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Stroke recovery

So many questions, so few answers

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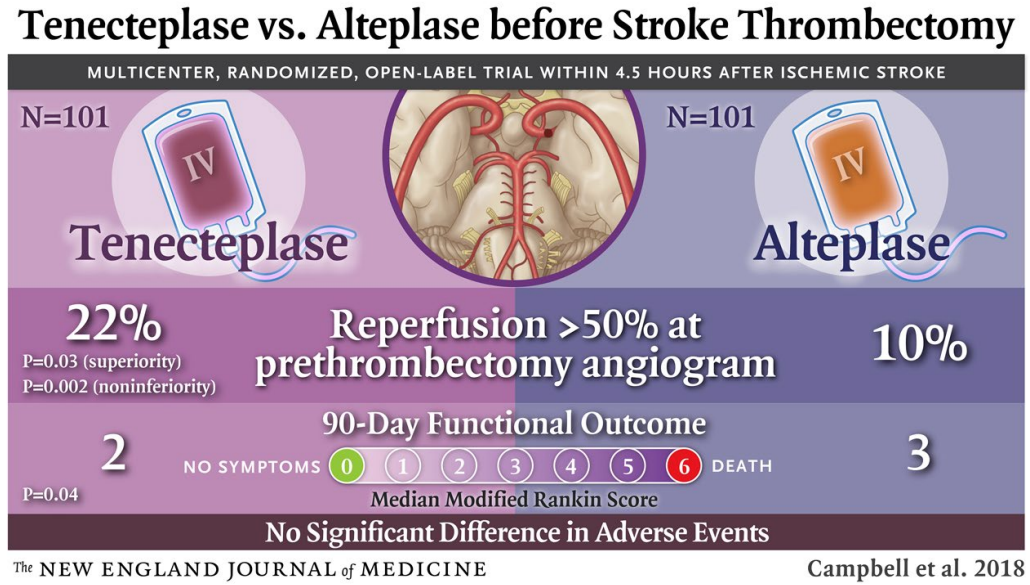
October 21, 2022

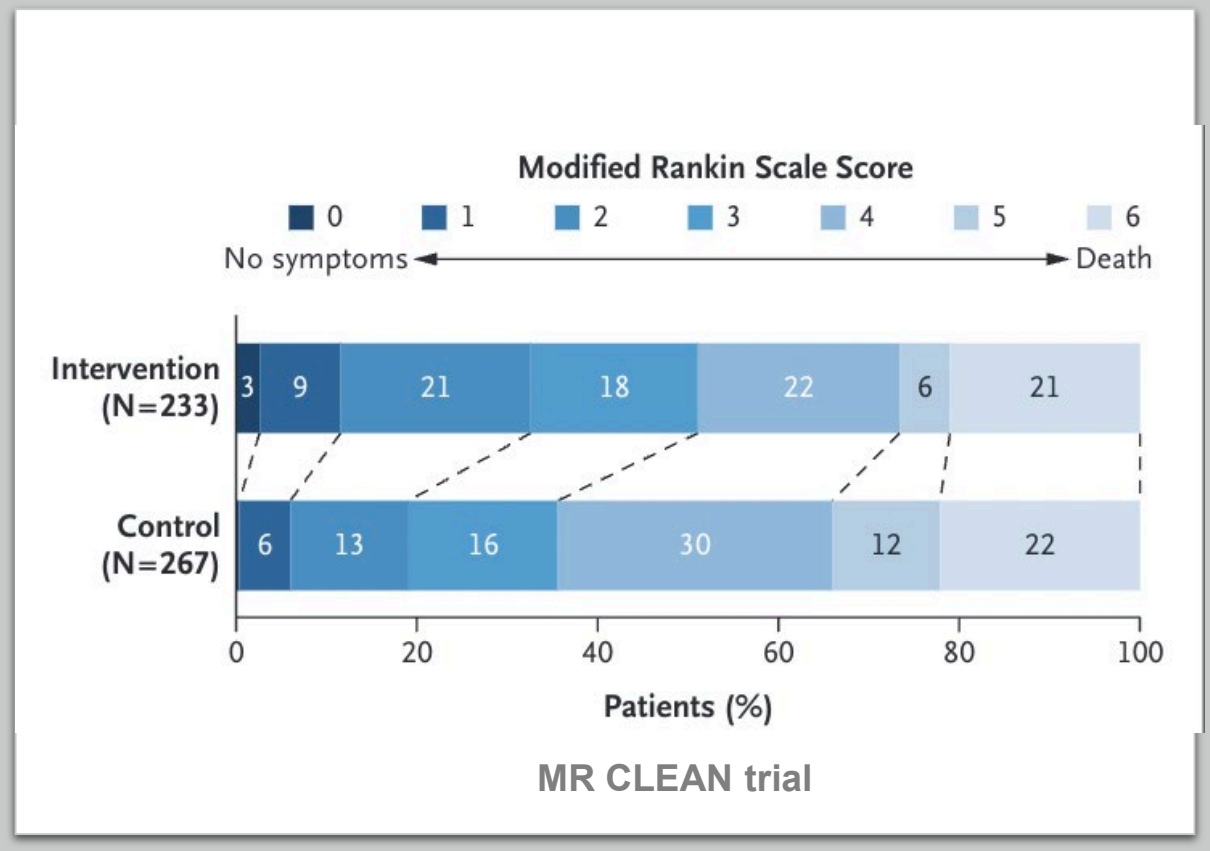
Outline of talk

- Stroke related disability
- Clinical recovery: what is the recovery that we see?
- Molecular recovery: what is the recovery that we do not see?
- Interventions: what works and what does not.

Acute Stroke interventions

- Thrombolysis: alteplase (tPA) or tenecteplase (TNK)
- Mechanical Thrombectomy
- Hemicraniectomy

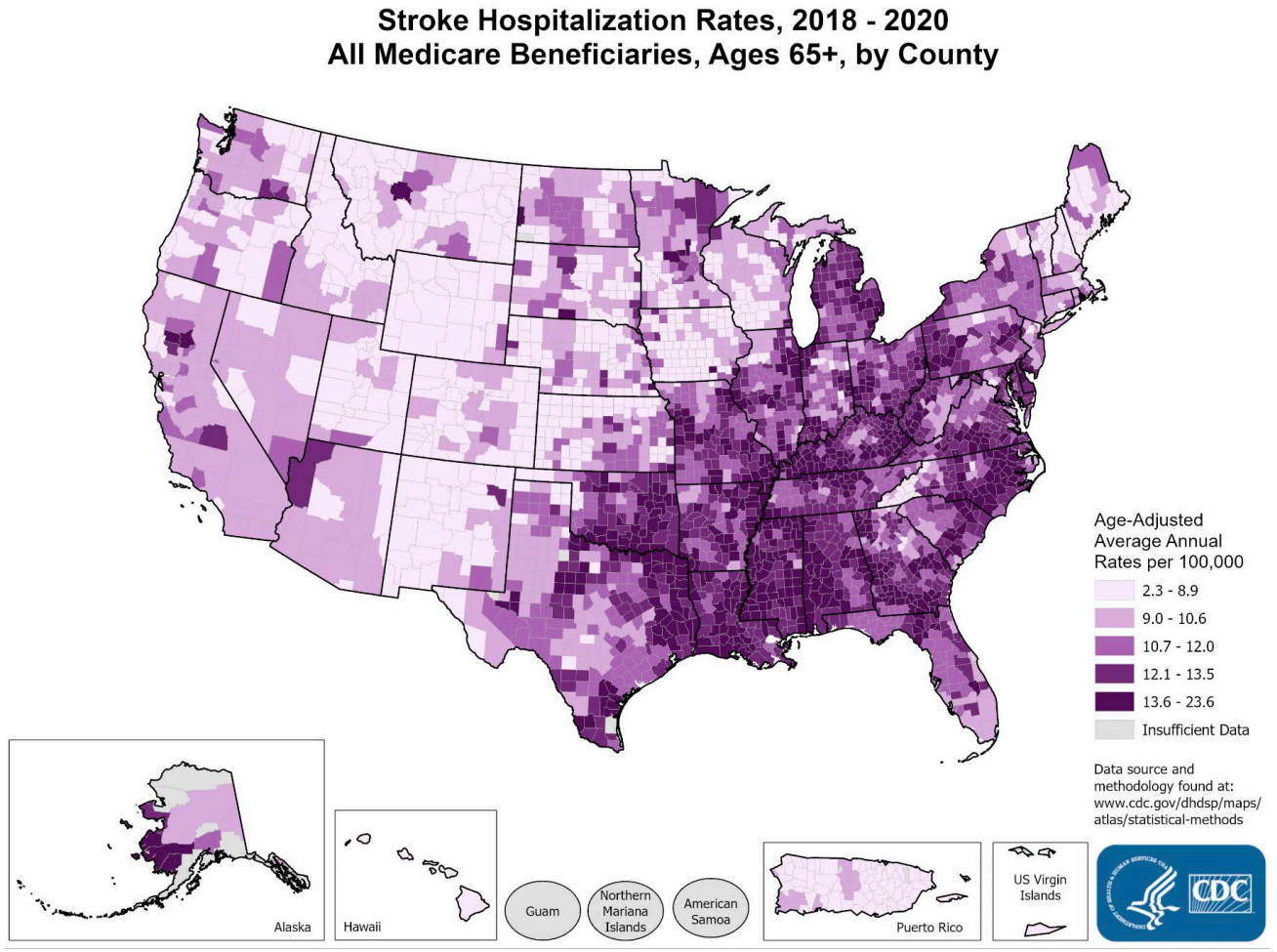




N Engl J Med 2015; 372:11-20

Stroke by the numbers

- **1 in 6 deaths** from cardiovascular disease was due to stroke.
- **795,000 new strokes per year** in the United States.
  - 610,000 of these are first or new strokes.
- **87%** of all strokes are ischemic
- **$53 billion**: stroke-related costs in the United States between 2017 and 2018. (Cost of health care services, medicines to treat stroke, and missed days of work).
- **Number 1:** Stroke is a leading cause of serious long-term disability.



1.Centers for Disease Control and Prevention. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Centers for Disease Control and Prevention; 2018.

Framingham Heart Study
Three Generations of Dedication

6-month outcomes in stroke survivors greater than 65 years old

- Hemiparesis (50%)
- Cognitive deficits (46%)
- Depressive symptoms (35%)
- Unable to walk unassisted (31%)
- Social disability (30%)
- **Poor subjective health (40%)**

	Women (n = 63)	Men (n = 45)	Total (n = 108)
Neurological deficits (%)			
Hemiparesis	57.4	40.0	50.0
Cognitive deficits	49.2	42.2	46.2
Hemianopsia	17.7	22.2	19.6
Aphasia	23.8	11.6	18.9
Sensory deficits	21.7	6.8	15.4
Disability measures (%)			
ADL: Barthel <60	33.9	15.6	26.2
Unable to walk unassisted	40.3	17.8	30.8
Bladder incontinence	28.6	13.3	22.2
Depression symptoms	31.9	39.5	35.3
Social disability	36.8	23.1	29.9
Institutionalization	34.9	13.3	25.9
Poor subjective health	40.7	38.1	39.6

Kelly-Hayes M. The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis. 2003;12(3):119–26.

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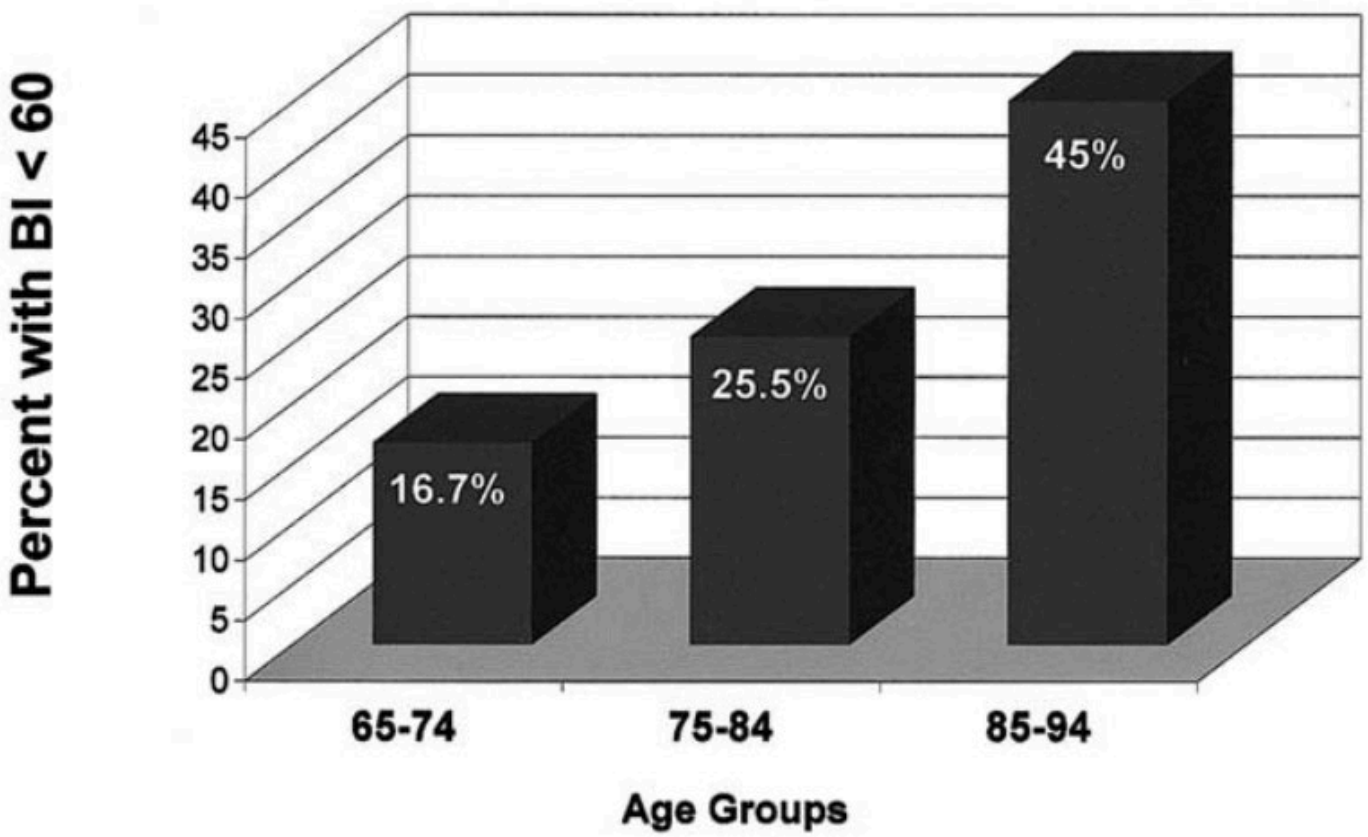
Framingham Heart Study
Three Generations of Dedication

Influence of Age on Disability After Stroke



- Severe disability in activities of daily living ((ADL) function following stroke
- Defined as Barthel Index < 60
- As age increased, the percent of severely disabled survivors also increased

Kelly-Hayes M. The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis. 2003;12(3):119–26.

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What factors are associated with post-stroke disability?

Table 2. Independent correlates of disability at 5 years in stroke patients (multiple logistic regression analysis with the group without disability as reference group).

	Stroke patients*		
Variables	**p**	**OR**	**95% CI**
Age	**<0.001**	1.06	1.04,1.08
Male	0.20	0.7	0.4,1.1
High school or above	**0.02**	0.6	0.4,0.9
Diabetes	0.75	1.06	0.7,1.6
Cardiac Disease	0.69	1.09	0.7,1.6
Current smoking	0.09	1.4	0.9,2.2
Moderate/Heavy Drinking	0.65	1.1	0.6,1.9
Stroke History	**<0.001**	2.6	1.7,4.1
NIHSS score at admission	**<0.001**	1.1	1.05,1.1
Depression at 3 months	**0.009**	1.8	1.1,2.9
Cognitive impairment at 3 months	**<0.001**	2.7	1.6,4.7
Stroke Recurrence within 5 years	**<0.001**	4.1	2.7,6.3

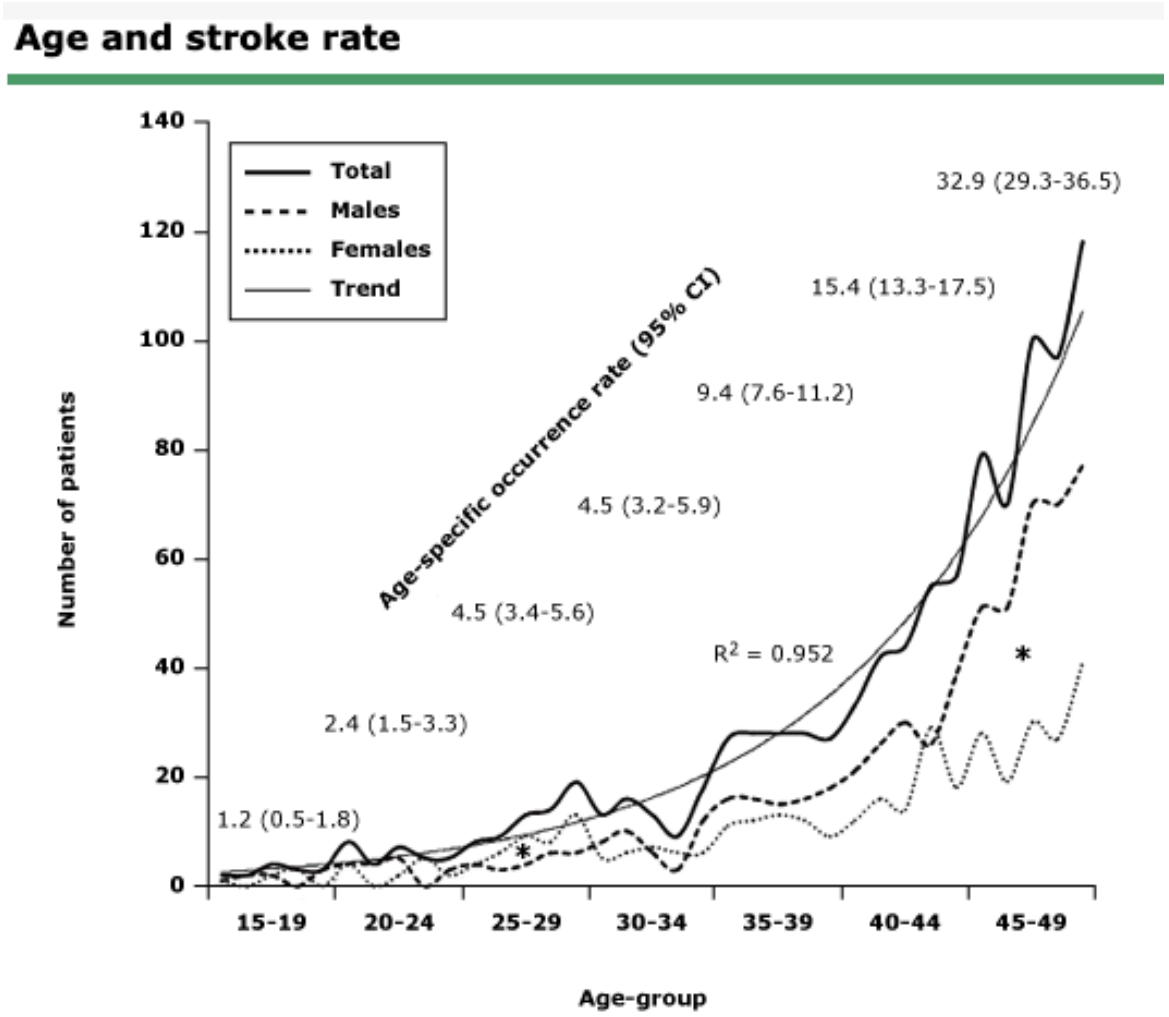
Bold values are p<0.05

* adjusting for study site; NIHSS = National Institutes of Health Stroke Scale

Age
Education level
History of stroke
Stroke severity
Depression (3 months)
Cognitive Impairment (3 months)
Stroke recurrence

Strokes don’t just strike the old

- 35% of strokes were in people less than 65

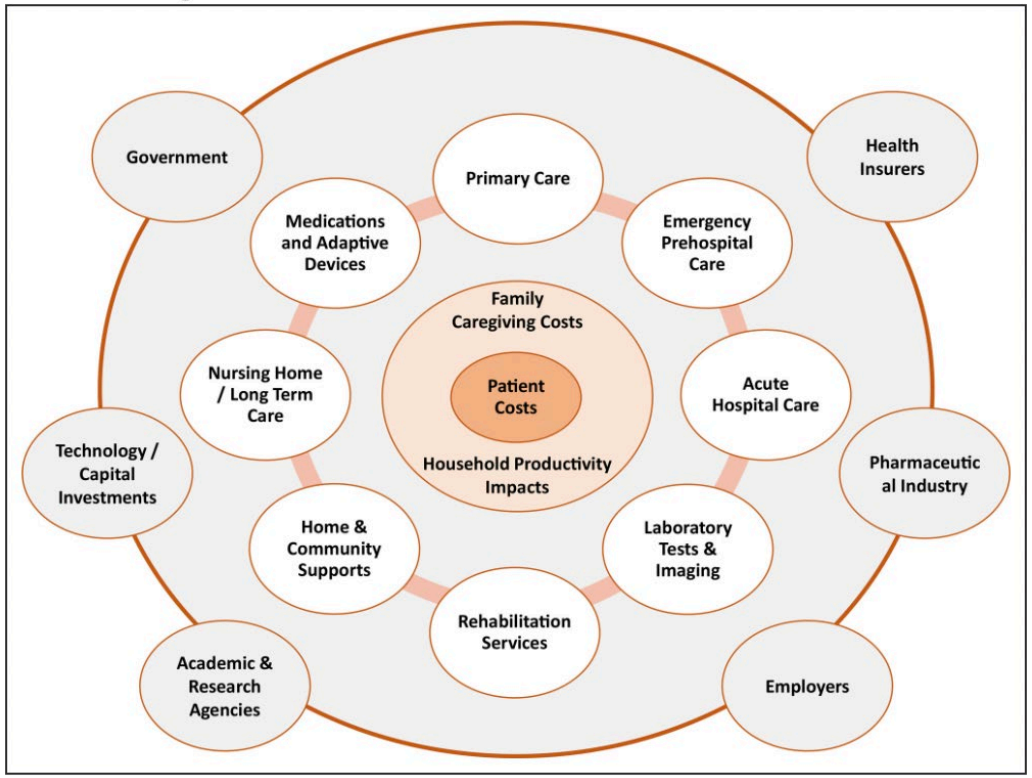


Number of patients according to age and age-specific occurrence rates per 100,000.

Stroke. 2009;40(4):1195.

Cost considerations

- Acute hospitalization: $20,396 ± $23,256
  - Hemorrhagic stroke costs $14,499 more
- At discharge, patients have an average of 11.3 medications (range 3 to 27) with a total monthly cost of ~ $725
- Direct healthcare costs in the first year after stroke were mean 54,012 (SD 54,766)
  - 1-year cost of post-stroke aphasia: $1703
  - 1-year cost for outpatient rehabilitation services and medications: $11 145
- Mean lifetime cost of ischemic stroke: $140,048
- Cost of lost productivity ($15.5 billion) nearly equaled the direct cost of treating stroke ($18.8 billion) in 2008



Stroke. 2022 June; 52(6): 2078-2081

Stroke. 2007 May; 38(5):1557-64

Outline of talk

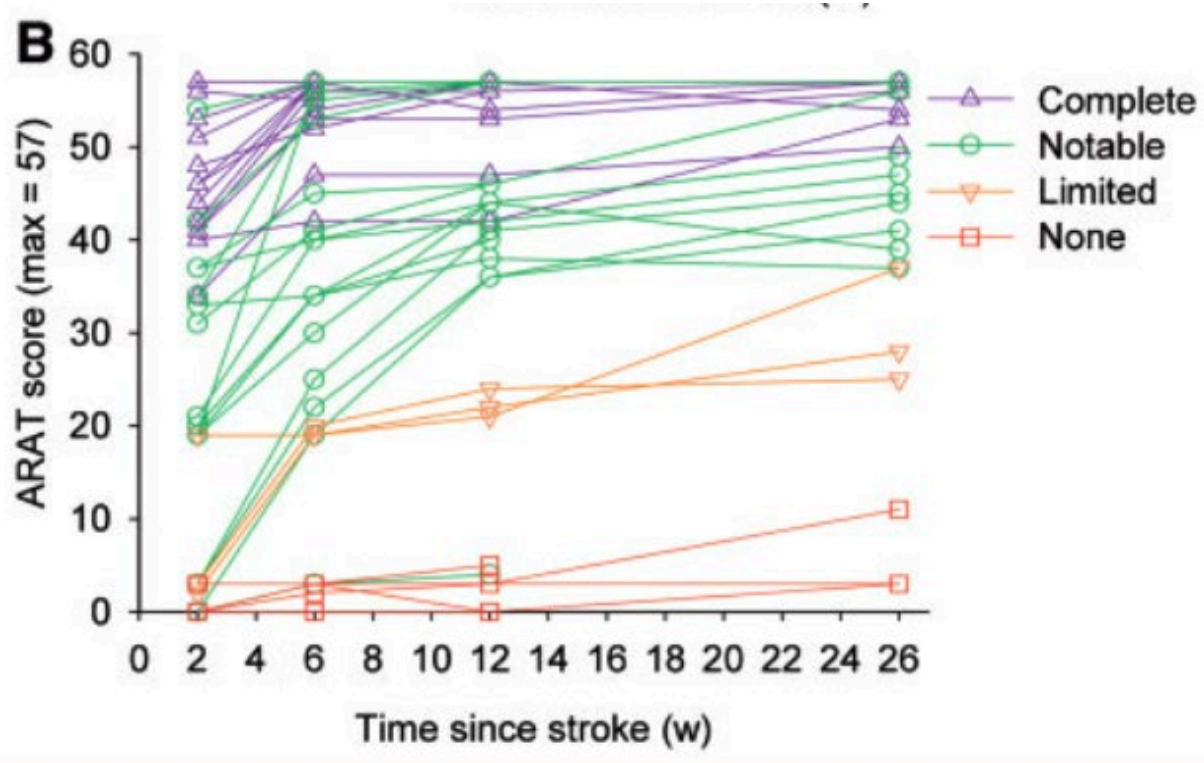
- Stroke related disability
- **Clinical recovery: what is the recovery that we see?**
- Molecular recovery: what is the recovery that we do not see?
- Interventions: what works and what does not.

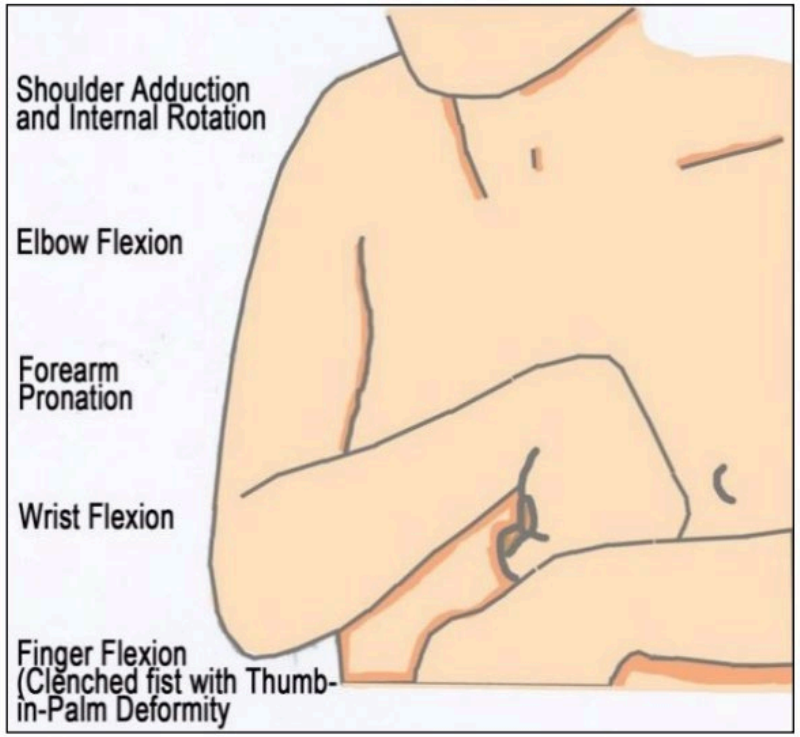
Clinical recovery: what is the recovery that we see?

Motor

Cognitive

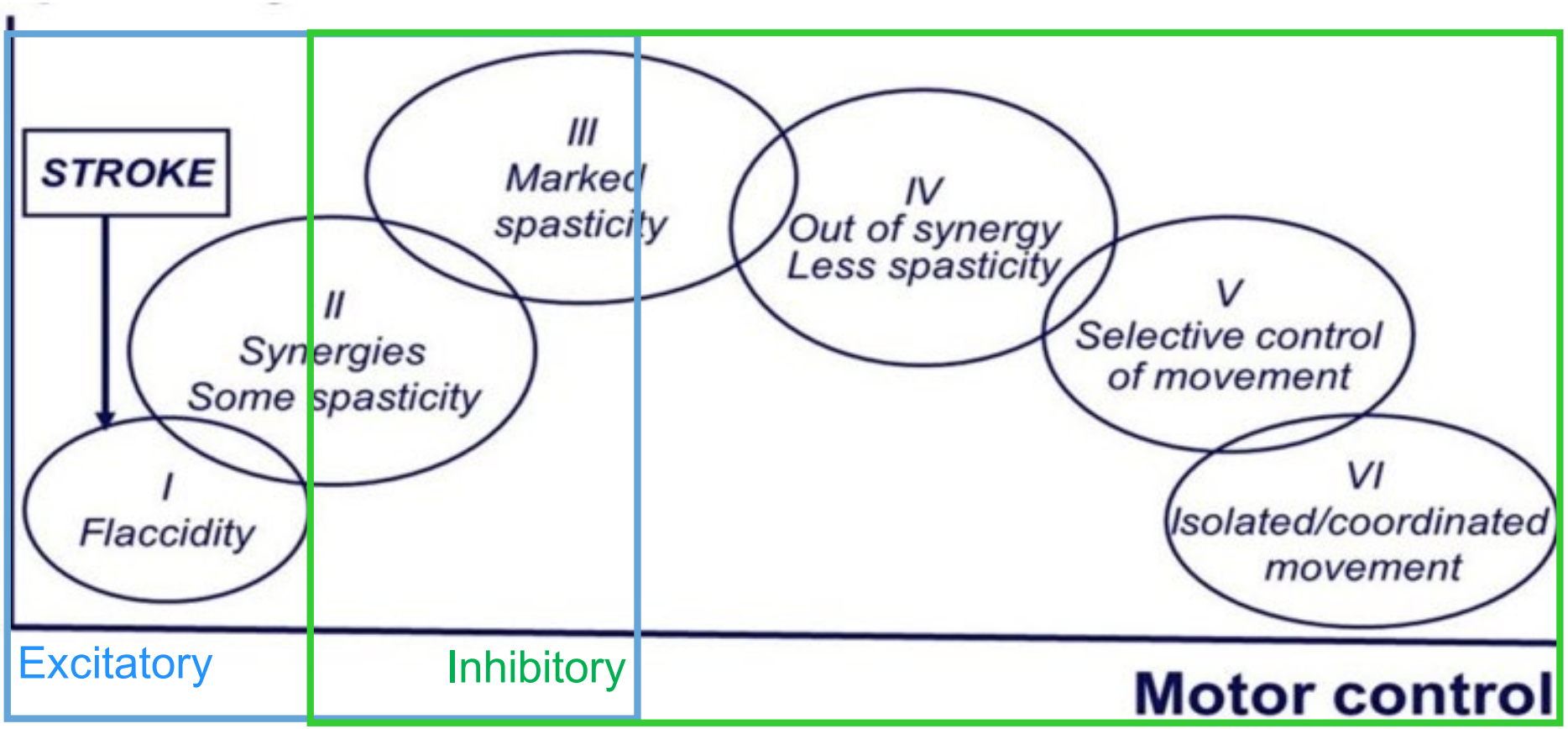
Motor recovery





Brain. 2012 Aug;135(Pt 8):2527-35.

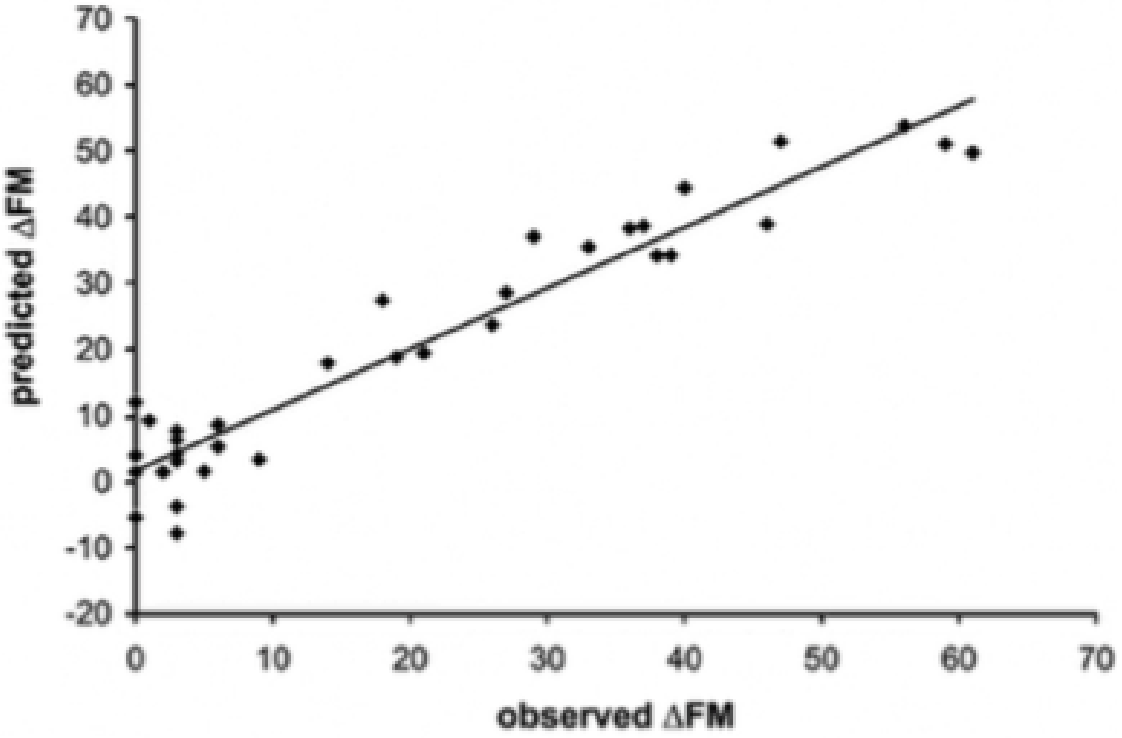
Progression of motor recovery, Twitchell (1951) and Brunnstrom (1956)



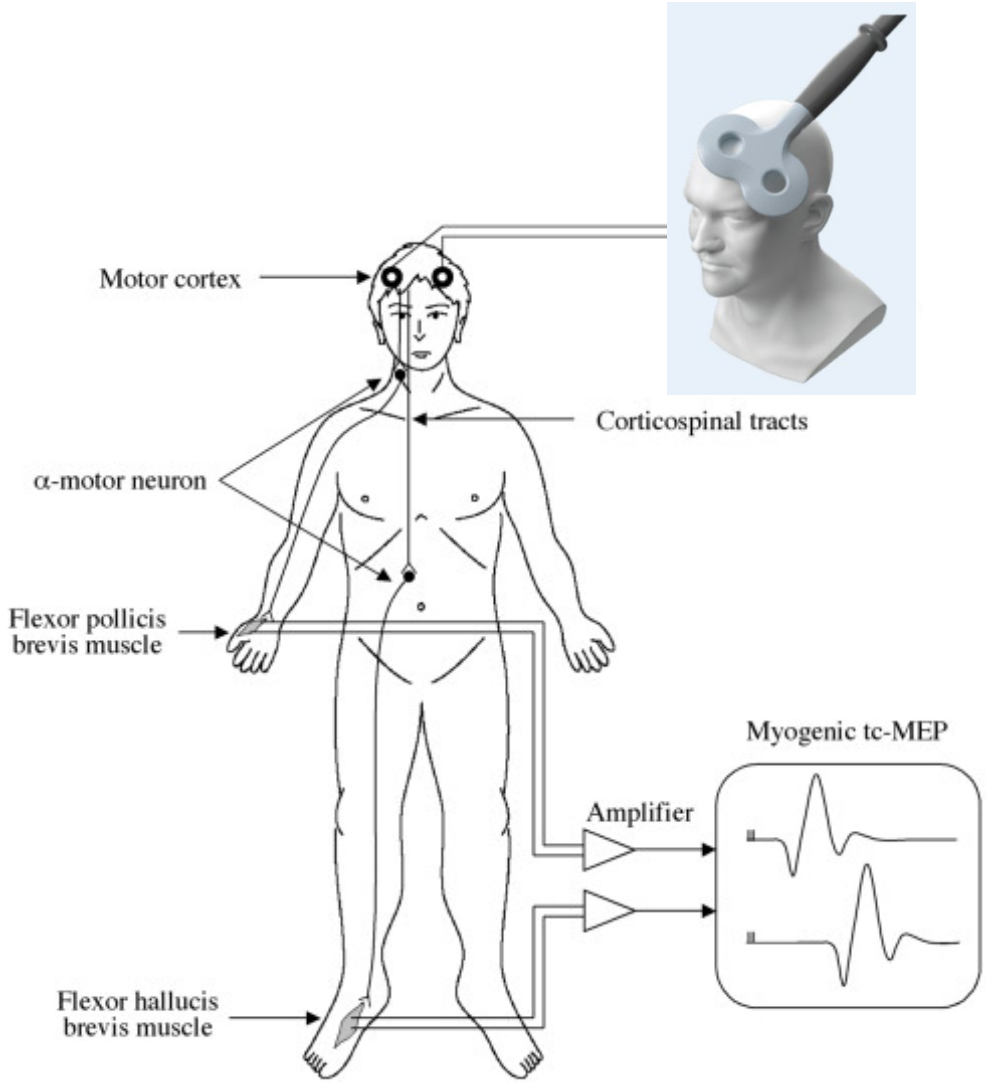
When will I get my arm function back?

Inter-individual Variability in the Capacity for Motor Recovery After Ischemic Stroke

Shyam Prabhakaran, MD, Eric Zarahn, PhD, Claire Riley, MD, Allison Speizer, MS, Ji Y. Chong, MD, Ronald M. Lazar, PhD, Randolph S. Marshall, MD, MS, and John W. Krakauer, MD



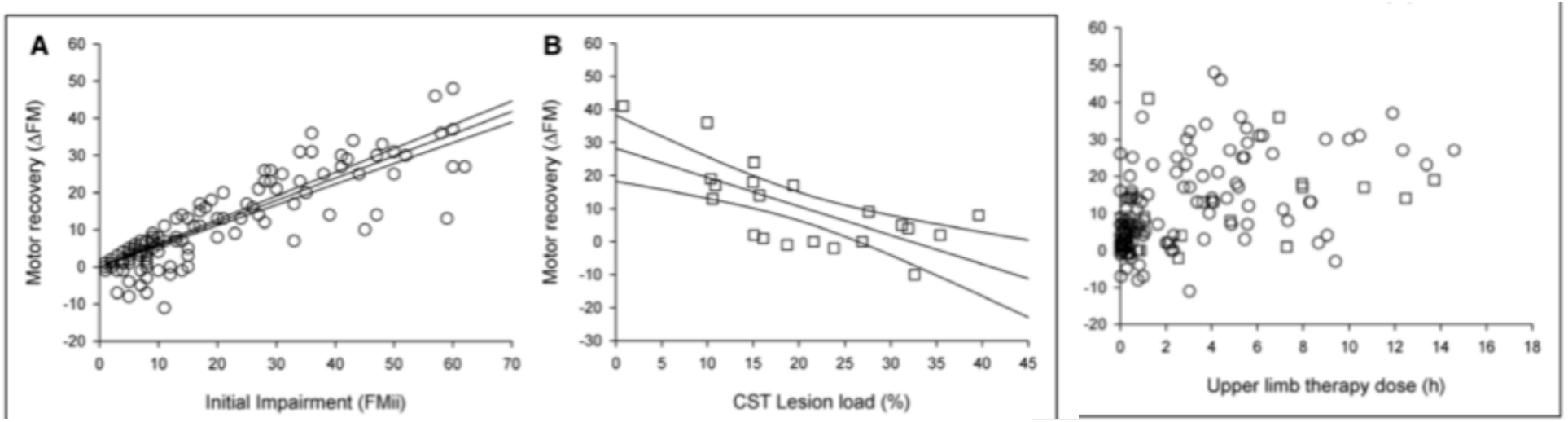
- 41 patients with first time stroke and some degree of arm motor impairment
- Fugl Meyer Scale to assess motor function
- Inpatient, 3 months, 6 months
- Controlled for age, gender, lesion location, cortical lesion volume
- **≈ (0.70) x maximal recovery potential**



And who proportionally recovers?

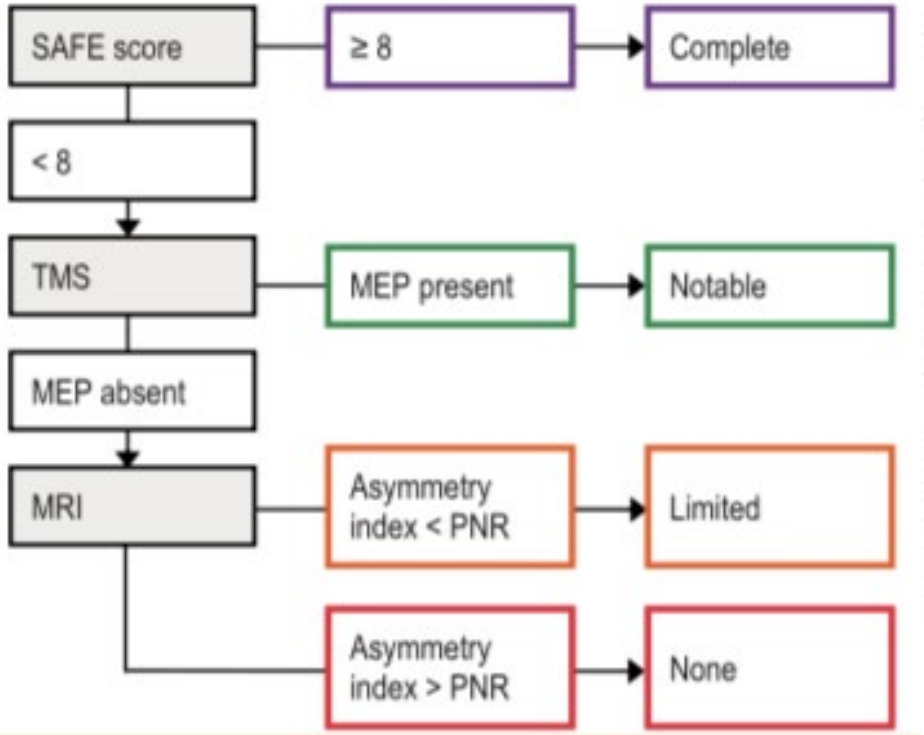
- Transcranial Magnetic Stimulation
  - Can assess integrity of corticospinal tract (CST)
  - Intact CST → better recovery potential

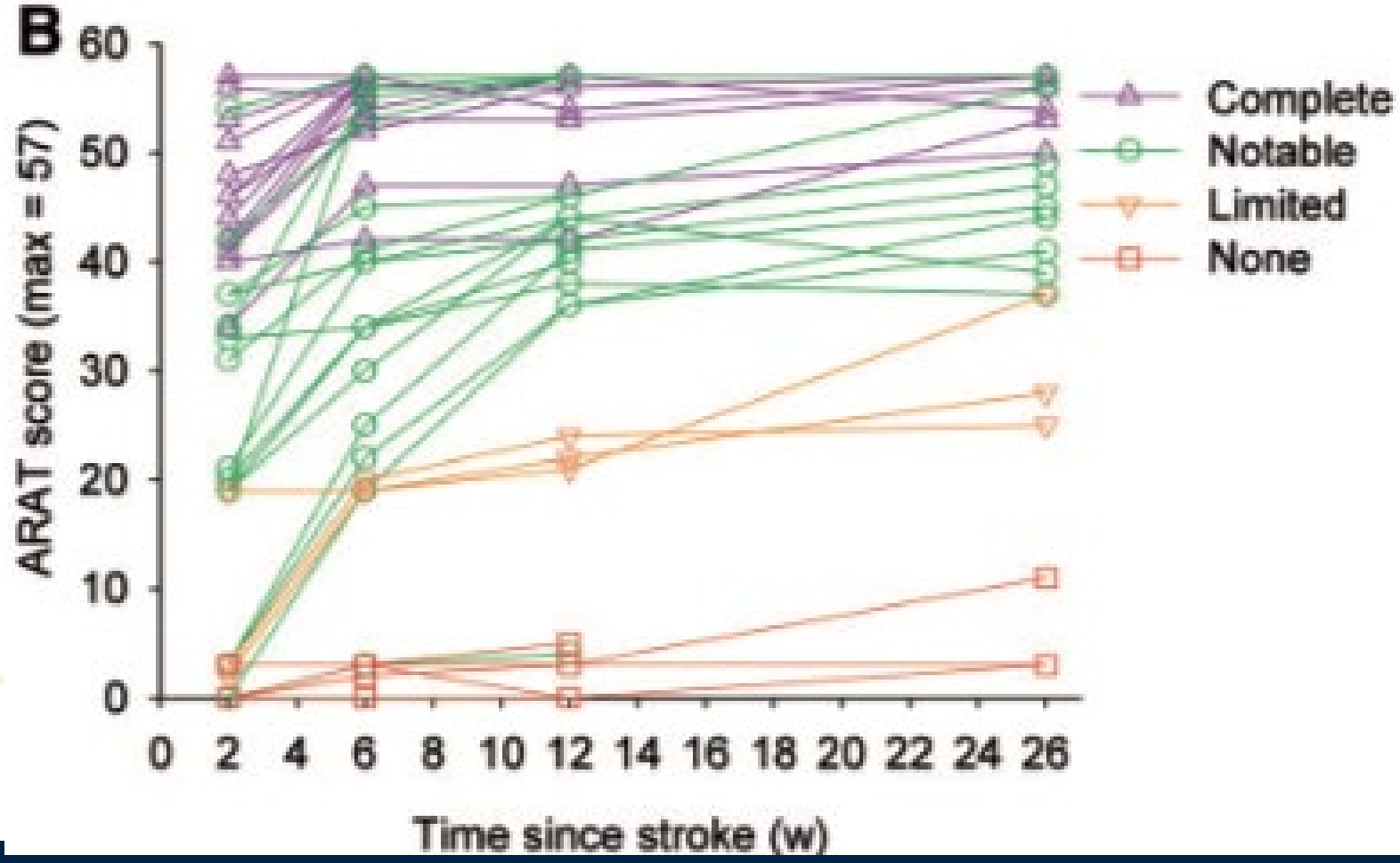
Byblow WD,. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol*. 2015;78:848–859.



Ann Neurol. 2015 Dec;78(6):848-59.

Predicted potential for motor recovery

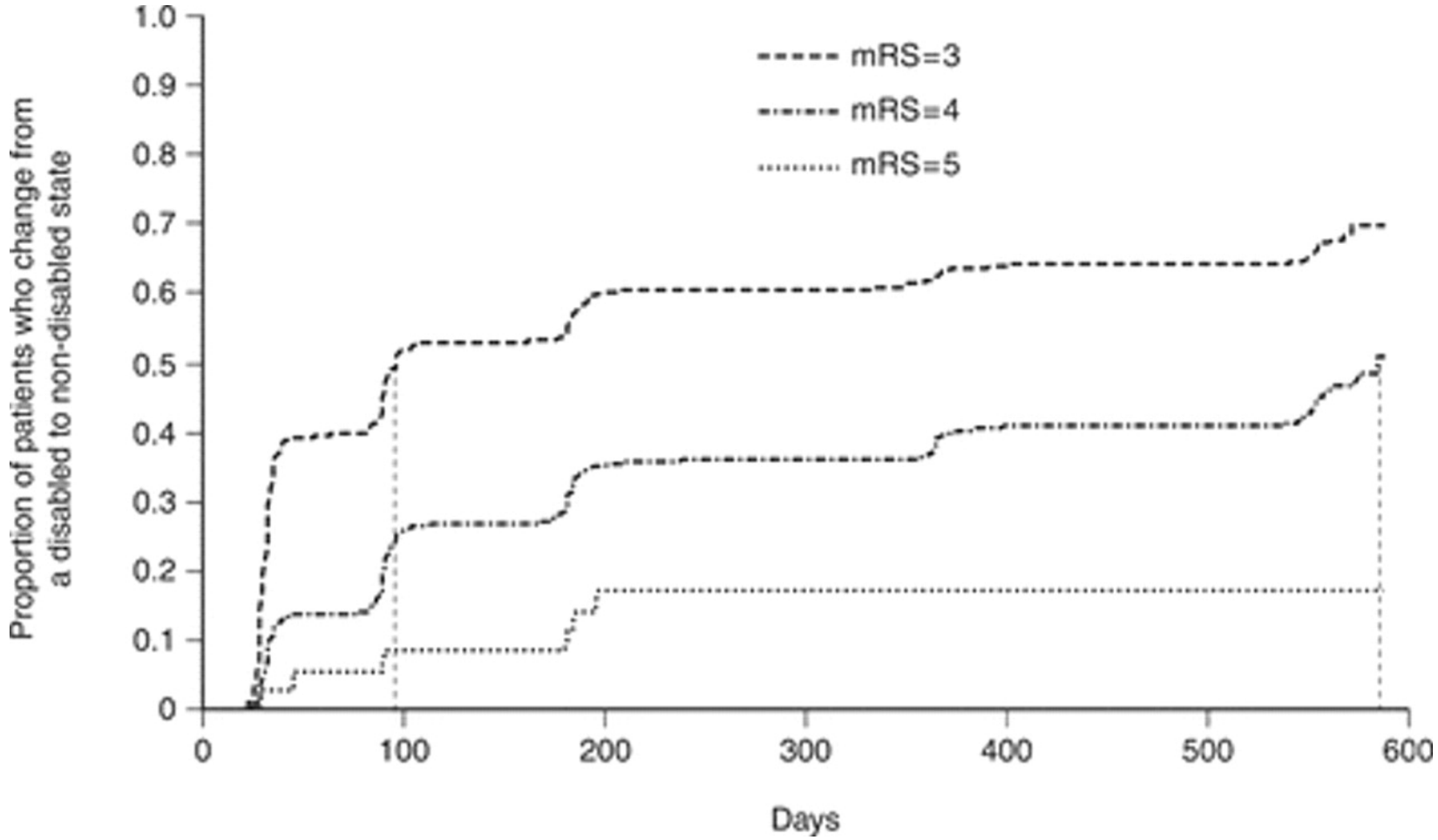




Brain. 2012 Aug;135(Pt 8):2527-35.

Can recovery continue beyond the initial period?

- Kaplan–Meier survival curve: Recovery to modified Rankin Scale score [mRS] < 3 according to their initial mRS.
  - mRS 3 → 63 % recovered
  - mRS 4 → 40 % recovered
  - mRS 5 → 17 % recovered



NEUROLOGY 2007;68:1583–1587

Clinical recovery: what is the recovery that we see?

Motor

Cognitive

How prevalent is cognitive impairment?

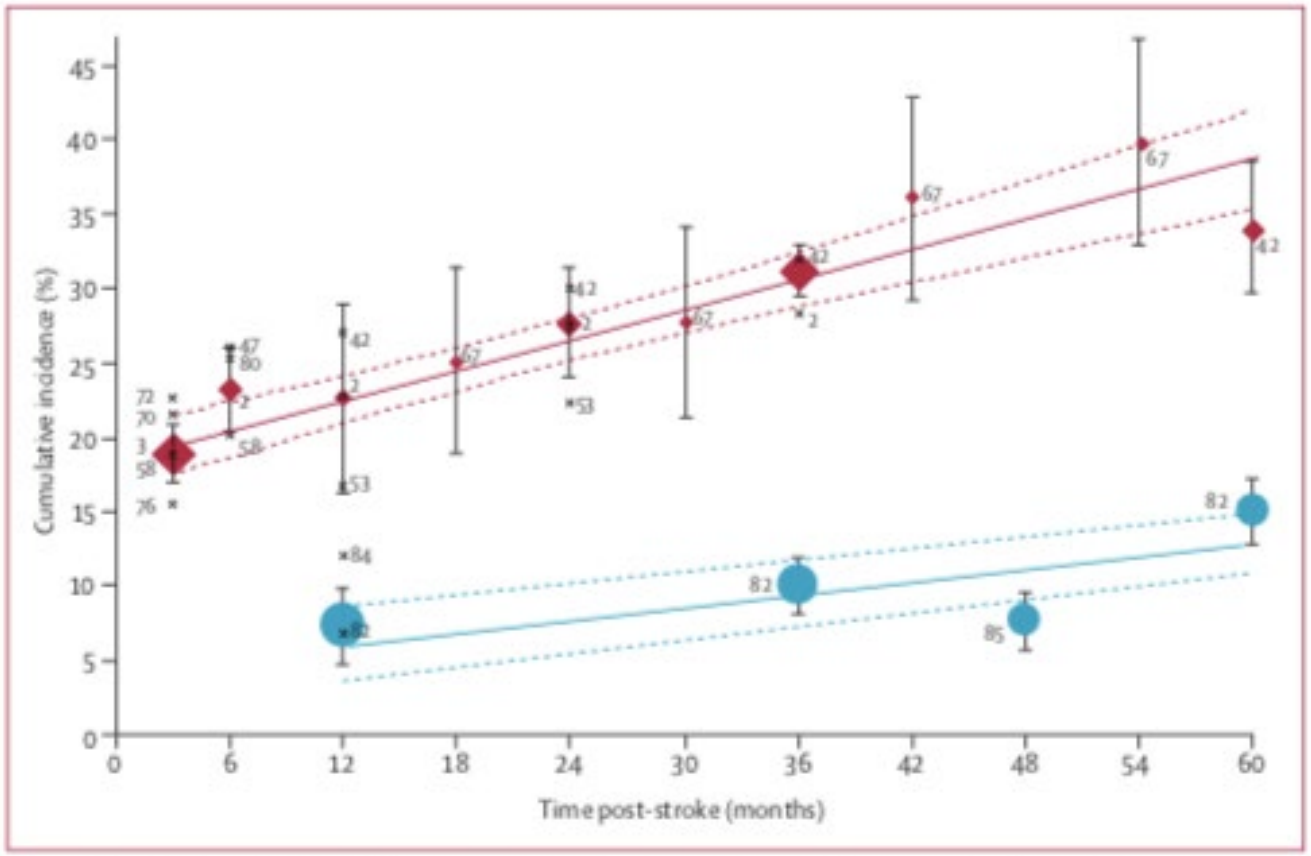
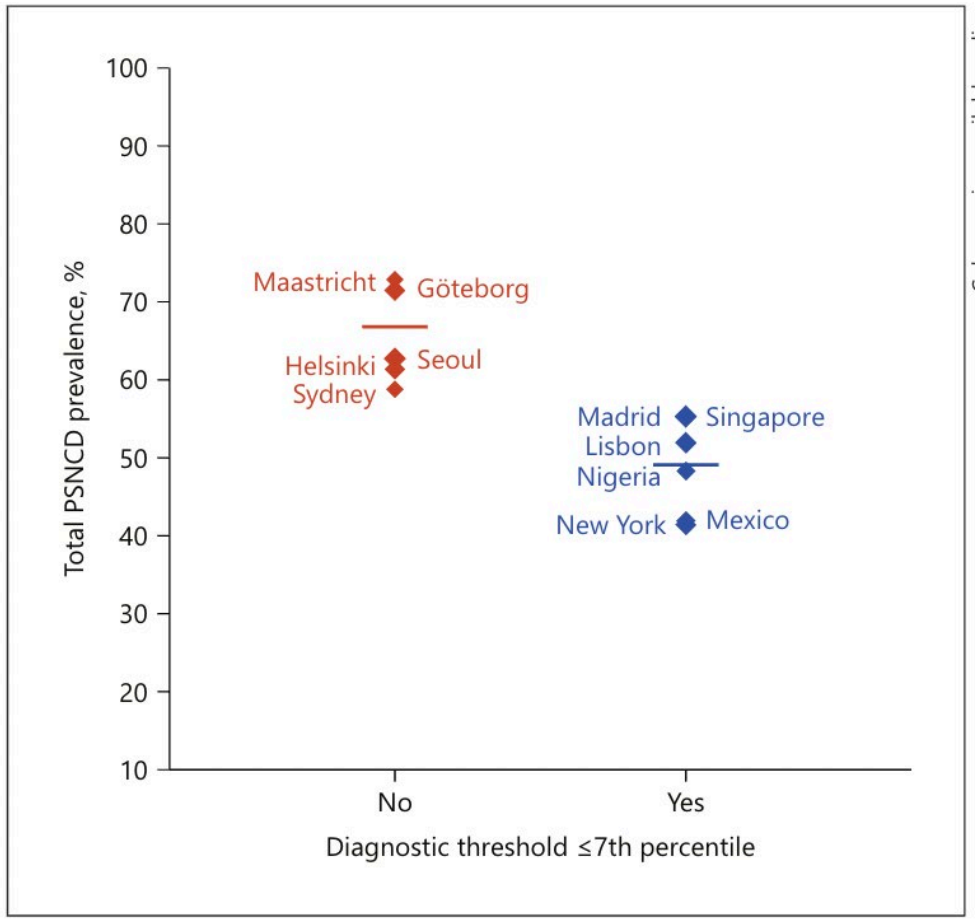


Figure 4: Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts

- Prevalence estimates vary based on how cognitive information is collected and in what setting.
- Post-stroke dementia or post-stroke cognitive impairment?

Neurol Neurosurg Psychiatry 1994; **57:** 202–07.
Stroke 2009; **40:** 2473–79.
Lancet Neurol. 2009 Nov;8(11):1006-18

How prevalent is post-stroke cognitive impairment?



- How is cognition defined?
- With neuropsychological testing, what is the threshold for diagnosis?

Dement Geriatr Cogn Disord 2018;46:322–334

The full extent of cognitive impairment may not be captured during normal screening

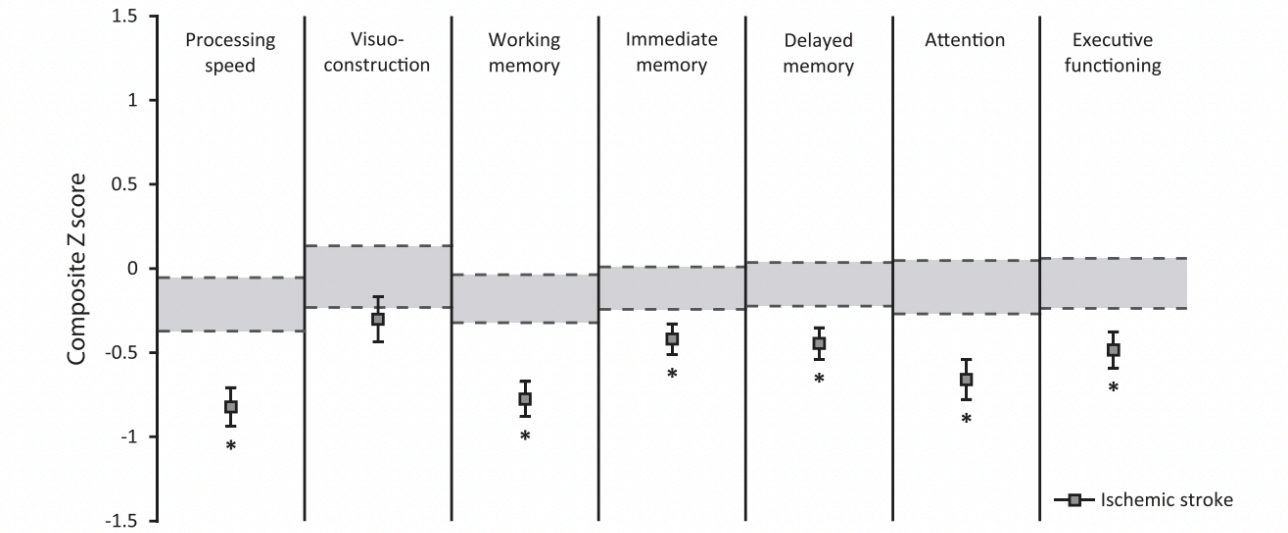
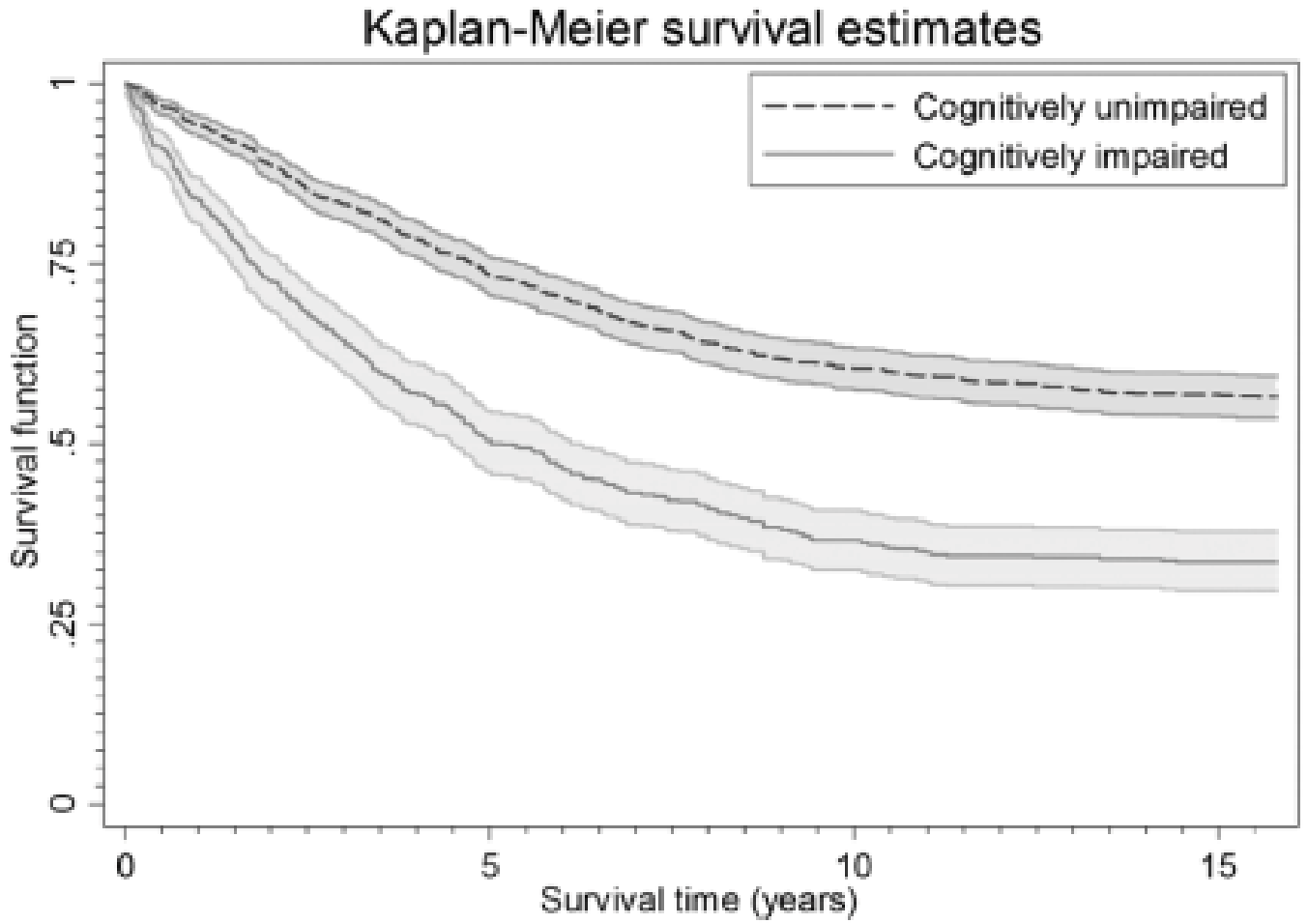


Figure 2. Cognitive performance ≈11 years after first-ever ischemic stroke in young adults compared with controls. Adjusted mean composite *Z* score (95% confidence interval [CI]) per cognitive domain (adjusted for age, sex, education, depressive symptoms, and fatigue). Gray band represents the 95% CI of the adjusted mean composite *Z* score of controls. Missing values in different domains: 0.7% to 6.5%. No missing values in the control group. *Significant difference between patients with ischemic stroke and controls. *P* value <0.0071 was considered significant.

- Adults with stroke at age < 50 years old underwent cognitive testing ~ 11 years later
- Performed worse than healthy controls on all cognitive domains except visuospatial construction

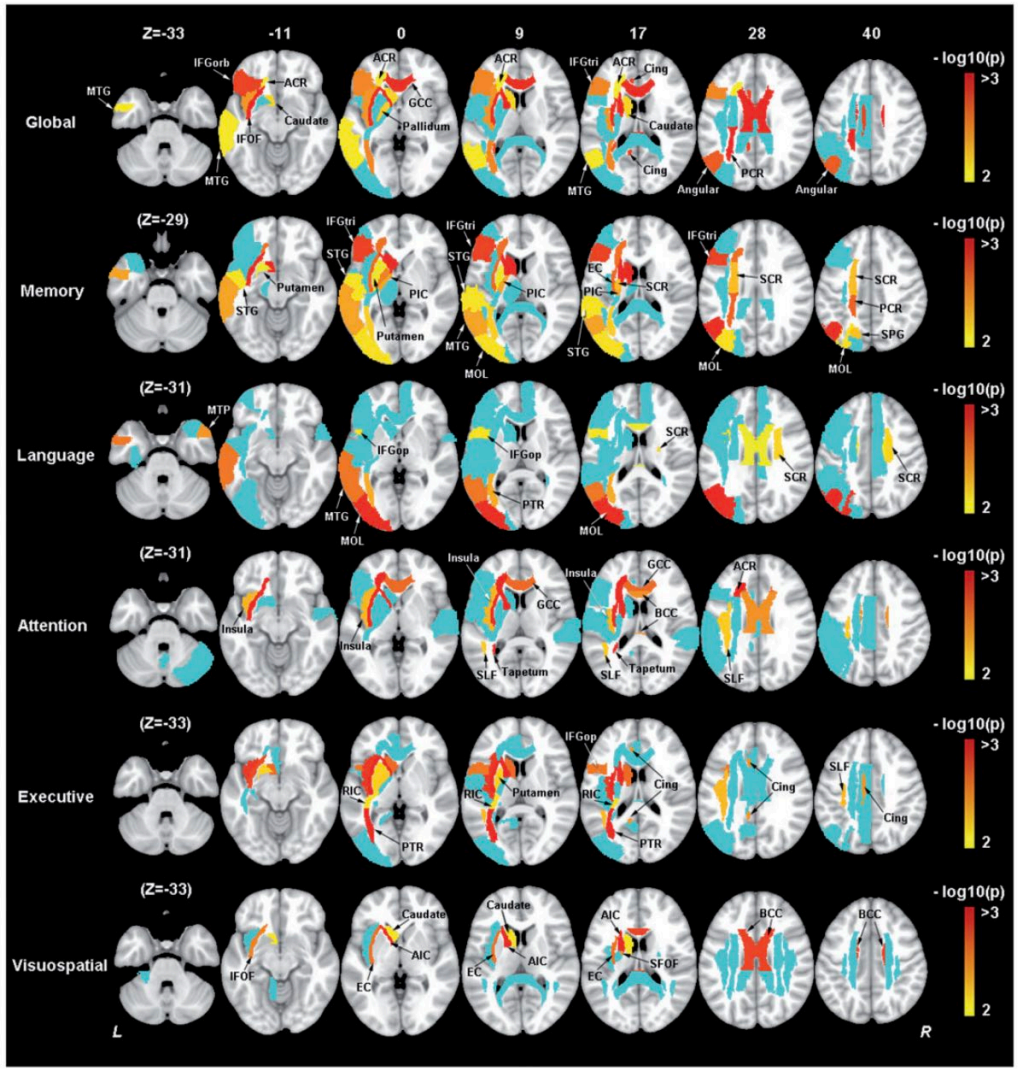
South London cohort: longitudinal study



- Cumulative survival after stroke stratified by 3 months cognitive status
- DSM IV or MMSE < 24

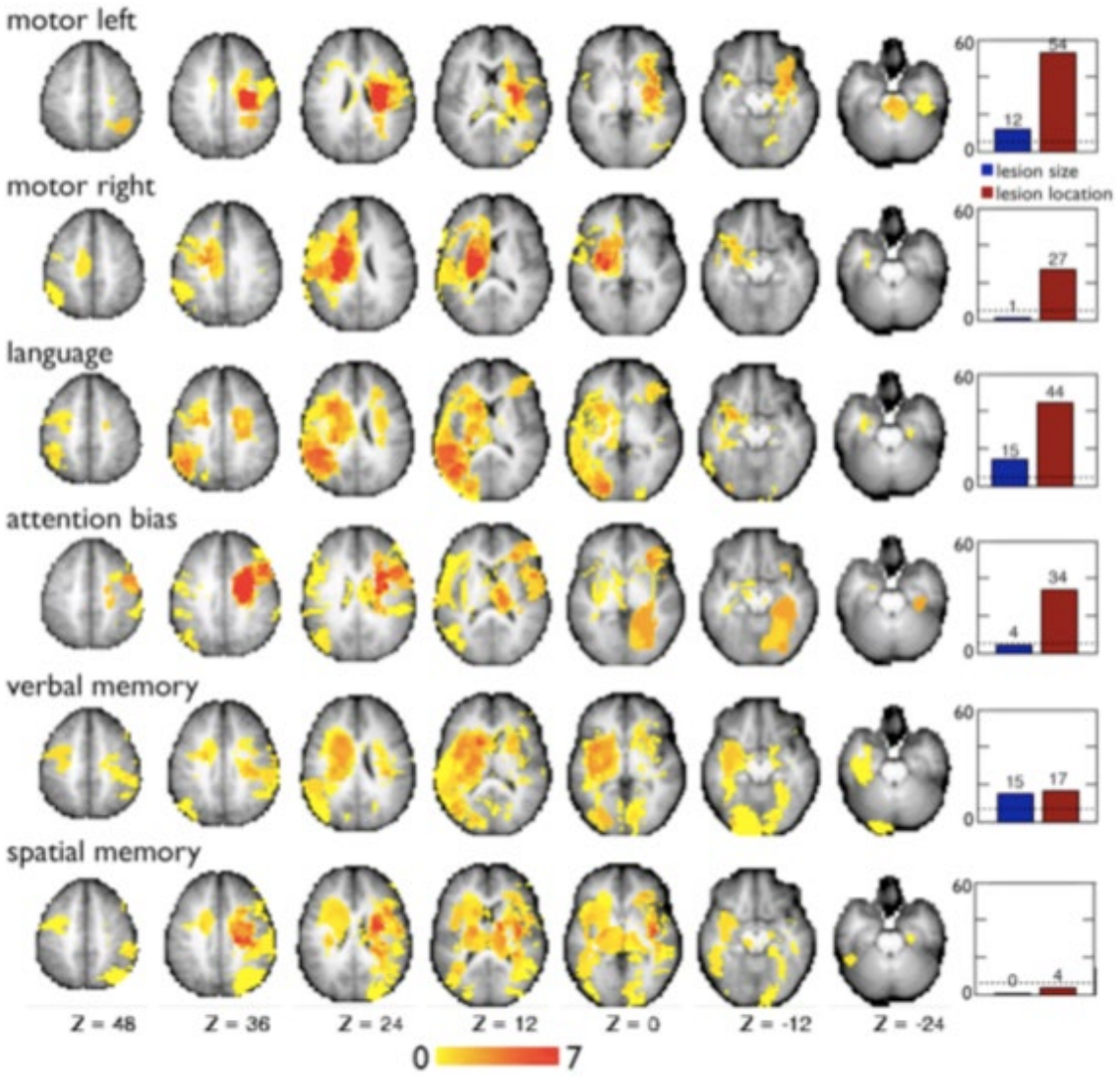
(Stroke. 2013;44:138-145.

Factors associated with post-stroke cognitive impairment



- Stroke volume
- Strategic location
  - Right corticospinal tract, left anteromedial thalamus, left arcuate fasciculis, left middle frontal gyrus, left postero-inferior cerebellum, left angular gyrus
- Total brain volume
- Medial temporal lobe atrophy
- White matter disease
- Presence of microbleeds

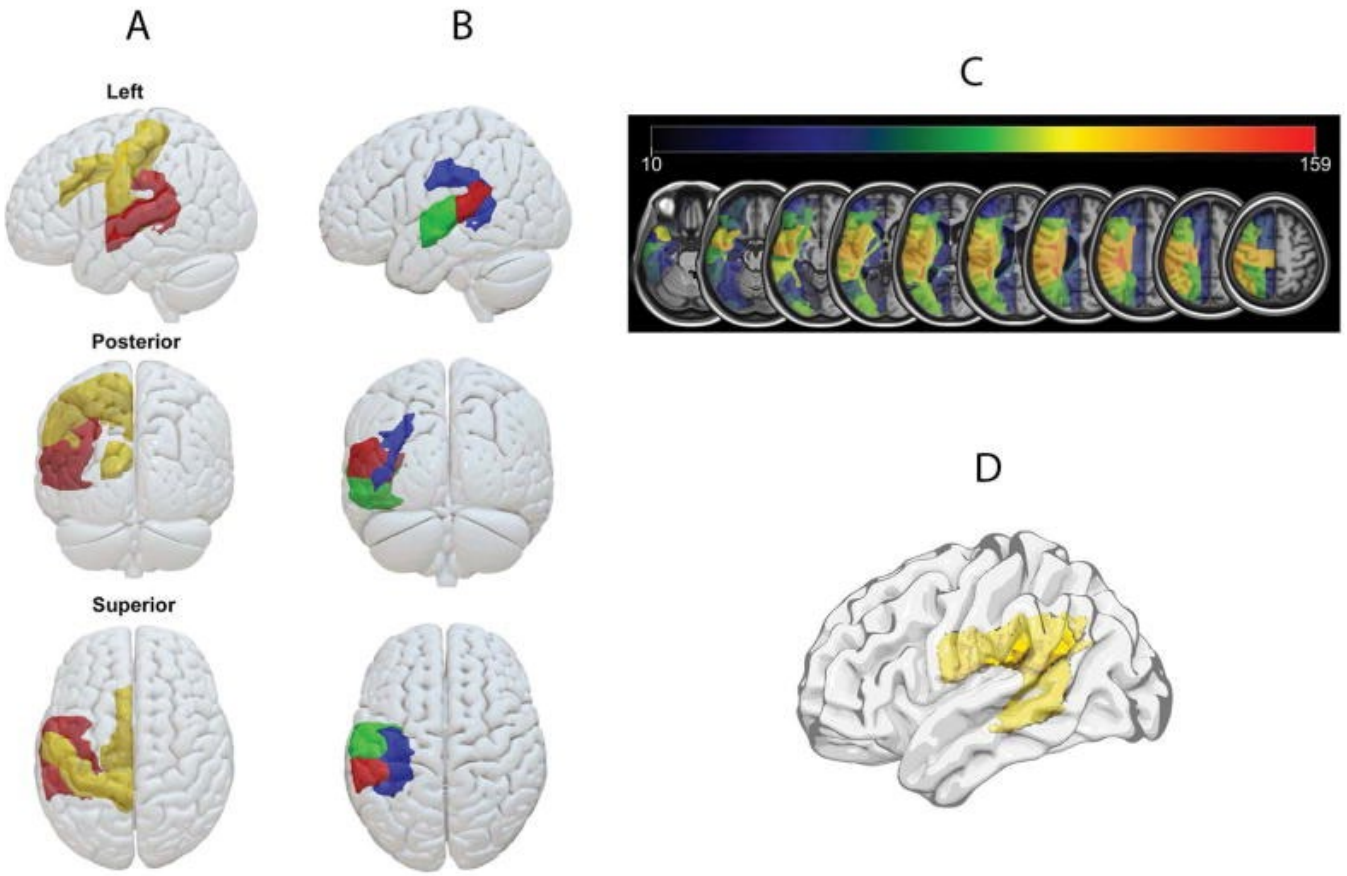
Stroke. 2018;49:2666- 2673.
Journal of Cerebral Blood Flow & Metabolism 2018, Vol. 38(8) 1299–1311



Common Behavioral Clusters and Subcortical Anatomy in Stroke

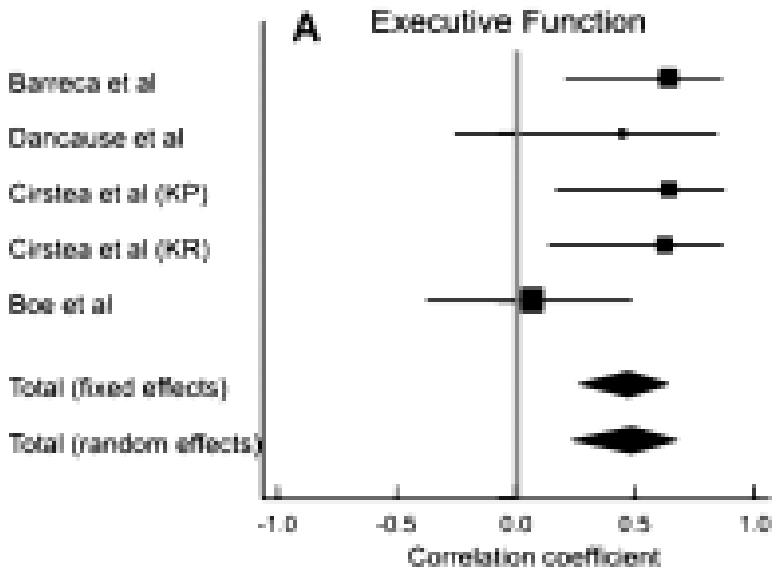
Corbetta et al., 2015, Neuron 85, 927–941

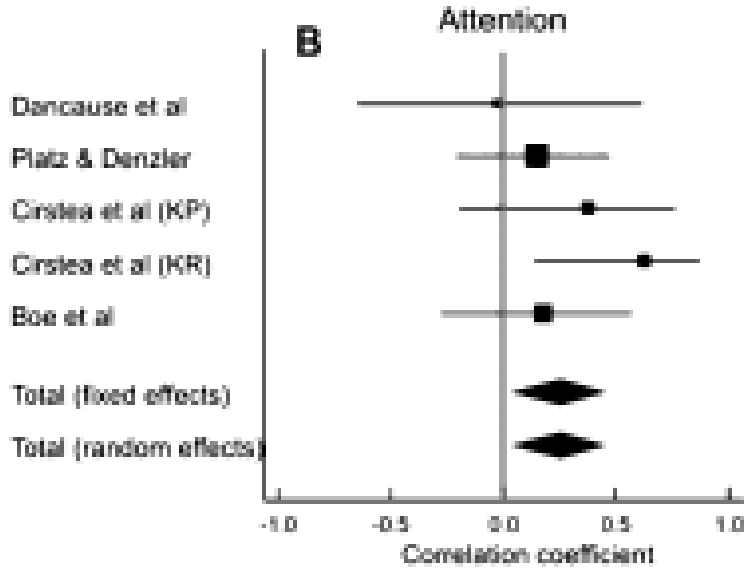
Post-stroke aphasia

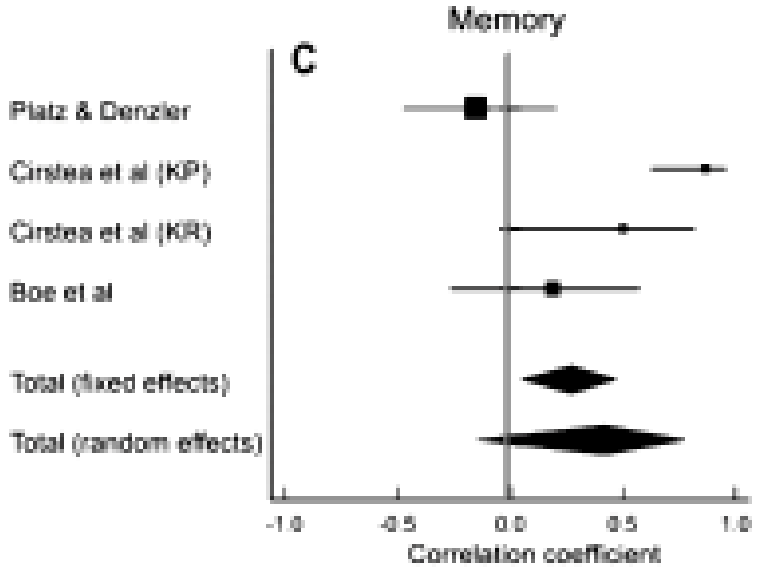


- Left posterior superior temporal gyrus
- Left superior longitudinal fasciculus
- Arcuate fasciculus

Cognitive and motor impairments are intertwined







Restorative Neurology and Neuroscience, vol. 33, no. 3, pp. 389-403, 2015

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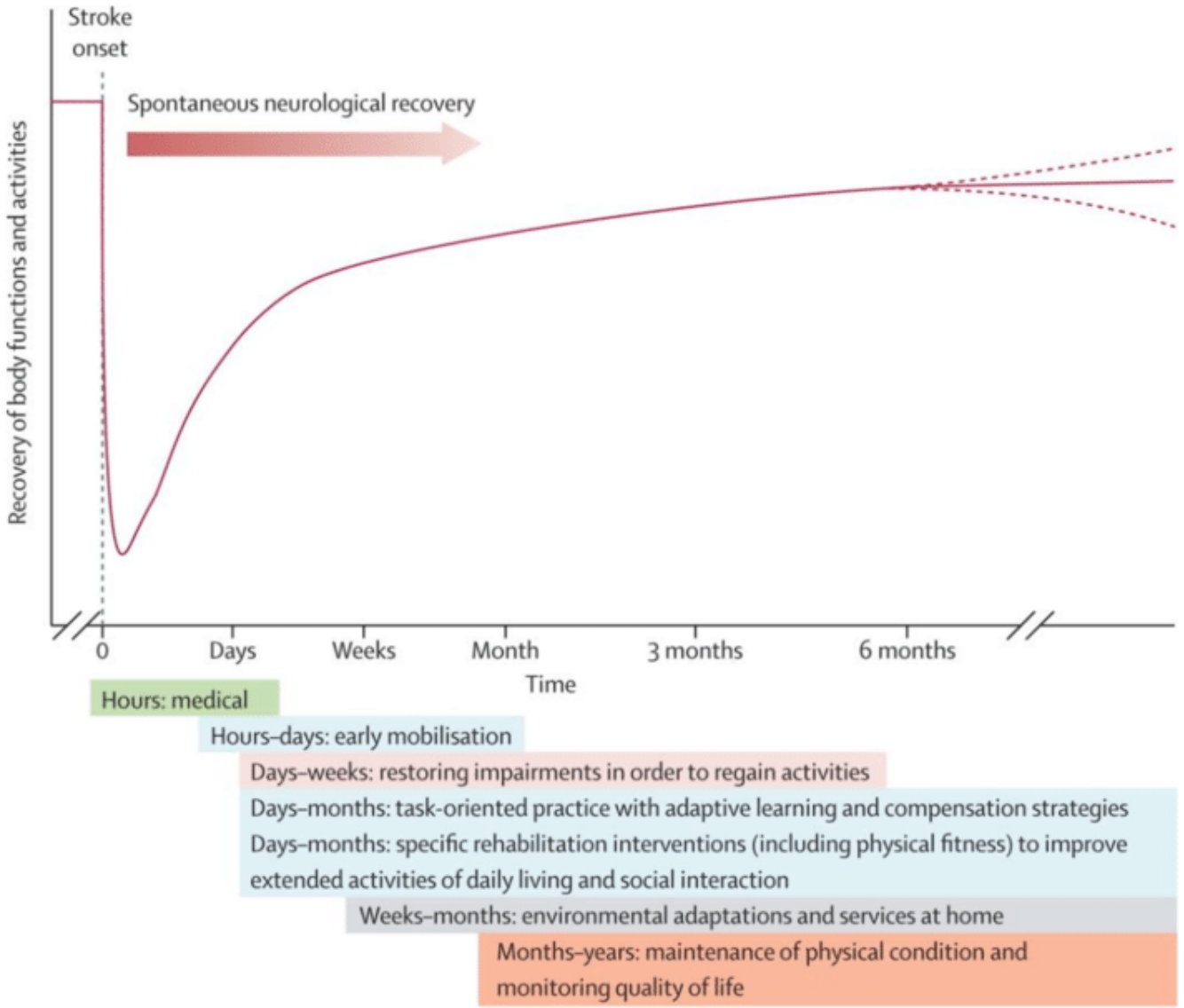
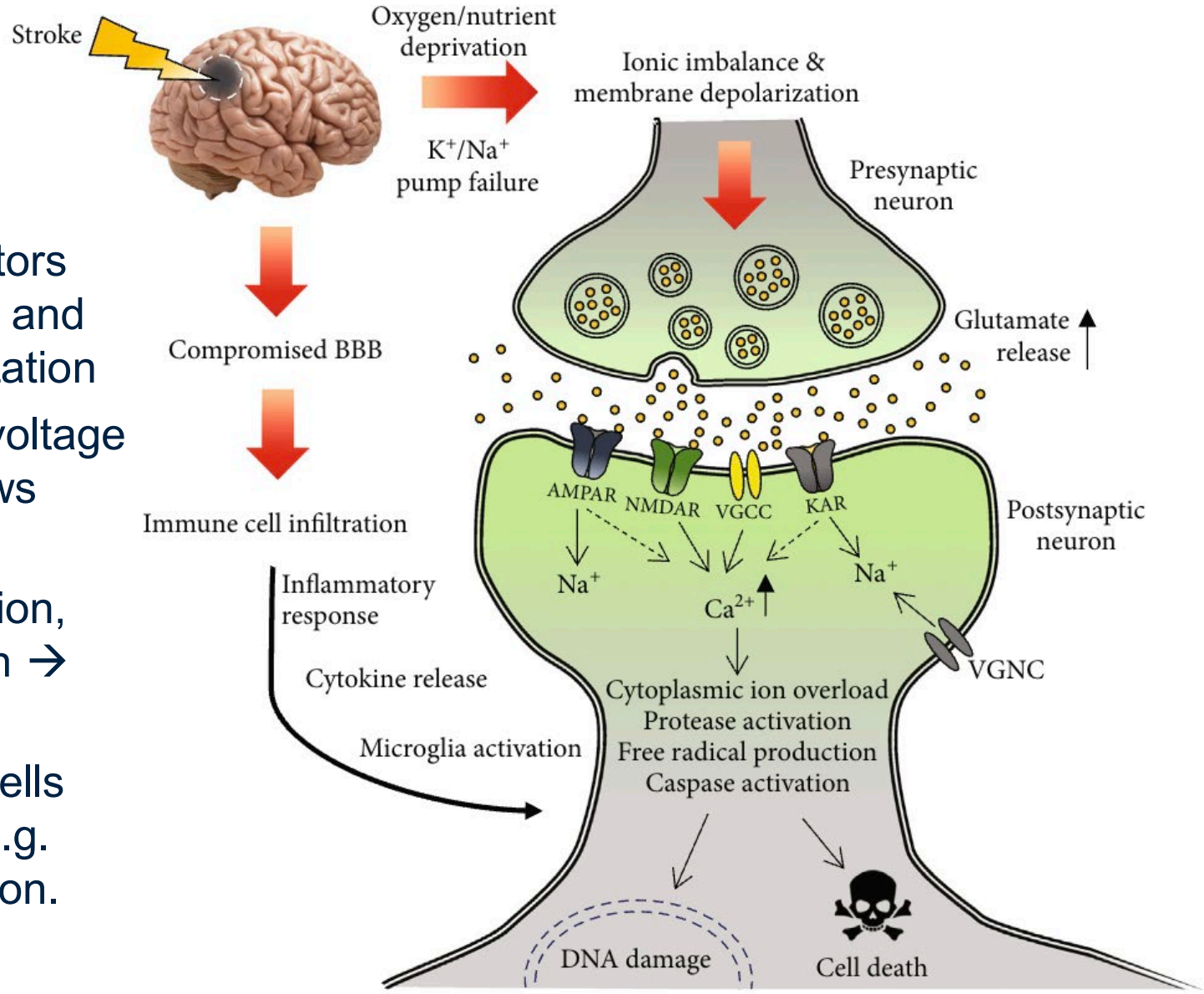
Understanding the mechanisms underlying recovery after stroke

- Spike of spontaneous recovery in the first 6 weeks to 3 months, followed by plateau
- “Sensitive period” or period of heightened neuroplasticity corresponding to this time of rapid clinical improvement



Cellular consequences of stroke

- Activation of postsynaptic glutamate receptors (AMPAR, NMDAR, and KAR) leads to Na+ and Ca2+influxes and cell membrane depolarization
- Opening of membrane potential-sensitive voltage gated Na+ and Ca2+ channels, which allows further Na+ and Ca2+ influx
- Cytoplasmic ion overload, protease activation, free radicals production, caspase activation → DNA damage, neuronal cell death.
- Through the compromised BBB, immune cells infiltrate to elicit inflammatory responses, e.g. cytokine release and microglial cell activation.



Neural Plast. 2020; 2020: 1969482.

Reestablishment of Inhibitory Neural Networks After Stroke

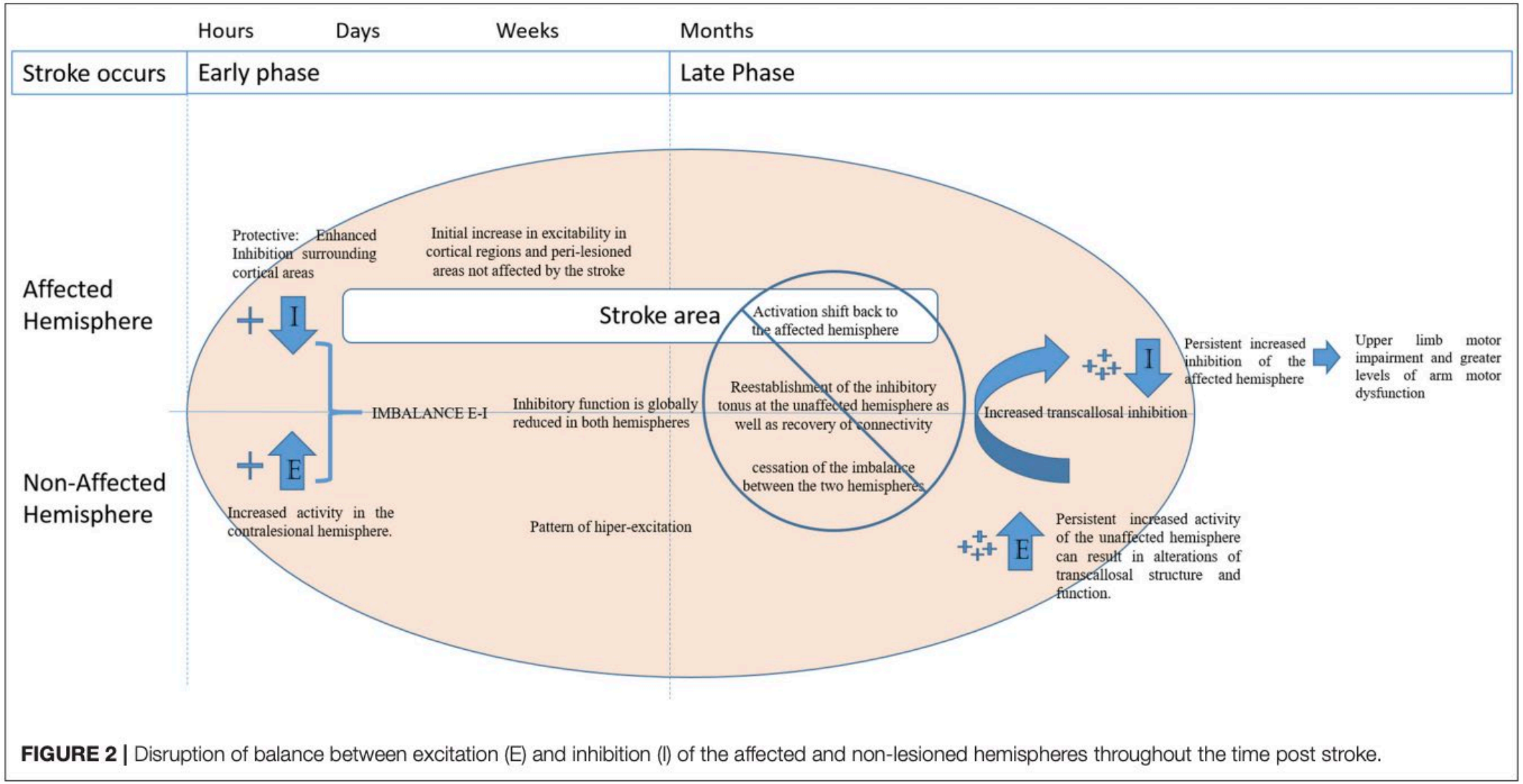
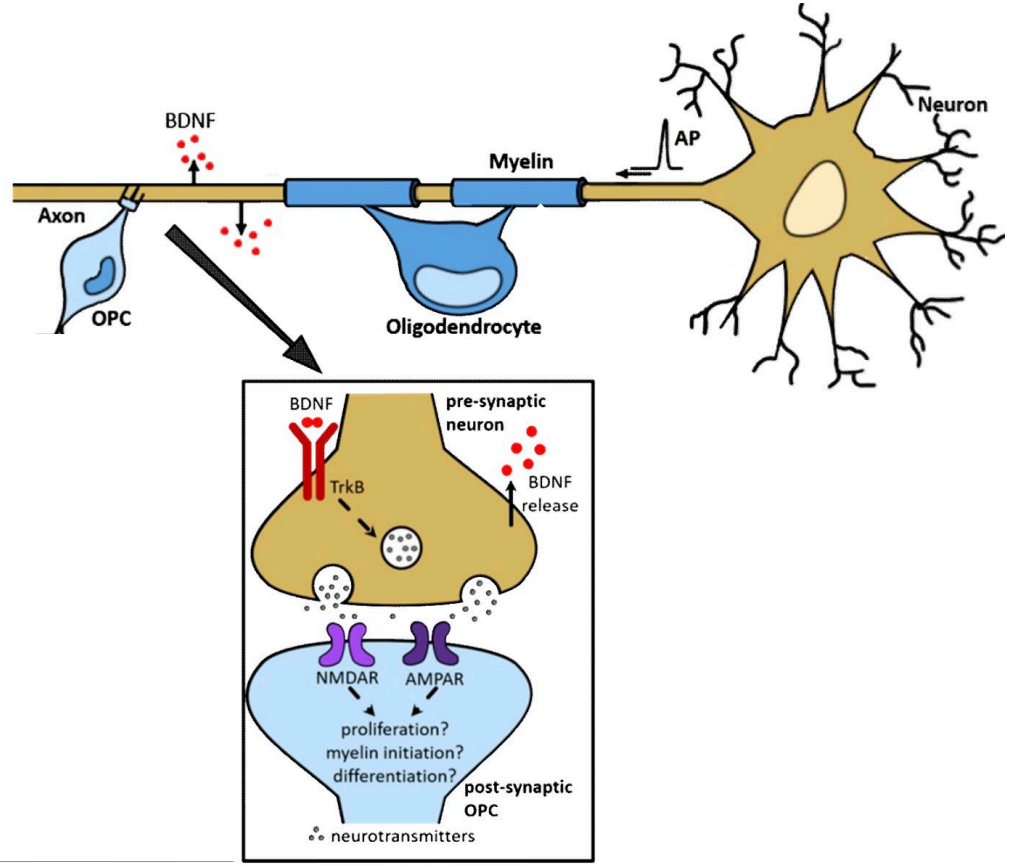


FIGURE 2 | Disruption of balance between excitation (E) and inhibition (I) of the affected and non-lesioned hemispheres throughout the time post stroke.

Molecular pathways that are important in stroke recovery



Brain Derived Neurotrophic Factor (BDNF)

- Promotes neurite outgrowth and neurogenesis post-stroke via TrkB pathway
- Promotes synaptic plasticity
- Genotype can be a predictor of motor and language recovery

NMDA and AMPA receptors

- play central roles in synaptic plasticity, brain development, learning and memory
- In acute ischemia, mediate excitotoxcity

Neural Plast. 2020; 2020: 1969482

International Journal of Molecular Sciences. 2018; 19(12):4131.

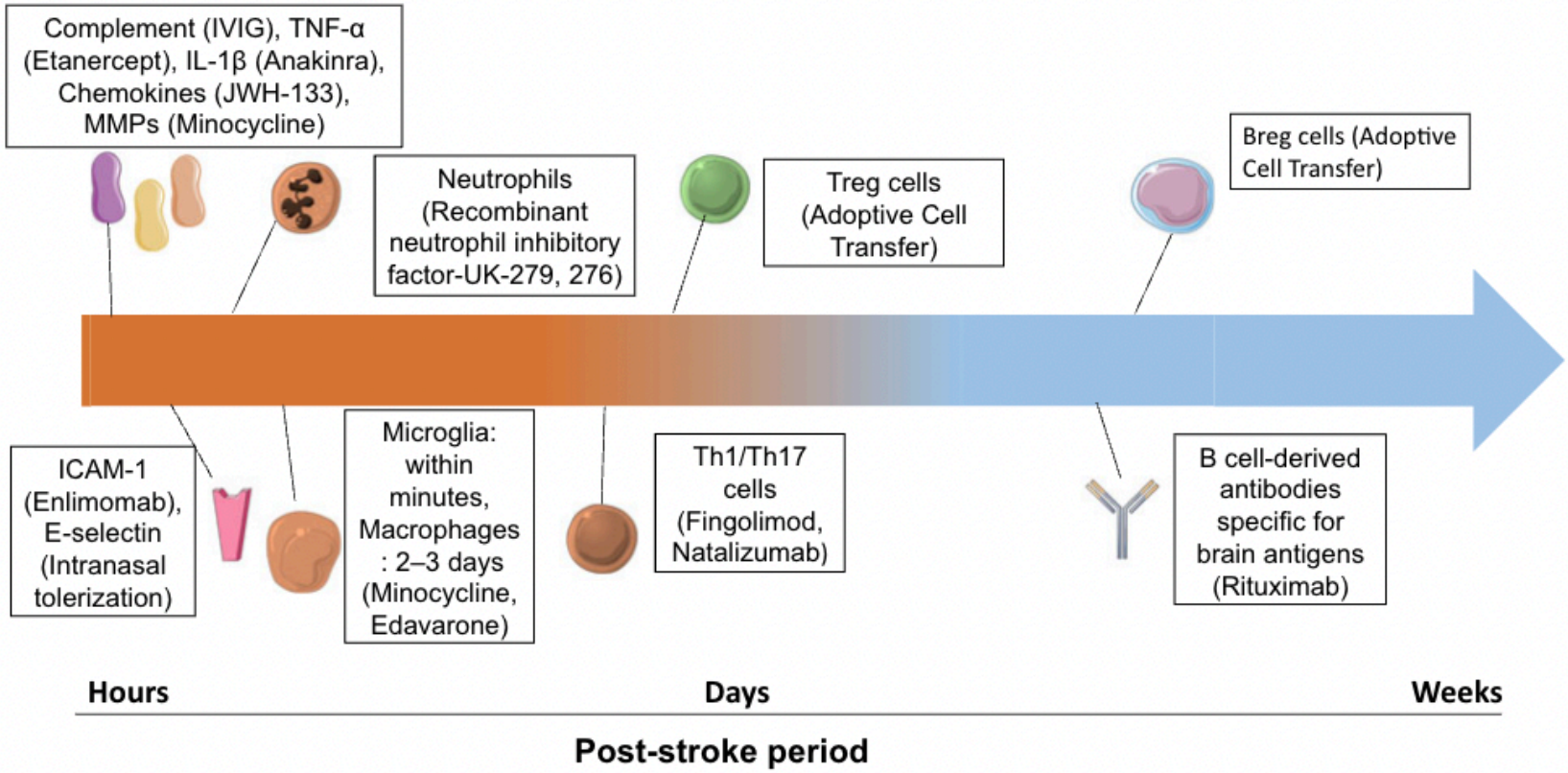


Figure 2. A time course of immune targets in stroke. Targets are placed according to the predominant role each plays in either neurotoxicity (hours to days post-stroke) or tissue remodeling and repair (weeks post-stroke). Potential therapies are highlighted in parentheses. (Adapted from Servier Medical Art). [The color version of this figure can be viewed at www.wileyonlinelibrary.com/journal/icb]

Malone et al. Immunol Cell Biol. 2019 Jan;97(1):5-16.

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Unique Challenges to Stroke Recovery

- Multiple transitions in care
- Rehabilitation is variable and often not driven by clinical need
- Stroke affects the individual in individual ways
- Pragmatic factors of post-stroke subject retention

Stroke Recovery is multidimensional

Lesion Characteristics

Amount and Type of Rehabilitation

Cortical Network involvement

Neuroactive Medications

Initial Impairment

Genetics

Age

Depression

Social Support Structures

Premorbid Disability

Fatigue

Socio-economic Demographics

Resilience

Medical Complications & Comorbidities

Interventions to Enhance Plasticity After Stroke

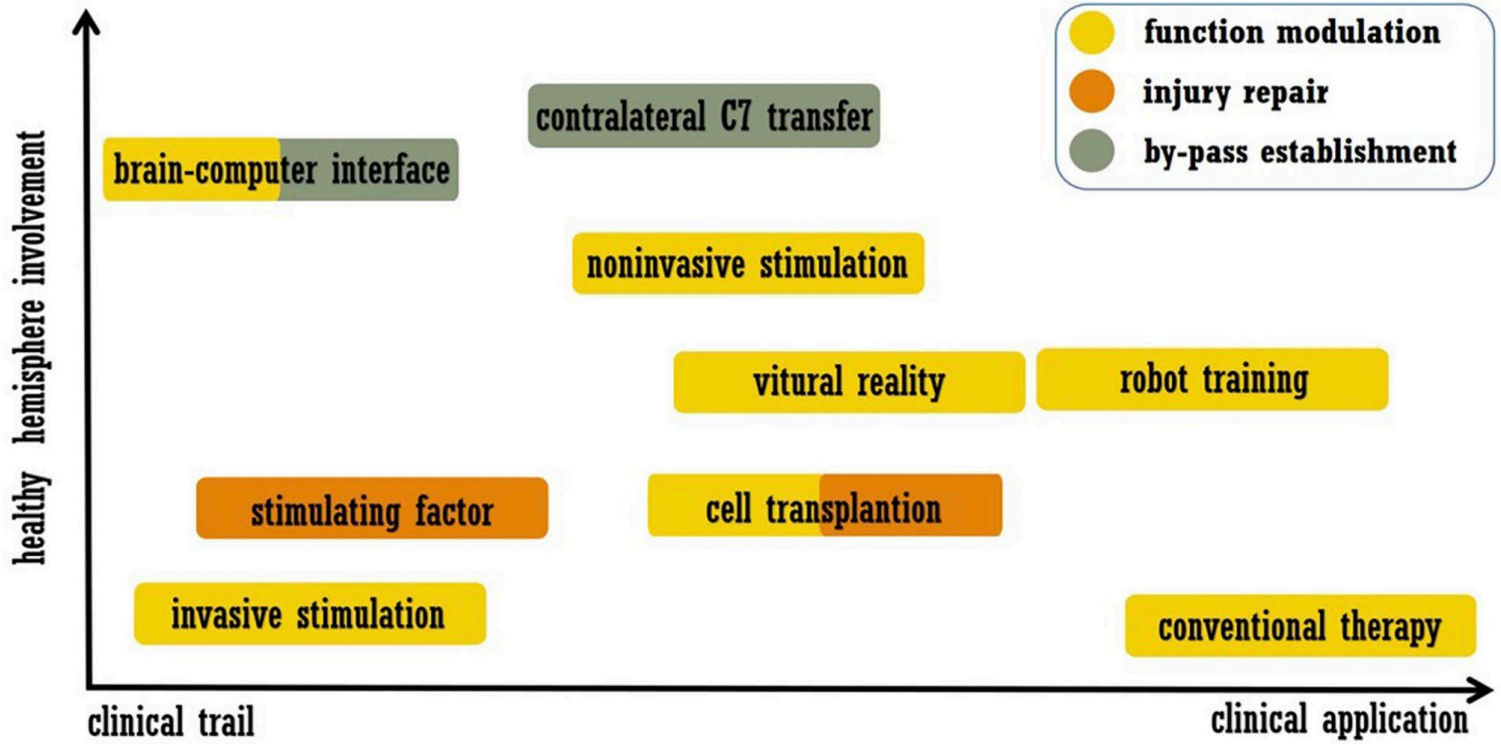


FIGURE 1 | Summary of treatment approaches discussed in this review. The abscissa indicates the readiness of clinical application, and the ordinate indicates the involvement of the healthy hemisphere.

Su F and Xu W (2020) Enhancing Brain Plasticity to Promote Stroke Recovery. Front. Neurol. 11:554089

Interventions: what works and what does not.

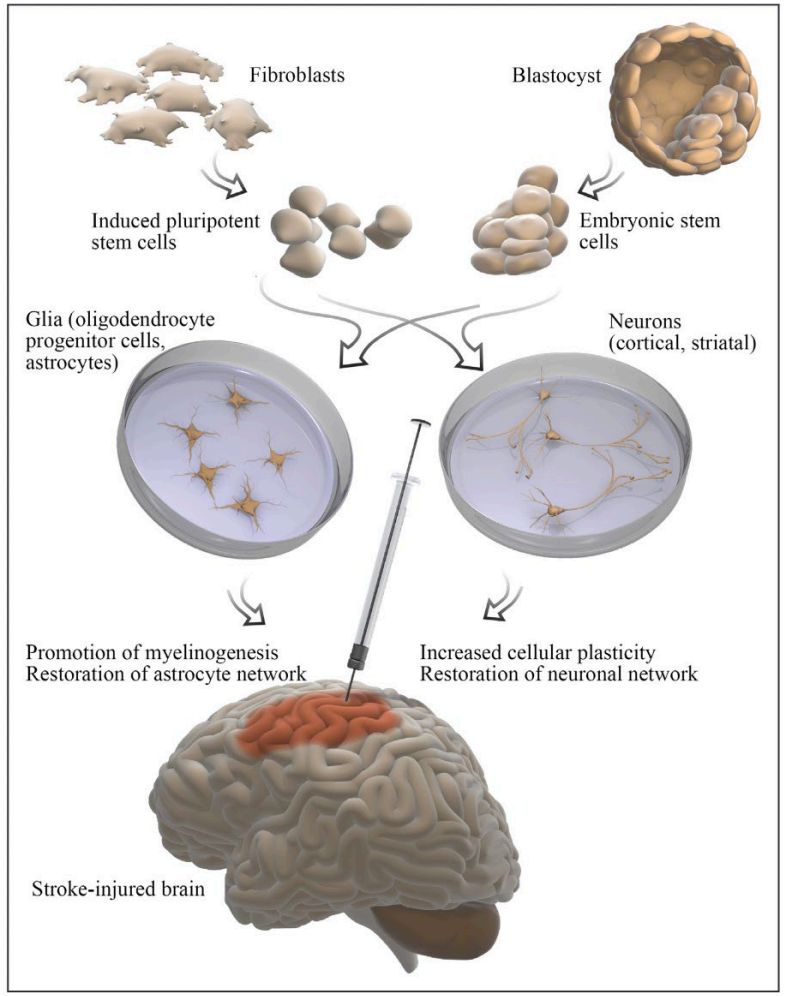
Molecular Targets for Stroke Recovery

- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

Device-based Targets for Stroke Recovery

- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation

Pluripotent stem cell therapy



Embryonic stem cells [ESCs] or induced pluripotent stem cells (iPSCs) can be treated in vitro to generate glia and neurons.

Transplantation of glial and neuronal cells at early stages of their development into stroke-injured brain can lead to promotion of myelinogenesis and restoration of astrocyte network or by increasing cellular plasticity and restoring neuronal network.

Thus far, there have been 9 randomized controlled trials and 7 non-randomized studies (NRSs), involving 740 participants.

There was no significant difference in mortality between the stem cell group and the control group.

Most commonly reported adverse effects: Fever, headache, and recurrent stroke.

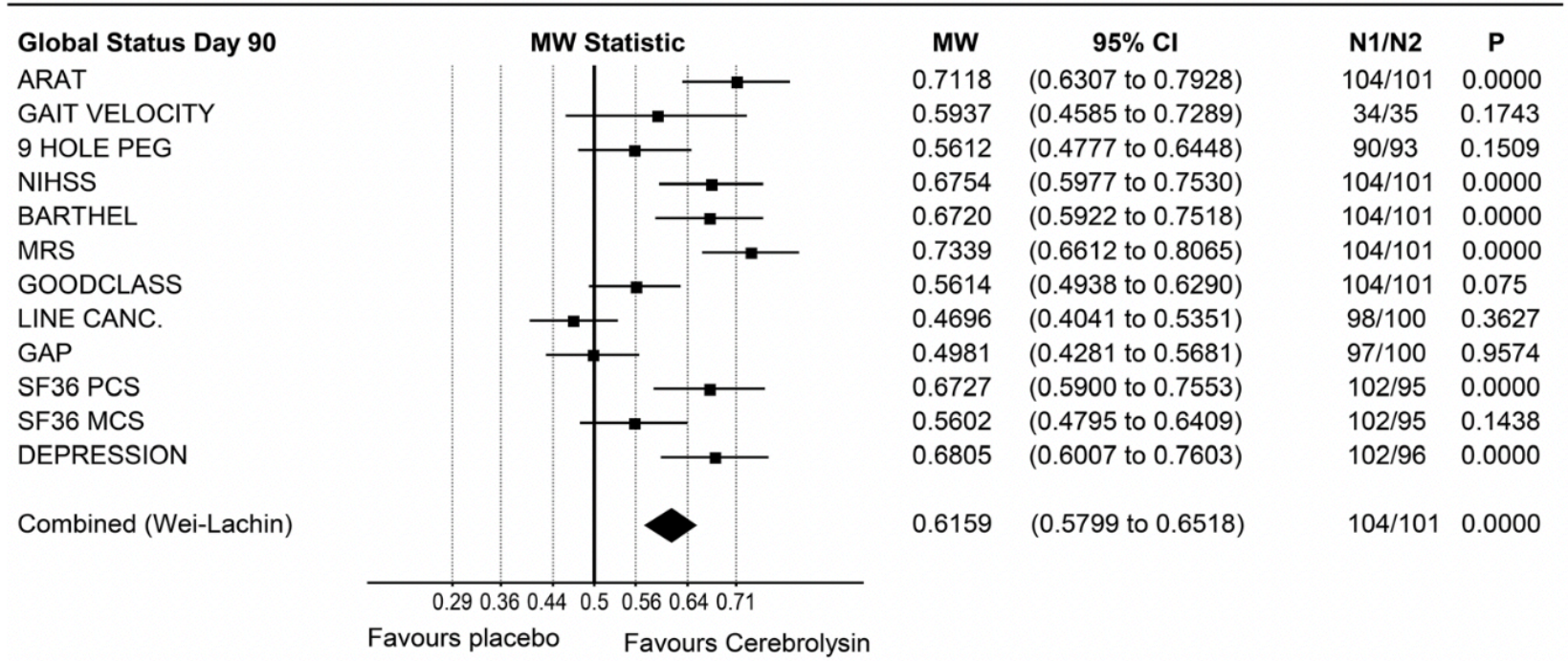
Kokaia Z, Llorente IL, Carmichael ST. 2018 May;49(5):1091-1098.
Li, Z., Dong, X., Tian, M. *et al.* *Stem Cell Res Ther* **11**, 252 (2020).

Cerebrolysin

- mixture of enzymatically treated peptides derived from pig brain whose constituents can include **brain-derived neurotrophic factor (BDNF),** glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and ciliary neurotrophic factor (CNTF).

CASTA trial: Administered within 12 hours of symptoms onset to Cerebrolysin daily or placebo for 10 days → no benefit

CARS trial: Administered within 24-72 hours of symptom onset to Cerebrolysin placebo daily for 21 days. Paired with a standardized rehabilitation program for 21 days that was initiated within 72 hours after stroke onset → benefit



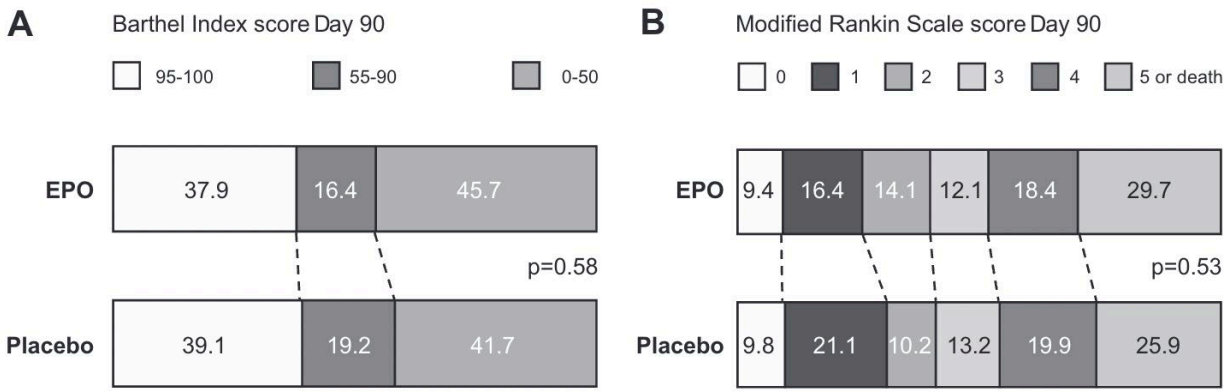
Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z; Stroke. 2012 Mar;43(3):630-6.
Stroke. 2016;47:151-159

Erythropoietin

- Binds specifically to neuronal EPO receptors
- Antiapoptotic, antioxidant, anti-inflammatory, neurotrophic, neural stem cell–modulating and neuroplasticity-enhancing fashion.

Beta-hCG+Erythropoietin in Acute Stroke (BETAS) study: multisite, open-label, safety trial that gave 3 doses beginning 1 to 2 days post-stroke followed by 3 erythropoietin doses beginning 7 to 8 days after stroke. This study identified no safety concerns,

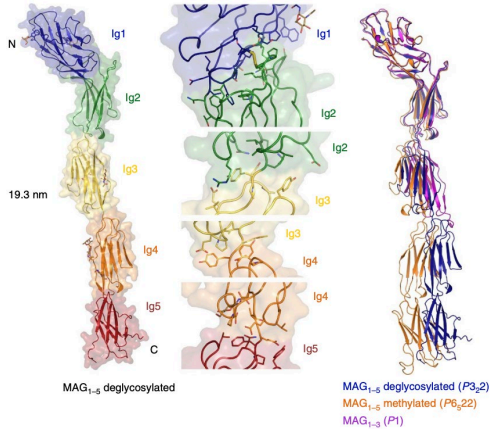
REGENESIS study: randomized, double-blind, placebo-controlled trial of 522 subjects with acute MCA ischemic stroke within 6 hours of symptom onset that gave 2 doses of EPO IV (40 000 IU each) at 24 and 48 hours.



Stroke. 2009;40:e647-e656.

Myelin-associated glycoprotein [MAG]

	Placebo	GSK249320
Change in gait velocity, baseline to day 90, mean±SD (ITT)	n=44 0.56±0.50	n=47 0.55±0.46
Change in gait velocity, baseline to day 180, mean±SD (ITT)	n=38 0.56±0.48	n=41 0.60±0.44
Change in box and blocks score, baseline to day 90, mean±SD (PP)	n=41	n=40
Stroke-affected arm	17.1±19.1	14.9±16.5
Nonstroke arm	18.6±15.2	14.6±16.4
Subjects falling to day 90 (safety)	15	12
Modified Rankin scale score, day 90 (PP)	n=46	n=45
0	0	2
1	7	6
2	13	11
3	10	11
4	14	14
5	2	1
NIHSS score, day 90, median (IQR) (PP)	4 (1.25–8.75)	4 (1–7)

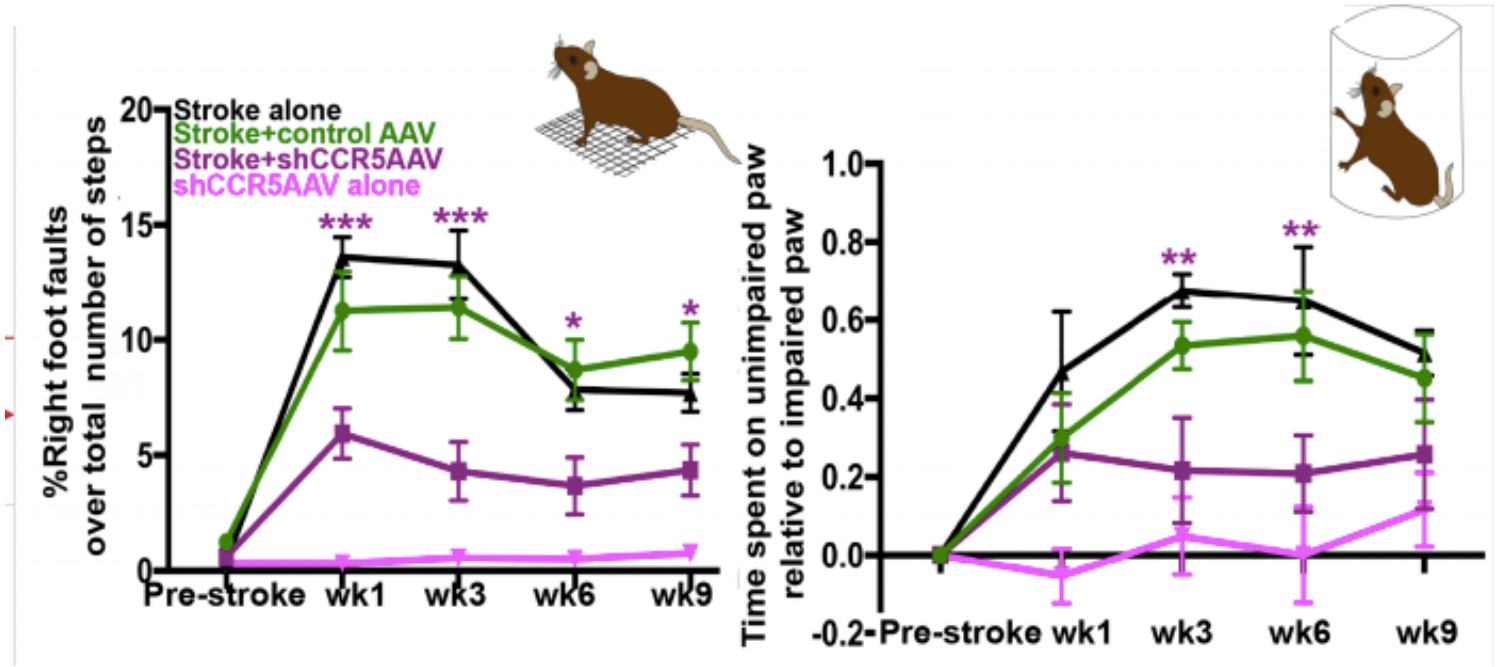


- Myelin-associated glycoprotein, along with other CNS inhibitors oligo-myelin glycoprotein, and Nogo-A, can block myelin-based inhibitory proteins that inhibit axon outgrowth and therefore neuronal repair.
- Randomized trial of 134 subjects: 2 IV infusions of MAG at 24 to 72 hours after stroke onset
- Primary outcome was gait velocity

Pronker, M., Lemstra, S., Snijder, J. *et al. Nat Commun* **7**, 13584 (2016).
Cramer SC, Stroke. 2017 Mar;48(3):692-698.

CCR5 impact on motor recovery

- CCR5:
  - White blood cells display CCR5 on their surface to intercept signals from chemokines and coordinate an immune response.
  - HIV exploits CCR5 to invade host cells.
  - High levels of CCR5 in stroke patients



Reducing CCR5 function in pre-motor cortex neurons induces early motor recovery after stroke.

Joy et al., 2019, Cell 176, 1143–1157

Interventions: what works and what does not.

Molecular Targets for Stroke Recovery

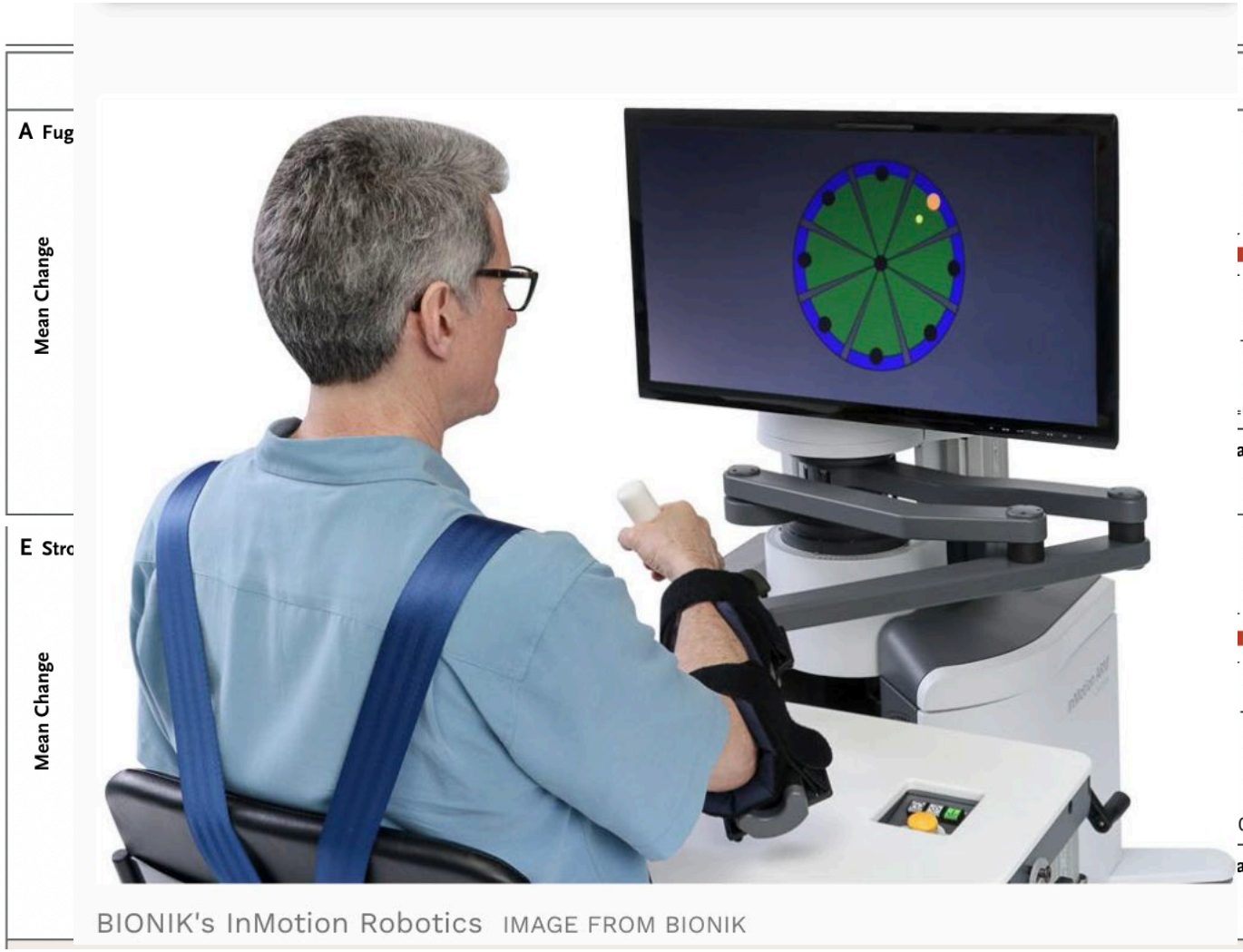
- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

Device-based Targets for Stroke Recovery

- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation

Robotics

- Multicenter, randomized, controlled trial involving 127 patients > 6 months after stroke.
  - 49 patients to receive intensive robot-assisted therapy, 50 to receive intensive comparison therapy for 12 weeks of treatment (up to 36 sessions). Twenty-eight were randomized to receive usual care.
  - Robot-assisted therapy did not significantly improve motor function after 12 weeks



BIONIK's InMotion Robotics IMAGE FROM BIONIK

Lo AC, et al N Engl J Med. 2010 May 13;362(19):1772-83.

Robotics

- **SMARTS2 trial:** multicenter, single-blinded, parallel randomized controlled trial comparing the efficacy of a neuro-animation therapy with time-matched conventional occupational therapy to enhance upper-limb motor recovery after stroke (2 hours a day of therapy for 5 consecutive days over 3 weeks).

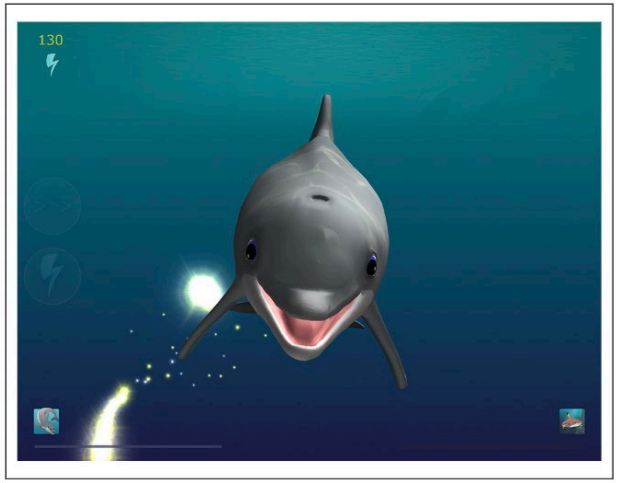
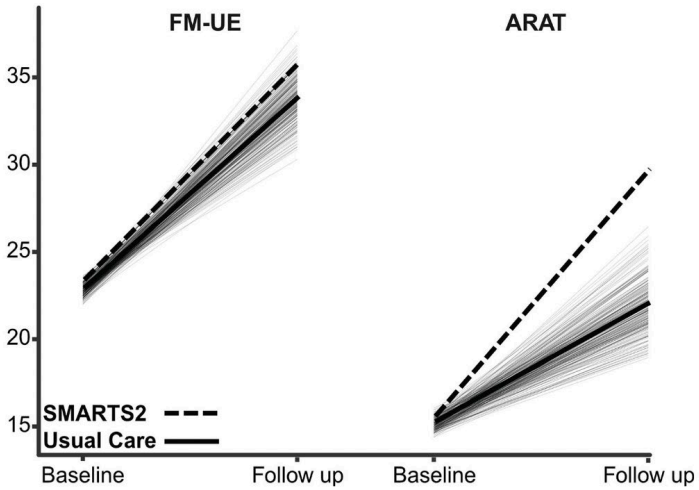


Figure 1. Participants in the neuroanimation therapy group played MindPod Dolphin.



Krakauer JW, et al. Neurorehabil Neural Repair. 2021 May;35(5):393-405.

Telerehabilitation

- Randomized, assessor-blinded, noninferiority trial of 124 participants across 11 US sites, 124 patients who had experienced stroke 4 to 36 weeks prior and had arm deficits

Figure 2. Examples of Telerehabilitation Therapy Content

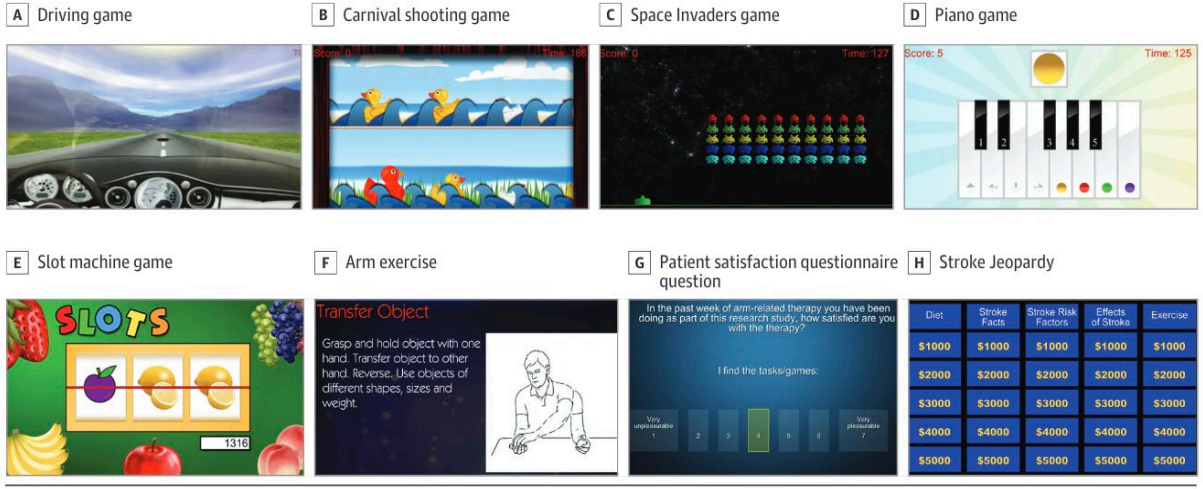


Table 2. Treatment-Related Change in FM Motor Score[a]

Model	Patients, No.			FM Score for IC Group, Mean Change	FM Change (TR-IC), Difference Between Groups (95% CI)[b]
	TR	IC	Total		
Primary analysis					
ITT with multiple imputation of missing outcomes	62	62	124	8.23	0.06 (−2.14 to 2.26)
Secondary analyses					
ITT with substitution of "worst-best-case" missing outcomes	62	62	124	8.58	−0.19 (−2.29 to 1.92)
Complete case ITT	59	55	114	8.36	0.00 (−2.27 to 2.27)
Complete case PP	58	55	113	8.36	−0.15 (−2.41 to 2.10)

Cramer et al. JAMA Neurol. 2019 Sep 1;76(9):1079-1087.

Brain-Computer Interface

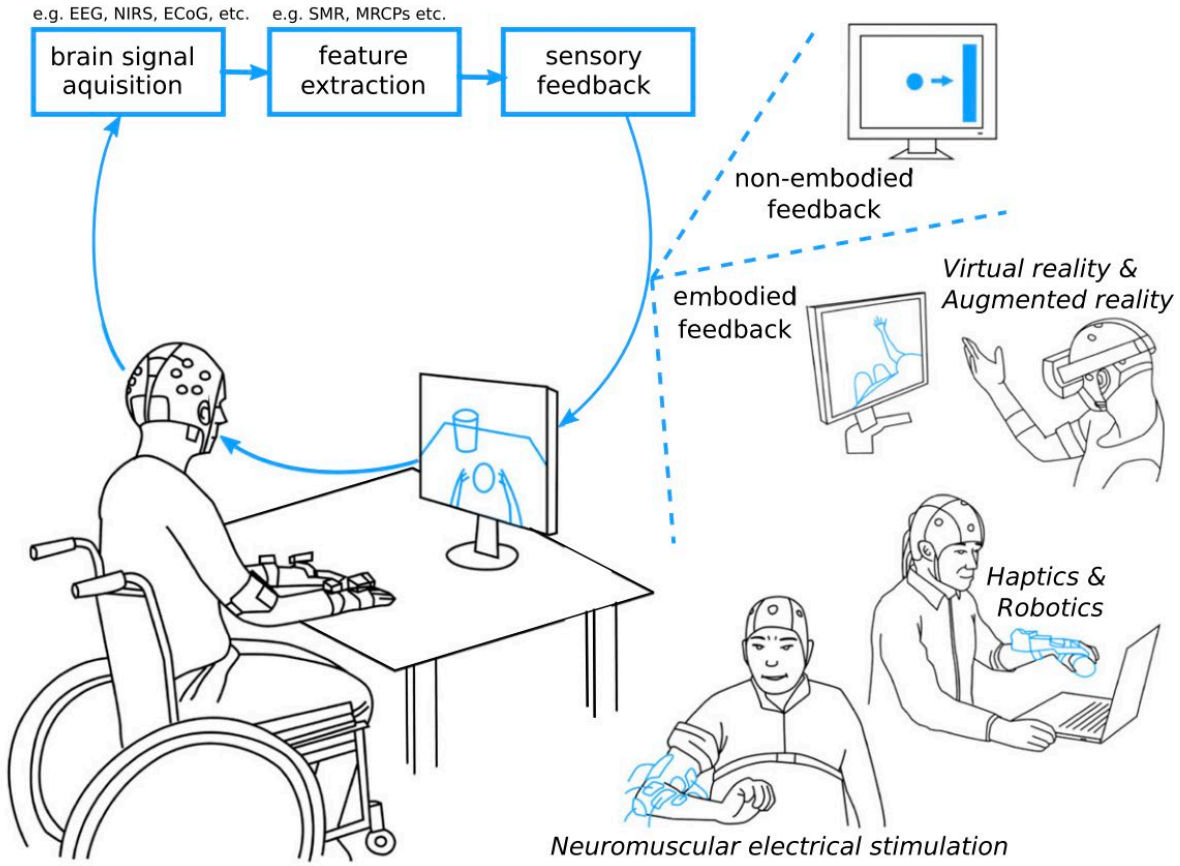


Figure 1. Illustration of typical brain-computer interface (BCI) systems used in post-stroke motor rehabilitation highlighting sensory feedback modalities. EEG = electroencephalography, NIRS = near-infrared spectroscopy, ECoG = electrocorticography, SMR = sensorimotor rhythm, MRCP = motor-related cortical potential.

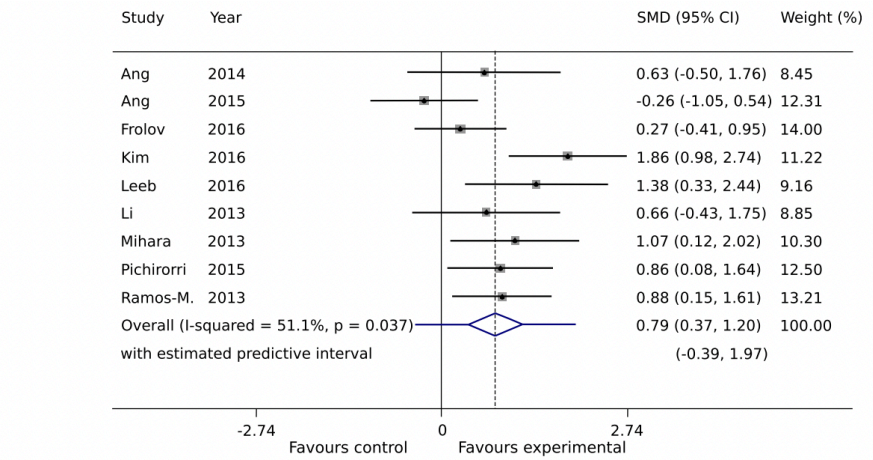
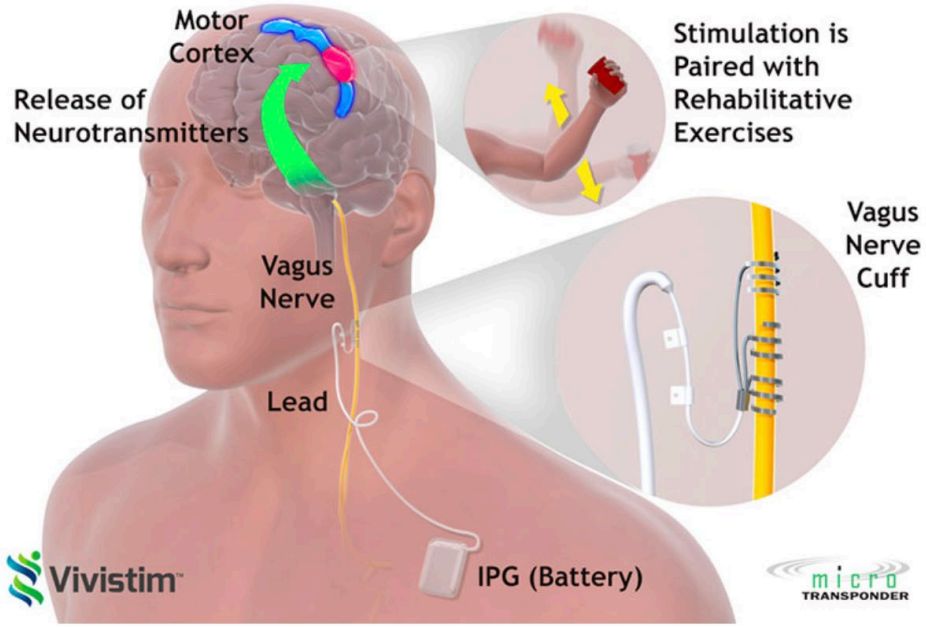


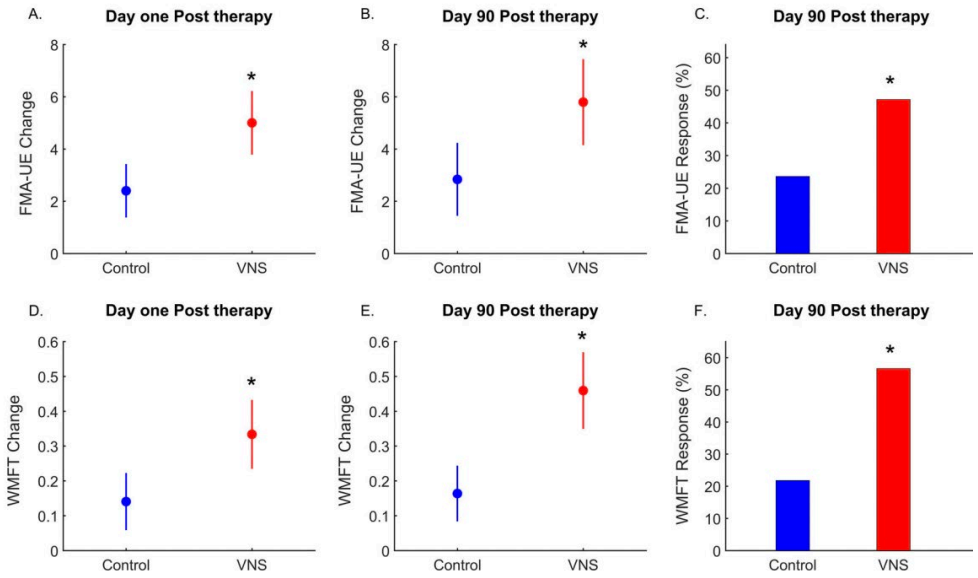
Figure 3. Intervention effect measured as changes in upper-extremity Fugl-Meyer Assessment (FMA-UE) scores between pre- and postintervention (standardized mean difference (SMD), Random-Effects). The mean effect is represented as a diamond in the forest plot, whose width corresponds to the 95% CI, whereas the PI is shown as a bar superposed to the diamond. Box sizes reflect the contribution of the study toward the total intervention effect.

Annals of Clinical and Translational Neurology 2018; 5(5): 651–663

(Non) invasive brain stimulation: Vagal Nerve Stimulator

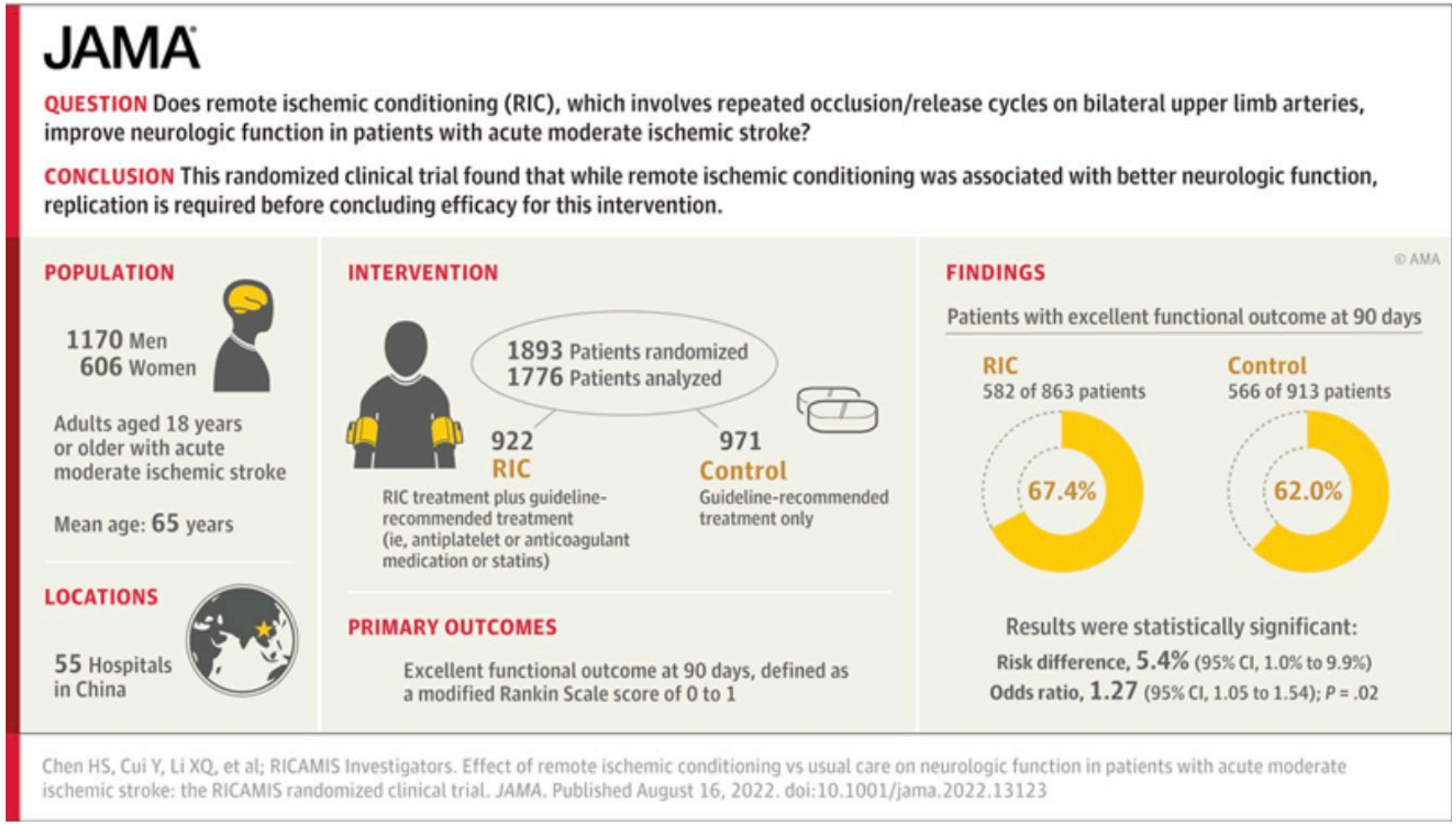
- To enhance the reorganization potential of the brain following stroke is via cholinergic and monoaminergic modulation of motor cortex neurons
- VNS-REHAB: randomized, triple-blind, sham-controlled trial, we assigned participants with moderate to severe arm weakness, at least nine months after ischemic stroke
  - FDA approval following this study





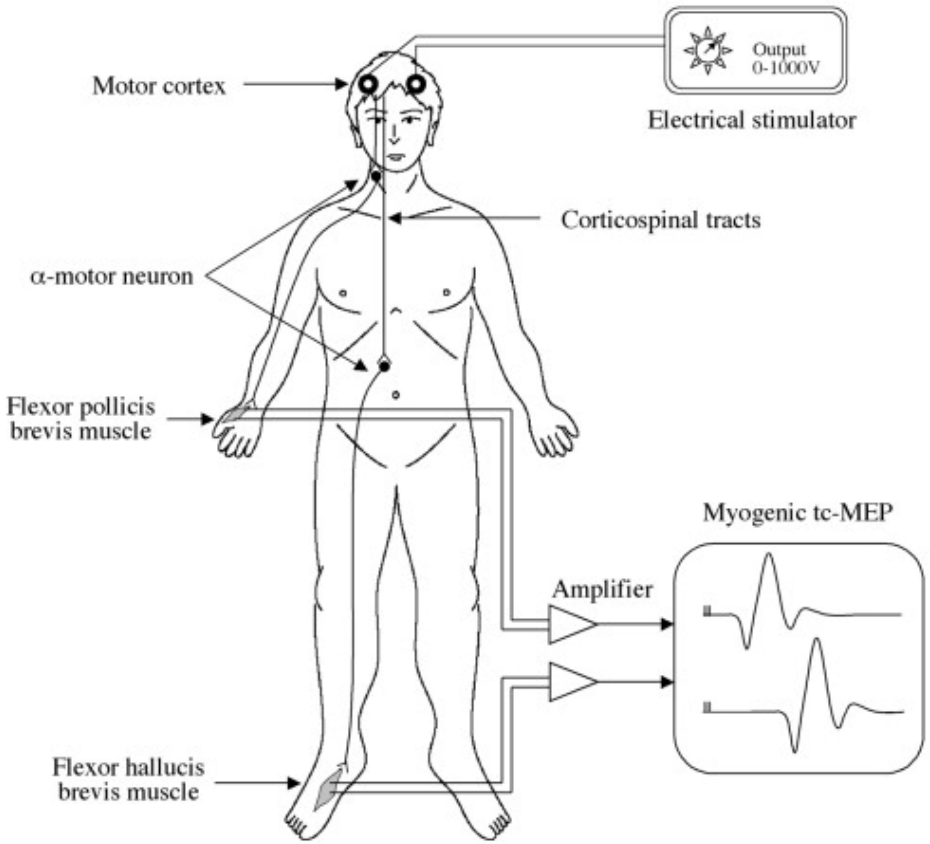
Dawson J, et al. Lancet. 2021 Apr 24;397(10284):1545-1553.

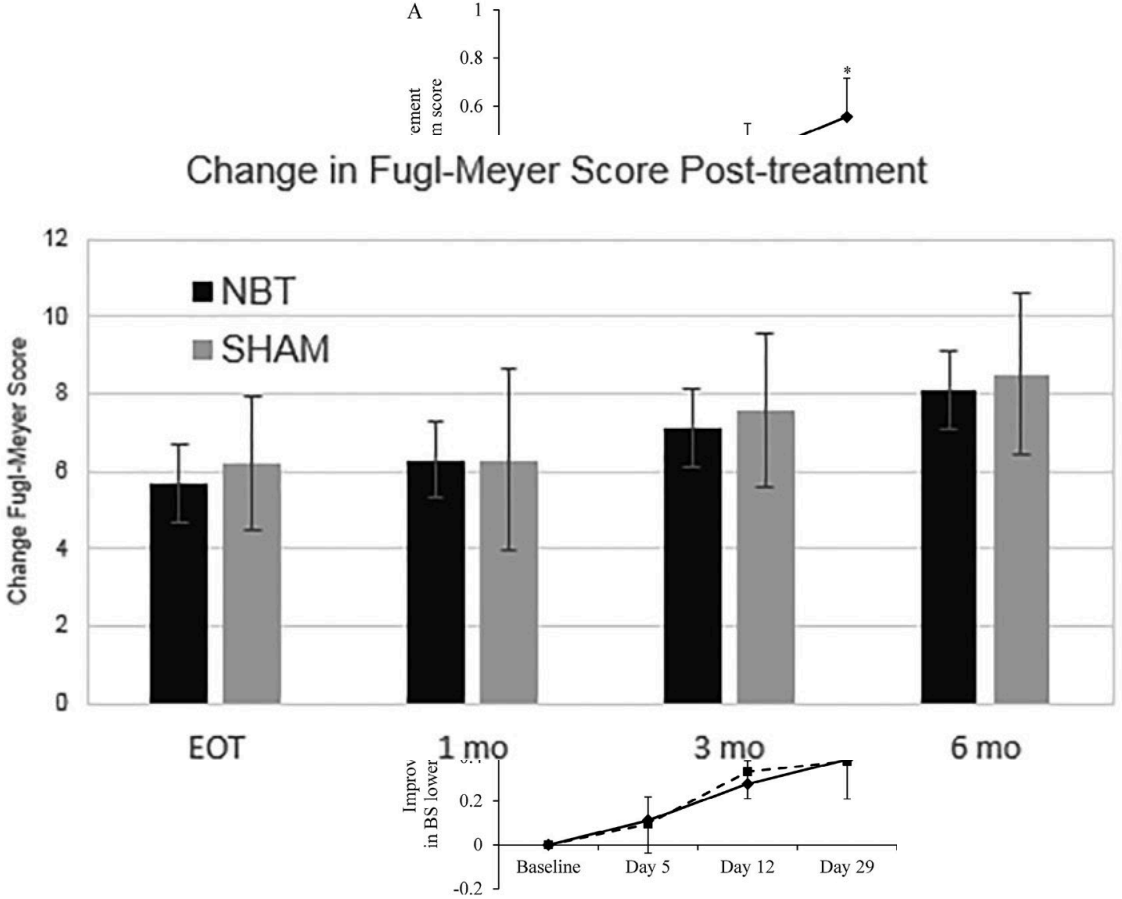
Non-invasive stimulation: Remote ischemic conditioning



Chen H, Cui Y, Li X, et al. The RICAMIS Randomized Clinical Trial. *JAMA.* 2022;328(7):627–636.

Non-invasive brain stimulation: Transcranial Magnetic Stimulation





Hosomi K, et al. J Stroke Cerebrovasc Dis. 2016 Jul;25(7):1655-1664.
Harvey RL, et al. Stroke. 2018 Sep;49(9):2138-2146.

Non-invasive brain stimulation: Transcranial Magnetic Stimulation

- Aphasia:
  - Common impairment after stroke
  - Standard of care is currently therapy with a speech and language pathologist

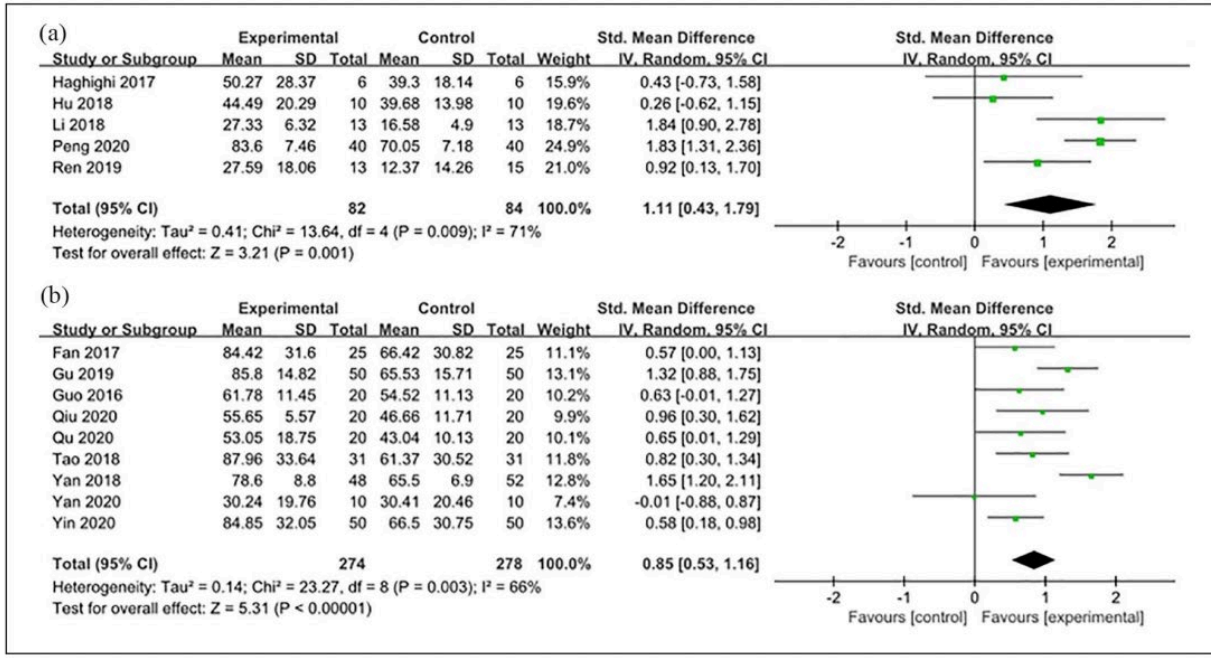


Figure 7. Forest plot for aphasia quotient: (a) rTMS versus Sham rTMS, and (b) rTMS versus Conventional rehabilitation.
Source: Conventional rehabilitation (speech and language training, physical exercises, or acupuncture, etc.); SD: standard deviation; 95% CI: 95% confidence interval; Std. mean difference: standard mean difference; IV: inverse variance.

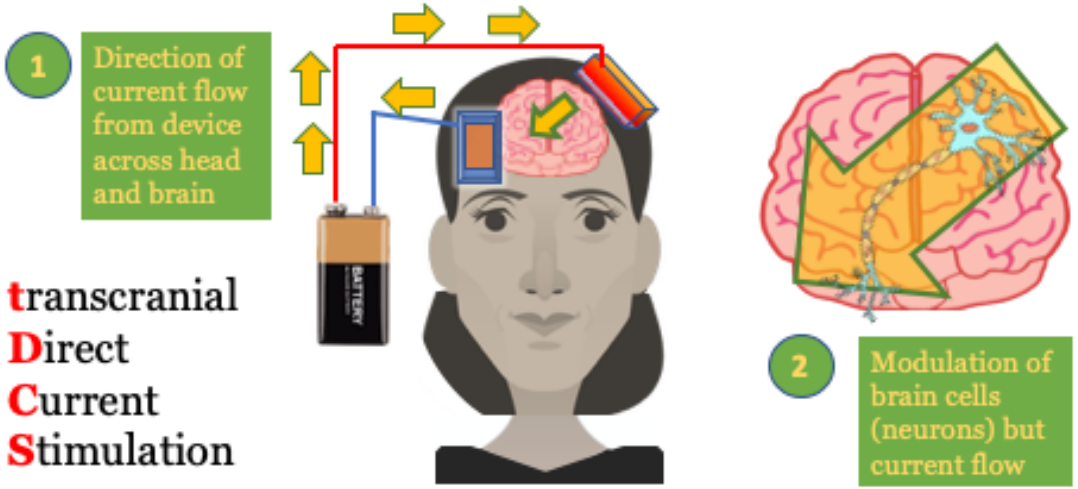
Non-invasive brain stimulation: Transcranial Direct Current Stimulation

- **Motor**

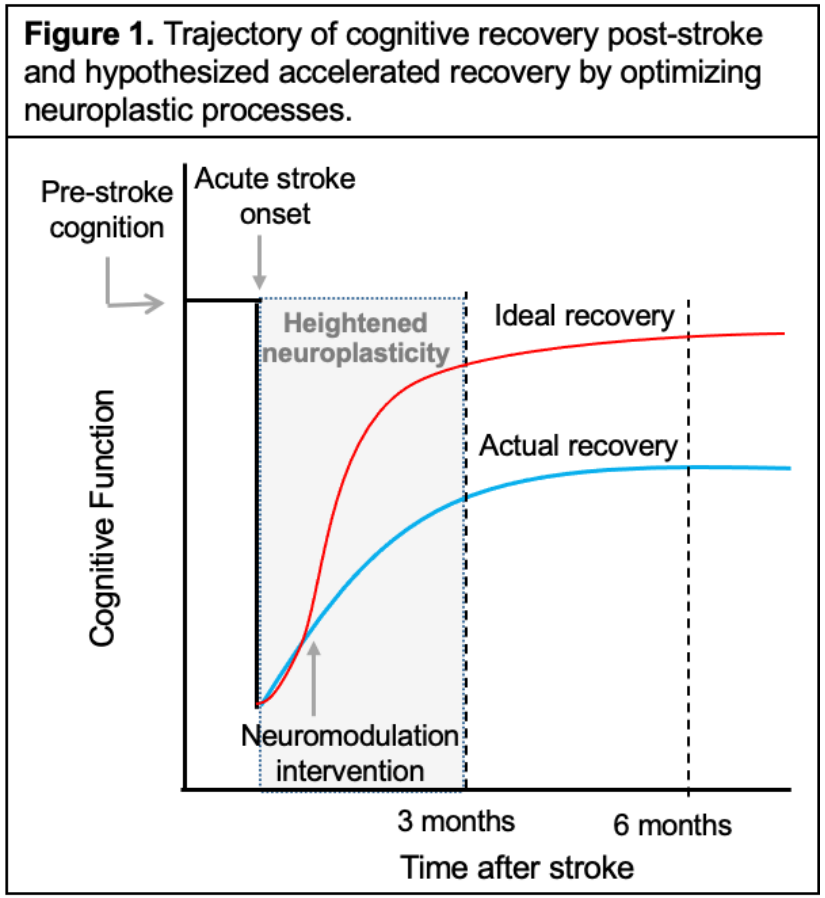
TRANSPORT2: tDCS + Constraint-Induced Movement Therapy to improve arm function within 30 days to 6 months of acute stroke

- **Cognitive**

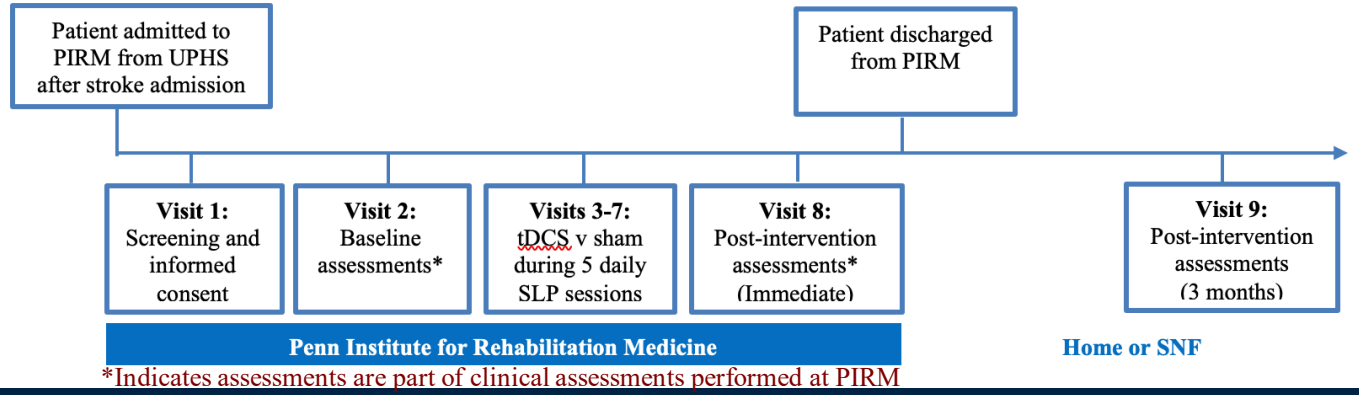
TRAINS: tDCS + cognitive therapy to improve attention and other cognitive functions within 3 months of acute stroke



TRAINS: Transcranial Direct Current Stimulation and Rehabilitation to Ameliorate Impairments in Neurocognition after Stroke



- tDCS potentiates depolarization of neurons, leading to hyperexcitability and learning
- Different effects depending on site stimulated and task performed while stimulated
- In our study, we are stimulating the left dorsolateral prefrontal cortex with a learning task involving memory and attention.



Molecular Targets for Stroke Recovery

- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

Device-based Targets for Stroke Recovery

- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation

What works?

Many interventions have potential
Few have consistent results
Only one (VNS) has FDA approval

Stroke recovery: Summary

- Stroke is the leading cause of adult disability in the United States.
- Predictive models are being developed to estimate motor recovery potential: currently, the proportional recovery rule indicates that 70% of lost function has the potential to be recovered.
- Many promising interventions are in various stages of conception, development, clinical testing.
- Stroke recovery is complex, multifaceted and predictably unpredictable
- Studies are needed to comprehensively evaluate “recovery”

Thank you!

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Branch Coslett, MD
Scott Kasner, MD
Pranav Ramkumar
Daniela Sacchetti

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