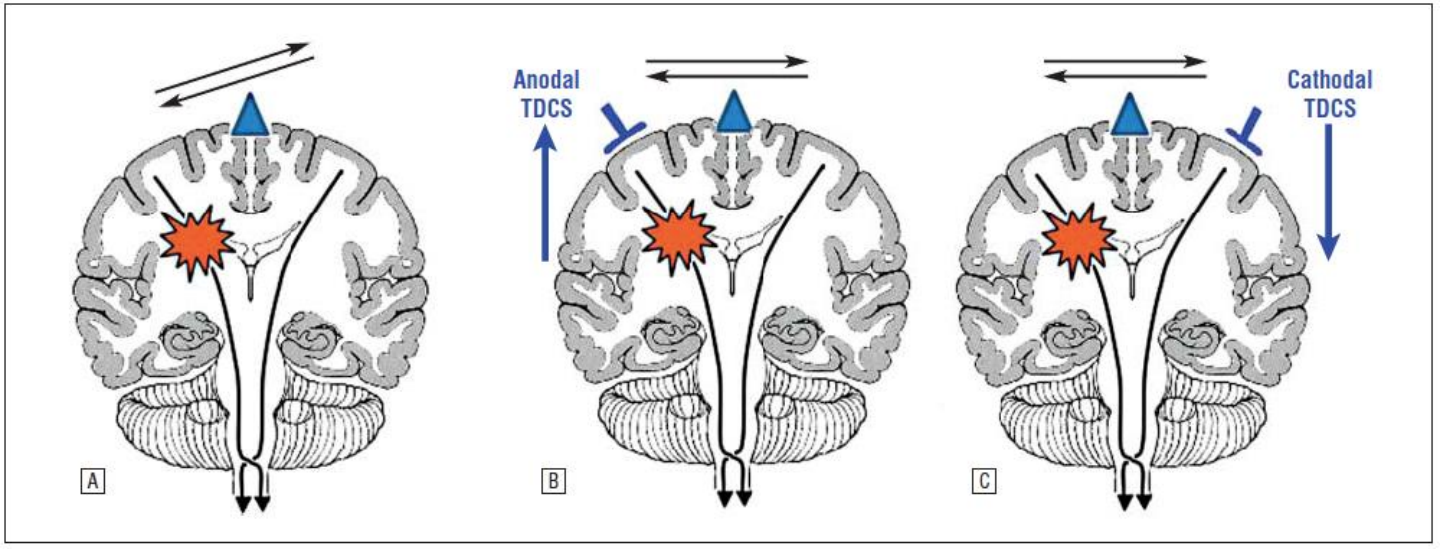
Transcranial Direct Current Stimulation



Fridriksson et al. JAMA Neurol 2018
Schlaug G. et al. Arch Neurol. Dec. 2008

Transcranial Direct Current Stimulation

Active electrode over target regions, reference electrode over control region



Anodal electrode → excitability increased.
Current flow is reversed (cathodal) → excitability decreased

Schlaug G. et al. Arch Neurol. Dec. 2008

In Conclusion

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Thank you